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Causes and prognosis of neovascular glaucoma after pars plana vitrectomy in patients with diabetic retinopathy

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Abstract

Background This study aims to investigate factors and prognosis of neovascular glaucoma (NVG) after pars plana vitrectomy (PPV) in patients with proliferative diabetic retinopathy (PDR).

Methods A total of 200 PDR patients with 225 eyes from May 2017 to January 2023 were retrospectively analyzed, including 115 males (128 eyes) and 85 females (97 eyes) with ages ranging from 30 to 75 years. All 25G PPV surgeries were completed by the same experienced chief physician. During the surgery, the anterior retinal fibrous vascular membrane was fully removed, and laser panretinal photocoagulation (PRP) was performed, phacoemulsification was combined in 114 patients. The average postoperative follow-up time was 10.65 ± 6.84 months and occurrence of NVG was recorded. Potential risk factors of NVG included age, glycated hemoglobin (HbAlc), blood urea nitrogen (BUN), severity of preoperative fundus lesion, preoperative treatment of anti-vascular endothelial growth factor (VEGF), preoperative PRP application, combination of phacoemulsification.

Results Among the total 225 eyes, 15 (6.7%) eyes developed NVG 1–12 months after surgery, including 11 cases within 6 months. Incidence of NVG was associated with age (t=-3.974), preoperative treatment of anti-VEGF ($\chi^2 = 5.706$), preoperative PRP application ($\chi^2 = 4.744$), comorbid tractional retinal detachment (TRD) ($\chi^2 = 3.883$), comorbid fibrovascular proliferation (FVP) ($\chi^2 = 4.093$), and combination of phacoemulsification ($\chi^2 = 6.179$), with all *P* values less than 0.05. On the other hand, no differences were found in HbAlc (t = 0.733) and BUN (t = 0.470), with both *P* values greater than 0.05. By the end of follow-up, all NVG cases after PPV underwent intravitreal injection of anti-VRGF drugs and supplementary retinal laser therapy, of which 8 patients had stable intraocular pressure control, 5 patients received drainage valve implantation surgery to control intraocular pressure, 1 patient abandoned surgery due to no light perception at presentation, and 1 patient underwent cyclophotocoagulation. The postoperative best corrected visual acuity (BCVA) after NVG was statistically significant compared with that before NVG ($P < 0.05$).

Conclusions Occurrence of NVG in PDR was related to preoperative PRP and anti-VEGF, and might further have impact on prognosis. In addition, comprehensive consideration of patient's age, severity of preoperative fundus lesion and appropriate surgical method (i.e., whether combined with phacoemulsification) could be protective factors of NVG.

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Keywords Proliferative diabetic retinopathy, Pars plana vitrectomy, Neovascular glaucoma

Background

Currently, pars plana vitrectomy (PPV) serves as the primary treatment of proliferative diabetic retinopathy (PDR). As one the most severe postoperative complication, neovascular glaucoma (NVG) can lead to visual loss or even blindness. Pathogenesis of NVG is mainly the formation of new blood vessels through the angle and iris, which in turn to contraction and traction of microvascular membrane, resulting in angle closure and elevated intraocular pressure [1]. The primary pathological mechanism of NVG caused by PDR is multiple cytokines produced after retinal ischemia and hypoxia are mediated, among which vascular endothelial growth factor (VEGF) is the most important [2]. In recent years, with the development of minimally invasive surgery and the massive perioperative application of anti-VEGF therapy, surgical procedure and efficacy for PDR has been changed. However, study [3] has shown that the number of various cytokines including VEGF in the vitreous will increase greatly after PPV among PDR patients, and at the same time, with the progression of diabetes after surgery, some patients are complicated with NVG. Therefore, NVG is still a serious blinding disease after PPV among PDR cases. This retrospective study aims to investigate factors and prognosis of NVG after PPV in patients with PDR.

Methods

The institutional review board of Hebei Eye Hospital approved this retrospective study. A total of 200 PDR patients with 225 eyes from May 2017 to January 2023 in our hospital were recruited, including 115 males (128 eyes) and 85 females (97 eyes) with ages ranging from 30 to 75 years. All participants were comorbid with type II diabetes.The study adhered to the principles of the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Hebei Eye Hospital.

High-performance liquid chromatography and automatic enzyme analyzer was used to measure glycated hemoglobin (HbAlc) and blood urea nitrogen (BUN), separately. The mean HbAlc was 7.4 ± 1.5%, ranging from 6.3 to 11.1%. The mean BUN was 6.5 ± 2.5mmol/L, ranging from 2.9 to 11.8mmol/L. Visual acuity, best corrected visual acuity, intraocular pressure, slit-lamp microscopy combined with anterior endoscopy and indirect ophthalmoscopy were performed in all affected eyes. Color fundus photography and ultrasound were conducted according to the refractive media. Based on preoperative examinations and intraoperative exploration, we determined the comorbidities of tractional retinal detachment (TRD) and fibrovascular proliferation (FVP). The best corrected visual acuity(BCVA) was light perception ~ 0.4 and intraocular pressure was all in normal range (< 21mmHg). Of all 225 affected eyes, 69 eyes were complicated with TRD and 94 eyes were complicated with FVP.

Inclusion criteria were as follows: (1) confirmed diagnosis of PDR; (2) vitreous hemorrhage not absorbed for more than 1 month, presence of TRD, or traction of the retinal microvascular membrane severely affecting vision; (3) follow up for at least 1 year after surgery, and for those with silicone oil filling, followed up for at least 1 year after removing the silicone oil.

Patients were excluded if (1) they had high preoperative intraocular pressure, or family history of glaucoma; (2) they had previous vitreous surgery or other ocular surgery; (3) there was preoperative iris neovascularization in the affected eye or contralateral eye, or they had preoperative uveitis and other intraocular diseases; (4) follow-up time was shorted than the time of inclusion criteria.

All 25G PPV surgeries were completed by the same experienced chief physician. Among all 225 eyes, 140 eyes underwent intravitreal injection of anti-VEGF 3 to 7 days before surgery. Besides, patients with lens opacification underwent phacoemulsification combined with PPA, and intraocular lenses were implanted at early stage as much as possible. A total of 96 eyes received phacoemulsification, during which the peripheral vitreous was fully resected, triamcinolone acetonide staining was used to completely remove the residual vitreous cortex, and if necessary, the epiretinal proliferative membrane was thoroughly removed with the help of 25G microscissors. During the operation, PRP was performed to the serrated margin in the top pressure state. Except for those who had completed PRP (148 cases) before the operation, the other basic intraoperative retinal laser points were 1800–2900 points. Different fillers were selected according to the degree of fundus lesions, including 95 eyes filled with silicone oil, 46 eyes filled with C3F8 gas, and 84 eyes filled with perfusate.

Incidence of NVG was calculated. Baseline information was analyzed in terms of age, HbAlc, BUN, severity of preoperative fundus lesion, preoperative anti-VEGF, preoperative PRP application, and combination of phacoemulsification, in order to investigate causes and prognosis of NVG.

Numerical differences between groups were assessed by independent t test for continuous variables (e.g., age, HbAlc, BUN) and chi-square test for categorical variables (e.g., preoperative PRP and anti-VEGF, combination of phacoemulsification, comorbid TRD and FVP). The best

Table 1 Comparison of baseline information between NVG and non-NVG (continuous data)

NVG	Cases/eyes (*n*)	Age (years)	HbAlc (%)	BUN (mmol/L)
NVG	15/15	49.50 ± 6.55	7.6 ± 1.5	6.6 ± 2.4
Non-NVG	185/210	56.60 ± 7.83	7.3 ± 1.8	6.3 ± 2.1
t		-3.974	0.733	0.470
P value		0.001	0.473	0.645

corrected visual acuity (BCVA) between NVG after surgery was compared using t test. The threshold for significance was set at $P < 0.05$. All statistical analyses were conducted using SPSS Statistics, Version 26.0.

Results

The first best corrected visual acuity after surgery was finger count ~ 1.0.

Among the total 200 patients and 225 eyes, 15 (6.7%) eyes (15 patients) developed NVG and 210 (93.3%) eyes (185 patients) did not develop NVG. Incidence of NVG was associated with age, preoperative treatment of anti-VEGF, preoperative PRP application, comorbid TRD, comorbid FVP, and combination of phacoemulsification, with all *P* values less than 0.05 (Table 1). On the other hand, no differences were found in HbAlc and BUN, with both *P* values greater than 0.05 (Table 2).

NVG happened 1–12 months after surgery, including 11 cases within 6 months. All NVG cases after PPV underwent intravitreal injection of anti-VRGF and supplementary retinal laser therapy, of which 8 patients had stable intraocular pressure control, 5 patients received drainage valve implantation surgery to control intraocular pressure, 1 patient abandoned surgery due to no light perception at presentation, and 1 patient underwent cyclophotocoagulation. The postoperative BCVA after NVG was statistically decreased compared with that before NVG ($P < 0.05$) (Table 3).

Table 3 Comparison of BCVA before NVG and after NVG

NVG	BCVA	t	*P* value
Before NVG	0.41 ± 0.14	2.838	0.008
After NVG	0.27 ± 0.14		

Discussion

Incidence of NVG among PDR was 6.7% in our study, which was slightly lower than previous study who reported that the probability of NVG occurrence at 12 months after vitrectomy was 7.1% [4]. The possible explanation may be the development of minimally invasive vitreoretinal surgery and the massive perioperative application of anti-VEGF therapy. Previous study identified close relationship between high expression of VEGF and NVG [5–6]. Retinal vessels can promote endothelial cells to synthesize VEGF under stimulation conditions of ischemia and hypoxia, and subsequently VEGF can catalyze the synthesis of nitric oxide synthase (NOS) by binding to its receptor, thereby increasing the production of nitric oxide (NO). NO inhibit the activity of protein kinase Cdelta (PKCδ) while strengthen the activity of integrin alphavbeta3 (αvβ3) to achieve endothelial cell migration and proliferation, and then trigger angiogenesis. A randomized controlled study by Yazdani et al. [7] investigated the effect of intravitreal bevacizumab, an anti-VEGF agent, on NVG in 26 eyes of 26 patients. All eyes were treated routinely with NVG and randomized to three 2.5 mg intravitreal injections 4 weeks apart or sham surgery. The authors concluded that intravitreal bevacizumab reduced iris neovascularization and maintained intraocular pressure stability in NVG. In this study, we found that both preoperative PRP and anti-VEGF could reduce the risk of NVG, which might be associated with the decreased VEGF level in intravitreal. PRP induces oxygen diffusion from the choroid to retinal or retinal pigment epithelial cells, thus improving the microenvironment of retinal hypoxia, finally downregulating VEGF [8–11]. Takayama et al. [12] also reported that preoperati. ve uncombined PRP was a risk factor for secondary NVG after PPV, suggesting that preoperative improvement of PRP, intraoperative supplementation of retinal photocoagulation according to the condition, as well as elimination of non-perfused areas to reduce VEGF release, could effectively reduce the occurrence of postoperative NVG. While anti-VEGF (e.g., conbercept, ranibizumab) targets to decrease VEGF expression, which in turn inhibits neovascularization at retina, iris, and angle, as well as reduces the risk of NVG development [13–16]. Our study also indicated a higher risk of NVG after combined phacoemulsification, which might be due to the destroyed barrier between the anterior and posterior

Table 2 Comparison of baseline information between NVG and non-NVG (categorical data)

NVG	Cases/eyes (*n*)	TRD eyes (*n*)	FVP eyes (*n*)	Preoperative PRP eyes (*n*)	Phacoemulsification eyes (*n*)	Preoperative anti-VEGF eyes (*n*)
NVG	15/15	8	10	6	11	5
Non-NVG	185/210	61	84	14 2	85	135
χ^2		3.883	4.093	4.744	6.179	5.706
P value		0.049	0.043	0.029	0.016	0.017

segments in PDR patients after cataract removal [17], resulting in the forward spread of VEGF, inflammatory cytokines and other promoting vascular proliferative substances. In addition, anterior chamber oxygen diffuses posteriorly into the vitreous cavity thus exacerbating the hypoxic condition of the iris [18], which in turn increases the possibility of NVG. Chung et al. [19] demonstrated that compared with PPV group (0.0%), incidence of postoperative NVG was 21.6% in combined phacoemulsification group, thus concluding that the combination of PPV and phacoemulsification was risk factor of NVG. Of course, this view has also been controversial, especially the current phacoemulsification owns advantages of short operation time, less trauma and good incision closure. Also, with the continuous improvement of surgical techniques, the posterior lens capsule can basically be completely preserved, and occurrence of NVG is significantly lower [20]. Another finding in our study was the increased risk of postoperative NVG among patients with preoperative comorbid TRD or FVP. The potential explanation of the above result is that in severe intraoperative fundus disease, retinal ischemia and hypoxia is also relatively serious, thus vitrectomy surgery will be more difficult with longer operation time, especially intraoperative combination of retinal laser treatment, postoperative inflammatory factors and VEGF expression will be highly up-regulated [21], and then increase the risk of postoperative NVG. HbAlc and BUN levels are the embodiment of recent blood glucose control and renal function. Prior study [22] pointed out that patients with higher HbAlc and BUN were more vulnerable to NVG, especially in the progressive stage of diabetic retinopathy. However, such association was not reported by our study, which might be related to the regular personal physical management after surgery, sample size or morbidity, or multiple factors could be limited in one study.

Once NVG occurs, anti-VEGF therapy and complete PRP need to be performed as soon as possible, and if necessary, anti-glaucoma surgery should be conducted to strive for effective control of intraocular pressure and maximize the preservation of the patient's visual function [23]. All our NVG patients (15 eyes) after PPV underwent intravitreal injection of anti-VRGF and supplementary retinal laser therapy, of which 8 patients had stable intraocular pressure control, 5 patients received drainage valve implantation surgery to control intraocular pressure, 1 patient abandoned surgery, and 1 patient underwent cyclophotocoagulation. But for these patients, visual acuity decreased after the development of NVG, and even some patients had permanent loss of visual function. Therefore, it is particularly important to prevent and reduce the occurrence of postoperative NVG in PDR. Current application of anti-VEGF drugs and early preoperative PRP have greatly enhanced the prognosis of PDR patients. Besides, comprehensive consideration of patient's age, severity of preoperative fundus lesion and appropriate surgical method (i.e., whether combined with phacoemulsification) could be protective factors of NVG. Limitation of this study is the insufficient sample size which may leave out some significant factors in the process of postoperative NVG among PDR. Hence, it is hoped that with the deepening of the study, our understanding of NVG will become more and more clear, thus to minimize the risk of postoperative NVG in PDR patients.

Abbreviations

PDR	Proliferative diabetic retinopathy
NVG	Neovascular glaucoma NVG
PPV	Pars plana vitrectomy
VEGF	Vascular endothelial growth factor
BUN	Blood urea nitrogen
TRD	Tractional retinal detachment
FVP	Fibrovascular proliferation
PRP	Panretinal photocoagulation

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Author contributions
"CL, JP conceived and designed the study. XQ, participated in information gathering and editing, analyzed and interpreted all the data.CL wrote and edited the manuscript. BG, FW reviewed the manuscript. All authors read and approved the ffnal manuscript".

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Data availability
The authors confirm that the data supporting the findings of this study are available within the article. More detailed raw data are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
The study was performed in accordance with the Declaration of Helsinki and was approved by the ethics committee of Hebei Eye Hospital, China. Written informed consent was obtained from each patient or their parents (for children < 18 years of age) prior to participation in the study.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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References

1. Havens SJ, Gulati V. Neovascular glaucoma. Dev Ophthalmol. 2016;55:196–204.

2. Hwang S, Hong EH, Kang MH, et al. Early postoperative bevacizumab for preventing neovascular glaucoma in phacovitrectomy for proliferative diabetic retinopathy. Sci Rep. 2025;15(1):1231.
3. Song S, Yu X, Zhang P, Dai H. Increased levels of cytokines in the aqueous humor correlate with the severity of diabetic retinopathy. J Diabetes Complications. 2020;34(9):107641.
4. Goto A, Inatani M, Inoue T, et al. Frequency and risk factors for neovascular glaucoma after vitrectomy in eyes with proliferative diabetic retinopathy. J Glaucoma. 2013;22(7):572–6.
5. Simha A, Braganza A, Abraham L et al. Anti-vascular endothelial growth factor for neovascular glaucoma. Cochrane Database Syst Rev. 2013;(10):CD007920.
6. Rodrigues GB, Abe RY, Zangalli C, et al. Neovascular glaucoma: a review. Int J Retina Vitreous. 2016;2:26.
7. Yazdani S, Hendi K, Pakravan M, et al. Intravitreal bevacizumab for neovascular glaucoma: a randomized controlled trial. J Glaucoma. 2009;18(8):632–7.
8. Ogata N, Ando A, Uyama M, et al. Expression of cytokines and transcription factors in photocoagulated human retinal pigment epithelial cells. Graefes Arch Clin Exp Ophthalmol. 2001;239(2):87–95.
9. Olmos LC, Sayed MS, Moraczewski AL, et al. Long-term outcomes of neovascular glaucoma treated with and without intravitreal bevacizumab. Eye (Lond). 2016;30(4):463–72.
10. Magargal LE, Brown GC, Augsburger JJ, et al. Efficacy of panretinal photocoagulation in preventing neovascular glaucoma following ischemic central retinal vein obstruction. Ophthalmology. 1982;89(7):780–4.
11. Kriechbaum K, Bolz M, Deak GG, et al. High-resolution imaging of the human retina in vivo after scatter photocoagulation treatment using a semiautomated laser system. Ophthalmology. 2010;117(3):545–51.
12. Takayama K, Someya H, Yokoyama H, et al. Risk factors of neovascular glaucoma after 25-gauge vitrectomy for proliferative diabetic retinopathy with vitreous hemorrhage: a retrospective multicenter study. Sci Rep. 2019;9(1):1–6.
13. Park SC, Su D, Tello C. Anti-VEGF therapy for the treatment of glaucoma: a focus on ranibizumab and bevacizumab. Expert Opin Biol Ther. 2012;12(12):1641–7.
14. Wittstrom E, Holmberg H, Hvarfner C, Andreasson S. Clinical and electrophysiologic outcome in patients with neovascular glaucoma treated with and without bevacizumab. Eur J Ophthalmol. 2012;22(4):563–74.
15. Zhou MW, Wang W, Huang WB, et al. Adjunctive with versus without intravitreal bevacizumab injection before Ahmed glaucoma valve implantation in the treatment of neovascular glaucoma. Chin Med J (Engl). 2013;126(8):1412–7.
16. Zhou M, Chen S, Wang W, et al. Levels of erythropoietin and vascular endothelial growth factor in surgery-required advanced neovascular glaucoma eyes before and after intravitreal injection of bevacizumab. Invest Ophthalmol Vis Sci. 2013;54(6):3874–9.
17. Senn P, Schipper I, Perren B. Combined pars plana vitrectomy, phacoemulsification, and intraocular lens implantation in the capsular bag: a comparison to vitrectomy and subsequent cataract surgery as a two-step procedure. Ophthalmic Surg Lasers. 1995;26(5):420–8.
18. Stefansson E, Landers MB 3rd, Wolbarsht ML. Increased retinal oxygen supply following pan-retinal photocoagulation and vitrectomy and lensectomy. Trans Am Ophthalmol Soc. 1981;79:307–34.
19. Chung TY, Chung H, Lee JH. Combined surgery and sequential surgery comprising phacoemulsification, pars plana vitrectomy, and intraocular lens implantation: comparison of clinical outcomes. J Cataract Refract Surg. 2002;28(11):2001–5.
20. Lahey JM, Francis RR, Kearney JJ. Combining phacoemulsification with pars plana vitrectomy in patients with proliferative diabetic retinopathy: a series of 223 cases. Ophthalmology. 2003;110(7):1335–9.
21. Wang J, Chen S, Jiang F, et al. Vitreous and plasma VEGF levels as predictive factors in the progression of proliferative diabetic retinopathy after vitrectomy. PLoS ONE. 2014;9(10):e110531.
22. Kwon JW, Jee D, La TY. Neovascular glaucoma after vitrectomy in patients with proliferative diabetic retinopathy. Med (Baltim). 2017;96(10):e6263.
23. Sun Y, Liang Y, Zhou P, et al. Anti-VEGF treatment is the key strategy for neovascular glaucoma management in the short term. BMC Ophthalmol. 2016;16(1):150.

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