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

Vitreous hemorrhage in diabetes patients with proliferative diabetic retinopathy undergoing hemodialysis

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Keywords
Diabetic retinopathy, Dialysis, Vitreous hemorrhage

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J Diabetes Investig 2020; 11: 688–692

doi: 10.1111/jdi.13161

ABSTRACT

Aims/Introduction: For diabetes patients undergoing hemodialysis, vitreous hemorrhage seems to be a hemodialysis-induced hemorrhagic complication because of the effect of systemic anticoagulation. However, it is unclear whether hemodialysis is associated with vitreous hemorrhage in diabetes patients. We therefore carried out this cohort study to clarify the relationship between hemodialysis and vitreous hemorrhage in diabetes patients with proliferative diabetic retinopathy.

Materials and Methods: This was a single-center, retrospective, cohort study. We compared the incidence of vitreous hemorrhage in non-vitrectomized proliferative diabetic retinopathy eyes between the hemodialysis group (145 eyes) and peritoneal dialysis group (36 eyes), which does not require the use of systemic anticoagulation (parallel-group study), and in hemodialysis patients in the 12-month period before and after the start of hemodialysis (before–after study). We also determined the risk factors for vitreous hemorrhage after the start of hemodialysis based on the patients' systemic and ophthalmic characteristics.

Results: There was no significant difference in the first-year incidence of vitreous hemorrhage between the hemodialysis (23.4%) and peritoneal dialysis groups (22.2%, $P = 1.000$). The incidence of vitreous hemorrhage in the dialysis period (23.4%) was significantly lower than that in the predialysis period (35.2%, $P = 0.008$). Only application of panretinal photocoagulation within the 6 months immediately before hemodialysis was significantly associated with the incidence of vitreous hemorrhage after the start of hemodialysis ($P < 0.001$).

Conclusions: Hemodialysis therapy does not seem to be associated with a higher risk of vitreous hemorrhage in diabetes patients with proliferative diabetic retinopathy.

INTRODUCTION

Vitreous hemorrhage is a major cause of unexpected and severe visual deterioration in diabetes patients with proliferative diabetic retinopathy (PDR). Diabetes patients with PDR are also likely to have end-stage kidney disease requiring renal replacement therapy, because retinopathy and nephropathy usually progress in parallel as a result of long-term diabetic microvasculopathy[1–5]. For this reason, many nephrologists might be concerned that starting hemodialysis in diabetes patients with PDR could be associated with an increased risk of subsequent vitreous hemorrhage, as routine hemodialysis requires systemic anticoagulation using unfractionated heparin[6]. However, somewhat surprisingly, numerous studies have reported that the severity of retinopathy[1,2,7,8], visual acuity[1,2,8] and macular edema[9–12] in diabetic eyes stabilized or even improved after initiation of hemodialysis, although the precise mechanisms are still being debated. If hemodialysis per se has stabilizing effects on PDR that lead to vitreous hemorrhage, hemodialysis might be associated with a decreased risk of vitreous hemorrhage. However, no previous reports have studied the incidence of vitreous hemorrhage in patients undergoing hemodialysis as a primary end-point. This end-point is more reasonable than the severity of diabetic retinopathy because of the specific concerns regarding anticoagulation in hemodialysis.

Received 29 July 2019; revised 24 September 2019; accepted 14 October 2019

To determine the association between hemodialysis and vitreous hemorrhage, randomized controlled trials comparing heparin versus heparin-free hemodialysis would be ideal; however, long-term heparin-free dialysis might be impractical due to concerns over the high frequency of dialyzer clotting. We therefore carried out the present retrospective study to clarify the relationship between hemodialysis and vitreous hemorrhage in diabetes patients with PDR from the two points of view. First, we compared the incidence of vitreous hemorrhage in hemodialysis and peritoneal dialysis patients (i.e., comparison of the incidence of vitreous hemorrhage based on the use or not of anticoagulant therapy during dialysis). Second, the incidence of vitreous hemorrhage was compared before and after the start of hemodialysis to assess a stabilizing effect of hemodialysis on vitreous hemorrhage. Furthermore, we determined the risk factors for vitreous hemorrhage after the start of hemodialysis.

METHODS

Materials

This was a single-center, retrospective, observational, cohort study based on electronic hospital records. The study procedures complied with the Declaration of Helsinki, and the institutional review board of Tokyo Women's Medical University approved the study protocol (approval number: 2348-R). The need for informed consent was waived by the institutional review board of Tokyo Women's Medical University, because the study was carried out retrospectively. Among consecutive patients with end-stage diabetic kidney disease who were starting hemodialysis at the Division of Nephrology and Hypertension, Department of Medicine, Diabetes Center of Tokyo Women's Medical University Hospital during the period between 2000 and 2016, those who met the following criteria were included in the study: (i) the presence of PDR defined according to the proposed international scale for the severity of clinical diabetic retinopathy[13]; (ii) and regular fundus follow-up examinations at least once every 3 months (or more frequently) during the study period for up to 12 months after the start of hemodialysis. The exclusion criteria were: (i) a history of vitrectomy in the study eye; (ii) vitreoretinal pathology other than diabetic retinopathy in the study eye; (iii) the presence of a severe vitreous hemorrhage or other factors (e.g., cataract, corneal opacity) that affected the visualization of the fundus at the start of hemodialysis; and (iv) administration of oral anticoagulant drugs. Patients were also excluded if they were switched to other renal replacement therapies during the study period. In patients with bilateral eye disease, each eye was independently studied. A total of 145 eyes of 102 patients had sufficient baseline and follow-up data to qualify for inclusion.

Outcome measurement

The primary outcome measure was the first-year incidence of vitreous hemorrhage after the start of hemodialysis. In the current study, the presence of a vitreous hemorrhage that was not observed at the last fundus examination was defined as a vitreous hemorrhage event during the follow-up period; the amount of the vitreous hemorrhage, the grade of visual deterioration or whether it was new-onset or recurrent vitreous hemorrhage were not considered.

Comparison of the incidence of vitreous hemorrhage in hemodialysis and peritoneal dialysis patients

To determine whether the use of anticoagulation drugs during hemodialysis was associated with an increased (or even decreased) risk of vitreous hemorrhage, we compared the first-year incidence of vitreous hemorrhage after the start of dialysis in hemodialysis and peritoneal dialysis patients. A total of 36 eyes of 21 patients who began peritoneal dialysis during the same period between 1990 and 2016 at our center and met the same inclusion criteria were studied as a control group.

Comparison of the incidence of vitreous hemorrhage before and after the start of hemodialysis

To assess the stabilizing effect of hemodialysis on vitreous hemorrhage in PDR eyes, we investigated the difference in the incidence of vitreous hemorrhage between prehemodialysis and hemodialysis periods (for 12 months in each period).

Risk factors for the incidence of vitreous hemorrhage after the start of hemodialysis

To determine the risk factors for vitreous hemorrhage in patients with PDR undergoing hemodialysis, we divided the patients into two groups according to the presence or absence of vitreous hemorrhage during the first year after the start of hemodialysis, and examined the systemic and ophthalmic differences between the groups. The variables at the start of hemodialysis (baseline) that were evaluated in both groups were duration of diabetes, hemoglobin level, hemoglobin A_{1c} level, systolic blood pressure, diastolic blood pressure, prescribed medications (insulin therapy, antiplatelet agent, erythropoiesis-stimulating agent), type of anticoagulant drugs at the start of hemodialysis (heparin, low-molecular-weight heparin, nafamostat mesilate), pseudophakia and application of panretinal photocoagulation (PRP) within the 6 months immediately before the start of hemodialysis.

Statistical analysis

Continuous variables are expressed as the mean ± standard deviation, and categorical data are expressed as the percentage or number. Continuous variables were compared using the two-tailed unpaired *t*-test. Comparisons between categorical variables were carried out using Fisher's exact test. The cumulative first-year incidence of vitreous hemorrhage was determined using the Kaplan–Meier method, and compared by means of the Wilcoxon test. Within-group comparisons of the incidence of vitreous hemorrhage between the period before the start of hemodialysis and the period after the start of hemodialysis were analyzed using the McNemar's test. To consider the correlations between the two eyes of the same patient, Thompson's proposed formula was

fitted to the data[14,15]. All statistical analyses were carried out using JMP software, version 12.1.0 (SAS Institute Inc., Cary, NC). $P < 0.05$ was considered significant.

RESULTS

To compare the incidence of vitreous hemorrhage in dialysis patients according to the use of anticoagulant therapy, 145 eyes of 102 patients who were treated with hemodialysis and 36 eyes of 21 patients who were treated with peritoneal dialysis were examined. Only one eye in the hemodialysis group had neovascular glaucoma associated with PDR. The number of individuals with vitreous hemorrhage in both assessed eyes was two patients in the hemodialysis group and one patient in the peritoneal dialysis group; there was little or no correlation between the eyes. Table 1 shows the clinical characteristics at the start of hemodialysis and peritoneal dialysis. The differences between the groups did not reach statistical significance, except for age ($P < 0.001$). During the first year after the start of hemodialysis, vitreous hemorrhage developed in 34 of 145 eyes (23.4%) in the hemodialysis group, and in eight of 36 eyes (22.2%) in the peritoneal dialysis group, with no significant difference between the two groups ($P = 1.000$, Fisher's exact test). The cumulative incidence of vitreous hemorrhage was also comparable ($P = 0.941$, Wilcoxon test; Figure 1). Although the vitreous hemorrhage resorbed spontaneously in most cases, severe vitreous hemorrhage that required vitrectomy developed in six of 34 eyes (17.6%) in the hemodialysis group, whereas it developed in one of eight (12.5%) eyes in the peritoneal dialysis group, with no statistically significant difference between the groups ($P = 1.000$, Fisher's exact test).

When the incidence of vitreous hemorrhage was compared only in eyes in hemodialysis patients longitudinally, the incidence during the 12-month dialysis period (23.4%, 34/145 eyes) was significantly lower than that in the 12-month predialysis period (35.2%, 51/145 eyes; $P = 0.008$, McNemar's test; Table 2).

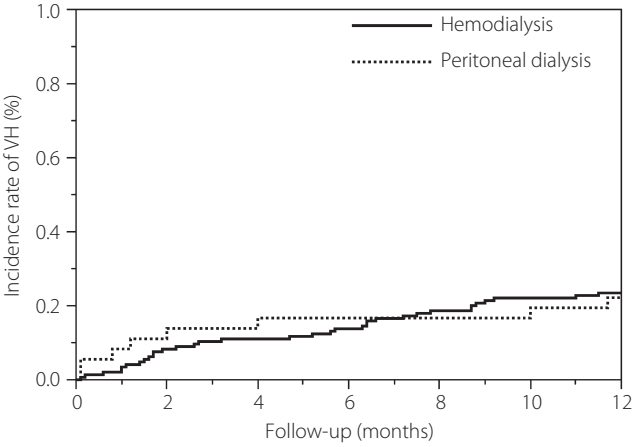

Figure 1 | First-year development rate of vitreous hemorrhages (VH) after the start of dialysis (hemodialysis vs peritoneal dialysis groups). The difference between Kaplan–Meier estimates for the two groups is not significant ($P = 0.941$, Wilcoxon test).

Table 3 shows the univariate analysis for the risk factors associated with the development of a vitreous hemorrhage during the first year after the start of hemodialysis. The risk factor identified was only application of PRP within the 6 months immediately before the start of hemodialysis ($P < 0.001$, Fisher's exact test).

DISCUSSION

For patients with diabetic kidney disease undergoing hemodialysis, vitreous hemorrhage seems to be a hemodialysis-induced hemorrhagic complication, because hemodialysis requires systemic anticoagulation therapy[6]. However, to the best of our knowledge, just two studies on vitreous hemorrhages in patients undergoing hemodialysis have been published[1,16]. In the first prospective uncontrolled study, Berman *et al.*[1] reported that a comparison of diabetic eyes in the dialysis (hemodialysis and

Table 1 | Clinical characteristics of the hemodialysis and peritoneal dialysis groups at the start of dialysis therapy

	HD (n = 145)	PD (n = 36)	P-value
Age (years)	56.3 ± 9.8	47.4 ± 9.5	<0.001
Male, n (%)	87 (60)	26 (72)	0.248
Duration of diabetes (years)	17.0 ± 8.9	19.8 ± 9.8	0.096
Hb (g/dL)	9.6 ± 1.2	9.5 ± 1.5	0.740
HbA1c (%)	6.5 ± 1.1	6.8 ± 1.5	0.203
Systolic BP (mmHg)	150.1 ± 21.9	146.8 ± 14.7	0.284
Diastolic BP (mmHg)	77.7 ± 12.1	79.5 ± 10.0	0.426
Insulin therapy, n (%)	119 (82)	34 (94)	0.075
Antiplatelet agent, n (%)	93 (64)	19 (53)	0.251
Erythropoiesis-stimulating agent, n (%)	133 (92)	31 (86)	0.338
Pseudophakia, n (%)	31 (21)	6 (17)	0.648
PRP just before HD†, n (%)	19 (13)	5 (14)	1.000

†Application of panretinal photocoagulation (PRP) within the 6 months immediately before the start of hemodialysis (HD). BP, blood pressure; Hb, hemoglobin; HbA1c, hemoglobin A_{1C}; PD, peritoneal dialysis.

peritoneal dialysis) and transplant groups showed that two (5%) of the 44 eyes in the dialysis group and none (0%) of the 18 eyes in the transplant group required vitrectomy for vitreous hemorrhage; the difference did not reach statistical significance. In the second case series study, Hayashi *et al.* reported surgical outcomes and complications after vitrectomy for patients with PDR who were undergoing hemodialysis. They found that a recurrent vitreous hemorrhage occurred after vitrectomy in one (1.3%) of 76 eyes that was washed out 2 weeks after onset. The authors concluded that hemodialysis did not appear to have a detrimental effect on the outcome of vitrectomy[16]. These clinical studies were limited by a small number of patients, and they indirectly evaluated vitreous hemorrhage in different settings and patients with varying ocular status. The current study directly examined the incidence of vitreous hemorrhage in non-vitrectomized PDR eyes.

Regarding the effects of anticoagulation, the current study showed that among patients with PDR who were undergoing hemodialysis and peritoneal dialysis, there were no significant differences in the first-year incidence of vitreous hemorrhage and the percentages of eyes with severe vitreous hemorrhage that required vitrectomy between the two dialysis groups. It should be emphasized that the number of patients in the peritoneal dialysis group was relatively small and the patients were younger (47.4 years) than those in the hemodialysis group (56.3 years) – factors that might have affected the outcomes. However, in the current study, none complained of vitreous hemorrhage-induced visual disturbances during hemodialysis sessions; that is, in a hypercoagulable state. Furthermore, the vitreous hemorrhage resorbed naturally in most cases in the hemodialysis group. For these reasons, we hypothesized that the vitreous hemorrhage that developed in diabetes patients undergoing hemodialysis has little association with systemic anticoagulation during hemodialysis.

In addition, in the current cases, the incidence of vitreous hemorrhage in the dialysis stage was significantly lower compared with that in the predialysis stage. This is noteworthy, because the results confirmed our opinion about the anticoagulative effects of hemodialysis for vitreous hemorrhage, and suggested a stabilizing effect of hemodialysis. Numerous studies have been published on the beneficial effects of hemodialysis for diabetic retinopathy[1,2,7,8]; one clinical study reported that the severity of retinopathy through every stage remained stable in 80% of patients at the 1-year follow-up examination after the start of hemodialysis[7]. The current study examined the incidence of vitreous hemorrhage, but not the severity of diabetic retinopathy. Even so, our observational data were comparable to the previously mentioned studies, because 76.6% of the eyes (111/145 eyes) in the current study were stable (i.e., they were event-free for the first year after the start of hemodialysis), despite PDR only. Therefore, we hypothesized that the stabilizing effect of hemodialysis might suppress the pathogenesis of vitreous hemorrhage, as well as progression of diabetic retinopathy.

The precise mechanisms by which hemodialysis stabilizes the disease progression remain uncertain, but a possibility is that patients often already have had prophylactic and aggressive laser photocoagulation, mainly PRP, for PDR before the start of hemodialysis[8,17]. In the current study, most participants had already been treated with PRP for PDR before the start of hemodialysis. Whereas PRP is well established as the standard of

Table 2 | Incidence rates of vitreous hemorrhage in the predialysis and dialysis stages of 12 months' duration each in 145 eyes

		For 12 months after HD	
		VH (+)	VH (–)
For 12 months before HD	VH (+)	22 eyes	29 eyes
	VH (–)	12 eyes	82 eyes

The difference between the two groups is significant ($P = 0.008$, McNemar's test). HD, hemodialysis; VH, vitreous hemorrhage.

Table 3 | Clinical characteristics of the two groups according to the incidence of vitreous hemorrhage at the start of hemodialysis

	VH (+) ($n = 34$)	VH (–) ($n = 111$)	*P*-value
Duration of diabetes (years)	15.6 ± 9.3	17.4 ± 8.8	0.319
Hb (g/dL)	9.8 ± 0.9	9.6 ± 1.2	0.363
HbA_{1c} (%)	6.4 ± 0.9	6.5 ± 1.1	0.550
Systolic BP (mmHg)	149.3 ± 27.4	151.4 ± 20.0	0.622
Diastolic BP (mmHg)	78.3 ± 12.8	77.6 ± 11.9	0.772
Insulin therapy, *n* (%)	29 (85)	90 (81)	0.799
Antiplatelet agent, *n* (%)	19 (56)	74 (67)	0.308
Erythropoiesis-stimulating agent, *n* (%)	30 (88)	103 (93)	0.476
Heparin use on HD, *n* (%)	20 (59)	75 (68)	0.411
Pseudophakia, *n* (%)	5 (15)	26 (23)	0.345
PRP just before HD†, *n* (%)	12 (35)	7 (6)	< 0.001

†Application of panretinal photocoagulation (PRP) within the 6 months immediately before the start of hemodialysis (HD). BP, blood pressure; Hb, hemoglobin; HbA1c, hemoglobin A_{1c}; VH, vitreous hemorrhage.

care for stabilizing and improving PDR[18], vitreous hemorrhage as a complication of laser treatment has been reported in 32% of patients at the 1-year follow up after PRP[19,20], and 37–39% at >12 months[21,22]. In the current study, application of PRP within 6 months immediately before the start of hemodialysis was significantly related to the development of vitreous hemorrhage during the dialysis stage. Conceivably, in the cases in which vitreous hemorrhage developed after the start of hemodialysis, patients with laser-induced vitreous hemorrhage might have been included. Hence, it is important to inform patients with PDR before dialysis, for whom PRP is crucial, that vitreous hemorrhage is a complication of laser treatment, to prevent the misunderstanding; hemodialysis might have a detrimental effect on vitreous hemorrhage.

The current study had some limitations. First, the study was a retrospective observational study of a relatively small number of patients and thus might have been subject to selection bias. Second, a retrospective analysis is likely to underestimate the incidence of vitreous hemorrhage, because a small episode of bleeding might be overlooked, unlike a prospective study. Finally, the current patients were followed only for the first year after the start of hemodialysis, and the cumulative effects over a longer follow-up period could not be estimated. The generalizability of the present findings should be confirmed in future prospective studies. Nevertheless, the results of the current study suggest that hemodialysis might have few detrimental effects on the incidence of vitreous hemorrhage in patients with PDR.

DISCLOSURE

The authors declare no conflict of interest.

REFERENCES

1. Berman DH, Friedman EA, Lundin AP. Aggressive ophthalmological management in diabetic end-stage renal disease: a study of 31 consecutively referred patients. *Am J Nephrol* 1992; 12: 344–350.
2. Watanabe Y, Yuzawa Y, Mizumoto D, *et al*. Long-term follow-up study of 268 diabetic patients undergoing haemodialysis, with special attention to visual acuity and heterogeneity. *Nephrol Dial Transplant* 1993; 8: 725–734.
3. Grenfell A, Bewick M, Parsons V, *et al*. Non-insulin-dependent diabetes and renal replacement therapy. *Diabet Med* 1988; 5: 172–176.
4. Takei I, Yamauchi A, Nakamoto S, *et al*. Retrospective analysis of hemodialyzed diabetic patients in Japan. *Diabetes Res Clin Pract* 1995; 29: 173–177.
5. Goldstein DA, Massry SG. Diabetic nephropathy. *Nephron* 1978; 20: 286–296.
6. Janssen MJ, Vandermeulen J. The bleeding risk in chronic haemodialysis: preventive strategies in high-risk patients. *Neth J Med* 1996; 48: 198–207.
7. Diskin CJ, Stokes TJ, Dansby LM, *et al*. A hypothesis: can erythropoietin administration affect the severity of retinopathy in diabetic patients with renal failure? *Am J Med Sci* 2007; 334: 260–264.
8. Yoshimoto M, Matsumoto S. Changes in diabetic retinopathy and visual acuity in patients with end-stage diabetic nephropathy after the introduction of hemodialysis. *Nippon Ganka Gakkai Zasshi* 2006; 110: 271–275. (in Japanese).
9. Bresnick GH. Diabetic maculopathy. *Ophthalmology* 1983; 90: 1301–1317.
10. Perkovich BT, Meyers SM. Systemic factors affecting diabetic macular edema. *Am J Ophthalmol* 1988; 105: 211–212.
11. Matsuo T. Disappearance of diabetic macular hard exudates after hemodialysis introduction. *Acta Med Okayama* 2006; 60: 201–105.
12. Ichikawa K, Kanie K, Kaga T. Diabetic macular edema and hemodialysis therapy. *Folia Ophthalmol Jpn* 2004; 55: 258–264.
13. Wilkinson CP, Ferris FL 3rd, Klein RE, *et al*. Proposed international clinical diabetic retinopathy and diabetic macular edema disease severity scales. *Ophthalmology* 2003; 110: 1677–1682.
14. Thompson JR. The χ^2 test for data collected on eyes. *Br J Ophthalmol* 1993; 77: 115–117.
15. Murdoch IE, Morris SS, Cousens SN. People and eyes: statistical approaches in ophthalmology. *Br J Ophthalmol* 1998; 82: 971–973.
16. Hayashi H, Kurata Y, Imanaga Y, *et al*. Vitrectomy for diabetic retinopathy in patients undergoing hemodialysis for associated end-stage renal failure. *Retina* 1998; 18: 156–159.
17. Aiello LP, Cahill MT, Wong JS. Systemic considerations in the management of diabetic retinopathy. *Am J Ophthalmol* 2001; 132: 760–776.
18. The Diabetic Retinopathy Study Research Group. Photocoagulation treatment of proliferative diabetic retinopathy, DRS Report Number 8. *Ophthalmology* 1981; 88: 583–600.
19. Kaiser RS, Maguire MG, Grunwald JE, *et al*. One-year outcomes of panretinal photocoagulation in proliferative diabetic retinopathy. *Am J Ophthalmol* 2000; 129: 178–185.
20. Rema M, Sujatha P, Pradeepa R. Visual outcomes of panretinal photocoagulation in diabetic retinopathy at one-year follow-up and associated risk factors. *Indian J Ophthalmol* 2005; 53: 93–99.
21. Kleinmann G, Hauser D, Schechtman E, *et al*. Vitreous hemorrhage in diabetic eyes previously treated with panretinal photocoagulation. *Int Ophthalmol* 2008; 28: 29–34.
22. Vander JF, Duker JS, Benson WE, *et al*. Long-term stability and visual outcome after favorable initial response of proliferative diabetic retinopathy to panretinal photocoagulation. *Ophthalmology* 1991; 98: 1575–1579.