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ORIGINAL RESEARCH

Frequency and Risk Factors for Neovascular Glaucoma After Vitrectomy in Eyes with Diabetic Retinopathy: An Observational Study

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ABSTRACT

Introduction: Vitrectomy is one of the main treatments for proliferative diabetic retinopathy (PDR). Postoperative neovascular glaucoma, in which it is difficult to obtain satisfactory results using conventional filtering surgery, is one of the most serious complications of vitrectomy. It often requires destructive surgery, such as ciliary body photocoagulation or freezing, and the outcome with regard to visual acuity (VA) is extremely poor. The purpose of this study was to evaluate the prevalence of neovascular glaucoma (NVG) after modern vitrectomy techniques and investigate how variables assessed before and after vitrectomy are associated with patients who develop NVG after PDR surgery.

Methods: This was an observational study including the medical records of patients who underwent vitrectomy for PDR at Tianjin Eye Hospital from June 2014 to July 2016, were followed for at least 24 months postoperatively, and NVG developed within 2 years after surgery was recorded. Each patient underwent complete preoperative ophthalmic examinations in both preoperative and follow-up appointments. Factors associated with survival were determined using the Kaplan–Meier (KM) survival analysis to calculate the incidence of NVG after vitrectomy for PDR. Multivariable analysis was performed with the Cox regression proportional hazards model to verify the results of the analysis and eliminate interference factors between variables. All statistical analyses were performed using R statistical software (http://www.r-project.org) for Windows.

Results: In all, 238 patients (238 eyes) fulfilled the study criteria. NVG occurred in 11 of 238 eyes (4.6%). The percentages of NVG development after vitrectomy at 6, 12, and 24 months were 0.42%, 3.3%, and 4.6%, respectively. After step analysis, multivariable regression identified

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preoperative high intraocular pressure (IOP) combined with retinal vein occlusion (RVO), severe PDR, no postoperative intravitreal injection of ranibizumab (IVR), and higher HbA1c levels as significant predictors of NVG.
Conclusion: Preoperative high IOP combined with RVO, severe PDR, no postoperative intravitreal injection of ranibizumab (IVR), and higher HbA1c levels are significant predictors of NVG after vitrectomy.

Keywords: Diabetic retinopathy; Neovascular glaucoma; Vitrectomy

INTRODUCTION

Proliferative diabetic retinopathy (PDR) is a complication observed in diabetic patients and the most common cause of blindness in working-age populations [1]. The main severe complications of PDR are vitreous haemorrhage (VH), traction retinal detachment (TRD), and fibrovasculature of the retina. Pars plana vitrectomy (PPV) is the main treatment for this disease and is widely practised in a clinical setting.

However, previous studies have shown that PPV for PDR is associated with postoperative neovascular glaucoma (NVG) in 4–12% of cases [2, 3]. As an end-stage complication of PDR, it is difficult to obtain satisfactory results in NVG using conventional filtering surgery. It often requires destructive surgery, such as ciliary body photocoagulation or freezing, and the outcome with regard to visual acuity (VA) is extremely poor. NVG occurrence in PDR patients has been reported after PPV, in which it was significantly associated with combined pars plana lensectomy or preoperative aphakia, in the 1980s [4, 5]. Recently, a combination of lens extraction with PPV has been performed by phacoemulsification, and the technology underlying vitreous cutter devices is more advanced. The relationship between combined lens removal during PPV surgery and rubeosis needs to be reassessed.

The purpose of this study was to evaluate the prevalence of NVG after modern PPV techniques and investigate how variables assessed before and after PPV are associated with patients who develop NVG after PDR surgery.

METHODS

This observational study included the medical records of patients who underwent PPV for PDR at Tianjin Eye Hospital from June 2014 to July 2016 and were followed for at least 24 months postoperatively or developed NVG within 2 years after surgery. The research followed the tenets of the Declaration of Helsinki, and approval of 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.

Inclusion criteria for this study were (1) age at least 18 years old; (2) patients who had diabetic PPV due to PDR, including non-clearing vitreous haemorrhage for more than 3 months, fibrovascular membranes of the retina, or traction retinal detachment (TRD). The study exclusion criteria included (1) eyes with a history of glaucoma, neovascularization of the iris (NVI), ocular trauma, uveitis, intraocular injection or PPV, or evidence of other vitreoretinal disease; and (2) patients who were not satisfied with glycaemic or blood pressure control before surgery.

We retrospectively reviewed the patients' records for baseline data, including age and the duration of diabetes mellitus at the time of index PPV. Each patient underwent complete preoperative ophthalmic examinations, including refraction, and best-corrected visual acuity (BCVA), which was tested at a standardized distance (4 m) under standardized lighting conditions. Slit-lamp biomicroscopy, intraocular pressure (IOP) measurement using applanation tonometry, fundus examination by binocular indirect ophthalmoscopy, and B-scan ultrasonograpy were performed.

All PPVs were carried out using a 25-gauge 3-port system (Bausch Lomb 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 by increasing the height of the irrigation bottle height. An endolaser was applied 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 an air–fluid change, the injection of air or silicone was performed according to the severity of PDR. The severity of retinopathy (according to pre- or during surgery) was classified into three grades as follows: mild (only VH), moderate (fibrovascular membranes of the retina without retinal detachment), and severe (TRD). The definition of vascular occlusion (VO) was vascular occlusion or white line (according to pre- or during surgery) [1, 6]. All surgeries were performed by one surgeon (Yue Zhang, MD).

Follow-up examinations included blood pressure, glycosylated haemoglobin A1c (HbA1c) levels (detected every 3 months and averaged), IOP, BCVA, and complications of PPV (such as postoperative diabetic vitreous haemorrhage (PDVH), retinal re-detachment, and rubeosis). Within 2 months after PPV, when the IOP was at least 22 mmHg and no iris neovascularization was observed, the end point of the event was not considered. Once iris neovascularization was found and the IOP was elevated, observation was terminated.

Kaplan–Meier (KM) survival analyses were used to evaluate the incidence of NVG following PPV. Factors associated with NVG after PPV for PDR were determined using the KM survival analysis, log-rank test, and Cox regression. Multivariable analysis was performed on the meaningful variables from univariate analysis with the Cox regression proportional hazards model to verify the results of the analysis and eliminate interference factors between variables. The Akaike information criterion (AIC) was used in model order identification. The time-dependent covariate was not statistically significant, suggesting that the proportional hazard assumption was valid. Estimates for hazard ratios (HRs) and 95% confidential intervals (CIs) were calculated from these regression models. All statistical analyses were performed using R statistical software (http://www.r-project.org) for Windows and findings were considered statistically significant at $P < .05$.

RESULTS

A total of 238 patients (238 eyes) fulfilled the study criteria. Table 1 summarizes the demographic characteristics at baseline: 103 men and 135 women were included. The mean age of the included patients was 55.76 ± 10.1 years old, the mean duration of DM at baseline was 14.47 ± 7.63 (years), and an anti-VEGF drug was used to treat 186 eyes (78.0%) for PDR. Phaco-PPV was performed in 103 eyes (43.3%), phacoemulsification was performed simultaneously, the intraocular lens was implanted in the capsular bag, and there was no patient with posterior capsule rupture. Tamponade was performed in 104 patients, including 12% C_3F_8 and silicone oil in 19 and 85 patients, respectively. The demographic characteristics of the patients are shown in Table 1. A total of six patients underwent neodymium-YAG laser treatment due to posterior capsule opacification after surgery, and none of them suffered from NVG.

NVG occurred in 11 of 238 eyes (4.6%). The percentage of patients who developed NVG after PPV at 6, 12, and 24 months was 0.42%, 3.3%, and 4.6%, respectively (Fig. 1). After step analysis, multivariable regression identified preoperative high IOP combined with vascular occlusion (VO), severe PDR, no postoperative intravitreal injection of ranibizumab (IVR), and higher HbA1c levels as significant predictors of NVG (Table 2).

DISCUSSION

The incidence of postoperative NVG after PPV in our study was considerably lower than has been found in previously published series in which it was only 4.6% [3–5, 7–9]. The low

Table 1 Patient demographic characteristics

Characteristics	Value
Number of the eyes	238
Age (mean ± SD)	55.76 ± 10.1
Gender	
Male (%)	103 (43.28%)
Female (%)	135 (56.72%)
Intravitreal injection ranibizumab	
Yes (%)	186 (78.15%)
No (%)	52 (21.852%)
Type of DM	
1 (IDDM)	28 (11.72%)
2 (NIDDM)	210 (88.27%)
Duration of DM (mean ± SD)	14.47 ± 7.63 (years)
Cataract phacoemulsification (%)	103 (43.32%)
Severity of retinopathy[a]	
Mild	159 (66.81%)
Moderate	18 (7.6%)
Severe	61 (25.63%)
Tamponade	
Air	134 (56.3%)
C_3F_8	19 (7.98%)
Silicone	85 (35.71%)
IOP (mean ± SD)	14.26 ± 3.85
Occurrence of NVG at 2 years	11 (4.6%)

Values are presented as mean ± standard deviation
C_3F_8 perfluoropropane gas, *DM* diabetes mellitus, *IDDM* insulin-dependent diabetes, *IOP* intraocular pressure
[a] Severity of retinopathy, mild (only VH), moderate (fibrovascular membranes of the retina without retinal detachment), and severe (tractional detachment of retina)

incidence may be associated with significant advancements in surgical techniques, such as the use of a wide-angled viewing system, high cutter speed, minimally invasive PPV, and anti-vascular endothelial growth factor adjuvants before surgery. A recent study of 127 eyes with PDR reported that the occurrence of NVG was 11.8% after PPV [10], and this was also higher than the results of our study. The reasons may be that the inclusion criteria of our study were more stringent.

The main aim of this study was to detect the risk factors for postoperative NVG in PDR eyes after PPV. Our results show that preoperatively high IOP combined with VO, no intravitreal injection of anti-VEGF drugs, more severe PDR, and higher HbA1c levels were significant predictors of NVG (Table 3).

As many studies have reported [3, 10], a high baseline IOP is a risk factor for NVG. In the early stage, NVI usually appears as small vascular tufts that result from the leakage of protein and cells from the micro-NVI [11], and the IOP may be elevated before the NVI can be observed by gonioscope. A small NVI can sometimes be detected by iris fluorescein angiography (IFA) [12], and we will explore the significance of IFA in the early diagnosis of NVI in future studies. Many large epidemiological studies have found that diabetic patients are at high risk for glaucoma: The Rotterdam study found that diabetes is correlated with primary open-angle glaucoma [13]. The Blue Mountain study also obtained similar conclusions [14]. Finally, some scholars believe that elevated IOP may be one of the symptoms of diabetic autonomic dysfunction [15, 16].

Many studies on retinal vein occlusion (RVO) have clearly shown ischaemic RVO eyes are at risk of developing ocular neovascularization. Moreover, many studies have shown that diabetes mellitus is significantly associated with RVO [17, 18], especially when present with central retinal vein occlusion (CRVO) [19]. Diabetic patients with microvascular and microcirculatory disorders due to long-term hyperglycaemia had a higher risk than other patients of vascular occlusion. In addition, the appearance of a vascular white line is predicted to be a serious manifestation of PDR. The condition causing retinal ischaemia is aggravated, and the concentration of VEGF is increased. Studies of clinical specimens have shown that there is a strong correlation between increases in intraocular VEGF levels and the development

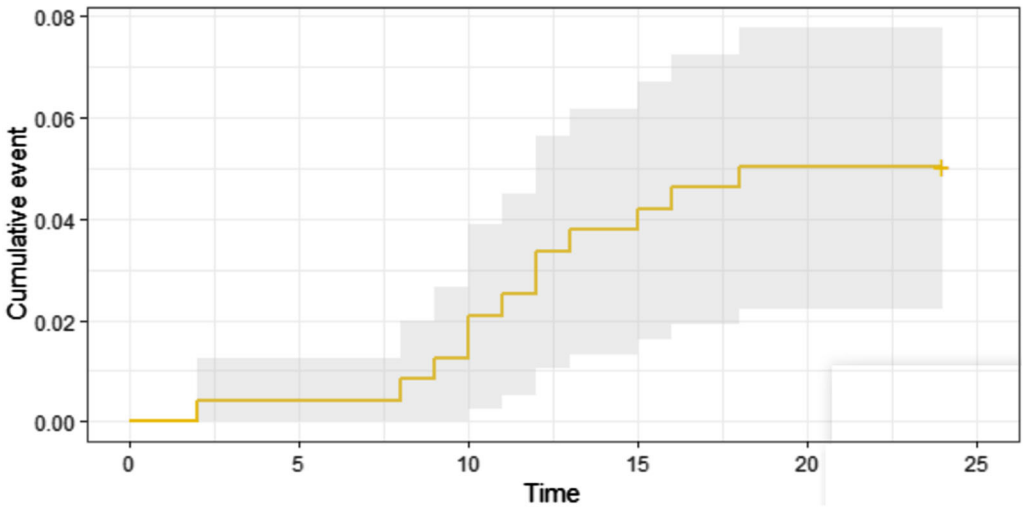

Fig. 1 Estimated cumulative probability of neovascular glaucoma (NVG) development after vitrectomy for proliferative diabetic retinopathy, as calculated by Kaplan–Meier survival analysis

Table 2 Univariate analysis of variables

Value	χ^2 (log-rank test)	*P*
Age	2.76	0.1
Duration of DM	0.55	0.5
HbA1c	45.5	< 0.001*
Preoperative IOP	51.32	< 0.001*
Gender	0.2	0.6
IVR	29	< 0.001*
Type of DM	0.1	0.7
Cataract phacoemulsification	2.7	0.1
Severity of retinopathy	29.5	0.004*
Tamponade	1	0.6
VO	13.2	0.03*

DM diabetes mellitus, *HbA1c* glycated haemoglobin, *IOP* intraocular pressure, *IVR* intravitreal injection ranibizumab, *VO* vascular occlusion
*$P < 0.05$

Table 3 Likelihood of postoperative NVG (multivariable analysis)

Variables	HR	95% CI	*P*
VO	2.85	1.54–8.33	0.025*
Severity of retinopathy	15.11	2.00–30.56	0.02*
IVR	0.07	0.02–0.13	0.03*
HbA1c	3.91	1.08–14.15	0.016*
Preoperative IOP	7.72	1.15–34.62	0.007*

HR hazard ratio, *CI* confidence interval, *VO* vascular occlusion, *IVR* intravitreal injection of ranibizumab, *HbA1c* glycated haemoglobin, *IOP* intraocular pressure
*$P < 0.05$

of PDR [20], and retinal vascular occlusion often indicates poor vascular function in the whole body. Studies have shown that carotid plaque is associated with RVO [21] when vascular occlusion is found pre- or during PPV, and there is a substantial risk of ocular ischaemic syndrome, which causes NVG. Fewer studies have explored the combination of PDR with VO, and there are also few corresponding epidemiological studies. In our opinion, awareness of this syndrome needs to highlight diabetes-related ocular disease.

Our results illustrate the fact that different grades of PDR for PPV are associated with widely different results. The more serious DR, especially the detached retina, has lost its supply of

blood from the choroid, is more ischaemic, and may produce greater amounts of vaso-proliferative factors. In addition, in patients with severe PDR, the systemic disease is also more severe, leading to a greater likelihood of carotid plaque, resulting in a higher occurrence of NVG [22]. An earlier study published in 1998 demonstrated that PDR patients with TRD are more prone to NVG [23], and some other studies have shown that more serious PDR is more dangerous to low vision and increases the incidence of NVG [24, 25].

Treatment with an intravitreal injection of anti-VEGF has been shown to be an efficient and safe treatment for NVG in multiple studies [26–28]. Castillo et al. reported that 156 patients who received preoperative IV anti-VEGF drugs 5–10 days prior to PPV demonstrated significantly better BCVA and fewer postoperative complications at 6 months. Similarly, previous studies have administered preoperative IV anti-VEGF drugs from 1 to 33 days before PPV for PDR-related complications [26, 27, 29–31]. All these results indicate that preoperative treatment with IV anti-VEGF drugs may represent a strategy to make PPV safer and more effective for severe PDR. However, few studies have reported whether preoperative IV anti-VEGF drugs are associated with postoperative NVG. To our knowledge, bevacizumab induces the regression of retinal neovascularization in patients with PDR, and the regression of the vascular component of fibrovascular complexes after treatment with IV anti-VEGF drugs facilitates the segmentation and delamination of membranes and thereby greatly reduces the likelihood of intraoperative bleeding. The resolution of VH and less intraoperative bleeding may in turn provide a clear surgical field and shorten surgical times. A clearer surgical field can reduce iatrogenic retinal breaks, improve panretinal photocoagulation (PRP), and decrease the incidence of NVG. Contrary to our conclusion, Kwon et al. reported that postoperative intravitreal bevacizumab (IVB) is a risk factor for postoperative NVG [10]; however, when comparing their and our results, it must be noted that the optimal timing of preoperative IVB is very important. Surgeons performing PPV on patients with PDR should consider administering preoperative IVB 5–10 days prior to PPV, especially in cases with severe grades of vitreoretinal adhesion, and this information was not clearly presented in their paper. Overall, further clinical trials should be performed in the future to determine the association between preoperative IV administration of anti-VEGF drugs and postoperative NVG.

Glycated haemoglobin, which has an average lifetime of 120 days and the blood level of which represents the average blood glucose concentration for that period, is an important index of systemic factors. In a previous report, when HbA1c levels were 6.5% or higher, the risk of diabetic retinopathy was exacerbated [32]. A large epidemiological survey performed in the USA, the Diabetes Control and Complications Trial (DCCT), showed that when glycosylated haemoglobin is reduced by 10% (e.g., from 7% to 6.3%), the progression of retinopathy is reduced by 35–40%, that is, patients with 10% glycosylated haemoglobin will have a risk of developing diabetic retinopathy when glycosylated haemoglobin decreases to 7% [33]. The results of the United Kingdom Prospective Diabetes Study (UKPDS) also show that for every 1% reduction in glycated haemoglobin, the complications of diabetic retinopathy were reduced by 35% [34]. Another clinical study performed in 2017 also showed that if blood glucose control is not satisfactory after PPV, the risk of postoperative neovascular glaucoma is greater [10]. This may be because PPV for PDR will cause damage to the retina, and postoperative ischaemia–reperfusion injury will also lead to increased retinal inflammation and if combined with postoperative hyperglycaemia will lead to increased microcirculatory damage to the retina, eventually leading to a large release of VEGF. In addition, in patients with proliferative diabetic retinopathy, promoting neovascularization factor functions are stronger than those of inhibiting neovascularization factors. Vitreous barrier function is weakened after vitreous surgery, resulting in faster diffusion of VEGF, making the vascular endothelium of the anterior segment an area of increased concentration of growth factor which causes neovascularization of the iris, and postoperative hyperglycaemia also exacerbates this process.

Furthermore, in addition, hyperglycaemia can cause systemic microcirculatory disorders, leading to hypoperfusion retinopathy (ocular ischaemic syndrome) and causing rubeosis iridis [35].

Contrary to this work, previous studies have found that PPV combined with cataract extraction is a risk factor for postoperative NVG [4, 36–38]. This may be because the previous research time was relatively early; during that time, cataract surgery could damage the barrier function of the posterior capsule and suspensory ligament. With the development of cataract phacoemulsification technology, surgical trauma is greatly reduced.

We also found that male sex, younger age, type 1 diabetes, and a longer duration of diabetes were also considered risk factors for postoperative neovascular glaucoma in previous studies [3, 5, 8, 10]. In this study, of the patients who developed NVG, six were male and five were female; the youngest was 42 years old and the oldest was 72; the prevalence of type 1 and type 2 diabetes was similar; and the shortest the duration of diabetes was 2 years, while the longest was 30 years. None of these results were statistically significant.

CONCLUSION

The occurrence of NVG after diabetic PPV is caused by multiple factors, including preoperative high IOP, combined with VO, severe PDR, no postoperative intravitreal injection of ranibizumab (IVR), and higher HbA1c levels. Regardless of the risk factors, the result depends on whether the retina and ocular anterior segment are ischaemic. The major limitation of the present study is that the number of participants was not large enough, the number of the eyes with NVG was only 11 eyes, as this limited the statistical power for identifying risk factors. Another limitation is that the duration of follow-up was too short. Further studies involving a larger number of patients and a longer follow-up period are therefore needed to verify our results.

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Compliance with Ethics Guidelines. This research followed the tenets of the Declaration of Helsinki, and approval of 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.

Data Availability. Requests for access to the study data can be submitted via email to zhongguol985@163.com.

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