Chapter

Diabetic Vitrectomy

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Abstract

Diabetic retinopathy (DR) in its advanced stage is a leading cause of blindness and visual impairment. Despite efforts at early detection of DR, disease monitoring, and medical therapy, significant proportions of people living with diabetes still progress to develop the advanced proliferative disease, which is characterized by neovascularization, actively proliferating fibrovascular membranes, and retinal traction. The surgical removal of this proliferating tissue and the treatment of the retinal ischemic drive can be very rewarding, providing significant stability of the retina and in several cases improved retinal anatomy and vision. Diabetic vitrectomy comprises a broad range of surgical techniques and maneuvers, which offer the surgeon and patient opportunity to reverse deranged vitreoretinal anatomy and improve or stabilizes vision. Advances in vitreoretinal technology have contributed greatly to more recent improved outcomes; it is expected that future advances will offer even more benefit.

Keywords: diabetic retinopathy, vitreous hemorrhage, proliferative diabetic retinopathy, tractional retinal detachment, macular edema, vitrectomy

1. Introduction

Global estimates of diabetes have been on the rise [1]. Diabetic retinopathy (DR) is a leading cause of blindness among the working age group, with increasing numbers of persons being affected worldwide [2, 3]. It is a microvascular complication of diabetes which progresses to advanced disease in several cases. It is a global concern as indicated by a recent review published in Lancet [4]. The microvascular complications of diabetes result in macular leakage or exudation and vasoproliferative retinal disease, which are the hallmarks of advanced DR. Despite treatment of earlier stages of DR with medical therapy, which include intravitreal injection of anti-vascular endothelial growth factor (VEGF), intravitreal injection of steroids, and retinal laser photocoagulation, several eyes will progress to require surgical treatment [5–8].

Surgical treatment for the advanced complications of DR can range from more straightforward cases involving the removal of a non-clearing vitreous hemorrhage from an eye in which vitreous separation has already occurred, to more complicated surgical techniques such as in dealing with a combined tractional and rhegmatogenous retinal detachment (TRD/RRD) or tractional retinal detachment (TRD) involving the macula [9, 10]. The preoperative considerations, intraoperative techniques, and the postoperative outcome, including the complications of surgery, could vary considerably, depending on the risk factors and complexity of the vitreoretinal presentation associated with each case. Therefore surgical planning should be done on a case-by-case basis.

Furthermore, in recent times, there have been significant improvements in preoperative care and evaluation, and intraoperative surgical technique, including the administration of preoperative intravitreal pharmacotherapy, development of small-gauge transconjunctival instrumentation [11–13], and availability of multifunctional vitrectomy probes with high cut rates [14]. These advances have made surgical outcome more predictable and have resulted in an expansion of the indication for vitrectomy in the management of the tractional complications seen in DR. This review will focus on highlighting the indications, pathophysiology and principles of surgery, preoperative considerations, intraoperative surgical techniques, and outcome of diabetic vitrectomy in contemporary times.

2. Indications for surgery

The indications for vitrectomy in advanced DR have increased over the years from the situation in the early years of diabetic vitrectomy, when surgery was used for removing non-clearing vitreous hemorrhage. The first vitrectomy performed by Machemer was for the removal of non-clearing vitreous hemorrhage in a patient living with diabetes, and suffering from proliferative diabetic retinopathy (PDR) [15]. The Diabetic Retinopathy Vitrectomy Study (DRVS) was the first randomized, large series study evaluating the outcome of early versus deferral of vitrectomy in eyes with vitreous hemorrhage secondary to advanced DR [16]. It highlighted the benefit of early vitrectomy especially in type 1 diabetics with more severe disease. The DRVS also demonstrated that the benefit of surgery was maintained over a 4-year study period. Since then, the indications for diabetic vitrectomy (DV) are now known to include non-clearing vitreous hemorrhage, TRD, combined RRD/TRD, vitreomacular traction, traction-induced diabetic macular edema (DME), rubeosis iridis, and macular distortion (including dragging of the macula), to mention a few [17–21].

1. Vitreous hemorrhage (VH): vitrectomy for vitreous hemorrhage removal, in several studies, remains the most common indication for diabetic vitrectomy [20, 22, 23]. The scope of this will depend on the surgeon's personal experience, state of the fellow eye, previous retinal laser, recurrence of VH, and systemic control of glycemic levels. Non-clearing vitreous hemorrhage cases with complete separation of the posterior hyaloid are rather uncommon and the vitreous can be easily removed with expectation of improved vision in a majority of eyes. Vitrectomy for a case in which prior retinal laser photocoagulation has been applied also tends to progress quite well as the prior laser would have reduced the activity of the retinopathy, treated the retinal ischemia, and slowed the momentum of the disease. Moreover, in eyes with prior preoperative retinal laser, the occurrence of iatrogenic breaks within the areas of retinal laser scars prevents progression to retinal detachment. VH can at times be associated with more severe proliferative retinal disease such as a macula involving TRD. In this case both VH and TRD are indications for surgery and eventual visual outcome will be affected by the occurrence of TRD. This situation can be identified using a preoperative B scan ultrasound, which will reveal the TRD.

2. Retinal traction involving the macula can be an important indication for vitrectomy. This can occur as a result of an epiretinal membrane (ERM), TRD, TRD/RRD and vitreomacular traction (VMT). Fibrovascular proliferation (FVP) in the sub-hyaloid space is responsible for the retinal traction, which could initially occur in an extra macular site, and then progress to involve the macular area. Also, TRD could develop primarily in the macula and have an early impact on vision.

Surgery is indicated when the traction occurs in the macula or if there is obvious progression of an extra macular TRD towards the macula. In some cases the retinal traction is significant and creates a retinal tear. This adds a rhegmatogenous component to the already existing TRD. In combined TRD/RRD, progression to involve the macula could be rapid, and early surgery is advised.

In these situations of significant traction involving the macula or threatening the macula, surgery is indicated to relieve the traction and reattach the retina or to prevent progression of TRD to the macula. However, there are several cases in which extra macular TRD remains stable after adequate panretinal laser photocoagulation (PRP) and good control of systemic parameters have been achieved. Such cases can be observed since there is no progression.

In one review comparing African-Americans with Caucasians requiring diabetic vitrectomy, patients of African-American descent were found to be more likely to have TRD/RRD than Caucasians, and it was concluded that African-Americans might have a greater risk of developing this advanced complication [24]. In the light of this, African-Americans and others at increased risk could benefit from earlier vitrectomy, before the onset of vision damaging advanced tractional complications.

3. Persistent retinal neovascularization despite adequate laser PRP may result in recurrent VH and requires surgical removal of the vitreous scaffolding on which such neovascularization would progress. In such cases, adequate retinal laser fails to cause a complete regression of neovascularization. The vascular tuft invades the vitreous scaffold and forms neovascular pegs. This vitreous attachment to the neovascular peg has to be removed to prevent the recurrent VH, which recurs whenever there is significant vitreous traction on the neovascular tuft.

4. Severe FVP, especially if associated with significant traction involving or threatening the macula, or if obscuring the macula, may require surgical removal. In some instances, FVP occurs in the retina periphery and may be associated with proliferation extending from sclerotomy sites. This was more common in the era of large sclerotomies using the 20-gauge vitrectomy systems. Residual postoperative peripheral vitreous and significant untreated ischemia in the peripheral retina using either endoretinal laser photocoagulation or cryotherapy predispose to the formation of this complication better known as anterior hyaloidal fibrovascular proliferation (AHFVP) [25]. This is a known complication of diabetic vitrectomy which has also been reported to occur after cataract surgery in poorly controlled diabetic patients [25, 26].

Other indications for diabetic vitrectomy include macular ectopia and rubeotic glaucoma.

3. Preoperative systemic considerations

Diabetes is a multisystem disease. The presence of DR suggests microvascular affectation, which may include an effect on the microvasculature in other organs, especially the kidney resulting in diabetic nephropathy. Advanced retinopathy requiring surgery has been found to be associated with reduced life expectancy [27]. Also patients with diabetic macular edema have been noted to have a higher incidence of cerebrovascular accidents and myocardial infarcts [28].

As the patient for diabetic vitrectomy could be ill before or after the surgery, careful review by the internist and anesthesia team is required before the decision to proceed to surgery is taken. If the patient is on routine dialysis, heparin-free dialysis may be beneficial in reducing the incidence of intraoperative and postoperative hemorrhage. Preoperative administration of intravitreal VEGF injection has become popular in recent times and has been shown to decrease the rate of intraoperative and postoperative hemorrhage; it also improves intraoperative visibility and reduces surgery time.

Importantly, an internist clearance is required before preoperative adjunctive anti-VEGF is administered to avoid a situation in which following the administration of anti-VEGF, surgery is postponed due to the patient's ill health. This may result in an overactivity of the anti-VEGF with severe contraction of the fibrous component of the fibrovascular membrane resulting in a worsening TRD (and perhaps more retinal ischemia); this is known as a "Crunch." The use of anti-VEGF will be discussed in more detail later on.

4. Preoperative ocular considerations

1. Visual acuity: preoperative acuity has been shown to be an important factor in determining the eventual postoperative visual outcome, with eyes having better preoperative vision tending to have improved postoperative vision. Also, TRD involving the macula will have poorer preoperative vision than a "macular sparing" TRD. Therefore surgery should be performed once the macula is perceived to be threatened. Macular ischemia remains an important reason for poor preoperative and postoperative vision; this can be determined by the use of fundus fluorescein angiography (FFA) to assess for macular non-perfusion. Optical coherence angiography (OCT angiography or OCTA) can also be used and has the advantage of repeatability of the test. However, in several cases, it is not possible to perform this FFA assessment of the macular vasculature before surgery because of opacities in the medium, including VH and FVP, which obscure the view of the macula.

2. Intraocular pressure (IOP): this may be normal or elevated. When IOP is elevated, it is important to assess the anterior chamber angles and anterior uvea carefully, in search of rubeosis. The finding of rubeosis suggests very significant retinal ischemia and further worsens the prognosis for recovery of vision. The rise in IOP may also have damaging effects on the cornea, including cornea edema, and result in decreased visibility during surgery.

3. Cornea: the clarity of this structure is required for proper access and visibility required for diabetic vitrectomy. The use of contact lens viewing systems significantly increases the incidence of cornea opacity and may require the removal of cornea epithelium during the surgery. Such scrapping off of cornea epithelium could result in postoperative cornea defects, which could take some time to heal. The aforementioned situation has been greatly reduced with the more frequent use of non-contact lens viewing systems.

4. Pupil: it is vital to assess for adequate pupillary dilatation prior to surgery. A poorly dilating pupil may require more than pharmacological mydriasis. In some instances pupillary synechiae may exist and will require mechanical dilatation such as using iris hooks.

5. Lens: the presence of significant cataract may require that a combined vitrectomy and cataract removal be performed during the same surgery. The cataract is first removed using a phacoemulsification technique, then the diabetic vitrectomy is performed. The intraocular lens (IOL) could be inserted before or at the conclusion of the vitrectomy. This combined procedure has become a popular technique in recent years. It provides a clearer view and lends itself to improved access to the retina periphery with the use of a wide-angle viewing lens. However, it can also be associated with significant complications of the anterior segment, since there could be enhanced diffusion of the growth factors including VEGF from the posterior segment to the anterior segment of the eye, resulting in the formation of rubeosis iridis and its sequelae.

6. A B scan ultrasound is a useful ocular investigation to have, especially in situations in which there is limited or no view of the retina as a result of vitreous hemorrhage, opacities in the vitreous, and cataract. A B scan can detect the presence or absence of posterior vitreous detachment (PVD) and provide information useful for preparing the eye for diabetic vitrectomy. For instance, some surgeons would give preoperative intravitreal anti-VEGF in eyes without a PVD and refrain from doing so in eyes in which a PVD already exists. Also a B scan can detect the presence of vitreoschisis (aka second membrane). Vitreoschisis is common in diabetic retinopathy eyes, and for this reason re-staining using multiple intravitreal triamcinolone injections is important to detect the residual vitreous layer when vitreoschisis is present. Vitreoschisis is thought to be due to vitreous hemorrhage in the gel splitting the vitreous fibers. Recognizing its presence is essential for good outcome.

5. Relevant pathophysiology and surgical principles

Advanced stages of DR are characterized by retina edema and ischemia, consequent to vascular hyperpermeability and vascular occlusion, respectively. The chronic hyperglycemia results in progressive damage to the retinal capillary network resulting in retinal hypoxia and release of hypoxia-inducible factor (HIF) from the affected areas of the retina. The resultant ischemic retina due to the action of HIF then releases pro angiogenesis growth factors which include basic fibroblast growth factor (FGF), insulinlike growth factor 1 (IGF 1), erythropoietin, and, the most known growth factor, VEGF [29]. Also, cytokines such as IL-6, IL-8, and MCP-1 are released. The interaction of these growth factors and cytokines stimulate angiogenesis. VEGF-mediated new blood vessels sprout out from the surrounding vessels, i.e., capillaries and venules, and invade the vitreous. Progressive vasoproliferation occurs in response to increasing levels of the growth factors; and this is associated with proliferation of fibrous tissue resulting in the characteristic fibrovascular membranes. The fibrovascular tissue proliferates and extends across the retina in the preretinal space (or sub hyaloid space). In eyes with PVD, fibrovascular membranes can only grow on the surface of the retina; therefore, retinal detachments do not tend to occur. However in eyes without a PVD (which is often the case), the posterior hyaloid acts as a scaffold that allows the fibrovascular tissue to grow, leading to traction on the retina and retinal detachments. Tractional forces within the vitreous exert effect on these rather brittle new blood vessels resulting in different degrees of hemorrhage. The resulting hemorrhage can range from a small leakage of blood on the surrounding retina to larger preretinal hemorrhage (**Figure 1a**) and to a more severe break through intragel vitreous hemorrhage.

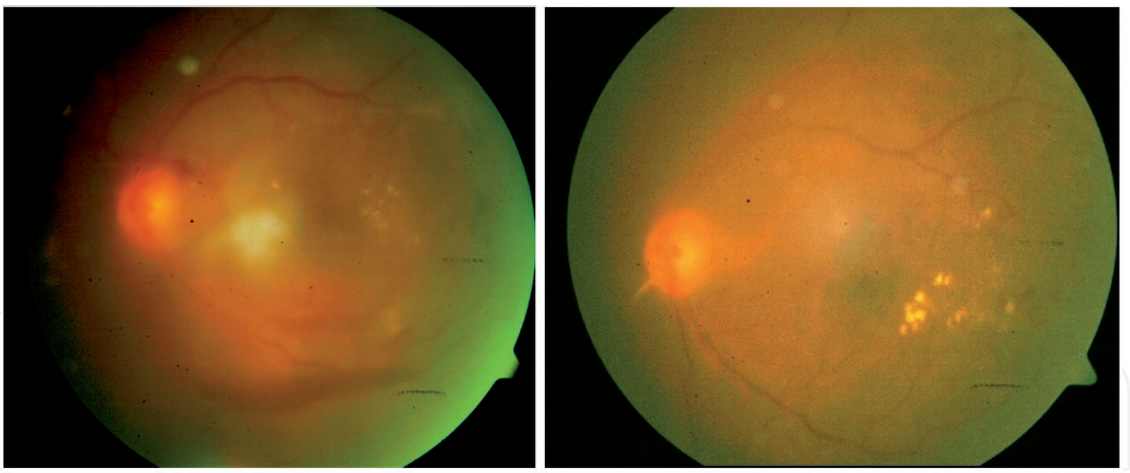

Figure 1.
Fundus photograph of PDR. (a) Left eye showing diffuse vitreous hemorrhage and preretinal hemorrhage in an eye diagnosed to have PDR. Notice also the absence of retinal laser marks and presence of macula hard exudates, with some significant cataract. (b) Same eye as in 1a after vitrectomy; view of the fundus is clearer and some hard exudates persist in the macular area.

This hemorrhage can often be removed using vitrectomy technique (**Figure 1b**). The fibrous component of the fibrovascular tissue contracts, due to a myofibroblastic effect [30], and causes traction on the inner retina, resulting in a TRD that may initially involve an extra macular site, and then subsequently progresses to the macula and damages vision. In some cases the traction results in a split in the layers of the retina (retinoschisis or foveoschisis) that can be appreciated on optical coherence tomography (OCT) scan. Similarly, ERM may be present in the macular area and result in considerable macular traction, worsening already existing macular edema. Since such diabetic macular edema (DME) has a traction-induced component as its causation, surgery will be required to remove the traction if resolution of the edema is to be achieved. VEGF suppression alone is unlikely to achieve complete resolution of this sort of DME, and this needs to be recognized.

The surgical principles of diabetic vitrectomy include performing a core vitrectomy. In some cases, a posterior vitreous separation already exists preoperatively and the goal of surgery is simply vitreous hemorrhage removal. This is a rather uncommon presentation. In cases of vitreous hemorrhage removal, in addition to the hemorrhage (since the vitreous cavity acts as a reservoir of several pro-inflammatory and pro-angiogenic factors that result in macular edema, neovascularization, and proliferation of fibrous tissue), diabetic vitrectomy also achieves immediate removal of these factors and cytokines. It facilitates access to the retina and permits release of the posterior hyaloid and further dissection of the tractional fibrotic membranes that create the TRD.

Separation of the anterior vitreous from the more posterior cortical vitreous can be easily accomplished using any standard vitreous cutter, allowing the release of the anteroposterior traction induced by the vitreous. Careful dissection of the posterior vitreous cortex from the underlying retina and the removal of proliferating fibrovascular membranes and fibrous bands from the retina surface (and at times from the subretinal space) are the highlights of the surgery. This should be done, avoiding the creation of iatrogenic breaks and creation of false passages. Identification of the right plane of vitreoretinal separation is the key to proper dissection and avoiding unnecessary iatrogenic breaks. One tip to achieve entry into the right vitreoretinal plane in difficult situations is to commence dissection from the optic disc and then move out towards the macula and retina periphery, the "inside out approach." In

practice, it is possible to detach the vitreous at the optic disc with gentle traction on the adjoining vitreous or fibrous tissue close to the optic disc using an intraocular forceps or the aspiration port of a vitreous cutter. This lifts the vitreous off the disc and ensures a safe entry into the vitreoretinal space, from where dissection can continue outward. In some cases a moderate to large amount of retrohyaloid blood already exists; this provides a useful entry point into the desired vitreoretinal space.

Techniques for fibrovascular proliferation removal have been well described and include en bloc dissection in which vitreous and proliferating tissue is removed as one, segmentation of fibrovascular tissue into islands of tissue using straight scissors or small-gauge cutter, and delamination involving careful removal of the islands of tissue using a small-gauge cutter or a curved intraocular scissors [31, 32]. Various ancillary instrumentation including picks, vertical and horizontal scissors, blades, membrane peeler cutters, forceps, scrapers, and other instruments can be used for the removal of proliferating fibrovascular membranes. However the use of newer high cut rate multifunctional vitreous cutters enables surgeons to often complete TRD repair using only the vitreous cutter [33, 34].

Upon completion of membrane dissection, ERM in the macular area may require identification and removal. Subretinal fluid drainage may be required. Existing retinal ischemia is treated with the application of laser panretinal photocoagulation [35]. PRP should be done up to the extreme retinal periphery, i.e., ora serrata. Scleral indentation is performed in search of iatrogenic retina breaks (which if undetected and treated can result in postoperative RRD and need for re-vitrectomy). Indentation is also done to ensure PRP has been extended to all areas of peripheral ischemia. Some surgeon will apply cryotherapy to the peripheral retina, to ensure maximum obliteration of the ischemic drive.

There may be a need for longer acting tamponade such as silicone oil in the more complex retina detachments such as in TRD cases with the occurrence of significant iatrogenic breaks, TRD/RRD situation, or in cases with existing traction [36]. Silicone oil is also used in monocular patients and patients who cannot position or who have to undertake air travel soon. Otherwise air, saline or shorter acting tamponade such as SF6 is sufficient in cases of low to medium complexity, especially if there are no iatrogenic breaks and release of traction is considered adequate. C3F8 can be used if longer duration of tamponade is required. It is important to ensure that sclerotomy ports are well closed, with no leakage. If required and judged to be necessary, sclerotomy sites should be sutured using, e.g., 8-0 vicryl suture, to prevent hypotony and reduce the risk of postoperative vitreous hemorrhage. A reported disadvantage of the sutured sclerotomy is postoperative patient discomfort and induction of cornea astigmatism, which tends to settle and return to preoperative status over some weeks.

6. Intraoperative considerations

Diabetic vitrectomy has benefited from the overwhelming advances that have occurred in vitrectomy over the past decade. This includes advances in surgical technique, instrumentation, improved preoperative patient work-up, and case selection. All this has resulted in improved surgical outcome, which has further increased surgeon confidence in performing surgery, even in the more complex vitreoretinal cases. Some of these advances in diabetic vitrectomy and their impact are as enumerated and discussed below:

1. Improvements in vitrectomy machines and probes, which includes faster cutting rates and smaller gauges (27 G, 25 G, and 23 G) trans conjunctival vitrectomy

systems, now means that these probes can be used as multifunctional tools. They can be inserted carefully beneath tractional membranes during surgery and used effectively for segmentation and delamination of the membranes without the need for intraocular scissors in several cases. Also the high cut rates provide for less traction on the retina, reduce the mobility of the retina, and reduce the rate of iatrogenic breaks. The presence of the vitrectomy cutting port closer to the tip of the probes means that membranes on the retina can be easily engaged. Indeed many complex cases can be safely completed with the use of only the vitreous cutter and no other ancillary instruments required. Similarly the protection conferred by the cannula system at the sclerotomy entry site provides for reduced incidence of entry sight breaks, vitreous incarceration at the wound edge, and leaking sclerotomies.

2. The introduction of intraoperative self-retaining lighting systems, such as the chandelier illuminating system, provides a free hand which can be used to grasp and stabilize intraocular tissue with a forceps while a fibrovascular membrane (FVM) is being dissected away. This led to the use of bimanual surgical technique. Bimanual surgery provides a very useful means of membrane dissection in difficult TRD and TRD/RRD cases, with broad attachment of fibrovascular membrane to the retina. Also various illuminated instruments, such as the lighted peaks, can provide considerable support in membrane dissection and relief of traction.

3. During the early days of diabetic vitrectomy, as the era of the DRVS, the ability to perform endoretinal photocoagulation was lacking. The presence of endoretinal photocoagulation probes has provided additional stabilization to the surgery outcome, since panretinal laser photocoagulation can now be done during the surgery irrespective of the occurrence of postoperative vitreous cavity hemorrhage. Supplemental retinal laser photocoagulation may be required in addition to already existing retinal laser marks. PRP should be adequate and done up to the retina periphery to cover the ischemic retina and prevent postoperative complications such as recurrent hemorrhage or AHFVP.

4. The intraoperative use of triamcinolone crystals to highlight the posterior vitreous cortex has helped visualization and improves complete removal of the vitreous. In some cases vitreoschisis is present, and this can be detected if the additional triamcinolone is used. Also vital dyes such as brilliant blue G (BBG) and membrane blue (MB) have been found to help in highlighting ERM and ILM, therefore facilitating its removal. While the removal of ILM is justified in the macula to prevent re-proliferation of membranes, in some cases this can be quiet difficult, especially in the presence of significant macular edema, with pathologically adherent ILM. In such cases with a risk of further trauma to the macula, ILM peel is best avoided. Injection of PFCL, which acts to stabilize the retina during the ILM peel, in some cases, may improve the chances of successful ILM peel.

5. Obtaining a preoperative OCT has become a standard work-up procedure for eyes with diabetic retinopathy (**Figure 2a**). Aside from providing useful histological overview of the retina and vitreous, it can be used to provide three-dimensional overlay including showing areas of vitreoretinal adhesion, pegs as they are called, and areas of vitreous separation, which is important for surgical planning. Also it provides additional information on prognosis for postoperative vision, since eyes with more preoperative preserved external

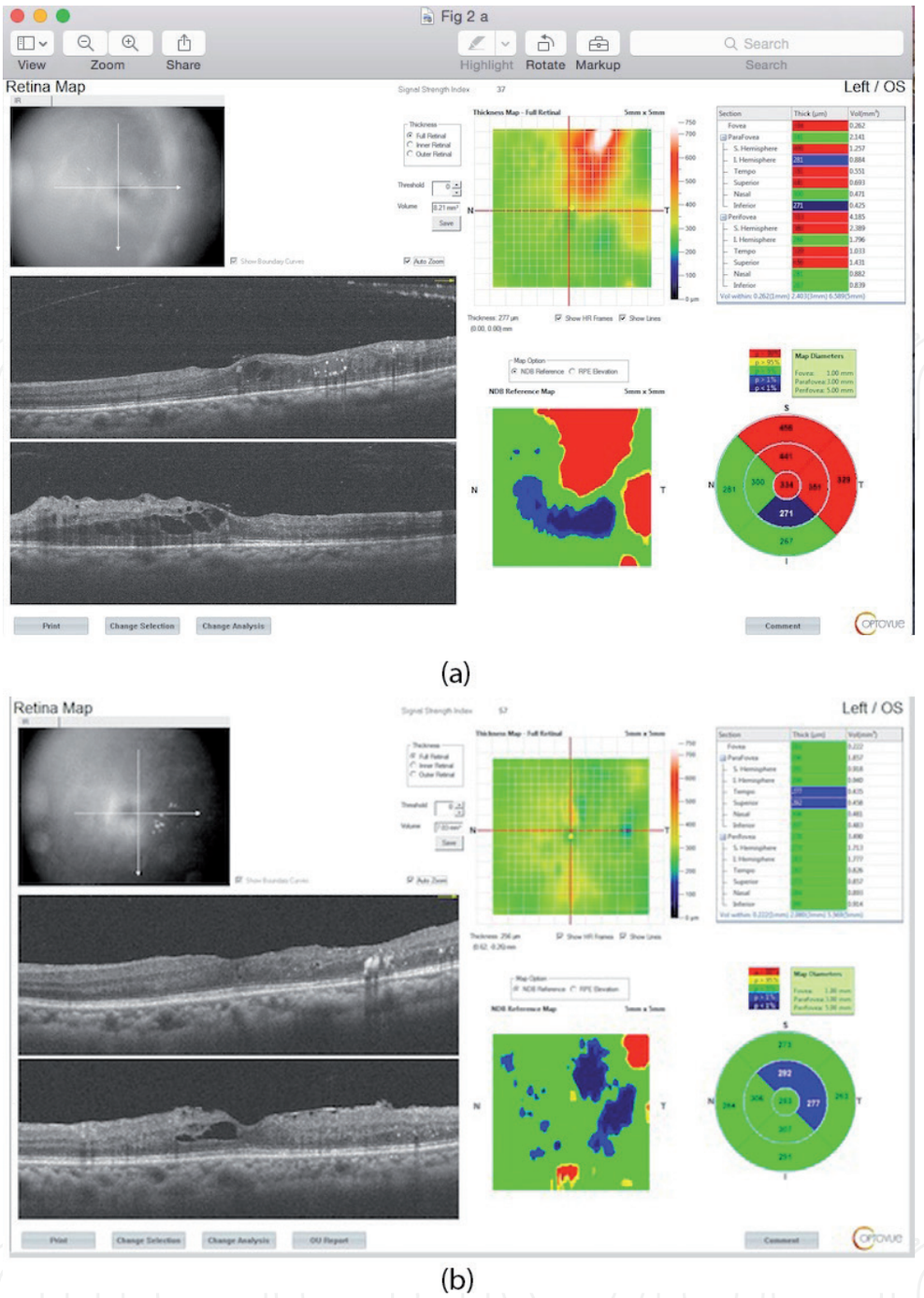

Figure 2.
*OCT images of same patient whose fundus picture is shown above. (a) Preoperative crossline OCT images of the same eye as in **Figure 1a**. Notice the presence of localized macular edema and vitreous hemorrhage with PVD. (b) Postoperative OCT images with normal subfoveal thickness but some intraretinal cystic spaces.*

limiting membrane (ELM) and ellipsoid zone (EZ) layers (as in **Figure 2a**) have been demonstrated to have better postoperative vision than eyes without, since a preserved EZ and ELM are also expected after surgery (**Figure 2b**). The postoperative presence of EZ and ELM, which are outer retinal layers, are essential predictors of postoperative recovery of vision.

Fairly decent OCT images can be obtained in eyes with a limited amount of vitreous hemorrhage as in **Figure 2a**. Unfortunately in some of the eyes with an obscured view of the retina, OCT is not possible. However, the successful incorporation of OCT technology into the operating microscope provides the intraoperative OCT (iOCT), which has shown usefulness in intraoperative

decision-making. The iOCT can help in determining the intraoperative presence of unremoved traction inducing ERM in the macula or the occurrence of a macular hole, which requires to be addressed during the surgery, since this can significantly affect postoperative visual outcome.

6. Timing of surgery: there is considerable interest in improving the visual outcome of eyes undergoing diabetic vitrectomy. This has resulted in some advocacy for earlier surgery in the category of patients with proliferative disease, instead of waiting for progression to more advanced TRD. Also efforts at inducing a pharmacologic separation of the vitreous from the retina using enzymatic vitreolysis have not been rewarding. Much of diabetic vitrectomy has to do with the separation of the attached vitreous. Induction of posterior vitreous separation could significantly halt the progression of PDR, since the attached vitreous is required for continued FVP.

   On the other hand, there are advocates for caution in diabetic vitrectomy, who argue for the more aggressive use of a combination of intravitreal anti-VEGF and retinal laser photocoagulation. They argue that the outcome of diabetic vitrectomy could be unpredictable and that even in seemingly straightforward cases, intra- and postoperative complications was not uncommon. Diabetic vitrectomy according to them should be undertaken only when necessary and other medical options exhausted.

7. Pharmacologic adjuvants: In recent times the use of pharmacological therapy has been introduced as adjuvant for use preoperatively and intraoperatively in diabetic vitrectomy. Intravitreal Injection of anti-VEGFs including Macugen, Avastin, and Lucentis has been used preoperatively and postoperatively, while steroid implants such as Ozurdex have been used pre- and intraoperatively.

   Bevacizumab (Avastin, Genentech, South San Francisco, CA, USA) appears to be the most commonly used preoperative anti-VEGF injection [37, 38]. Preoperative injection of anti-VEGF agents is known to considerably shrink neovascular fronds and has been shown to reduce intraoperative and postoperative bleeding and result in improved visual outcome [38–42]. However, an overaction of anti-VEGF can cause contraction of fibrovascular membrane and could exacerbate the traction and cause progression of TRD, in some cases causing a macular sparing TRD to involve the macula. This has been called the "crunch syndrome" which is characterized by a worsening tractional retinal detachment and development of denser fibrotic connections between the retina and overlying tissue, which makes it harder to identify tissue planes and results in more difficult dissection of the fibrous membranes [43].

   Therefore the optimum time for anti-VEGF injection preoperatively should be enough time to cause the desired effect, which is reduction in neovascularization, and not long enough to induce severe fibrotic contraction and worsening of TRD. It is generally thought that the ideal time frame is somewhere between 3 and 5 days prior to surgery, with considerable variation among surgeons. This time frame enables neovascular regression while limiting fibrovascular membrane contraction.

   Pegaptanib (Macugen, Bausch, and Lomb, Bridgewater, NJ, USA) has been used as an adjunct, when injected preoperatively. Pegaptanib is a PEGylated aptamer and only inhibits the VEGF isoform 165 [44]. It therefore has been suggested to have a more selective effect on the neovascularization component of the fibrovascular membrane and less tractional effect with lower systemic risks [44].

Therefore it can be used to induce regression of neovascularization, in a way similar to bevacizumab, and therefore reduces the risk of intraoperative bleeding, but does not have a similar tractional effect as seen with the use of bevacizumab [45]. This may allow for injection of Pegaptanib at any given time prior to surgery, even in the form of multiple injections, awaiting physician clearance, and good timing for surgery. There is however no wide spread use of Pegaptanib for this purpose, and comparison with bevacizumab has not been done. It may also be systemically advantageous due to the lower risk of vascular accidents in these high-risk patients [44]. It is instructive to mention that Pegaptanib is rarely used as an anti-VEGF of choice for suppression of VEGF in other neovascular ocular pathologies.

Ozurdex (Allergan, Dublin, Ireland) is a biodegradable 0.7 mg dexamethasone implant that is injected intravitreally via a 22-gauge needle and has been approved by the Food and Drug Administration (FDA) for the treatment of DME. It has been used in the pre- and postoperative control of the neovascularization process and tissue edema. As noted by Mahmoud et al., it can be injected preoperatively in an eye with extensive TRD in which it facilitates regression and consolidation of neovascularization in addition to inhibiting other inflammatory cytokines [45]. Unlike anti-VEGF agents, it is not known to increase risk of systemic complications, and there is no associated fibrovascular membrane or retinal tractional response. Tissue planes were found to be more distinct and not changed into flat fibrovascular tissue, making them more difficult to dissect, as was seen following administration of anti-VEGF agents. Due to these properties, it provides for flexibility with operative physician clearance planning (there is adequate time for preoperative clearance when Ozurdex is being used). In addition, the effect of Ozurdex can continue well into the postoperative period, since the Ozurdex implant can remain in position in the postoperative period under silicone oil [45]. Ozurdex implant releases the active drug over a period of 6 months and therefore keeps the eyes quiet, and the neovascular process is inactive during the postoperative period.

8. Techniques and tips for fibrovascular membrane dissection. Certain techniques are useful in the safe removal of fibrovascular tissue. The following are by no means exhaustive and are at best suggestions:

    a. Smaller-gauge (25 G and 27 G) transconjunctival surgery can provide opportunity for the vitrectomy probe to be inserted between the membrane and the retina. Using an aspiration mode, the membrane is lifted up with the cutting edge of the probe facing superiorly. As soon as resistance to the membrane lifting is encountered, the membrane is cut with the cutter. In this way the fibrovascular membrane is segmented; then the islands of fibrovascular tissue are removed from the retina using a delamination technique. Using the probe in this fashion, it can also serve as a blunt dissector and can be used without the need for additional instrumentation such as scissors or pick.

    b. Viscodissection is a very useful technique in cases of very adherent membranes [46, 47]. It was born from the idea that the use of liquid or fluid instead of metal or other materials to separate membranes from normal retina would have safety advantages. The use of small tip retractable cannulas, which can be inserted into small spaces between fibrovascular membranes and detached or attached retina, enables injection of hyaluronic acid (HA). The HA serves to separate the membrane from the retina,

and the viscodissection cannula can be used for blunt dissection as well. In addition, the HA provides hemostasis and improves visibility in the area of the dissection. Care should be taken to ensure adequate removal of the HA after the surgery to prevent a rise in IOP.

c. In the extremely difficult cases of TRD and TRD/RRD, characterized by thickened fibrotic membranes strongly adherent to the retina, a combination of forceps with curved scissors is a good option. With the use of a bimanual technique using a chandelier illumination placed at 12 O clock position (or any other position as chosen by the surgeon) and wide-angle viewing, the edge of thickened fibrovascular membranes can be engaged using a good gripping tissue forceps and then separated from the retina with scissors. After the separation, the membrane or clot can then be cut off with the small-gauge cutter using reduced cut rates.

d. Proportional reflux is a feature of the Constellation vitrectomy machine and other machines that have been used in the safe dissection of membranes from the normal retina [48]. The Constellation Vision System (Alcon Laboratories, Fort Worth, TX) has the pulse reflux mode, which allows a jet of fluid to be ejected from the port and is useful for ejecting accidentally incarcerated tissue during vitrectomy. In addition to this, it also has a proportional reflux mode. The proportional reflux mode allows for fluid to be ejected from the vitrectomy probe port in a gradual and controlled manner with foot pedal control, thus the term proportional reflux. The concurrent development of microincisional vitrectomy surgery with a smaller gauge and the port being closer to the tip as well as the development of proportional reflux has allowed for a new surgical technique known as "proportional reflux hydrodissection" [48, 49]. In this technique, credited to Dugel, the port of the cutter is placed between the fibrovascular tissue and the normal retinal tissue. Thereafter, with the foot pedal, the surgeon has complete control over fluid extrusion in a proportional fashion to create a separation between the fibrous tissue and the normal retina.

7. Complications of surgery

Vitrectomy in an eye that suffers from PDR can have significant complications. This ought to be considered and the risk for these intra- and postoperative complication considered before the decision to perform surgery is taken. Some of these complications include intra- and postoperative vitreous cavity hemorrhage (early or delayed), recurrent vitreous hemorrhage, hypotony, progression of diabetic retinopathy, iatrogenic retinal breaks (commonly occurring during fibrovascular tissue dissection), cornea edema, sclerotomy-related complications including vitreous incarceration (not as common with small-gauge vitrectomy compared to 20 G era), vascular ingrowths and AHFVP, rapid progression of cataract, phototoxicity (associated with chandelier illumination placement close to the retina), rubeosis and rubeotic glaucoma (more common in pseudophakia and aphakia), and severe loss of vision. Rubeotic glaucoma is a troublesome disease to manage and will require the use of intravitreal anti-VEGF, retinal laser photocoagulation, or cryotherapy. In some cases additional cyclodestructive procedure or glaucoma drainage tube surgery may be indicated. Fortunately the incidence of this complication is on the decline due to the use of laser endo photocoagulation, which enables more aggressive management of the peripheral ischemia.

Much of the complications can be avoided with meticulous attention to currently available surgical techniques. For instance, the rate of intra- and postoperative hemorrhage can be reduced by the use of preoperative intravitreal anti-VEGF as previously described and careful hemostasis during surgery either by the elevation of intraocular pressure, cautious diathermy, direct application of pressure to bleeding vessels, or application of viscoelastic to the point of bleeding. Also preoperative discontinuation of blood thinners and attention to the systemic blood pressure during and after surgery to ensure it is not elevated can be helpful.

8. Outcome

In recent times due to improvements witnessed in vitrectomy technology and technique as previously discussed, the anatomical and visual outcome of diabetic vitrectomy has generally improved. Compared to the earlier era, when endoretinal laser photocoagulation for treating retinal ischemia intraoperatively was not available (retinal ischemia is the main drive for the proliferative retinal changes), we now have a host of retinal laser photocoagulation probes available for use during vitrectomy. There have been reports of improvements in visual acuity in 75% and 87% of TRD eyes and vitreous hemorrhage eyes, respectively [50, 51]. With continued improvements and probably earlier timing of surgery, success rates will likely continue to improve and may exceed the 90% rates. Some of the poor prognostic factors include poor pre-op visual acuity, rubeosis, ectopia or displacement, and macula involving TRD. Significant fovea ischemia, which can be recognized with the use of fundus fluorescein angiography and OCTA, has a poor prognosis.

To conclude, diabetic vitrectomy has benefited from the advances in the sphere of vitreoretinal surgery. Though presentation of proliferative DR is very variable and can be complex, modern tools and technique can in most cases improve or stabilize vision. There is an ongoing discussion on possible identification of eyes at risk for progression and offering earlier surgery. This may result in further improvements. Perhaps the development of an ideal pharmacologic vitreolytic agent which will induce a PVD in eyes known to have PDR will usher in a new era in diabetic vitrectomy.

Acknowledgements

I wish to expresses my thanks to Dr Vipin Vig, vitreoretinal surgeon in Amritsar, India, who took the time to read through my manuscript and made useful suggestions.

Conflict of interest

None.

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