Original Article

Vitreous rebleed following sutureless vitrectomy: Incidence and risk factors

Prabhushanker Mahalingam, Tasneem Tameem Topiwalla, Geetha Ganesan

Purpose: This study aims to evaluate the incidence and risk factors for vitreous rebleed (VRB) following 25-gauge sutureless vitrectomy for vitreous hemorrhage (VH) in diabetic retinopathy. **Methods:** A retrospective review of 190 diabetic patients having undergone vitrectomy for VH at a tertiary eye care center was analyzed. Demographic data of patients along with risk factors such as blood sugar levels (BSL), blood pressure (BP), anticoagulant use, and pan-retinal photocoagulation status (PRP) were tabulated. Depending on the commencement of VRB, patients were divided into immediate rebleed-within 2 weeks and delayed rebleed-beyond 2–4 weeks. **Results:** Forty-one patients had VRB, out of which 18 patients had immediate VRB and 23 patients had delayed VRB. The average duration between vitrectomy and VRB was 3.28 months. Twenty-eight patients were male and 13 were females. Average age at presentation was 53.8 years. Thirty-four patients (82.9%) were found to have high BSL and 28 patients (68.3%) had high BP and they developed rebleed ($P < 0.01$) after an initial hemorrhage-free period (average = 5.15 months). Fifteen patients (36.6%) underwent first time PRP intraoperatively, and they had immediate rebleed ($P < 0.01$) without any hemorrhage-free period (average = 0.9 months). Eight patients (19.5%) were on perioperative anticoagulants; however, their statistical significance did not persist in the multivariable model. There were neither age nor gender predilection toward rebleed ($P > 0.05$). **Conclusion:** The incidence rate of VRB was found to be 21.6%. Age and gender did not contribute to rebleed. Intraoperative PRP was a risk factor for immediate rebleed. Poor glycemic and BP control was a risk factor for delayed rebleed.

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Vitreous hemorrhage (VH) is one of the most common causes for sudden vision loss in proliferative diabetic retinopathy (PDR).[1] Vitreous rebleed (VRB) after pars plana vitrectomy (PPV) is the most common complication in diabetes mellitus (DM) patients with PDR with incidence rate reported to occur in 12% to 63%.[2-5] Spontaneous resolution of VH occurs in most of the cases; however, resurgery for nonresolving VH is reported in 4% to 38%.[3,6,7] This incidence is higher in patients with PDR, in being 29% to 75%.[3,7,8] Early studies have found that the clearance of VH occurred on an average of 9.1 weeks postoperatively in phakic eyes.[4] The causes of VRB include fibrovascular ingrowth, residual neovascular membrane, insufficient pan-retinal photocoagulation (PRP), and postoperative hypotony.[5,9] The purpose of our study was to evaluate the incidence and identify the risk factors for VRB following 25-gauge sutureless PPV.

Methods

This was a retrospective case series wherein all patients with PDR who underwent PPV for VH and presented with VRB postsurgery were reviewed and evaluated from January 2013 to December 2015. IRB approval was taken for the study. Eyes with PDR that underwent PPV for reasons such as extensive fibrovascular proliferations and tractional retinal detachment were excluded from analysis. This study included patients with persistent VH that occurred within 1 day after surgery. Subject characteristics including patient age, gender, date of surgery and subsequent visits, indication for surgery, operative eye, visual acuity, intraocular pressure, duration of diabetes, history of PRP, lens status, anterior and posterior segment findings were noted from the patient's records. Preoperative tests such as blood sugar and blood pressure (BP) were noted. Attention to their diabetic management including any insulin dependence with concurrent use of anticoagulants was also recorded. Ultrasonography findings were documented in eyes, in which clear fundus view was not possible. Surgical characteristics such as intraoperative and postoperative complications were noted. Depending on the commencement of rebleed, patients were divided into immediate VRB (VH <2 weeks from surgery including present on postoperative day 1) and delayed (VH 2–4 weeks from surgery). All the patients were operated under peribulbar anesthesia. The operative technique for primary procedure was 3-port 25-gauge PPV with endolaser. To prevent postoperative ocular hypotony, all patients underwent fluid-air exchange at the end of surgery. After vitrectomy, the postequatorial retina was inspected for any possible sources of bleeding or tear. If the VH was sufficiently large to prevent clear visualization of the retina or was not absorbed after a month, secondary surgery like vitreous lavage

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was performed. For vitreous lavage surgery, different entry sites from the previous sclerotomies were used. Appropriate management for VRB was performed such as dissection or the cautery of neovascularization, removal of any residual vascular membrane, and the supplementation of laser photocoagulation as required.

Statistical analysis

Descriptive statistical analysis was used initially. To compare between groups, univariable analysis of either Chi-square test or Fisher's exact test was used as appropriate. Factors that were significantly associated with the outcome in the univariable analysis were considered for multivariable analysis. As part of multivariable analysis, logistic regression model was used. A two-sided "$P < 0.05$" was considered to be statistically significant. All analyses were done using the SPSS version 17.0 software for windows.

Results

A total of 190 vitrectomies were performed during the study period. Forty-one patients had VRB, out of which 18 patients (9.5%) had immediate rebleed and 23 patients (12.1%) had delayed rebleed. Four patients were excluded from the study as they had concurrent tractional retinal detachment. The mean age of the patients with VRB was 53.83 years (ranging from 33 years to 80 years). No statistical correlation between age and VRB was found ($P > 0.05$). Twenty-eight male patients out of the total 134 undergone vitrectomy presented with VRB (20.9%) and 13 female patients out of 56 (23.2%) presented with VRB. The correlation between gender and VRB was not statistically significant ($P > 0.05$). The mean duration between TPPV and presentation with VRB was 3.28 months (ranging from 0.3 to 15.4 months). Twenty-seven patients (24.5%) out of the 110 patients that were phakic had VRB and 14 out of the 80 pseudophakic patients presented with VRB (17.5%). No statistical correlation was found between lens status and incidence of VRB ($P > 0.05$).

The mean duration of DM in the patients was 13.41 years. It was noted that 34 patients of the 60 (56.7%) who had high blood sugar levels (BSL) presented with VRB (BSL taken as RBS >150 mg/dl and PPBS >180 mg/dl), and out of 130 patients with stable BSL, only 7 developed VRB (5.3%). The correlation between high BSL and VRB was significant ($P < 0.05$). All 34 patients were on oral hypoglycemic drugs with 27 of them on additional insulin therapy.

It was further noted that 28 patients (65.1%) out of 43 who had high BP (BP >140/90 mmHg) had VRB as opposed to 13 patients who developed VRB out of 147 patients with normal BP readings (8.8%). It thus proved to be statistically significant ($P < 0.05$).

In our study, we found that eight patients out of nine (88.9%) who were on oral anticoagulants had VRB. The anticoagulants were discontinued 5 days before the surgery and restarted on the first postoperative day. Perioperative usage of anticoagulants was significantly associated with rebleed in the univariable analysis ($P < 0.0001$). However, its statistical significance did not persist in the multivariable model after adjustment for other factors.

Out of the total 18 patients who underwent intraoperative PRP, 15 (83.3%) of them had VRB whereas only 3 patients who underwent intraoperative PRP did not develop VRB (16.7%). Statistical significance was hence established ($P < 0.05$). Interestingly, we noted that out of 123 patients that underwent preoperative PRP, only 24 (19.5%) developed VRB, and in the 67 patients that did not undergo preoperative PRP, 17 developed VRB (25.4%). No correlation was found between preoperative PRP and VRB ($P > 0.05$) [Graph 1].

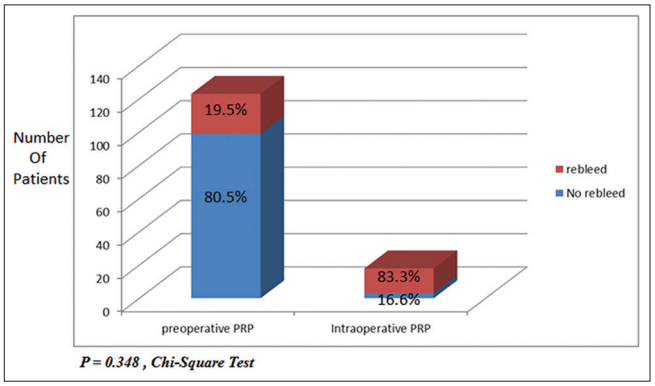
Patients with high blood sugar and BP reading presented with VRB with an average of 13.07 weeks and 10.54 weeks, respectively. Patients who continued with perioperative anticoagulants developed VRB with an average of 5.07 weeks and those who underwent first time intraoperative PRP developed VRB at an average of 4.08 weeks [Graph 2].

Discussion

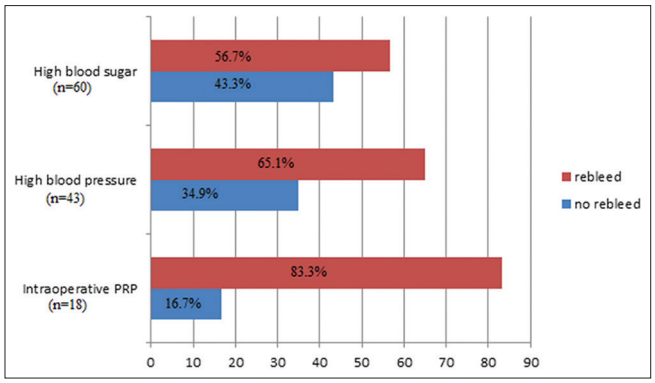
Recurrent bleeding after PPV hinders visual recovery, necessitates additional surgery, and prevents timely and thorough evaluation of fundus. It is defined as hemorrhage that is large enough to cause decrease in visual acuity preventing clear visualization of retinal vessels under indirect ophthalmoscopy.[1] The vitreous blood does not have the tendency to clear as spontaneously in patients with PDR as other patients.[10] VRB can appear within the first few weeks after surgery or occasionally months later. Depending on its severity, additional intervention may be necessary.

The incidence of VRB in PDR has significantly reduced from 75% in the 1980s to approximately 13%–40% due to the advances in surgical techniques.[11-13] In our study, the incidence rate of VRB after PPV was 21.5%, with 9.4% having immediate rebleed and 12.1% with delayed rebleed. Although the incidence for immediate rebleed was considerably lower than that found in a study by Lee and Yu[14] (45.2%), the delayed rebleed showed similar rate (11.8%). Lo *et al*.[15] reported a rate of 13%.

In a study by Khuthaila *et al*.[10] using 23-gauge PPV, the incidence was reported to be 32%. Lei Shi and Yi-Fei[1] reported 16.2%. These differences in the incidence rate can be attributed to the different ages and population studied, duration of diabetes, and severity of eye lesions of the patients in these studies. The average duration between VRB and PPV in our study was 3.28 months which was similar to the literature recorded previously.[16]



Graph 1: The number of patients underwent preoperative or intraoperative PRP and developed vitreous rebleed



Graph 2: The risk factors and percentage of patients developing vitreous rebleed. % of patients $P < 0.001$**, Chi-square Test

It is proven that hyperglycemia-induced inflammation causes the dysfunction of blood vessels, and Toll-like receptor 4 plays a key role in inflammation-induced angiogenesis which contributes to the pathogenesis of PDR.[17] In our study, 34 patients of VRB had high BSL. Twenty-eight patients had high BP level on presentation with VRB and 26 patients from them had concurrent high BSL and this may account for the VRB in these patients. Optimizing BP helps to reduce the necessity of laser photocoagulation and the risk of loss of vision.[18] Levels of about 140/80 mmHg should be aimed for. In a study by Ostri *et al*.,[19] it was shown that inadequate glycemic control caused increase in the risk of undergoing diabetic vitrectomy for VH, but no association was found for systolic BP ≥140 mmHg, diastolic BP ≥90 mmHg, or diabetes duration. However, good metabolic and BP control are essential for successful ophthalmic care of patients with DM and should be monitored on a regular basis. Pre- and post-operative BP was recorded for all the patients. Intraoperative BP recording was not done.

In our study, eight patients on anticoagulants (19.5%) developed VRB. Two patients were on aspirin and six patients on clopidogrel tablets. Anticoagulant usage was found to be significantly associated with rebleed in the univariable analysis ($P < 0.0001$). However, its statistical significance did not persist in the multivariable model after adjustment for other factors though early restarting of anticoagulants may be a risk factor for VH. Our result is in accordance with the study by Khuthaila *et al*.[10] and Brown and Mahmoud[20] who studied the significance between anticoagulation and VH and found no statistical correlation between these variables and also found no greater risk of undergoing reoperation. In contrast, Fabinyi *et al*.[21] stated that patients who were on anticoagulation/antiplatelet therapy at the time of surgery had an increase in the risk of postoperative VH and subsequent reoperation. Appropriate preoperative cessation of treatment appeared to reduce this risk; however, caution has to be taken with regard to the systemic risk. There is limited information about the risks of anticoagulation in vitrectomy and less so in diabetic vitrectomy.[22-24] Although anticoagulant or antiplatelet therapy has not been thought to represent a risk factor for VH, it is prudent to consult with the physician before stopping treatment, as stopping either one could increase the risk of morbidity or mortality in these patients.

We found that patients who underwent preoperative PRP had less chance of VRB than patients undergoing intraoperative PRP. Laser photocoagulation inhibits the production of angiogenic factors and reduces the proliferation of the fibrovascular membrane. In a study by Yan *et al*.,[25] VRB caused by insufficient retinal photocoagulation occurred in 22% that did not receive supplementary retinal photocoagulation. Retinal photocoagulation insufficiency has been reported to be one of the major causes of VRB. However, in a study by Lei Shi and Yi-Fei,[1] no case of VRB was found to be caused by insufficient PRP, as supplementary PRP was given which prevented VH. The rate of VH was lower in patients with complete scatter photocoagulation before undergoing PPV compared with patients with incomplete scatter photocoagulation as noted by Khuthaila *et al*.[10] Complete scatter photocoagulation before PPV leads to regression of neovascularization and may lower the risk of intraoperative and postoperative hemorrhage. As the regression can take several weeks, PRP should be performed to the fullest extent possible before PPV. However, in patients with dense VH which obscures the view of fundus, preoperative PRP may not be possible.

Other factors that caused higher VRB rate in other studies were reported as younger age ($P = 0.022$) and phakia ($P = 0.036$) by Khuthaila *et al*.[10] They hypothesized that in phakic patients, there may be less trimming of the vitreous skirt to prevent damage to the crystalline lens and increasing blood dispersion into the vitreous cavity. In younger patients, the disease may be more aggressive, and there may be greater difficulty in inducing a complete posterior vitreous detachment at the time of surgery. We did not find any statistical significance between age and gender and lens status with VRB ($P > 0.05$ for all variables). Lee and Yu[14] reported that patients who had postoperative hypotony had an increased risk of immediate postoperative VH. In our study, all patients underwent fluid-air exchange to prevent postoperative hypotony. Lei Shi and Yi-Fei[1] studied the various intraocular tamponade used for postoperative hemostasis such as air, gas, silicon oil, and their correlation with VRB and found that patients with silicon oil removal have an earlier onset of VRB. They hypothesized that this could be due to removal of silicone oil tamponade effect on the retinal vessels.

Early postoperative VRB may occur due to residual blood clots in the peripheral vitreous and retinal surface and its dispersion into the vitreous cavity, iatrogenic injury of retinal vessels, incomplete removal, and dissection of the fibrovascular tissue.[4,26] Sources of delayed VRB include fibrovascular proliferation from the sclerotomy sites,[13,16,27] neovascularization of the residual fibrovascular tissue, secondary hemorrhage from shedding of thrombus, or by detachment of the residual attached cortex and avulsion of fibrovascular tissue contained on it.[26] During vitreous lavage for VRB in our study, even though sclerotomy sites were checked for fibrovascular proliferation, ultrasound biomicroscopy was not used to confirm it and hence we could not study this factor.

Previous studies suggested potential sources for VRB after 20-gauge PPV.[2,3,13] However, in a study by Lee and Yu[14] and Park *et al*.,[28] they found no difference in the rate of VRB with different gauge vitrectomies. Various strategies to minimize VRB have been analyzed by several groups. Yang *et al*.[4] noted that long-acting C3F8 gas may be effective by exerting mechanical tamponade on retinal vessels and concentrating coagulation factors near to bleeding sites. Yeh *et al*.[13] reported that prophylactic cryotherapy treatment to the peripheral retina

or to the sclerotomies may prevent delayed VRB. However, Entezari *et al*.[29] claimed the opposite. Lo *et al*.[15] pretreated their patients with intravitreal bevacizumab before PPV and reported that it did not appear to affect rates of VRB or final visual acuity.

Some limitations of this study include its retrospective nature. Because of the inclusion of a few patients with shorter follow-up, it is possible that we may have missed some eyes in which delayed VRB occurred or repeat PPV was required. We did not include patients having undergone intraocular tamponade with gas or silicone oil and who received intravitreal bevacizumab and hence could not study their effects on VRB. Ultrasound biomicroscopy was not done to rule out sclerotomy site fibrovascular proliferation. Correlation between glycosylated hemoglobin level and VRB was not analyzed. The confounding factors in our study were high BP levels and sugar levels.

Conclusion

We found that the major risk factors for immediate VRB were lack of preoperative PRP. Inadequate blood sugar control and high BP level are major risk factors for delayed VRB.

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Conflicts of interest

There are no conflicts of interest.

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