Observational Study

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Intravitreal ranibizumab injection at the end of vitrectomy for diabetic vitreous hemorrhage (Observational Study)

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Abstract

To evaluate the outcomes and complications of intravitreal injections of ranibizumab in patients during pars plana vitrectomy for treatment of diabetic vitreous hemorrhage. This retrospective, observational, comparative study included 103 patients (103 eyes) who underwent pars plana vitrectomy for treatment of diabetic vitreous hemorrhage. Sixty-six patients received an intravitreal injection of 0.05 mg (0.05 cc) of ranibizumab at the end of surgery. Main outcome measures were the occurrence of recurrent early vitreous hemorrhage, reoperation, intraocular pressure, best corrected visual acuity. Mean follow-up time was 6 months. The rate of rebleeding in the intravitreal ranibizumab (IVR) group was 6.1% (4 eyes), which is significantly lower than the control group (24.3%, 9 eyes, $P < .01$). The incidence of postoperative diabetic vitreous hemorrhage (PDVH) was significantly lower in the IVR group than the control group, OR=0.26, 95% CI= (0.06, 0.95). Visual acuity 6 months after operation was better in IVR group ($P<.01$) There was no difference in mean intraocular pressure between the 2 groups ($P=.56$). The present clinical study suggests that intravitreal injection of ranibizumab is effective in the prevention of postoperative diabetic vitreous hemorrhage in eyes undergoing pars plana vitrectomy for the treatment of diabetic vitreous hemorrhage.

Abbreviations: BCVA = best-corrected visual acuity, CI = confidential interval, DR = diabetic retinopathy, IOP = intraocular pressure, IVB = intravitreal bevacizumab, IVR = intravitreal ranibizumab, IVT = intravitreal triamcinolone, logMAR = logarithm of the minimum angle of resolution, OCT = optical coherence tomography, OR = odds ratio, PDR = proliferative DR, PDVH = postoperative diabetic vitreous hemorrhage, PPV= pars plana vitrectomy, PRP = panretinal photocoagulation, TRD = tractional retinal detachment, VEGF = vascular endothelial growth factor, VH = vitreous hemorrhage.

Keywords: proliferative diabetic retinopathy, ranibizumab, vitrectomy

1. Introduction

Diabetic retinopathy (DR) is the leading cause of severe vision loss in adults of working age, worldwide.[1,2]. Its pathology and etiology have been extensively studied for half a century, most research has concentrated on the microvasculopathy.[3] Diabetic microangiopathy, including retinopathy, is characterized by abnormal growth and leakage of small blood vessels, resulting in severe diabetic eye complications including macular edema, vitreous hemorrhage (VH), tractional retinal detachment (TRD), and anterior segment neovascularization.[3–6]

Nonclearing VH and TRD are 2 common complications associated with DR.[7,8] Since the Diabetic Retinopathy Vitrectomy Study over 25 years ago, there have been significant advancements in surgical techniques[9], such as the use of a wide-angled viewing system, perioperative endolaser, minimally invasive vitrectomy, and antivascular endothelial growth factor adjuvants before surgery. However, postoperative diabetic vitreous hemorrhage (PDVH) occurs frequently in diabetic patients who undergo pars plana vitrectomy (PPV) to address complications of proliferative diabetic retinopathy (PDR).[10–12] In a case series of patients who underwent vitrectomy for PDR, PDVH (either persistent or recurrent) occurred in over 50% of patients.[13] While the prevalence of PDVH reported in another case series was lower, ranging from 13% to 23%, these proportions are nonetheless substantial.[14–16]

Diabetic patients who develop PDVH may require further surgery, such as revision of vitrectomy, and the complication may

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lead to impaired visual outcomes.[9,11,17] Sources of VH include postoperative neovascularization at the posterior retinal surface and entry sites.[15,18–20] Although the exact source is unclear, early recurrent VH may be caused by the dissolution of blood clots trapped in the remaining antero-peripheral vitreous gel, remnants of fibrovascular tissue, or reactivation of retinal sites that bled intraoperatively.[21–23]

Vascular endothelial growth factor (VEGF), a major player in the pathogenesis of DR, is expressed at high levels in the retina of diabetic patients, consequently accumulating at a relatively increased concentration in the vitreous. Previous studies have revealed that high intraocular VEGF levels detected at the time of PPV in patients with PDR are a significant risk factor for the occurrence of PDVH.[24,25] The past decade has seen dramatic changes in the management of retinal vascular disease through the introduction of injectable anti-VEGF agents. As the mainstay of treatment in exudative macular degeneration, anti-VEGF agents have been shown to be highly effective as adjunct therapy prior to performing PPV in PDR. However, it is unclear whether anti-VEGF injections during the PPV procedure are useful in the prevention of PDVH associated with PDR.

The purpose of this study was to investigate whether injections of anti-VEGF therapy (Ranibizumab) during the PPV procedure in patients with PDR correlate with the occurrence of postoperative complications, focusing on late VH after the surgery.

2. Methods

This retrospective, observational, comparative study included the medical records of patients who underwent vitrectomy for nonclearing due to PDR between August 1, 2016 and June 31, 2017 at the Tianjin Eye Hospital, Tianjin, China. The research followed the tenets of the Declaration of Helsinki and approval for the study was obtained from the institutional review board of Tianjin Eye Hospital, Tianjin, China. All patients received a detailed explanation of the study and provided written informed consent.

The inclusion criteria for this study were: age ≥ 18 years and patients who had vitrectomy due to nonclearing diabetic VH for more than 3 months, and were followed up for more than 12 months after surgery.

The study exclusion criteria for patients were: those with TRD or iris neovascularization; those with ocular trauma, macular degeneration, glaucoma, pathological myopia, other eye diseases that may affect corrected vision (excluding age-related cataract), or those who underwent previous ocular surgery (except age-related cataract surgery); previous intravitreal corticosteroids or anti-VEGF injection in either eye; patients with inadequate glycemic or blood pressure control as well as cardiac disease; pregnancy or current oral contraceptive intake; usage of antiplatelet or anticoagulant drugs (e.g., Clopidogrel Bisulfate or Coumadin); and uncontrolled renal or liver disease.

Baseline data included age and duration of diabetes mellitus at the time of index vitrectomy. Each patient underwent complete preoperative ophthalmic examinations, including refraction, corneal culture, axial length, slit-lamp biomicroscopy, intraocular pressure (IOP) measurement using applanation tonometry, fundus examination by binocular indirect ophthalmoscopy, and B-scan ultrasonography. The best-corrected visual acuity (BCVA) was tested at a standardized distance (4 m) under standardized lighting conditions and the Snellen fraction was converted into the logarithm of the minimum angle of resolution (logMAR) values for statistical analysis. All patients underwent standard PPV under regional anesthesia. In patients with cataract, phacoemulsification was performed simultaneously, and the intraocular lens was implanted in the capsular bag. Since the degree of macular edema could not be detected before the surgery due to VH, it was instead evaluated during surgery.

All PPVs were carried out by using a 25-gauge 3-port system (Stellaris PC, Bausch + Lomb) and a high-speed vitreous cutter (5000 cycles/min). After extensive removal of the vitreous gel at the vitreous base, vitreous base shaving was performed under scleral depression, and blood clots in the peripheral vitreous skirt were also removed using this process. Intraoperative bleeding was controlled either by endodiathermy or increasing the height of the irrigation bottle. The endolaser was used to complete panretinal photocoagulation (PRP) up to the ora serrata. In some patients with combined fibrovascular membranes, intraocular forceps were used to peel or remove epiretinal membranes. After the air-fluid exchange, 0.05 mg (0.05 mL) of commercially available Ranibizumab was injected from the limbus via the pars plana using a 30-gauge needle. All surgeries were performed by 1 surgeon (YZ).

Patients were given the option to receive an intravitreal Ranibizumab (IVR) 0.5 mg injection following vitrectomy and each individual choice was recorded in the chart review by the authors. Follow-up examinations were done postoperatively at 2 weeks and 1, 2, 3, and 6 months. For statistical analysis, "Counting fingers" vision was defined as 2.0 logMAR and "hand movements" vision was defined as 3.0 logMAR.[26,27] The severity of pre- and postoperative VH was classified into 4 grades as follows: none (no VH), mild (most of the optic disc and retinal vessels were visible), moderate (optic disc or retinal vessels were barely visible), and severe (VH was too dense to allow visualization of the optic disc).

The Shapiro–Wilk test was used to determine whether the data were normally distributed. To examine the differences in baseline features, including patient demographic data, surgical findings, additional surgical procedures, surgical outcomes, and the frequency of manifest recurrent between the 2 groups, the χ^2 and Fisher exact tests were performed. The paired and unpaired t tests were used to compare differences in resolution, visual acuity values, and IOP. Data analysis was performed with the R software, version 3.4.2 (http://www.r-project.org) and findings were considered statistically significant at $P < .05$.

3. Results

In this study, the IVR and control groups consisted of 66 and 37 cases, respectively. All participants undergoing PPV for VH were studied. All participants who underwent PPV with or without IVR had attached retinas at the end of the 6-month follow-up. Demographic data are summarized in Table 1. Patient characteristics were similar between both groups (IVR and control) at baseline and no statistically significant differences were noted between the groups. All patients underwent air-fluid exchange at the end of the surgery. The gas volume reduced to about 30% of the vitreous cavity 3 days after surgery and was reabsorbed completely in 10 days. All patients underwent FFA and completed PRP within 1 month after vitrectomy.

After surgery, PDVH occurred in 4 eyes (6.1%) in the IVR group and in 9 eyes (24.3%) in the control group. The incidence of PDVH was significantly lower in the IVR group than the control group ($P < .01$). Early manifest recurrent VH, within 1

Table 1

The features of all participants at baseline.

Characteristics	IVR	Control	*P* value
Number of the eyes	66	37	
Age (mean ± SD)	48.69 ± 6.53	47.51 ± 6.77	.89*
Gender			
Male	39	19	.69†
Female	37	18	
Type of DM			
IDDM	8	5	.33†
NIDDM	58	32	
VH			
None	0	0	.29†
Mild	0	0	
Moderate	12	5	
Severe	54	32	
IOP (mean ± SD)	15.80 ± 2.45	16.11 ± 5.26	.98*
Duration of years	9.21	9.71	.68*
HbA1c, %	5.30 ± 1.26	5.42 ± 1.88	.36*

Values are presented as mean ± standard deviation.
IVB = intravitreal ranibizumab, DM = diabetes mellitus, IDDM = insulin-dependent diabetes, IOP = intraocular pressure.
* *t* test.
† χ^2 test.

month after surgery, did not occur in any of the cases in the IVR group but did occur in 2 cases in the control group. Late PDVH, more than 1 month after surgery, occurred in 4 eyes (16.7%) in the IVR group and 7 eyes in the control group. All cases with PDVH in the IVR group displayed eventual clearing of the hemorrhage, whereas 5 patients in the control group required vitreous lavage. In the control group, 3 patients were diagnosed with macular edema using optical coherence tomography (OCT) in the last follow-up.

As seen in Fig. 1, both patient groups showed improvement in mean visual acuity within 6 months. In the IVR group, the BCVA (mean ± SD) improved significantly from 1.64 ± 0.52 logMAR at baseline to 1.43 ± 0.32, 0.76 ± 0.11, 0.73 ± 0.2, 0.72 ± 0.1, and 0.61 ± 0.1 logMAR at 2 weeks, 1, 2, 3, and 6 months after

Table 2

The features of all participants at last fellow-up.

Characteristics	IVR	Control	*P* value
BCVA (logMAR)	0.61 ± 0.32	0.8 ± 0.5	*P*<.001*
VH			
Severe	0	2	*P*<.001†
Moderate	1	2	
Mild	3	5	
None	62	28	
IOP (mean ± SD)	15.86 ± 3.68	16.1 ± 4.51	.33*
Secondary glaucoma	0	0	
Endophathalmitis	0	0	

Values are presented as mean ± standard deviation.
IVR = intravitreal ranibizumab, BCVA = best-corrected visual acuity, logMAR = logarithm of the minimum angle of resolution, VH = vitreous hemorrhage, IOP = intraocular pressure.
* *t* test.
† Fisher exact test.

treatment, respectively ($P < .001$). In the control group, the BCVA was 1.60 ± 0.22 logMAR at baseline, improved to 1.39 ± 0.3 logMAR within 2 weeks, increased to 0.77 ± 0.25 logMAR in 1 month, 0.81 ± 0.2 logMAR in 2 months, reached 0.74 ± 0.17 logMAR in 3 months, and finally decreased to 0.78 ± 0.42 in 6 months. The most significant improvement in BCVA occurred within the first 3 months. The mean BCVA of the IVR group was significantly better than the control group in the last follow-up ($P < .01$).

Any hemorrhage that occurs in the vitreous cavity after the initial clearing is defined as rebleeding. The occurrence of PDVH was significantly lower in patients taking IVR compared with the control group with 4 patients (0.6%) in the IVR group and 9 (10.52%) in the control group ($P < .01$). Although no reoperation was performed in the IVR group, 4 patients underwent reoperation (10.8%) in the control group ($P < .01$; Table 2, Fig. 2). The power calculation resulted in an odds ratio (OR) of 0.32 for the IVR group with a 95% confidence interval of 0.06 to 0.95, as shown in Fig. 3.

No major complications were observed.

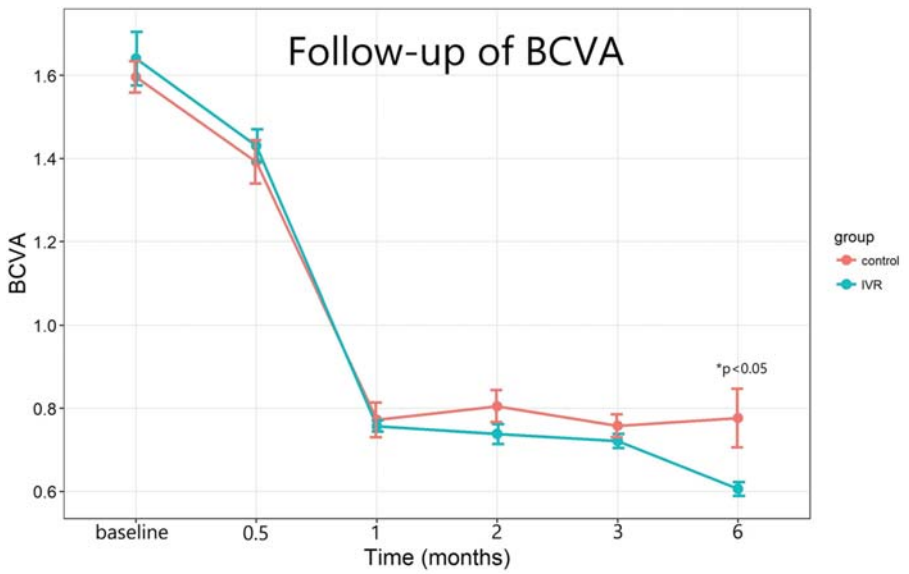

Figure 1. Follow-up of best corrected visual acuity after vitrectomy in 6 months. BCVA = best corrected visual acuity, IVR = intravitreal injection of ranibizumab.

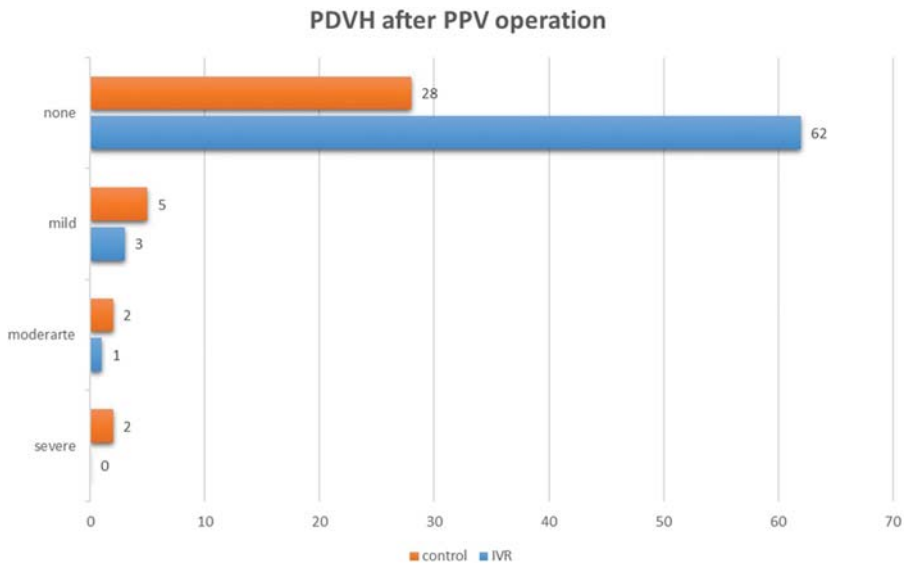

Figure 2. Follow-up of postoperative diabetic vitreous hemorrhage after vitrectomy. IVR = intravitreal injection of ranibizumab, PDVH = postoperative diabetic vitreous hemorrhage, PPV = pars plana vitrectomy.

4. Discussion

The purpose of this study was to evaluate a possible treatment to decrease the probability of PDVH occurring in patients who received PPV for VH due to PDR.

This study suggests a clinically important correlation between IVR and controlling the incidence of PDVH in eyes with VH from PDR is not entirely clear. In this study, for both groups, the BCVA after vitrectomy increased significantly. In the IVR group, the mean of BCVA gradually increased whereas, in the control group, the BCVA increased up to 3 months after surgery, and decreased slightly thereafter. The incidence of PDVH in the IVR group was significantly lower than the control group, and in the recurrent cases, all bleeding in the IVR group was self-absorbed, whereas in the control group, the vitreous cavity received partial vitreous lavage. The incidence of macular edema was significantly higher in the control group than in the IVR group. This could be a reason for the BCVA of some patients in the control group demonstrating a downward trend following 3 months.

Postoperative diabetic vitreous hemorrhage is a severe complication of PPV in patients with PDR and has long been recognized as a very difficult issue to manage. It may be noted as early as the first postoperative day or may occur on a more delayed timeline, that is, weeks or months after surgery. The reported prevalence of PDVH (occurring 1 or more weeks after surgery) is between 20% and 30%.[4,16] Many studies report that intravitreal anti-VEGF drugs administered before surgery can significantly reduce the probability of PDVH[1,16,28]; however,

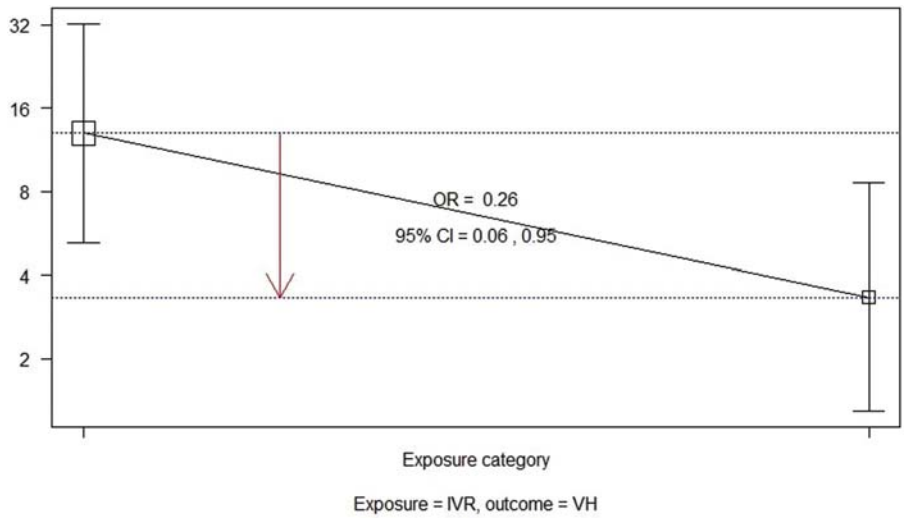

Figure 3. The odds ratio of postoperative diabetic vitreous hemorrhage after vitrectomy in 2 groups. CI = confidence interval, IVR = intravitreal injection of ranibizumab, OR = odds ratio, VH = vitreous hemorrhage.

other studies have contradicted these results and shown that these drugs fail to prevent PDVH.[23,29,30] Although definitive conclusions cannot be drawn, all studies[23,29,30] have shown that injection of anti-VEGF drugs (Bevacizumab and Ranibizumab) is helpful for limiting fibrovascular proliferation before vitrectomy, makes surgery easier, decreases surgical time, and reduces the frequency of endodiathermy. It is likely that the preoperative intravitreal anti-VEGF drug injections failed to prevent postoperative VH due to drug washout during PPV and air-fluid exchange, thereby making the drugs unavailable to inhibit remaining or future fibrovascular growth.

As such, we evaluated the effect of IVR as an adjunctive treatment administered after vitrectomy in patients with diabetic VH without TRD. The main cause of early PDVH is bleeding of the scleral surgery incision or rupture of sites of neovascularization at the optic disc and retina. As previous studies have shown, blockage of VEGF by Ranibizumab is expected to cause regression of neovascularization.[31,32] Therefore, IVR given at the end of air-fluid exchange can eliminate neovascularization either at the optic disc or retina. Due to the use of the endolaser during the procedures performed after the PPV, the neovascularization of the retina is limited, which in turn reduces the probability of bleeding after surgery.

Our study showed that patients who received IVR following vitrectomy had better BCVA compared with those who did not take IVR. Apart from the lower incidence of rebleeding, we believe that an improvement in BCVA in patients who received IVR was also due to a decrease in macular edema after injection. Unfortunately, although we did not evaluate the baseline characteristics of the maculae between the groups during PPV, given that macular edema was lower in the IVR group after the surgery and during follow-up, it is possible that this was the cause of improved vision in the IVR group.

Previous studies have reported that visual acuity after surgery was better in patients receiving intravitreal Triamcinolone (IVT) than in the control group.[17,33] However, an increased IOP after injection was the most common complication of IVT, as a potent dose of the corticosteroid leads to increased mean IOP in 28% to 52% of patients receiving IVT.[34–36] When comparing our results to those of other studies, it should be noted that the IOP between the IVR and control groups showed no statistical difference.

Other studies have shown intravitreal Bevacizumab (IVB) to be safe and effective in reducing the incidence of recurrent postoperative VH.[17,28,37] The IVB injection also does not carry the risk of an early temporary rise in IOP that is seen with the IVT injection. Both Bevacizumab and Ranibizumab have been reported to cause regression of neovascularization in eyes with active progressive PDR.

Although all patients received retinal air tamponade, the gas is almost fully replaced by liquid within 7 days. Therefore, the BCVA measurements are not likely to be affected by the tamponade.

The limitations of this study were its retrospective design, small sample size, short follow-up time, and lack of comparison of fluorescein angiography and OCT conducted at baseline and postvitrectomy. In addition to this, grouping was done according to each patient's choice to receive IVR, and as such, selection bias is an inherent limitation of this study.

Our results confirm that IVR injection is a good choice for diabetic patients with VH as it was effective in reducing PDVH complications and improved BCVA.

Author contributions

Involved in study design and conduct (XL, YZ); data collection, management, analysis (XL, YZ, W-RH), and interpretation (XL, J-XW, L-FW); and manuscript preparation, review, or approval (XL, XT).

Formal analysis: Xu Liang.

Investigation: Xu Liang, Li-Fei Wang, Wan-Rong Huang, Xin Tang.

Methodology: Xu Liang, Yue Zhang, Jia-Xing Wang.

Writing – review & editing: Xu Liang.

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