Characteristics of cases with postoperative vitreous hemorrhage after 25-gauge vitrectomy for repair of proliferative diabetic retinopathy

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Abstract

Purpose The purpose of this study was to compare ocular and systemic parameters between proliferative diabetic retinopathy (PDR) cases with postoperative vitreous hemorrhage (PVH) and those without PVH after 25-gauge vitrectomy, and to investigate the predictors of PVH.

Methods The medical records of 106 eyes of 78 consecutive patients who underwent primary 25-gauge vitrectomy were reviewed.

Results The incidences of early and late PVH were found to be 18.9 % (20/106 eyes) and 17.9 % (19/106 eyes) respectively. On multiple logistic regression analysis, intraoperative bleeding from new vessels on the disc was identified as the most important factor, with the greatest odds ratio, for the development of early PVH (odds ratio = 3.395, $P = 0.134$), while the HbA1c level was identified as the most important significant factor, with the greatest odds ratio, for the development of late PVH (odds ratio = 1.403, $P = 0.014$).

Conclusions Early PVH tends to occur in severe PDR cases, while late PVH tends to occur in cases with poor diabetic control.

Keywords Proliferative diabetic retinopathy · Vitrectomy · 25-gauge vitrectomy · Microincision vitrectomy surgery · Postoperative vitreous hemorrhage

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Introduction

Proliferative diabetic retinopathy (PDR) is one of the leading causes of blindness in adults, especially in developed countries [1]. Vitrectomy is performed for complicated PDR cases, such as non-clearing vitreous hemorrhage and tractional retinal detachment [2].

Since the introduction of 25-gauge transconjunctival vitrectomy surgery by Fujii et al. in 2002 [3], the indications for 25-gauge vitrectomy have expanded to include complicated vitreoretinal disorders, such as rhegmatogenous retinal detachment [4, 5], proliferative vitreoretinopathy [6, 7], and PDR [8, 9]. In our institution, 20-gauge vitrectomy was totally replaced with 25-gauge vitrectomy for PDR in 2009, and the recovery time was found to be shorter with 25-gauge vitrectomy than with 20-gauge vitrectomy [10].

Postoperative vitreous hemorrhage (PVH) is one of the most common complications after PDR vitrectomy. PVH not only prevents physicians from examining and treating the eyes appropriately, but also prevents patients from resuming their daily lives. PVH can occur at any time in the postoperative period, and its incidence has been reported to range from 5 to 45 %, with some patients requiring additional treatment [11–15].

The present study aimed to compare ocular and systemic parameters between PDR cases with PVH and those without PVH after 25-gauge vitrectomy, and to investigate the predictive factors for the development of PVH.

Material and methods

The procedures used in this study conformed to the tenets of the Declaration of Helsinki, and were approved by the institutional review boards of Osaka Rosai Hospital and

Osaka University School of Medicine (15328). All patients were informed of the nature and possible consequences of the procedures, and signed informed consent was obtained from all patients.

Patients

The medical records of patients who had undergone primary vitrectomy for PDR between January 2011 and April 2013 at Osaka Rosai Hospital were reviewed. All vitrectomies were performed by an experienced surgeon (TS). The indications for vitrectomy were PDR with non-clearing vitreous hemorrhage, active fibrovascular proliferation, and tractional retinal detachment involving or threatening the macula. Eyes that had undergone intraocular surgery within 6 months prior to vitrectomy, and eyes that had been followed up for less than 6 months were excluded from this study.

Baseline ocular and systemic parameters and intraoperative ocular parameters were compared between the cases with PVH and those without PVH. The baseline systemic parameters included age, sex, platelet level, prothrombin time-international normalized ratio, hemoglobin A1c (HbA1c) level, creatinine level, blood urea nitrogen level, and the absence or presence of hemodialysis. The baseline and intraoperative ocular parameters included preoperative: (1) best-corrected visual acuity (BCVA), (2) preoperative intraocular pressure, (3) lens status, (4) the absence or presence of preoperative panretinal photocoagulation, vitreous hemorrhage, fibrovascular membrane, intraoperative bleeding from new vessels on the disc, tractional retinal detachment involving the macula, and intraoperative retinal breaks, (5) use of gas, and (6) surgical time.

PVH was subdivided into the following two groups, according to the time interval from vitrectomy to PVH development: early PVH (less than 1 month after vitrectomy) and late PVH (1–6 months after vitrectomy). Additionally, PVH severity was graded according to a previous report [16].

Twenty-five-gauge vitrectomy

Twenty-five-gauge vitrectomy was performed under local anesthesia using either the Accurus® surgical system ($n = 23$) or the Constellation® vision system ($n = 83$) (Alcon Japan Ltd., Tokyo, Japan). Phacoemulsification and intraocular lens implantation were also performed in phakic eyes. Epinephrine was added to the irrigation solution (BSS plus®; Alcon Japan Ltd.). Preoperative injection of anti-vascular endothelial growth factor was not used in any of the cases enrolled in this study.

After core vitrectomy, posterior vitreous detachment was performed or confirmed. Peripheral vitrectomy and vitreous base shaving were performed with scleral indentation using the Resight® fundus viewing system (Carl Zeiss Meditec Co. Ltd., Tokyo, Japan) and chandelier illumination. Fibrovascular membranes were mostly cut and removed only

with the cutter; however, if needed, a bimanual technique was performed under chandelier illumination. Intraoperative bleeding was controlled by temporarily raising the intraocular pressure, pressing the bleeding site with the tip of the cutter directly, and/or applying endodiathermy. Panretinal photocoagulation was performed up to the peripheral retina with scleral indentation. The intraocular pressure was normalized to identify and treat any bleeding from new vessels. All retinal breaks were treated with photocoagulation. Fluid–air exchange was performed for eyes with retinal breaks and rhegmatogenous retinal detachment, and if needed, a long-acting gas was applied to the vitreous cavity. If a leak was noted, the sclerotomy site was sutured at the end of surgery to prevent postoperative transient hypotony.

All patients were hospitalized after the vitrectomy. The criteria for hospital discharge were no signs of infection for 5 consecutive days after the vitrectomy [17], no postoperative complications, and no patient discomfort. After discharge, patients were regularly followed up 1, 3, and 6 months after the vitrectomy, and were instructed to visit the outpatient clinic when they noticed decreased vision.

Statistical analysis

Data are presented as mean ± standard deviation. BCVA was measured using a Landolt C acuity chart, and the decimal BCVA was converted to logarithm of the minimal angle of resolution (logMAR) units for statistical analyses. Based on previous reports [18, 19], counting fingers, hand motion, light perception, and no light perception vision were set to 1.85, 2.30, 2.80, and 2.90 logMAR units respectively.

The significance of differences between the cases with PVH and those without PVH was determined using t-tests, if the data were normally and equally distributed, and the Mann–Whitney rank sum test if the data were not normally and equally distributed. The significance of differences in preoperative and postoperative BCVA and intraocular pressure was determined using the Wilcoxon signed-rank test, as the data were not normally and equally distributed. The significance of differences in the ratios between the cases with PVH and those without PVH was determined using the chi-square or Fisher exact test. All statistical analyses were performed using Sigma Plot 12 (Systat Software, Inc., San Jose, CA, USA). A P-value <0.05 was considered statistically significant.

Results

The study included 106 eyes of 78 consecutive patients with PDR (30 eyes of 21 female patients and 76 eyes of 57 male patients). The mean age of the patients at vitrectomy was 59.6 ± 12.2 years (range, 30–86 years), and the mean postoperative follow-up period was 11.9 months (range, 6–31 months).

Table 1 Incidences of early (<1 month) and late (1–6 months) PVH

	Cases with early PVH (n = 20)	Cases with late PVH (n = 19)
Mild vitreous hemorrhage with visible fundus details (n [%])	9 (45)	12 (63)
Moderate vitreous hemorrhage with no visible fundus details but with an orange fundus reflex (n [%])	0	3 (16)
Severe vitreous hemorrhage with no retinal details and no orange fundus reflex (n [%])	11 (55)	4 (21)

Vitreous hemorrhage was graded according to the classification by diabetic retinopathy vitrectomy study report #1 (1985)

PVH postoperative vitreous hemorrhage

The mean preoperative and final logMAR BCVAs were 0.96 ± 0.70 (decimal range, light perception–1.0) and 0.49 ± 0.58 (decimal range, no light perception–1.2) respectively. The final BCVA was significantly greater than the preoperative BCVA ($P < 0.001$). The mean preoperative and final intraocular pressures were 14.6 ± 3.6 mmHg (range, 7–26 mmHg) and 15.6 ± 4.6 mmHg (range, 8–30 mmHg) respectively. There was no significant difference between the pressures. No eye developed postoperative hypotony (≤ 5 mmHg). Additionally, no eye developed retinal detachment postoperatively; however, in one eye with preoperative neovascular glaucoma, the preoperative BCVA of counting fingers worsened to no light perception vision 6 months after surgery.

The incidences of early and late PVH were 18.9 % (20/106 eyes) and 17.9 % (19/106 eyes), respectively. The severity of PVH is presented in Table 1. Additional treatments, such as intravitreal injection of anti-VEGF, fluid–fluid exchange,

Table 2 Characteristics of cases with and without early (<1 month) PVH

	Cases with early PVH	Cases without early PVH	P value
Eyes	20	86	
Baseline systemic parameters			
Age (years, mean ± SD)	54.9 ± 15.8	60.2 ± 11.8	0.134[*]
Gender (female: male)	5:15	25: 61	0.930[†]
Platelet (×10³/μl, mean ± SD)	222.1 ± 71.9	241.8 ± 73.4	0.415[*]
PT-INR (mean ± SD)	1.1 ± 0.2	1.0 ± 0.2	0.533[*]
Hemoglobin A1c (%, mean ± SD)	7.7 ± 2.1	7.2 ± 1.7	0.394[*]
Creatinine (dl/ml, mean ± SD)	2.2 ± 2.6	2.0 ± 2.3	0.671[*]
Blood urea nitrogen (dl/ml, mean ± SD)	26.6 ± 15.3	24.2 ± 15.8	0.474[*]
Hemodialysis (yes: no)	3:17	14: 72	1.000[‡]
Baseline ocular parameters			
Best-corrected visual acuity (logMAR, mean ± SD)	1.10 ± 0.71	0.93 ± 0.70	0.319[*]
Intraocular pressure (mmHg, mean ± SD)	14.3 ± 4.1	14.8 ± 3.5	0.601[*]
Lens status (phakia: intraocular lens)	15: 5	61: 25	0.930[†]
Panretinal photocoagulation (presence: absence)	18: 2	74: 12	1.000[‡]
Intraoperative ocular parameters			
Vitreous hemorrhage (presence: absence)	13: 7	54: 32	0.942[†]
Fibrovascular membrane (presence: absence)	13: 7	37: 49	0.127[†]
Bleeding from NVD (presence: absence)	13: 7	19: 67	<0.001[†]
TRD involving macula (presence: absence)	1: 19	3: 83	1.000[‡]
Encountering retinal breaks (presence: absence)	8: 12	8:78	0.002[†]
Use of gas (yes: no)	10: 10	11: 75	<0.001[†]
Surgical time (minutes, mean ± SD)	90.0 ± 31.0	74.4 ± 24.5	0.021*

SD standard deviation, *PT-INR* prothrombin time-international normalized ratio, *logMAR* logarithm of the minimal angle of resolution, *NVD* new vessels on the disc, *TRD* tractional retinal detachment, *PVH* postoperative vitreous hemorrhage. [*] Mann–Whitney rank sum test was performed to compare between the two groups. [†] chi-square or [‡] Fisher's exact test was performed to compare the ratio between the two groups

Table 3 Characteristics of cases with and without late (1–6 months) PVH

	Cases with late PVH	Cases without late PVH	P value
Eyes	19	87	
Baseline systemic parameters			
Age (years, mean ± SD)	58.8 ± 10.0	59.3 ± 13.3	0.589[*]
Gender (female: male)	5:14	25: 62	0.945[†]
Platelet (×10³/μl, mean ± SD)	264.2 ± 86.5	232.4 ± 69.2	0.045[*]
PT-INR (mean ± SD)	1.1 ± 0.1	1.0 ± 0.2	0.071[*]
Hemoglobin A1c (%, mean ± SD)	8.2 ± 2.1	7.1 ± 1.7	0.018[*]
Creatinine (dl/ml, mean ± SD)	2.2 ± 2.1	2.0 ± 2.5	0.429[*]
Blood urea nitrogen (dl/ml, mean ± SD)	27.9 ± 14.3	24.0 ± 16.0	0.148[*]
Hemodialysis (yes: no)	3:16	14: 73	1.000[‡]
Baseline ocular parameters			
Best-corrected visual acuity (logMAR, mean ± SD)	1.16 ± 0.78	0.92 ± 0.68	0.272[*]
Intraocular pressure (mmHg, mean ± SD)	14.5 ± 3.1	14.7 ± 3.7	0.784[**]
Lens status (phakia: intraocular lens)	13: 6	63: 24	0.945[†]
Panretinal photocoagulation (presence: absence)	16: 3	76: 11	1.000[‡]
Intraoperative ocular parameters			
Vitreous hemorrhage (presence: absence)	14: 5	53: 34	0.434[†]
Fibrovascular membrane (presence: absence)	9: 10	41: 46	0.815[†]
Bleeding from NVD (presence: absence)	7: 12	25: 62	0.673[†]
TRD involving macula (presence: absence)	0: 19	4: 83	1.000[‡]
Encountering retinal breaks (presence: absence)	2: 17	14: 73	1.000[‡]
Use of gas (yes: no)	2: 17	19: 68	1.000[‡]
Surgical time (minutes, mean ± SD)	77.3 ± 20.5	77.3 ± 27.6	0.561[*]

SD standard deviation, *PT-INR* prothrombin time-international normalized ratio; *logMAR* logarithm of the minimal angle of resolution, *NVD* new vessels on the disc, *TRD* tractional retinal detachment, *PVH* postoperative vitreous hemorrhage. [*]Mann–Whitney rank sum test or [**]*t*-test was performed to compare between the two groups. [†]chi-square or [‡]Fisher's exact test was performed to compare the ratio between the two groups

fluid–air exchange, and/or reoperation, were required in 15 (75 %) early PVH cases and 11 (58 %) late PVH cases.

The ocular and systemic parameters in the eyes with and those without early or late PVH are presented in Tables 2 and 3. There were no significant differences in baseline systemic and ocular parameters between cases with and those without early PVH (Table 2). However, there were significantly higher probabilities of intraoperative bleeding from new vessels on the disc and encountering retinal breaks intraoperatively in cases with early PVH than in those without early PVH ($P < 0.001$ and 0.002 respectively; Table 2). Additionally, intraocular gas was required more often and the surgical time was longer in cases with early PVH than in those without early

PVH ($P < 0.001$ and 0.021 respectively). On multiple logistic regression analysis, intraoperative bleeding from new vessels on the disc was identified as the most important factor, with the greatest odds ratio, for the development of early PVH; however, the association was not significant (Table 4).

There were no significant differences in baseline and intraoperative ocular parameters between cases with and those without late PVH (Table 3). However, the platelet and HbA1c levels were significantly higher in cases with late PVH than in those without late PVH ($P = 0.045$ and 0.018, respectively; Table 3). On multiple logistic regression analysis, the HbA1c level was identified as the most important significant factor, with the greatest odds ratio, for the development of late PVH (Table 5).

Table 4 Logistic regression model for detecting the risk for development of early PVH

Factor	Odds ratio (95 % CI)	P value
Intraoperative bleeding from new vessels on the disc	3.395 (0.686–16.788)	0.134
Encountering retinal breaks intraoperatively	1.455 (0.186–11.359)	0.720
Use of gas	1.753 (0.188–16.348)	0.622
Surgical time	1.003 (0.982–1.024)	0.799

Table 5 Logistic regression model for detecting the risk for development of late PVH

Factor	Odds ratio (95 % CI)	P value
Blood level of platelet	1.006 (1.000–1.013)	0.062
Blood level of hemoglobin A1c	1.403 (1.072–1.838)	0.014

Discussion

In the present study, the incidences of early and late PVH were found to be 18.9 % (20/106 eyes) and 17.9 % (19/106 eyes) respectively. Previous studies have reported that the incidence of PVH varied from 5 to 45 % [11–15]. The PVH incidence in this study is comparable with the PVH incidences reported in those previous studies, although the preoperative characteristics of the patients may have differed between this study and the previous studies, the postoperative follow-up period differed between this study and the previous studies, and preoperative anti-VEGF injection was used in some of the previous studies [11–13, 15].

Early PVH occurred in 18.9 % (20/106) of the PDR cases, and was subdivided into mild PVH (9 cases, 45 %) and severe PVH (11 cases, 55 %). One of the causes of early PVH appeared to be the dispersion of residual blood from the peripheral vitreous skirt and/or retinal surface. The main reason for blood dispersion was that the removal of blood attached to the peripheral vitreous skirt completely without retinal and/or capsular breaks was challenging. Another reason was that the coagula attached to the dissected new retinal vessels were often left in place to prevent re-bleeding. Thus, the blood from the vitreous skirt and the coagula attached to the dissected new vessels would have dispersed after vitrectomy, which may have caused early PVH.

Another cause of early PVH may be re-bleeding from dissected new vessels on the disc and/or on the retina. Intraoperative bleeding from the new vessels on the retina was controlled not only by temporarily raising the intraocular pressure and pressing the bleeding site with the tip of the cutter directly, but also by applying endodiathermy. However, endodiathermy could not be applied to the new vessels on the disc because of the risk of central vein occlusion. In addition, endodiathermy should probably be avoided at the nerve head to prevent damage to the nerve fibers directly. The intraocular pressure was normalized to identify and treat any bleeding from new vessels at the end of surgery. Additionally, leaky sclerotomy sites were sutured at the end of surgery because postoperative hypotony can increase the rate of early PVH. No eye developed postoperative hypotony (≤5 mmHg). However, fluctuations in the intraocular pressure during the suturing of the leaky sclerotomy sites and body movement after vitrectomy may lead to re-bleeding from the new vessels on the disc as well as on the retina, which may cause early PVH.

A previous study reported that new vessels on the disc contributed greatly to severe vision loss in patients with PDR [20]. The present study showed that there was a significantly higher probability of intraoperative bleeding from new vessels on the disc in cases with early PVH than in those without early PVH. Additionally, there was a higher probability of encountering retinal breaks intraoperatively, which required intraocular gas tamponade, in cases with early PVH than in those without early PVH. Iatrogenic retinal breaks appeared to occur very often in cases with a thick and wide fibrovascular membrane that is attached tightly to the retina. In addition, the surgical time was longer in cases with early PVH than in those without early PVH. These findings suggest that early PVH tends to occur in cases with severe PDR.

Late PVH occurred in 17.9 % (19/106 eyes) of the PDR cases. Most of the cases were subdivided into mild PVH (12 cases, 63 %). The main cause of late PVH has been reported to be bleeding from fibrovascular ingrowth at sclerotomy sites [21–23]. We did not perform any examinations, such as ultrasound biomicroscopy, to identify fibrovascular ingrowth at sclerotomy sites after the surgery; however, fibrovascular ingrowth appears to be much less likely to develop after 25-gauge vitrectomy than after 20-gauge vitrectomy because of the smaller sclerotomy size, less inflammatory surgical procedure, intensive vitreous base shaving using the wide-angle viewing system, and suturing of leaky sclerotomy sites [24].

Another cause of late PVH appears to be neovascularization from residual fibrovascular tissue [11]. A previous study found that the plasma HbA1c level was positively correlated with the plasma VEGF level in patients with type 2 diabetes [25], and another study found a significant association between the serum VEGF level and the severity of retinopathy in patients with type 2 diabetes mellitus [26]. Shichiri et al. demonstrated that intensive glycemic control can delay the onset and progression of diabetic microvascular complications in Japanese patients with type 2 diabetes [27]. In the present study, the HbA1c level was significantly higher in cases with late PVH than in those without late PVH. Thus, neovascularization from residual fibrovascular tissue might develop after vitrectomy in patients with high HbA1c levels, which would lead to late PVH. Therapeutic alternatives, such as closer follow-up and prophylactic administration of anti-VEGF drugs, should be considered to avoid late PVH in cases of poor diabetic control.

The present study had some limitations. This was a retrospective single-center study, in which all vitrectomies were performed by a single surgeon. Nevertheless, the data obtained from our relatively large number of consecutive PDR cases that underwent 25-gauge vitrectomy without anti-VEGF pretreatment provided new information about the ocular and systemic characteristics of PDR cases with PVH.

In conclusion, the probabilities of intraoperative bleeding from new vessels on the disc and encountering retinal breaks intraoperatively might be higher in cases with early PVH than

in those without early PVH. Additionally, intraocular gas might be needed more often and the surgical time might be longer in cases with early PVH than in those without early PVH. The platelet and HbA1c levels might be higher in cases with late PVH than in those without late PVH. Furthermore, intraoperative bleeding from new vessels on the disc might be a predictor for early PVH, while the HbA1c level might be a significant predictor for late PVH. Early PVH tends to occur in cases with severe PDR, while late PVH tends to occur in cases with poor diabetic control.

Compliance with ethical standards

Conflict of interest   All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge, or beliefs) in the subject matter or materials discussed in this manuscript.

Ethical approval   All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent   Informed consent was obtained from all individual participants included in the study.

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