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Neovascular glaucoma after vitrectomy in patients with proliferative diabetic retinopathy

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Abstract

To evaluate the prevalence and risk factors of neovascular glaucoma (NVG) after vitrectomy in patients with vitreous hemorrhage associated with proliferative diabetic retinopathy (PDR). This retrospective, noncomparative, observational study included 127 eyes of 127 patients with PDR who received vitrectomy with a follow-up period of at least 6 months. The prevalence of NVG and associated risk factors were assessed including sex, age, previous panretinal photocoagulation, baseline intraocular pressure, combined phacovitrectomy, and pretreatment with intravitreal bevacizumab (IVB) before vitrectomy for the treatment of vitreous hemorrhage. NVG developed in 15 (11.8%) of 127 patients. Of the 15 eyes with NVG, 11 cases (73.3%) postoperatively developed NVG within 6 months. Postoperative NVG was associated with preoperative IVB treatment (odds ratio, 4.43; $P=0.019$). The prevalence of NVG after vitrectomy was 11.8%, and an associated risk factor for NVG was preoperative IVB for the treatment of vitreous hemorrhage.

Abbreviations: CI = confidential interval, CTGF = connective tissue growth factor, DR = diabetic retinopathy, IOP = intraocular pressure, IVB = intravitreal bevacizumab, NVG = neovascular glaucoma, OR = odds ratio, PDR = proliferative DR, PRP = panretinal photocoagulation, VEGF = vascular endothelial growth factor.

Keywords: bevacizumab, neovascular glaucoma, phacovitrectomy, proliferative diabetic retinopathy, retinal ischemia

1. Introduction

Neovascular glaucoma (NVG) is a serious ocular disease characterized by neovascularization of the iris and anterior chamber angle. The fibrovascular membrane eventually obstructs the trabecular meshwork and contracts, resulting in progressive angle closure and an increase in intraocular pressure (IOP).[1] Neovascularization of the iris and angle occurs in response to retinal ischemia, uveitis, trauma, and radiation.[2] Of these conditions, retinal ischemia due to diabetic retinopathy (DR) is the most common cause of NVG.[2,3] The mechanism underlying NVG in proliferative DR (PDR) is mainly mediated by various cytokines and enzymes induced by retinal ischemia and inflammation.[4,5] The most suspected and studied cytokine is vascular endothelial growth factor (VEGF), and anti-VEGF agents have been used to treat various diseases involving retinal ischemic conditions such as PDR.[6] Treatments for PDR patients, including panretinal photocoagulation (PRP), vitrectomy, and anti-VEGF agents, are targeted to reduce cytokine levels in the vitreous.[7–9] In cases of vitreous hemorrhage associated with PDR, vitrectomy and intravitreal anti-VEGF agents have been used as first-line treatments.[10,11] Anti-VEGFs including intravitreal bevacizumab (IVB) can be used as a single modality or can be combined with a vitrectomy.[11–13] Combinational IVB pretreatment before vitrectomy was recently reported,[14–16] with some studies reporting the efficacy of IVB pretreatment.[16,17] However, although these treatment modalities reported promising results, many patients presented with NVG after surgical treatments. Few studies have described NVG after PDR treatments; therefore, we evaluated the prevalence of NVG after vitrectomy, as well as the risk factors of NVG in patients with PDR treated with vitrectomy and intravitreal IVB.

2. Methods

This study adhered to the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board of the Catholic University of Korea (Seoul). Informed consent was not required because the study used chart reviews and patient records, and the information was anonymized before the analyses.

This retrospective study was conducted from 2010 to 2012 at St. Vincent Hospital (Suwon, South Korea) and included 127 consecutive eyes of 127 patients who underwent phacovitrectomy or vitrectomy because of PDR vitreous hemorrhage. Eyes with a history of glaucoma, preoperative IOP > 22 mm Hg, rubeosis iridis, ocular trauma, uveitis, intraocular injection or vitrectomy, or evidence of other vitreoretinal disease were

Editor: Alparslan Şahin.

Funding/support: The authors wish to acknowledge the financial support of the National Research Foundation of Korea Grant funded by the Korean Government (MSIP) (no. NRF-2016R1D1A1B03932606).

The authors have no conflicts of interest to disclose.

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Medicine (2017) 96:10(e6263)

Received: 8 October 2016 / Received in final form: 19 January 2017 / Accepted: 9 February 2017

http://dx.doi.org/10.1097/MD.0000000000006263

excluded. By reviewing the medical records, we determined the prevalence and duration until the development of NVG, which was defined as the presence of neovascularization in the anterior chamber angle or iris with an IOP > 21 mm Hg after vitrectomy. We also evaluated possible risk factors including sex, age, lens status before vitrectomy, time from PRP to vitreous hemorrhage, previous PRP, surgery type (combined phacovitrectomy or conventional vitrectomy), duration from the onset of vitreous hemorrhage to vitrectomy, and IVB treatment.

IVB treatment was recommended to all of the patients as an optional treatment. These patients had definite PDR and persistent vitreous hemorrhage >2 weeks, and PRP was not performed because of an invisible fundus.[18] If there was a possibility of retinal detachment using an ultrasonogram (Echograph Axis II; Quantel Medical, Marcoussis, France), a history of myocardial infarction and cerebral vascular accidents, or evidence of ocular infection, IVB treatment was excluded.[19,20] We did not consider lens status in the IVB treatment.

We waited for resolution up to a maximum of 10 weeks.[21–23] During this observation period, there was close follow-up every 2 weeks that included an ultrasonogram for detection of any possible retinal detachment. If the patient requested early surgery, if sustained vitreous hemorrhage occurred for more than 10 weeks, or if there were any findings of suspicious retinal detachment, a vitrectomy was performed without waiting for resolution of the vitreous hemorrhage. Phacovitrectomy was performed in cases with significant cataract, which sometimes prevented visualization of the retina during surgery; otherwise, conventional vitrectomy was performed. PRP was performed in patients when PDR was identified; however, it could not be used to treat patients with vitreous hemorrhage to preclude the retina at the first visit. During the follow-up after vitrectomy, an additional PRP was performed in cases of new developments of retinal neovascularization, instead of additional treatment with IVB.

Surgical procedures involved the following. Vitrectomy was performed by a single retinal specialist, who used a standard 3-port, 23-ga pars plana vitrectomy procedure. After total vitrectomy with vitreous hemorrhage removal, endolaser retinal photocoagulation was performed. Air or perfluorocarbon gas was used to fill the vitreous cavity at the end of surgery to reduce recurrent vitreous hemorrhage.[24,25] In cases of phacovitrectomy, additional phacoemulsification and implantation of an artificial intraocular lens using an in-the-bag procedure was performed before the vitrectomy.

Kaplan–Meier survival analyses were used to evaluate the rate of NVG following vitrectomy. Factors associated with survival were determined using the Cox regression proportional hazards model. Two approaches were used to assess the validity of the proportional hazard assumptions. First, the assumption was assessed using a log-minus-log survival function and was valid. Second, to confirm the assumption of proportionality, a time-dependent covariate was used. The time-dependent covariate was not statistically significant, suggesting that the proportional hazard assumption was valid. Estimates for odds ratio (OR) and 95% confidential interval (CI) were calculated from these regression models. All of the statistical analyses were performed using SPSS statistical software for Windows, version 20.0 (SPSS, Chicago, IL).

3. Results

The mean duration of the follow-up period was 35.9 ± 12.5 months (range: 6.7–54.3 months). The average age of the patients was 52.0 ± 11.5 years, and 66 patients (52.0%) were male. Preoperative PRP was conducted in 85 eyes (66.9%). IVB was used to treat 14 eyes (11.0%) for vitreous hemorrhage. Phacovitrectomy was performed in 102 eyes (80.3%), and vitrectomy was performed in 25 eyes (19.7%). Of the 102 eyes with phacovitrectomy, there was no patient with posterior capsule rupture. The characteristics of the patients are summarized in Table 1.

NVG occurred in 15 of 127 eyes (11.8%). The percentages of NVG development after vitrectomy at 6, 12, 24, and 36 months were 8.7%, 11.1%, 11.1%, and 11.8%, respectively (Fig. 1). Of the 15 eyes with NVG, 11 cases (73.3%) postoperatively developed within 6 months (Table 2). The mean duration from surgery to the development of NVG was 5.8 ± 6.9 months

Table 1

Patient demographic characteristics according to subjects with or without NVG.

Characteristics	Total (n = 127)	Without NVG (n = 112)	With NVG (n = 15)	*P*
Sex (man)	66 (52.0%)	58 (51.8%)	8 (53.3%)	0.910
Age, y	52.0 ± 11.5	52.8 ± 11.5	48.2 ± 8.8	0.133
Hypertension	72 (56.7%)	65 (67.0%)	7 (50.0%)	0.213
Duration of diabetes, y	11.5 ± 7.6	11.7 ± 7.9	9.8 ± 5.2	0.222
Cardiovascular events	6 (4.7%)	4 (3.6%)	2 (13.3%)	0.148
Lens (phakic, before vitrectomy)	115 (90.6%)	101 (90.2%)	14 (93.3%)	0.695
Time from PRP to vitreous hemorrhage	25.5 (27.1)	27.7 (27.5)	14.3 (22.2)	0.143
Preoperative PRP	85 (66.9%)	76 (67.9%)	9 (60.0%)	0.544
Phacovitrectomy	102 (80.3%)	87 (77.7%)	15 (100%)	0.223
Postoperative retinal detachment	4 (3.1%)	3 (2.7%)	1 (6.7%)	0.399
Time to vitrectomy, d	32.8 ± 20.4	32.3 ± 19.7	36.6 ± 25.5	0.440
Preoperative IVB	14 (11.0%)	9 (8.0%)	5 (33.3%)	0.003
Baseline intraocular pressure, mm Hg	13.1 ± 4.3	12.9 ± 3.2	14.7 ± 9.3	0.462
Follow-up period, mo	35.9 ± 12.5	42.0 ± 10.1	20.9 ± 7.1	<0.001
Systolic blood pressure, mm Hg	143.7 ± 22.8	143.1 ± 22.6	151.1 ± 26.1	0.344
Diastolic blood pressure, mm Hg	86.6 ± 14.9	86.1 ± 12.1	92.3 ± 35.5	0.637
Serum glucose, mg/dL	257.5 ± 104.8	256.6 ± 105.6	264.4 ± 101.9	0.804
Seum hemoglobin A1c, %	8.6 ± 1.6	8.4 ± 1.6	9.1 ± 1.6	0.210
Serum creatinine, mg/dL	2.6 ± 1.3	2.4 ± 1.0	3.4 ± 2.7	0.358

IVB = intravitreal injection of bevacizumab, NVG = neovascular glaucoma, PRP = panretinal photocoagulation.

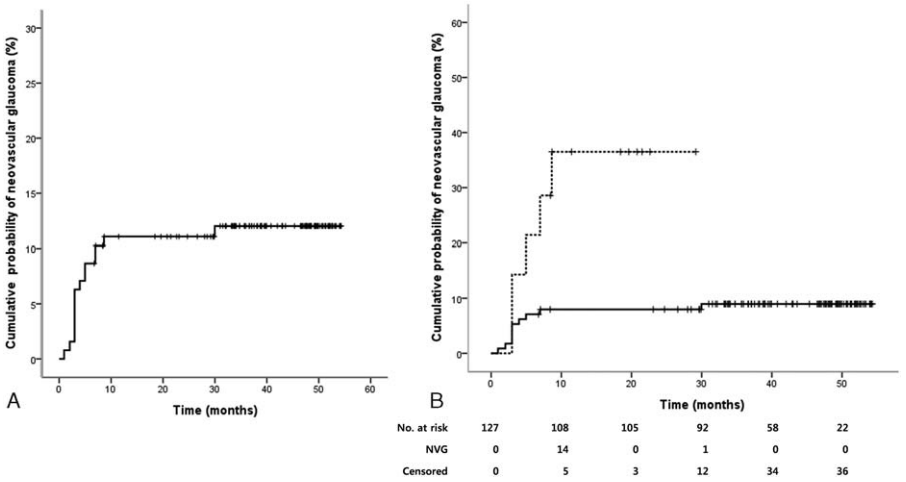

Figure 1. Cumulative probability of neovascular glaucoma after vitrectomy in patients with vitreous hemorrhage associated with proliferative diabetic retinopathy using Kaplan–Meier survival analyses. (A) Total patients. (B) Patients with or without intravitreal bevacizumab (IVB) treatment. The solid line designates patients without IVB treatment, and the dotted line designates patients with IVB treatment. IVB = intravitreal injection of bevacizumab, NVG = neovascular glaucoma.

(median, 3.0 months; range, 0.9–29.9 months). All of the eyes with NVG were administered the maximal tolerable dose of IOP-lowering drugs and were promptly treated using PRP. Of the 15 eyes with NVG, 7 (46.6%) ultimately required an Ahmed valve implantation. Using Cox proportional hazard multiple regression analyses, the IVB injection strategy for resolution of vitreous hemorrhage was independently associated with the development of NVG after adjusting for serum glucose levels, hemoglobin A1c levels, blood pressure, preoperative PRP, lens status, and the time from PRP to vitreous hemorrhage, which were all possible confounding factors affecting retinal ischemia (OR, 4.43; CI, 1.28–15.27; $P=0.019$; Table 3).

4. Discussion

The prevalence of NVG in our study was 11.8%, which is comparable to previous studies that reported percentages of 2% to 17%.[26–29] However, most of these studies were performed in the 1980s and early 1990s, and did not include recent developments in treatment modalities such as phacovitrectomy, high cutter speed, and IVB. Recently, a study of 512 patients with PDR reported an NVG percentage of 7.1% at 12 months after vitrectomy,[30] which was lower than the results of our study.

The development of NVG after vitrectomy in this study was associated with IVB treatment for the resolution of vitreous hemorrhages. This is an unexpected result because IVB is reportedly effective for the treatment of NVG as an adjunctive or primary therapy.[31–33] One possible mechanism for this unexpected finding is that IVB increased fibrosis leading to peripheral anterior synechia formation, which is an important mechanism involved in NVG development. These results are consistent with a recent study, which reported that intravitreal anti-VEGF treatment increased fibrosis in PDR patients.[34] In this study, connective tissue growth factor (CTGF) increased, while VEGF levels decreased after IVB treatment. The CTGF/VEGF, which was a good predictor of fibrosis, was shifted toward increased levels of CTGF that led to accelerated fibrosis.[34,35] Clinically, the progression and development of

Table 2

Survival tables for 15 cases of neovascular glaucoma after vitrectomy in diabetic retinopathy using a Kaplan–Meier analysis.

NVG event	Time to event, mo/d	Numbers at risk	Censored	Cumulative proportion, %	IVB
1	0.8 (23)	126	0	0.8	
2	2.0 (61)	125	0	1.6	
3	3.0 (89)	124	0	2.4	IVB
4	3.0 (89)	123	0	3.1	IVB
5	3.0 (89)	122	0	4.7	
6	3.0 (89)	121	0	5.5	
7	3.0 (89)	120	0	6.3	
8	3.0 (89)	119	0	6.3	
9	4.0 (119)	118	0	7.1	
10	5.0 (149)	117	0	7.9	IVB
11	5.0 (149)	116	0	8.7	
12	7.0 (209)	114	1	9.4	IVB
13	7.0 (209)	113	0	10.2	
14	8.6 (259)	109	3	11.1	IVB
15	30.0 (899)	92	16	11.8	

IVB = intravitreal injection of bevacizumab, NVG = neovascular glaucoma.

Table 3

Associated factors with neovascular glaucoma after vitrectomy in diabetic retinopathy using multiple Cox proportional hazard regression model.

Variables	Univariable analysis		Multivariable analysis	
	Odds ratio (95% CI)	*P*	Odds ratio (95% CI)	*P*
Sex (woman)	0.95 (0.34–2.61)	0.914	0.68 (0.21–2.12)	0.511
Age, y	0.97 (0.93–1.01)	0.122	0.98 (0.92–1.03)	0.399
Hypertension	0.49 (0.16–1.52)	0.219	0.97 (0.15–6.11)	0.971
Preoperative PRP	0.73 (0.26–2.05)	0.548	0.53 (0.18–1.55)	0.251
Lens (phakic, before vitrectomy)	1.55 (0.20–11.79)	0.672	0.52 (0.00–high)	0.522
Time from PRP to vitreous hemorrhage	0.97 (0.94–1.101)	0.158	0.97 (0.84–1.12)	0.971
Phacovitrectomy	3.96 (0.81–5.06)	0.223	3.76 (0.64–6.25)	0.379
Time to vitrectomy	1.01 (0.96–1.03)	0.494	1.00 (0.98–1.02)	0.760
IVB	4.74 (1.59–14.17)	0.005*	4.43 (1.28–15.27)	0.019*
Baseline IOP	1.07 (0.99–1.15)	0.080	1.049 (0.94–1.16)	0.364
Systolic BP	1.01 (0.99–1.04)	0.346	1.05 (0.82–1.35)	0.681
Diastolic BP	1.02 (0.98–1.06)	0.271	1.02 (0.97–1.06)	0.383
Serum glucose, mg/dL	1.00 (0.99–1.01)	0.802	1.01 (0.99–1.01)	0.468
Seum hemoglobin A1c	1.32 (0.85–2.05)	0.212	1.39 (0.23–8.55)	0.717
Serum creatinine, mg/dL	1.14 (1.97–1.34)	0.117	1.38 (0.11–3.74)	0.372

BP = blood pressure, CI = confidential interval, IOP = intraocular pressure, IVB = intravitreal injection of bevacizumab, PRP = panretinal photocoagulation.
* $P < 0.05$.

tractional retinal detachment have been reported shortly after IVB treatment.[20] Moreover, a histopathological study reported a fibrotic switch toward diabetic fibrovascular membrane formation after IVB treatment.[36] Our hypothesis was further supported by another study that reported a sudden decrease in VEGF levels after IVB treatment, resulting in compensatory increases in other inflammatory cytokines such as interleukin-6, which is associated with fibrosis.[37] However, the CTGF/VEGF ratio was not evaluated in this study. Therefore, additional studies are needed to examine CTGF and VEGF levels.

Another possible explanation was that IVB might have aggravated retinal ischemia, because the diabetic retina could have been susceptible to ischemic damage by nonspecific VEGF suppression. Although the systemic use of bevacizumab is associated with an increased risk of ischemia in cancer patients,[38,39] there has been controversy regarding whether IVB exacerbates ischemia in DR.[40,41] Enlargement of the foveal avascular zone after IVB treatment was reported in 1 patient with DR.[40] In contrast, another study using fluorescence in angiography, before and 1 month after IVB treatment in 19 patients with PDR, reported no evidence of increasing retinal ischemia after IVB treatment.[41] However, an adequate explanation involving aggravation of ischemia remains unknown due to a lack of supporting evidence.

A recent study showed that in vitro VEGF-A concentrations increased in the retinal pigment epithelium after exposure to ranibizumab or aflibercept due to a compensatory response from the cells and suggested the possibility of differing responses according to the VEGF subtype. We propose that a similar mechanism may affect the prevalence of NVG.[42]

The duration from onset of a vitreous hemorrhage after vitrectomy was evaluated as a risk factor for the development of NVG. The time delay caused by waiting for resolution of the vitreous hemorrhage after IVB treatment may have had adverse effects on its development. However, the time delay associated with vitrectomy was not associated with NVG, implying that the pharmacological action of bevacizumab itself, and not the time delay effect, may be a risk factor. In addition, we also examined several factors such as diabetic control and hypertension, which may have affected retinal ischemia in the patient. Even after adjusting for these possible confounding factors, IVB treatment was an independent risk factor for the development of postoperative NVG.

The results of this study should be cautiously applied to clinical practice, because IVB treatment has been shown to be an efficient and safe treatment for NVG in multiple studies.[31–33] In this study, patients receiving IVB treatment waited up to 10 weeks for resolution of vitreous hemorrhage, followed by PRP. The IVB treatment strategy for vitreous hemorrhage in PDR patients was designed to reduce the need for vitrectomy. A recent study reported that IVB, instead of early vitrectomy, reduced the need for vitrectomy by 35% in patients with vitreous hemorrhage associated with PDR.[18] In this study, the percentages of cases requiring vitrectomy were 10% in the IVB treatment group and 45% in the control group. Another study reported that IVB treatment resulted in the rapid resolution of vitreous hemorrhage with no short-term safety concerns.[43] Therefore, this strategy using IVB treatment for the resolution of vitreous hemorrhage differs from preoperative IVB treatment to reduce intraoperative hemorrhage during vitrectomy or IVB treatment to treat developed NVG.

An association between NVG and phacovitrectomy was not found in this study. There has been controversy concerning whether phacovitrectomy is a risk factor for NVG in patients with PDR. Phacovitrectomy may increase the risk of NVG by destroying the barrier between the anterior and posterior segments of the eye, leading to anterior diffusion of vasoproliferative substances such as VEGF and inflammatory cytokines.[44] In addition, anterior chamber oxygen diffuse posteriorly into the vitreous cavity.[45] A retrospective study comparing combined and sequential surgeries reported that NVG only occurred in the combined phacovitrectomy group (15.4%) and not in the vitrectomy-alone group (0%).[46] In contrast, more extensive PRP to the peripheral retina using phacovitrectomy reduced the probability of NVG.[47] Tseng et al[48] reported that the incidence of NVG was significantly lower in the phacovitrectomy group (0%) than in the vitrectomy-alone group (15.1%). Regarding the extent of PRP, our study showed that there was also the possibility of insufficient PRP intraoperatively, because there was a difference in the operation field between

phacovitrectomy and vitrectomy. Additional studies such as randomized clinical trials are needed to resolve this controversy.

To date, no study has reported the direct association between metabolic control and the prevalence of NVG. However, many studies have reported an association between metabolic control and the progression stage of DR.[49–51] Although it has been reported that NVG occurs because of retinal ischemia,[52] we could ignore this association. The basic mechanism of retinal ischemia is affected by the progression of DR, and NVG is included in PDR, so we considered the possible association of NVG and metabolic control. However, in this study, there was a difference in glycated hemoglobin levels between patients with and without NVG. Thus, future studies with a larger sample size are needed to confirm the possible association of metabolic control and NVG.

PRP, which induced increased diffusion of oxygen from the choroid to the retina or retinal pigmented epithelial cells and downregulated angiogenic factors, has been an important treatment for NVG.[53–56] However, many patients need glaucoma surgery, and the prognosis of NVG is very poor.[2,54,57] In addition, after using anti-VEGF agents as an adjuvant therapy with glaucoma surgery, the results have been better than previous treatments.[58–60] There have even been studies reporting NVG regression after treatment with anti-VEGF agents, with or without PRP.[61–63]

A major limitation of the present study was the relatively small number of cases, which limited the statistical power to identify risk factors. Further studies involving a larger number of patients are therefore needed to verify our results. Another limitation of this study was that the Cox proportional hazard ratio model used in this study is heavy, which suggested that more variables than appropriate were included in the model. However, a recent study reported that the rule of thumb suggesting that the Cox model use a minimum of 10 outcome events per predictor variable was too conservative and could be relaxed.[64] Finally, the retrospective nature of this study limited an accurate comparison between subjects with or without IVB treatment under controlled conditions.

To the best of our knowledge, this is the first study evaluating the prevalence and risk factors for NVG after vitrectomy that included the new treatment modality of IVB. In our study, the prevalence of NVG was 11.8%, and most NVG (73.3%) developed postoperatively within 6 months. Patients undergoing vitrectomy after IVB treatment for the resolution of vitreous hemorrhage were associated with postoperative NVG. These findings indicate that IVB treatment may have adverse effects on the development of NVG, although IVB treatment can reduce the vitrectomy burden. Instead of waiting up to 10 weeks, early vitrectomy would be another option in patients who show no resolution of vitreous hemorrhage. However, further studies are needed to verify this possibility.

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