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Current Management of Vitreous Hemorrhage due to Proliferative Diabetic Retinopathy

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Abstract

Diabetic vitreous hemorrhage secondary to proliferative diabetic retinopathy is a cause of severe vision loss in diabetic patients. Laser photocoagulation remains the primary treatment when the view allows. Intravitreous anti-VEGF injections do not appear to have a role as primary treatment but may have an invaluable role as adjuvant to surgery. Pars plana vitrectomy with endolaser panretinal photocoagulation remains the procedure of choice for non-clearing vitreous hemorrhage. The vast majority of patients with vision of 5/200 or less due to diabetic vitreous hemorrhage do not clear spontaneously even after 1 year. With improvements in surgical techniques leading to better outcomes, fewer complications, less discomfort and a faster recovery time it is reasonable to operate on such patients sooner than the 3–4 months that had been generally accepted in the past, if there has been no significant spontaneous improvement.

In 1970, Robert Machemer performed the first pars plana vitrectomy (PPV) on a patient with a nonclearing diabetic vitreous hemorrhage (NCVH) of 5 years' duration, achieving an improvement in visual acuity from 2/200 to 20/50.[1–3] Indeed, NCVH was one of the main indications for retinal surgery in the early days of vitrectomy. [4] The role of PPV for vitreous hemorrhage was further refined in 1985 when the first results of the Diabetic Retinopathy Vitrectomy Study (DRVS) were reported.[5–6] Since that time there have been a multitude of refinements in surgical instrumentation and techniques improving surgical outcomes, and the role of anti-VEGF medications as potential adjuvant or treatment has been evaluated. This review focuses on the current medical and surgical management of NCVH.

Pathophysiology

Retinal ischemia results in hypoxia which results in the production of hypoxia induced factor (HIF). HIF enhances the expression of angiogenic factors including insulin-like growth factor 1, basic fibroblast growth factor, erythropoietin, and vascular endothelial growth factor (VEGF) amongst others.[7–12] Such angiogenic factors are present in the vitreous,[7,10–11, 13–15] fibrovascular membranes [8, 16–17] and whole retinas [18] of patients with proliferative diabetic retinopathy and lead to the development of neovascular buds from retinal blood vessels. [19] This neovascular tissue proliferates and invades the potential space between the retina and the posterior hyaloid face and later the posterior lamellae of the cortical vitreous, producing a firm adhesion.[20–21] The vessels continue to proliferate and subsequently develop an increasingly fibrous component. Localized traction from the posterior hyaloid face or contraction of the fibrous element of this fibrovascular complex leads to traction on the friable neovascular tissue and retina, leading to a vitreous

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hemorrhage. This may stimulate further fibrosis and vitreous contraction, and ultimately lead to a traction retinal detachment. [22]

Laser Photocoagulation

Vitreous hemorrhage in the presence of any neovascularization at the optic disc (NVD) or moderate/severe neovascularization elsewhere (NVE) was shown in the Diabetic Retinopathy Study (DRS), a randomized controlled study comparing observation to peripheral retina ablation using photocoagulation, to significantly increase the risk of severe visual loss (defined as vision <5/200) without treatment ('high-risk characteristic'). [23] For example, the risk of severe visual loss without treatment for eyes with moderate or severe NVE increased from 6.9% to 29.7% in the presence of VH. [23] Similarly, the risk of severe visual loss in eyes with mild NVD increased from 10.5% to 25.6% in the presence of VH. [23] Panretinal photocoagulation (PRP) was shown to significantly reduce the risk of long-term severe visual loss.[23] The endpoint to laser photocoagulation should be the complete resolution of NVD and NVE.[24]

Panretinal photocoagulation does not appear to increase the rate of clearance of the vitreous hemorrhage itself. However, PRP does prevent further episodes of vitreous hemorrhage and by interrupting fibrovascular proliferation, PRP prevents the progression to tractional retinal detachment. Vitreous hemorrhage will often resolve spontaneously, especially if is mild-moderate. Pars plana vitrectomy may be considered for non-clearing vitreous hemorrhage (see below).

Recurrent vitreous hemorrhage indicates that active NVD or NVE is still present and that additional peripheral scatter retinal photocoagulation is required. It should be noted that VH developing *shortly following* (within 4 weeks) panretinal photocoagulation sometimes occurs due to contraction of the fibrous component as the vascular component of the fibrovascular membrane regresses: such VH is not an indication for fill-in panretinal photocoagulation.

The presence of pre-existing panretinal photocoagulation scars is associated with better outcomes following PPV for VH,[2526–27] including a reduced risk of post-operative recurrent VH.

Anti-VEGF to Resolve Vitreous Hemorrhage

Intravitreous (IVT) bevacizumab results in rapid regression of retinal neovascularization, as early as 24 hours following injection. [28] The effect, however, is transient and neovascularization tends to recur. [28] Several small retrospective series reported that IVT bevacizumab (followed by PRP in several of these series) might have a role in resolving vitreous hemorrhage. [28–31] Therefore the Diabetic Retinopathy Clinical Research network (DRCRnet) conducted a double masked randomized multicenter clinical trial (protocol N) investigating IVT ranibizumab (an anti-VEGF agent) versus IVT saline injection for eyes with VH of severity that precluded PRP. The study found no difference between the two treatments for the primary outcome which was the proportion of patients requiring a vitrectomy. It is likely that some of the effects attributed to anti-VEGF in the early series were a non-pharmacological effect of IVT injection (injection of any fluid causes increased vitreous syneresis and sometimes a posterior hyaloid face separation which results in faster clearance of vitreous hemorrhage). Moreover, secondary outcomes such as PRP completion by 4 months or rates of recurrent hemorrhage, while marginally favoring IVT ranibizumab impressed by the poor efficacy documented: for example, in only 44% of eyes in the IVT ranibizumab group compared with 31% of eyes in the IVT saline group could PRP be completed by 4 months. [32] Therefore, at present IVT anti-VEGF does not seem to have a

significant role in the treatment of diabetic vitreous hemorrhage other than as an pre-operative adjuvant to vitrectomy, as discussed elsewhere in this issue of *International Ophthalmology Clinics.*

Surgical Management of Diabetic Vitreous Hemorrhage

Timing of pars plana vitrectomy for Diabetic Vitreous Hemorrhage

Pars plana vitrectomy remains the treatment of choice for eyes in which the vitreous hemorrhage is not spontaneously resolving. Findings from the DRVS still inform the decision making process as to when to operate. This study evaluated eyes with severe vitreous hemorrhage reducing visual acuity to 5/200 or less for at least 1 month. Patients were randomized to early vitrectomy or deferral of vitrectomy for 1 year. The deferral group patients underwent vitrectomy if persistent vitreous haemorrhage was present after 12 months, or sooner if retinal detachment involved the center of the macula as demonstrated by ophthalmoscopic or ultrasonographic examination at any time during follow-up. This study showed that 25 % of the early vitrectomy group compared to 15% of the deferral group had a final visual acuity of 20/40 or better after 2 years follow-up, although the benefit seemed to be limited to patients with type I diabetes.[6] The benefits of early vitrectomy were still demonstrable after 4 years follow-up in this subgroup.[33] In patients with type 2 diabetes mellitus there was no demonstrable benefit of early vitrectomy in final visual acuity. However, only 20% of eyes in the deferral group had had resolution of vitreous hemorrhage by 1 year.

Two conclusions can be drawn from the DRVS: firstly, that there is a benefit of early vitrectomy eyes of type 1 diabetics with severe vitreous hemorrhage; secondly, that the majority (80%) of patients with type 2 diabetes and severe vitreous hemorrhage still require a vitrectomy to resolve the vitreous hemorrhage after 1 year. While there was no benefit in long-term outcome in this study by operating sooner than a year, it did mean that patients had to suffer poor vision in that eye during that period of time. The DRVS was conducted before it had been realized that dextrose should be added to the infusion to prevent intraoperative cataract formation in diabetic eyes (30% of eyes undergoing pars plana vitrectomy required pars plana lensectomy due intraoperative cataract formation). [34] Lensectomy with the resultant aphakia leads to a higher risk for neovascularization of the iris [35–37] and the additional operative time required and resultant inflammation may also compromise visual outcomes. Moreover, DRVS was conducted prior to the advent of endolaser photocoagulation which assures complete ablation of the peripheral retina which could sometimes be challenging with intraoperative laser delivered through the indirect ophthalmoscope. [38] Further, wide-field visualization, that evolved in the late 1990s, enables more complete endolaser photocoagulation treatment and may allow for better outcomes. [39]

The results of PPV with current techniques may therefore be better than in DRVS. Studies published within the last decade showed an improvement in visual outcome when compared with previously reported outcomes from the DRVS. In one series the mean visual acuity improved from 20/600 preoperatively to 20/90 postoperatively. [40] In another series, 87% of the eyes improved by at least three ETDRS lines at 12 months.[41] Additionally, complications are less common (see below). Moreover, the evolution of transconjunctival, sutureless, micro-incision (23-, 25- gauge) PPV has resulted in less inflammation, increased comfort to the patient and faster recovery in the early post-operative period with similar complication rates. [42–44] Further, the transition to performing PPV for NCVH under local anesthesia rather than general anesthesia has further increased the comfort and reduced the recovery time for the patient. Given the reduced systemic risk of surgery, improved visual and anatomic outcomes of PPV with current techniques and the reduced post-operative discomfort and recovery time, surgeons have been performing PPV for diabetic vitreous

hemorrhage earlier than the 3 months that had once been the widely adopted standard for observation.

Factors that should be considered when deciding on the timing of PPV for a diabetic vitreous hemorrhage include status of the fellow eye, occupational requirements/lifestyle requirements (e.g. a self-employed taxi cab driver may not be able to afford an observation period of 3 months or a champion golf player may not wish to have resolving vitreous hemorrhage coming into their field of vision), the degree of visual impairment in the affected eye, the requirement for clear media to monitor progression of concurrent pathology (e.g. tractional retinal detachment threatening the macula or diabetic maculopathy). It is important not to underestimate the visual impairment caused by vitreous hemorrhage that comes into the visual axis intermittently in patients with good visual acuity in the clinic.

In our practice, unless the patient has an over-riding reason why they need immediate visual rehabilitation, we observe both patients with type 1 and type 2 diabetes mellitus and a vitreous hemorrhage for 4 weeks. If at that point the patient is satisfied that there has been improvement we continue with observation; otherwise, we offer a PPV. In a system where resources (funds, operating room time etc) are limited, it is reasonable to observe vitreous hemorrhages in type 2 diabetics for 3 or 4 months for spontaneous resolution. It cannot be over-emphasized that the above discussion is for eyes with vitreous hemorrhage without a concurrent retinal detachment; all patients with a vitreous hemorrhage should have ocular b-mode ultrasonography to ensure that there is no retinal detachment.

Surgical techniques

We perform a 3-port transconjunctival sutureless vitrectomy (usually 23-gauge) with a cannula entry system. The infusion line is inserted in the inferotemporal quadrant. Using a light pipe and the vitreous cutter we perform a core vitrectomy and transect the peripheral hyaloid face 360 degrees, then trim the unformed vitreous over the posterior pole and if not already separated, lift the posterior hyaloid face to the ora, if possible. Caution needs to be exerted when lifting the posterior hyaloid face as it can be strongly adherent to areas of NVE. Hemorrhage can be controlled by elevating the infusion pressure and direct endolaser photocoagulation to the NVE, provided it is not in the macula. With the current wide-field viewing system, we are able to visualize and can remove most of the vitreous skirt. We apply complete panretinal photocoagulation, ablating retina to the ora as we believe that this reduces the risk of further vitreous hemorrhage or anterior segment neovascular complications.

Combined phacoemulsification with intraocular lens insertion/ PPV has also been performed when significant cataract limits visualization of the posterior segment or to spare the patient from a second procedure given that the rate of cataract progression is greatly increased by PPV. [45] It is important to be aware that rendering eyes with severe PDR pseudophakic (or aphakic) increases the risk of iris neovascularization and neovascular glaucoma[35, 46–47] Furthermore, the rate of cataract progression after PPV for diabetic vitreous hemorrhage is lower than after PPV for other indications, especially in younger patients. [48] It may therefore be preferable to postpone phacoemulsification cataract surgery until a visually significant cataract has developed after vitrectomy for vitreous hemorrhage. [49]

Special Considerations

In the special case where ghost-cell glaucoma is complicating very severe VH, and the intraocular pressure is uncontrollable despite maximal medical therapy PPV should not be delayed. [50–51] Aphakic eyes allow easy access for the vitrector to the anterior chamber to wash the ghost cells. In pseudophakic eyes, performing an opening in the posterior capsule

with the vitrector allows the accumulated ghost cells in the anterior chamber to freely move to the posterior vitreous cavity.

Complications after vitrectomy for VH

Common complications after vitrectomy for VH include corneal epithelial defects, cataract formation, elevated intraocular pressure, recurrent vitreous cavity hemorrhage (early, delayed or persistent), iatrogenic retinal breaks, rhegmatogenous retinal detachment, and neovascular glaucoma.[40, 52] The development of these complications can be minimized by meticulous surgical technique and cautious post-operative follow-up.

The incidence of corneal epithelial defects has decreased dramatically after the introduction of non-contact wide-angle viewing system.[53] Elevation in intraocular pressure commonly occurs secondary to trabecular meshwork obstruction by erythrocytes and/or the effects of intraocular gas tamponade. Under these circumstances the IOP can be usually readily controlled by medical treatment.[54]

Vitreous cavity hemorrhage

Vitreous cavity hemorrhage following PPV for VH has been reported in 7–63% of patients.[40, 55, 56–62] Vitreous cavity hemorrhage following PPV can be present from the first post-operative day (persistent- 20–63% of patients), or can occur within the first 4–6 weeks (early-5%) or thereafter (delayed- 8%).[40. 55, 61] Persistent and early vitreous cavity hemorrhage are mainly secondary to incomplete intraoperative hemostasis, bleeding from dissected fibrovascular tissue and release of erythrocytes from residual peripheral vitreous gel and iatrogenic injury to the retina or retina vessels. Postoperative hypotony increases the risk of post-operative vitreous hemorrhage as does pre-operative neovascularization of the iris. [55, 63] Previous lower extremity amputation and failure to take prescribed antihypertensives are also associated with increased risk of persistent or early vitreous cavity hemorrhage.[63]

Intraoperatively, more thoroughly removing the residual peripheral vitreous gel my reduce the red blood cells seeping into the vitreous cavity and resulting in persistent vitreous hemorrhage. Indeed, a small retrospective study by Cheema and colleagues reported that 2 of 28 (7.1%) compared to 10 of 31 (32%) patients in the groups that respectively did and did not undergo complete removal of the residual peripheral vitreous gel had a persistent vitreous hemorrhage.[56]

Intraocular tamponade with perfluoropropane gas has been hypothesized to either tamponade the retinal vasculature or stimulate clot formation. A small retrospective study did not find gas tamponade to be associated with a reduced rate of post-operative bleeding.[56] However, in a prospective, randomized controlled study of 61 eyes comparing eyes with intraocular gas tamponade with those without, while there was no difference in the mean time to initial clearing of VH in the two groups or the proportion of eyes that required over 5 weeks to clear their VH, there was a significant difference between rate of early recurrent VH in the two groups. Specifically, none of 31 eyes (0%) in the group that received 10% perfluropropane gas had an early recurrent VH compared to 5 of 30 (16%) in the group that did not receive intraocular gas tamponade. Criticisms of this study include the limited number of eyes recruited and that there was no statistical adjustment for multiple comparisons. Further, given that perfluoropropane will not allow clear vision for at least 2 weeks, will cause the patient to have annoying visual perceptions due to the gas bubble for an additional 4–6 weeks and will lead to restricted travel for 5–7 weeks, it is far from obvious why perfluoropropane is a valuable adjuvant: it may be that accepting a 16% rate of

early recurrent VH is better- especially since the majority of such VH will spontaneously resolve.

Intravitreous anti-VEGF therapy with bevacizumab administered 1–2 weeks pre-operatively has been reported to prevent the occurence of early postoperative hemorrhage but the evidence for routine use is still lacking; the topic of adjunctive use of anti-VEGF therapy with vitrectomy for proliferative diabetic retinopathy is covered by a different article in this issue of *International Ophthalmology Clinics*. [64]

Delayed vitreous hemorrhage (occurring 3 months or greater after surgery) occurs in approximately 8% of patients. [40] There are 3 common causes for delayed vitreous hemorrhage: firstly, from residual fibrovascular membranes; secondly, from sclerotomy entry site fibrovascular ingrowth, and thirdly, from reproliferative retinal or ciliary body neovascularisation. [60, 65] Complete dissection of fibrovascular membranes during surgery may reduce delayed VH from this source. To prevent re-proliferation of retinal neovascularization extensive intraoperative retinal ablation, including of the anterior peripheral retina should be undertaken. While this was done with cryopexy in the past, the ability to visualize the periphery to the ora with wide-field viewing systems and consequently better removal of peripheral vitreous allow this to be performed using intraoperative endolaser scatter photocoagulation to the anterior peripheral retina. [57,66]

Fibrovascular ingrowth has been shown to be responsible for the majority of delayed VH. [59–60, 65] Cryotherapy to the sclerotomy entry sites has been advocated to prevent fibrovascular ingrowth. [60] An early retrospective study of 81 eyes did indeed show that cryotherapy to the sclerotomies (with anterior peripheral retinal cryopexy) reduced the rate of postoperative VH from 37.5% to 4.3%,[62] However, a more recent, prospective randomized double masked clinical trial found that cryotherapy applied to the sclerotomy sites appeared to have the opposite effect: delayed VH was present in 28% of eyes treated thus compared to 10% of controls! [67] Therefore, the routine use of cryotherapy to sclerotomy sites does not appear to be justified at this point in time. It should be noted that the incidence of fibrovascular ingrowth in the era of small gauge vitrectomy has not been well-studied.

Persistent or recurrent VH clears fastest in aphakic (3–4 weeks) compared to phakic eyes (average 9 weeks), with the time to clearing being intermediate in pseudophakic eyes.[61] In pseudophakic patients with intact posterior capsule, Nd:YAG laser peripheral capsulotomy may be helpful in resolving the vitreous hemorrhage by allowing a track of the blood cells from the vitreous cavity to the anterior chamber and to clear through the trabecular meshwork. A spike in intraocular pressure can occur but is usually transient and well controlled with topical glaucoma drops. [58] Indeed, we routinely open the posterior capsule with the vitreous cutter when performing a PPV for a complication of diabetic retinopathy. In recent studies there is a 7– 22% rate of repeat surgery following PPV for VH due to persistent or recurrent VH. [40, 52, 55] It is uncommon for patients to require more than a single repeat PPV due to recurrent VH. [40, 68]

Retinal Breaks

Iatrogenic retinal breaks occurred at a rate of 8.1% in a series of patients who underwent PPV for complications of diabetic retinopathy; these occur most commonly with fibrovascular membrane dissection [57] The occurrence of these breaks did not increase the risk of postoperative vitreous hemorrhage. [57] RRD after vitrectomy for NCVH is a rare complication, the reported rate is 1%. It usually results from peripheral or, less commonly, posterior retinal breaks. [40, 57] RRDs can be further complicated by proliferative vitreoretinopathy and/or anterior segment neovascularisation.[52, 69] Hence, it is essential to

perform scleral depression and examination of the peripheral retina to rule out the presence of tears or breaks at the conclusion of surgery and laser retinopexy or cryopexy applied if a break is identified. [39] When a RRD occurs after a vitrectomy further surgical intervention is necessary to reattach the retina although the final visual outcome might be poor.[52, 69]

Neovascular Glaucoma

The incidence of neovascular glaucoma (NVG) is approximately 3%. NVG usually occurs in cases with severe ischemia and/or inadequate laser photocoagulation, although it may also occur following endolaser panretinal photocoagulation. [52, 57, 69] Urgent treatment with panretinal photocoagulation and adjunctive intravitreal anti-VEGF therapy is required to decrease the ischemic drive leading to neovascularization.[70]

Surgical Outcome

In the majority of studies visual outcomes of eyes that underwent PPV for repair of tractional retinal detachment are lumped together with those of eyes that underwent PPV for VH so that only a handful of studies provide useful data.[52, 71] Such recent series have documented mean postoperative visual acuity of 20/40-20/90, [40, 55] with 87% of the eyes improving by at least three ETDRS lines at 12 months.[41] Visual outcomes can be limited by macular ischemia, severe hard exudates, long-standing diabetic macular edema: the patient should be warned about the possibility of a limited visual outcome prior to surgery. Visual outcomes can also be limited by complications of the disease or surgery such as anterior segment neovascularization and neovascular glaucoma.

Conclusion

Scatter panretinal photocoagulation remains the mainstay of treatment when the view allows following VH due to PDR. Intravitreous anti-VEGF agents do not have a role in the primary treatment of VH, but may be invaluable adjuncts to pars plana vitrectomy. B-mode ultrasonography should be routinely performed upon presentation in a diabetic patient with vitreous hemorrhage and proliferative diabetic retinopathy to rule out retinal detachment. In the absence of a macula involving tractional retinal detachment, PPV should be undertaken early in patients with type 1 diabetes mellitus and VH due to PDR to improve long-term visual outcomes. In patients with type 2 DM and VH due to PDR the rate of spontaneous clearance of severe VH is only 20% at 1 year: the healthcare system limitations dictate the timing of surgery in such cases; if there has been no improvement after 4 weeks of observation the majority (80%) of patients would benefit from pars plana vitrectomy at that point in time. The most common complication of PPV for VH is recurrence of the VH: meticulous intraoperative hemostasis and aggressive panretinal photocoagulation reduce this risk, while adjunctive pre-operative or intra-operative IVT bevacizumab may also have a role. Visual outcomes are generally very satisfactory, although they may be limited by macular ischemia, longstanding diabetic macular edema, severe hard exudates or neovascular glaucoma.

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