JDI Journal of Diabetes Investigation Open access
Official Journal of the Asian Association for the Study of Diabetes
ORIGINAL ARTICLE

Predictors of postoperative bleeding after vitrectomy for vitreous hemorrhage in patients with diabetic retinopathy

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Keywords
Diabetic retinopathy, Postoperative bleeding, Vitrectomy

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J Diabetes Investig 2018; 9: 940–945

doi: 10.1111/jdi.12791

ABSTRACT

Aims/Introduction: To clarify the association between perioperative variables and postoperative bleeding in pars plana vitrectomy for vitreous hemorrhage in diabetic retinopathy.

Materials and Methods: The present retrospective study enrolled 72 eyes of 64 patients who were admitted to Osaka University Hospital between April 2010 and March 2014, and underwent vitrectomy for vitreous hemorrhage as a result of diabetic retinopathy.

Results: Postoperative bleeding developed in 12 eyes. Using binomial logistic regression analysis, we found that the duration of operation was the only significant variable associated with postoperative bleeding within 12 weeks after vitrectomy. Furthermore, Poisson regression analysis identified fasting blood glucose just before vitrectomy, no treatment with antiplatelet drugs and treatment with antihypertensive drugs, as well as duration of operation, to be significantly associated with the frequency of bleeding within 52 weeks after vitrectomy.

Conclusions: Long duration of operation can be used to predict bleeding within both 12 and 52 weeks after vitrectomy. In addition, fasting blood glucose just before vitrectomy, no treatment with antiplatelet drugs and treatment with antihypertensive drugs might be risk factors for postoperative bleeding up to 1 year after vitrectomy.

INTRODUCTION

Diabetic retinopathy is one of the major microvascular complications of diabetes mellitus. The treatment of diabetic retinopathy includes retinal laser photocoagulation, intravitreal injection of antivascular endothelial growth factor and vitrectomy[1–3]. Vitrectomy is regarded the first-line therapy for vitreous hemorrhage or traction retinal detachment causing visual loss[4–7]. Furthermore, vitrectomy is sometimes carried out for macular edema[8]. Therefore, vitrectomy could be considered a minor surgical procedure based on its wide application for diabetes patients. In this regard, there are just a few reports on the impact of various systemic conditions on postoperative complications after vitrectomy for diabetic retinopathy, and the relationship between various perioperative parameters and postoperative outcome in vitrectomy remains unclear.

The aim of the present study was to clarify the association between various perioperative parameters (e.g., glycemic control and surgical factors) and postoperative bleeding after pars plana vitrectomy for vitreous hemorrhage in patients with diabetic retinopathy. Specifically, we retrospectively examined patients who underwent vitrectomy for vitreous hemorrhage in order to identify parameters that might influence the postoperative outcome after vitrectomy.

METHODS

The participants of the present retrospective study represented all patients who were admitted to the Department of

Received 13 October 2017; revised 25 November 2017; accepted 10 December 2017

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Ophthalmology, Osaka University Hospital, Osaka, Japan, between April 2010 and March 2014, and underwent pars plana vitrectomy (PPV) for vitreous hemorrhage associated with proliferative diabetic retinopathy. We excluded those patients who were diagnosed with glaucoma or detachment of the retina at the time of vitreous hemorrhage. We also excluded those who underwent PPV by surgeons with <10 years of experience or were on hemodialysis due to chronic renal failure. The total number of the study participants was 72 eyes of 64 patients.

Data for the present study were obtained from the medical records kept at Osaka University Hospital. For preoperative variables, we collected the following parameters: age, sex, body mass index, systolic and diastolic blood pressure, estimated glomerular filtration rate, fasting blood glucose just before PPV (preoperative FBS), hemoglobin A1c (HbA1c) within 1 month before PPV (preoperative HbA1c) and HbA1c at approximately 3 months before PPV (3M-before HbA1c). We also collected information about diabetes management (diet only, use of oral hypoglycemic agents, or use of insulin), history of cardiovascular diseases and treatment with antihypertensive or antiplatelet drugs. The operative variables that were collected included duration of PPV, concomitant cataract operation and use of laser photocoagulation during PPV. For postoperative variables, we examined the mean blood glucose levels before meals within 1 week after PPV and also the incidence of hypoglycemia during the same period. For the outcome events, the postoperative complications after vitrectomy, including bleeding and glaucoma, were evaluated at 1, 4, 12, 26 and 52 weeks after surgery. In addition, the severity of postoperative bleeding was classified as follows: grade 1, clearly visible optic disk and retinal blood vessels on ophthalmoscopy; grade 2, partial visibility of retinal blood vessels; grade 3, poorly demarcated of ill-defined optic disk; and grade 4, no clear optic disk.

This study was approved by the Institutional Ethics Review Board of Osaka University Hospital and carried out in accordance with the Principles of the Helsinki Declaration. The study was announced to the public on the website of our Department at Osaka University Hospital and all patients were allowed to participate or refuse to participate in the study.

Statistical analysis

Binomial logistic regression analysis was carried out. The outcome was defined as the presence or absence of bleeding within 3 months of surgery. In addition, Poisson regression analysis was carried out, in which the outcome was defined as the frequency of bleeding (Fbd) within 52 weeks after surgery taking the severity of bleeding into account. 'Fbd' was calculated by the following formula: sum of the grade number/follow-up period (weeks). Furthermore, we analyzed missing data using multiple imputation. The data encompassed repeated observations (right and left eyes) in the same patient. Data analysis was carried out using methods that account for data clustering.

RESULTS

The clinical characteristics of the participants are shown in Table 1. A total of 64 non-obese normotensive patients with a mean estimated glomerular filtration rate of 53.6 mL/min/1.73 m^2 were studied (with 72 analyzed eyes). The mean age was 63.2 years. With regard to glycemic control, the mean preoperative HbA1c was 7.2% and mean 3M-before HbA1c was 7.5%. The mean decrease in HbA1c before surgery (Decrease HbA1c) calculated by (3M-before HbA1c) − (preoperative HbA1c) was 0.18%. The mean FBS measured just before surgery (preoperative FBS) was 118 mg/dL, while the mean blood glucose levels before a meal within 1 week after surgery was 142 mg/dL. With regard to the incidence of hypoglycemia within 1 week after surgery, 50 patients did not develop hypoglycemia, eight patients had one or two episodes, and two had more than three episodes. With regard to diabetes management, six were on diet only, 31 were using oral hypoglycemic agents alone and 30 were treated with insulin. Table 1 provides details about cardiovascular diseases, and the use of antihypertensive and antiplatelet drugs.

The operative variables are listed in Table 2. The mean number of laser photocoagulation shots during surgery was 1,033, and the mean duration of operation was 56 min. Furthermore, 41 cases had concomitant cataract surgeries, whereas 31 did not. The postoperative complications after vitrectomy included bleeding and/or glaucoma. A total of 12 cases developed

Table 1 | Clinical characteristics of the study participants

Sex (male/female)	47/25
Age (years)	63.2 ± 9.85
BMI (kg/m^2)	23.3 ± 3.40 (54)
Systolic blood pressure (mmHg)	128.1 ± 23.9 (63)
Diastolic blood pressure (mmHg)	68.7 ± 11.8 (63)
eGFR (mL/min/1.73 m^2)	53.6 ± 24.6 (69)
Preoperative HbA1c (%)	7.24 ± 1.27 (68)
3M-before HbA1c (%)	7.47 ± 1.27 (38)
Decrease HbA1c (%)	0.18 ± 1.08 (37)
Preoperative FBS (mg/dL)	118.3 ± 27.4 (52)
Mean blood glucose level before meal within 1 week after surgery (mg/dL)	142.4 ± 25.8 (61)
Incidence of hypoglycemia within 1 week after surgery (0/1/2–3)	50/8/2
Diabetes management (diet/oral hypoglycemic agents/insulin)	6/31/30
History of cardiovascular disease (yes/no)	17/51
Treatment with antiplatelet drugs (yes/no)	15/53
Treatment with antihypertensive drugs (yes/no)	44/24

Data are mean ± standard deviation and/or number of participants. 3M-before HbA1c, hemoglobin A1c at 12 weeks before surgery; BMI, body mass index; Decrease HbA1c, decrease in HbA1c before surgery; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; Preoperative FBS, preoperative fasting blood sugar; Preoperative HbA1c, hemoglobin A1c within 4 weeks before surgery.

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Table 2 | Operation-related variables

No. laser photocoagulation shots	1033 ± 677 (68)
Duration of operation (min)	56.1 ± 23.8 (70)
Concomitant cataract surgery (yes/no)	41/31

Data are mean ± standard deviation and/or number of participants.

Table 3 | Grade of postoperative bleeding in individual patients

Patientt#	Time after vitrectomy (weeks)					Fbd
	1	4	12	26	52	
Grade of postoperative bleeding†						
1	0	4	0	ND	ND	0.333
2	0	0	1	3	0	0.077
3	0	4	4	4	0	0.231
4	3	0	0	0	ND	0.115
5	0	0	1	0	ND	0.038
6	2	0	ND	ND	ND	0.5
7	1	0	0	0	ND	0.038
8	0	0	3	0	0	0.058
9	0	0	4	0	0	0.077
10	0	4	0	0	0	0.077
11	1	0	0	0	0	0.019
12	1	0	0	0	0	0.019
Postoperative glaucoma‡						Type of glaucoma
1	0	1	0	ND	ND	NVG
2	0	0	0	0	0	
3	0	0	0	0	1	OAG
4	0	0	0	0	ND	
5	0	0	0	0	ND	
6	0	0	ND	ND	ND	
7	0	0	0	0	ND	
8	0	0	0	0	0	
9	0	0	0	0	0	
10	0	0	1	1	1	OAG
11	0	0	0	0	0	
12	0	0	0	0	0	

Fbd, frequency of bleeding (calculated as follows: sum of degrees in bleeding grades/follow-up period [weeks]); ND, not determined; NVG, neovascular glaucoma; OAG, open angle glaucoma. †Bleeding was graded into 0 (no bleeding), 1 (optic disk and retinal blood vessels are observed clearly), 2 (retinal blood vessels are observed to some extent), 3 (optic disk is observed, but not clearly) and 4 (optic disk is not observed). ‡Development of glaucoma was classified as 0 (no glaucoma) and 1 (development of glaucoma).

postoperative bleeding, and the bleeding occurred in five cases within 1 week, three cases within 4 weeks and four cases within 12 weeks after surgery (Table 3). Thus, bleeding occurred within 12 weeks after surgery in all cases. The bleeding that occurred in the early phase (1 week) and in the late phase (12 weeks) after vitrectomy might reflect different pathology. The bleeding in the early phase might be derived from the vessels that could not be completely stanched during the surgical procedure resulting in oozing. In contrast, the bleeding in the late phase would be caused by re-bleeding from the vessels that were once stanched during the surgery, or represent new bleeding from other vessels after vitrectomy. Among the 12 cases, three also had postoperative glaucoma, and each glaucoma was observed within 4, 12 and 52 weeks, respectively, after surgery (Table 3). The types of glaucoma are also shown in Table 3. Another case developed postoperative glaucoma, but not bleeding (that case is not included in Table 3). Together with that case, there were just four cases with postoperative glaucoma in our cohort, thus we did not analyze them for glaucoma. Instead, we analyzed their data for bleeding as a postoperative complication in the present study.

The clinical characteristics of the individuals with or without postoperative bleeding are shown in Table 4. Age, preoperative HbA1c and duration of operation were significantly different between the participants with and without postoperative bleeding. A binomial logistic regression analysis was applied to determine the predictors of postoperative bleeding (Table 5). After adjustment for age, preoperative HbA1c was not selected as a significant predictor. Next, we analyzed the distinctive factors described in Table 5 after adjustment for both age and preoperative HbA1c. Among these factors, the duration of operation was identified as the only significant predictor of postoperative bleeding.

We also tried to analyze the frequency of bleeding taking its severity into account (we termed it 'Fbd') using Poisson regression analysis (Table 6). As described in the Methods section, the 'Fbd' was calculated as follows: total sum of bleeding grade/follow-up period (weeks), as described in Table 4. Similar to the results of binominal regression analysis, preoperative HbA1c was not a significant predictor after adjustment for age in Poisson regression analysis. Furthermore, after adjustment for both age and preoperative HbA1c, high preoperative FBS, treatment with antiplatelet drugs, treatment with antihypertensive drugs and duration of operation were associated with the frequency of bleeding based on its severity.

DISCUSSION

The main finding of the present study was the identification of the duration of operation as a predictor of postoperative bleeding (within both 12 and 52 weeks) after vitrectomy. The operation time includes the time for photocoagulation and hemostasis against neovascularization. As photocoagulation was not associated with postoperative bleeding in the present study, the duration of operation should represent the degree of neovascularization and severity of diabetic retinopathy, with the consequent association with bleeding after surgery. In fact, the duration of operation was a significant predictor, even after adjustment for photocoagulation (data not shown). This finding indicates that we should carefully follow patients after vitrectomy for a period proportionate with the duration of operation.

Although perioperative hyperglycemia is associated with postoperative complications in major surgeries[9], we could not find

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Table 4 | Characteristics of individuals with or without postoperative bleeding

	Bleeding	No bleeding	*P*-value
Sex (male/female)	6/6	41/19	0.32
Age (years)	59.5 (38–68)	65.0 (42–81)	0.0137
BMI (kg/m^2)	20.5 (18.8–29.1)	22.8 (17.0–34.3)	0.131
Systolic blood pressure (mmHg)	127 (82–188)	130 (82–176)	0.898
Diastolic blood pressure (mmHg)	76 (46–92)	66 (46–103)	0.288
Preoperative HbA1c (%)	6.4 (5.6–8.8)	7.2 (5.2–11.6)	0.02
3M-before HbA1c (%)	6.9 (5.3–11.4)	7.3 (4.8–14.4)	0.81
Preoperative fasting blood glucose (mg/dL)	125 (96–146)	108 (60–186)	0.63
Mean pre-meal blood glucose within 1 week after surgery (mg/dL)	139 (108–207)	134 (98–243)	0.75
Incidence of hypoglycemia within 1 week after surgery (0/1/2–3)	9/2/0	41/6/2	0.76
Diabetes management (diet/oral hypoglycemic agents/insulin)	1/5/6	5/26/24	0.603
History of cardiovascular diseases (yes/no)	1/11	16/40	0.269
Treatment with antiplatelet drugs (yes/no)	1/11	14/42	0.276
Treatment with antihypertensive drugs (yes/no)	10/2	34/22	0.19
No. laser photocoagulation shots	1192 (244–3900)	877 (0–2515)	0.434
Duration of operation (min)	71.5 (38–125)	50.0 (15–118)	0.0134
Concomitant cataract surgery (yes/no)	8/4	33/27	0.536

Data are mean ± standard deviation and/or number of participants and (range). 3M-before HbA1c, hemoglobin A1c at 12 weeks before surgery; BMI, body mass index. HbA1c, hemoglobin A1c; Preoperative FBS, preoperative fasting blood sugar; Preoperative HbA1c, hemoglobin A1c within 4 weeks before surgery.

Table 5 | Results of binomial logistic regression analysis for prediction of postoperative bleeding

Variables	25%	75%	Odds ratio	*P*-value
Preoperative HbA1c (%)[†]	6.6	7.7	0.5142	0.1354
Sex (1 = male/0 = female)	0	1	3.1964	0.1417
BMI (kg/m^2)	20.8	25.6	0.4044	0.1306
Systolic blood pressure (mmHg)	111	144	0.7030	0.4685
Diastolic blood pressure (mmHg)	60	76	0.9473	0.9175
Preoperative FBS (mg/dL)	98	141	1.2141	0.7279
3M-before HbA1c (%)	6.45	7.95	3.6021	0.0681
Decrease HbA1c (%)	–0.475	0.7	2.5900	0.0965
Mean pre-meal blood glucose levels within 1 week after surgery (mg/dL)	128	160	1.4718	0.4556
Incidence of hypoglycemia within 1 week after surgery	0	1	0.7419	0.6335
Treatment with antiplatelet drugs (1 = yes/0 = no)	0	1	0.4221	0.4442
Treatment with antihypertensive drugs (1 = yes/0 = no)	0	1	3.9043	0.1444
Log number of laser photocoagulation shots	6.40	7.24	0.7267	0.5451
Duration of operation (min)	40	70	3.2912	0.0199
Concomitant cataract surgery (1 = yes/0 = no)	0	1	1.2887	0.7528

[†]Hemoglobin A1c (HbA1c) was adjusted for age before analysis. The values of all variables, except preoperative HbA1c, were adjusted for age and preoperative HbA1c before analysis. 3M-before HbA1c, hemoglobin A1c at 12 weeks before surgery; BMI, body mass index; Decrease HbA1c, decrease in hemoglobin A1c before surgery; Preoperative FBS, preoperative fasting blood sugar; Preoperative HbA1c, hemoglobin A1c within 4 weeks before surgery.

such relationship during the early period (12 weeks) after vitrectomy in the present study. The mean HbA1c within 1 month before surgery was 7.2%, and at 12 weeks before surgery was 7.5%. In addition, the mean preoperative FBS just before vitrectomy was 118 mg/dL (range 60–186 mg/dL). Furthermore, the mean blood glucose level before a meal within 1 week after surgery was 142 mg/dL. These data indicate well-controlled diabetes in our patients during the preoperative period. It is possible that perioperative glucose levels measured in the present study had no relationship with postoperative bleeding during the early period after vitrectomy. In contrast, we found that fasting blood glucose just before vitrectomy was associated with the frequency of bleeding within 52 weeks after vitrectomy. One possible reason for the observed results is that

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Table 6 | Poisson regression analysis for the frequency and severity of bleeding

	Estimate of regression coefficient	*P*-value
Preoperative HbA1c (%)†	–0.0845	0.6476
Sex (male/female)	0.4142	0.2699
BMI (kg/m^2)	–0.0799	0.2454
Systolic blood pressure (mmHg)	–0.0035	0.6021
Diastolic blood pressure (mmHg)	0.0100	0.4989
Preoperative FBS (mg/dL)	0.0145	0.0284
3M-before HbA1c (%)	0.1305	0.4883
Decrease HbA1c (%)	0.1887	0.2985
Mean pre-meal blood glucose level within 1 week after surgery (mg/dL)	–0.0114	0.1698
Incidence of hypoglycemia within 1 week after surgery	–0.5430	0.2256
Treatment with antiplatelet drugs	–1.0574	0.0470
Treatment with antihypertensive drugs	1.9210	0.0014
Log number of laser photocoagulation shots	–0.2766	0.3790
Duration of operation (min)	0.0404	<0.0001
Concomitant cataract surgery	0.4729	0.2576

The values of all variables, except preoperative HbA1c, were adjusted for age and preoperative HbA1c before analysis. 3M-before HbA1c, hemoglobin A1c at 12 weeks before surgery; BMI, body mass index; Decrease HbA1c, decrease in hemoglobin A1c before surgery; Preoperative FBS, preoperative fasting blood sugar; Preoperative HbA1c, hemoglobin A1c within 4 weeks before surgery. †Hemoglobin A1c (HbA1c) was adjusted for age before analysis.

a high level of preoperative FBS reflects the difficulty of glycemic control during such a period, which could result in chronic hyperglycemia after surgery, leading to postoperative bleeding during the longer period. Anyway, it remains unknown whether postoperative bleeding can be prevented by lowering preoperative FBS levels relative to those found in the present study. Further studies are required to clarify this issue.

It is interesting that the use of antiplatelet drugs was negatively associated with the frequency of bleeding within 52 weeks after vitrectomy. Together with the fact that use of antiplatelet drugs was not associated with postoperative bleeding during the 12 weeks after vitrectomy, this finding suggests that antiplatelet drugs can be used safely during the perioperative period of vitrectomy. Furthermore, the use of these agents might contribute to improvement of local circulation and prevention of neovascularization, with consequent indirect prevention of bleeding during the longer postoperative period.

In contrast, the use of antihypertensive drugs was associated with the frequency of bleeding within 52 weeks after vitrectomy. In general, hypertension, as well as high blood glucose, promotes neovascularization and bleeding. In the present study, blood pressure in patients using antihypertensive drugs was not significantly different from that in patients not taking such medications. As the patients using them had been diagnosed with hypertension before the present study, they should have been exposed to hypertension for some time. Furthermore, the daily variance of blood pressure in these patients might be larger than that in those without antihypertensive drugs. Past exposure to hypertension or possible daily variation in blood pressure might contribute to postoperative bleeding during the longer period after vitrectomy.

The present study had certain limitations. First, the number of patients and the number of events were relatively small, thus we carried out binomial logistic regression analysis only using two or three confounding factors. Second, as shown in Table 1, there were some missing values in our data and we had to use the multiple imputation method in this analysis. However, we believe that the conclusions of this study are reasonable due to the use of proper statistical methods.

In conclusion, we retrospectively examined patients with vitrectomy for vitreous hemorrhage, and found the duration of surgery to be a significant and independent predictor of bleeding within both 12 and 52 weeks after vitrectomy. In addition, FBS just before vitrectomy, no treatment with antiplatelet drugs and treatment with antihypertensive drugs might be risk factors for postoperative bleeding up to 1 year after vitrectomy. These parameters should be of help in the selection of treatment and clinical care of diabetes patients after vitrectomy.

ACKNOWLEDGMENT

This study was supported in part by a Research Grant from MSD. We thank Word-Medex PTY Ltd. for assistance in manuscript preparation.

DISCLOSURE

The authors declare no conflict of interest.

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