Diabetic Vitrectomy – An Update

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Abstract

Aim: To review the literature relating to diabetic vitrectomy, providing an update on topics where new information is available. Method: Reference to articles in peer-reviewed journals, the minutes of international academic meetings and authoritative textbooks. Results: We discuss aspects of management that will assist the vitreoretinal surgeon in evidence-based decision-making, including indications and timing of surgery, the use of pharmacological adjuvants, the influence of lens status, choice of vitrectomy gauge and the use of tamponades. Conclusions: Improvements in safety and outcome from diabetic vitrectomy have led a trend towards earlier surgery. A growing body of evidence supports the role of vitrectomy in diabetic macular oedema in the presence of traction. Anti-vascular endothelial growth factor (anti-VEGF) may aid surgery, but the risk of progression of tractional retinal detachment should be considered. The evidence for the efficacy of other adjuvants is discussed. We examine the role of cataract surgery in diabetic vitrectomy, discuss the use of tamponades and recommend a pragmatic approach when selecting a vitrectomy gauge.

Keywords

Diabetic, vitrectomy, bevacizumab, ranibizumab, adjuvant, tamponade, cataract surgery, vitrectomy gauge, inflammation, haemorrhage

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Diabetic retinopathy remains the most common preventable cause of blindness in the working-age population in the industrialised world. However, in the UK degeneration of the macular and posterior pole (principally age-related macular degeneration [AMD]) remains the major cause of visual loss in the population as a whole. A review of UK blind and partial-sighted registration between April 1999 and March 2000 showed that macular disease accounted for 57.2% and 56%, respectively, followed by glaucoma (10.9 and 10.2%, respectively) and diabetic retinopathy (5.9 and 7.4%, respectively). The age-specific incidence of all three appears to be increasing, although this may reflect improved diagnosis and reporting. Nonetheless, increases in registration for diabetic retinopathy have been most marked, particularly in the over 65s, where the number of certifications has more than doubled over 10 years.1

Improved control of blood glucose, blood pressure and cholesterol reduce the risk of development and progression of diabetic retinopathy, and for those who develop proliferative diabetic retinopathy (PDR), pan-retinal laser photocoagulation (PPR) remains the first-line therapy. Despite this, at least 4.5% of eyes will still develop complications that require surgical intervention.12

The technique of pars plana vitrectomy (PPV) was first reported in 1971 by Machemer et al. using 17G instruments to clear diabetic vitreous haemorrhage.3 Although the technique has since evolved considerably, the basic goal of removing vitreous to relieve retinal traction and clear opacities remains the same. The principal indications for surgery in diabetic retinopathy are non-clearing vitreous haemorrhage and retinal detachment (tractional [TRD], rhegmatogenous [RRD] or combined tractional/rhegmatogenous [CTR]) and for fibrinous retinal detachment (FDR)3.4.5

A prospective study of 744 consecutive vitrectomies for diabetic retinopathy reported that surgery was performed for the following reasons: non-clearing vitreous haemorrhage, 43.1%; TRD affecting the macula, 32.8%; CTRD, 11.5%; recurrent vitreous haemorrhage, 6.3%; TRD threatening the macula, 4.6%; rubeosis and vitreous haemorrhage, 1.1%; and uncontrolled new vessels, 0.6%.5 Other indications for surgery include pre-macular haemorrhage, ghost cell glaucoma, neovascular glaucoma, proliferation of the anterior hyaloid and diabetic macular oedema (DMO).

Removal of the vitreous appears to have a stabilising influence in proliferative diabetic retinopathy. It is likely that several factors contribute to this effect. First, attached vitreous gel acts as a scaffold for fibrovascular proliferation and removing it not only hinders repopulation but also reduces the tractional forces that traumatis the fragile new vessels, causing haemorrhage.6 Second, the relief of traction on retinal blood vessels may improve their perfusion and reduce leakage. Increased retinal blood flow velocity and reduced restrictive index in the central retinal artery have been demonstrated in patients with PDR undergoing vitrectomy.7 Third, removing the vitreous may increase oxygen supply to the inner retina and prevent accumulation of vasoactive cytokines by allowing unrestricted circulation of fluid in the vitreous cavity.8

Vitrectomy Surgery – Indications and Timing

Diabetic Vitreous Haemorrhage

It is over 20 years since the Diabetic Retinopathy Vitrectomy Study (DRVS). In this trial, 616 eyes with severe diabetic vitreous
haemorrhage of at least one month duration were randomised to early vitrectomy or vitrectomy deferred for one year. The results showed a clear benefit of early vitrectomy in patients with type 1 diabetes and those with uncontrolled neovascularisation.\textsuperscript{1,5}

Since the publication of the DRVS findings, there has been a trend towards ever earlier and ever lower thresholds for vitrectomy in diabetic vitreous haemorrhage. This has been prompted by improvements in the safety of surgery\textsuperscript{6} and cost-effectiveness\textsuperscript{7} and a growing body of evidence to suggest a benefit to visual outcome.\textsuperscript{6,7} Patients seen in our unit are typically managed conservatively for approximately six weeks from the date of presentation to allow for spontaneous clearance. After this period a decision to operate is made based on the pace of improvement or evidence of progressing anterior segment neovascularisation.\textsuperscript{7} Other considerations include visual acuity in the fellow eye and patient preference.

**Retinal Detachment**

Retinal detachment remains the most common indication for vitrectomy in proliferative diabetic retinopathy, accounting for 48.9% of surgery (37.4% TRD, 11.5% CTRD) compared with 43.1% for non-clearing vitreous haemorrhage.\textsuperscript{3} The timing of surgery is strongly influenced by the aetiology of the detachment and the proximity to the macula.

TRD arises from progressive fibrovascular proliferation and contraction. The detached retina typically has a concave appearance with limited mobility and the condition is characterised by slow progression. Urgent surgery is rarely required except in the context of visual loss associated with rapid progression of traction and macular involvement. Extramacular TRD can usually be managed conservatively, although there is a trend towards prophylactic surgery as the detachment approaches the macula due to the poor prognosis once the macula is affected.\textsuperscript{4} In contrast to the indolent course of most TRD, the fibrosis and contraction may be sufficient to cause a localised break in the retina, resulting in CTRD. In this situation the detachment may progress rapidly and is typified by a convex appearance and greater mobility of the retina. Urgent surgery is required in this situation.

Because the pathophysiology of TRD and CTRD involves vitreoretinal adhesions at sites of fibrovascular proliferation, it is important to assess the extent and configuration of posterior vitreous attachments.\textsuperscript{8} The extent of vitreous attachment may be a useful grading system for eyes undergoing vitrectomy as more extensive attachment is a poor prognostic feature,\textsuperscript{9} and may also influence case selection for small-incision surgery and the use of adjuvant pharmacotherapy (see below).

**Pre-macular Haemorrhage**

The presence of extensive pre-macular haemorrhage is a further indication for early vitrectomy, with studies suggesting that blood trapped against the retina may cause toxic damage, exert traction on photoreceptors and form a physical barrier to diffusion of nutrients and metabolites.\textsuperscript{10} Furthermore, the presence of pre-retinal haemorrhage suggests an attached hyaloid face, which may promote vascular proliferation, recurrent haemorrhage and DMO.

**Diabetic Macular Oedema**

DMO affects around 29% of diabetics within 20 years of diagnosis.\textsuperscript{11} The benefits of focal laser photocoagulation for clinically significant DMO were established by the Early Treatment Diabetic Retinopathy Study (ETDRS),\textsuperscript{12,13} and in cases where vascular leakage is diffuse and associated with a generalised breakdown of the blood-retinal barrier, modified grid laser can stabilise or improve vision in 75.4% of eyes. However, 24.6% of eyes with diffuse DMO will still lose vision despite adequate laser treatment.\textsuperscript{14} There is a growing body of evidence to suggest a role for vitrectomy surgery in these refractory cases, although the studies are often small and retrospective with variable disease extent and outcome measures.

When considering the role of vitrectomy in the treatment of diffuse DMO the attachment of the posterior hyaloid is a critical observation. Eyes with DMO have a lower rate of posterior vitreous detachment than those without,\textsuperscript{15,16} and spontaneous posterior vitreous separation is associated with improvement in DMO.\textsuperscript{17} It is now widely agreed that the presence of traction is an indication for vitrectomy, with efficacy demonstrated both in vitreomacular traction (VMT)\textsuperscript{18} and in the presence of a taut thickened posterior hyaloid (TPTH).\textsuperscript{19} However, the role of vitrectomy in the absence of demonstrable traction remains unclear.

At the time of writing, eight randomised trials were found on Medline investigating vitrectomy surgery in DMO. Of these, six used optical coherence tomography (OCT) to compare surgery with laser,\textsuperscript{20–25} with four showing surgery to be more efficacious than laser at reducing macular thickness. However, of these four only two showed an improvement in visual acuity. Furthermore, there is no clear benefit to vitrectomy with internal limiting membrane (ILM) peeling over vitrectomy alone.\textsuperscript{26,27} Based on the available evidence, we would therefore recommend that vitrectomy for DMO be reserved for patients with evidence of traction on OCT. Data from the Diabetic Retinopathy Clinical Research Network are awaited to shed more light on this subject.

**Pharmacological Adjuvants in Vitrectomy Surgery**

The use of adjuvant drugs in diabetic vitrectomy is primarily targeted at reducing the risk of intra-operative and post-operative haemorrhage in the setting of active retinal neovascularisation or in the presence of very vascular fibrous fronds with TRD.\textsuperscript{28–30}

**Anti-vascular Endothelial Growth Factor Adjuvants**

The role played by vascular endothelial growth factor (VEGF) in angiogenesis is a complex one. While essential for embryonic development, it is known to cause pathological neovascularisation in ischaemic retinopathies such as diabetic retinopathy. Work in mice has shown that VEGF is important for healthy revascularisation following vaso-obliteration induced by hyperoxia, and there is concern that the use of anti-VEGF agents in diabetic retinopathy may impair physiological revascularisation. It is hoped that further research will identify the VEGF isoforms responsible for pathological neovascularisation, so that these may be selectively targeted pharmacologically while facilitating healthy vasoregeneration.\textsuperscript{31}

Studies have demonstrated a correlation between levels of VEGF and severity of diabetic retinopathy, and that levels of VEGF drop following PRP.\textsuperscript{32–34} Furthermore, the DRVS showed that eyes that had undergone PRP prior to vitrectomy were more likely to achieve better vision post-operatively.\textsuperscript{35} The link between reduced VEGF and improved vision following PRP is the rationale for the use of intravitreal anti-VEGF agents such as bevacizumab.\textsuperscript{36} These treatments have an important advantage over PRP in that they can be used
where media opacities such as cataract or vitreous haemorrhage prevent the application of laser. There are also cases of proliferative retinopathy that do not respond to PRP alone, where anti-VEGF agents may be a useful additional therapy. The pre-operative use of intravitreal bevacizumab has been shown to speed the clearance of vitreous haemorrhage prior to surgery and to reduce the risk of intraocular bleeding during surgery.43,45 It has also been shown to reduce operating time, with anecdotal reports that fibrovascular membranes become less adherent. The risk of early post-operative haemorrhage also appears to be reduced, although there is some evidence of late re-bleeding. This may reflect the pharmacokinetics of bevacizumab or its removal with the vitreous at the time of surgery. It is therefore recommended that vitrectomy be followed by supplementary PRP. The role of top-up intravitreal bevacizumab at the end of surgery remains unclear.47

A potential risk of anti-VEGF agents is the progression of TRD, with Arevalo et al. reporting a 5.2% (11 from 211 eyes) incidence of progression of TRD following intravitreal bevacizumab.48 The authors speculated that this may reflect the natural history of rapid involuting fibrovascular complexes rather than a risk specific to anti-VEGF agents. A single case report describes a good result with heparin.54 Although heparin has been shown to speed the clearance of haemorrhage during surgery,43,44 it has also been shown to increase risk of intraocular haemorrhage and possible retinal toxicity, and caution is advised.56

There are currently no published studies that have investigated the optimal timing of surgery following intravitreal bevacizumab. However, Yeoh et al. reported that bevacizumab given within 14 days of surgery caused regression of new vessels without maturation and thickening of the fibrous component.53 Their shortest duration between injection and surgery was six days, when the new vessels were already sufficiently regressed. Avery et al. found that all patients with neovascularisation demonstrated by fluorescein angiography had a reduction in leakage within one day, and that 59–82% showed complete cessation. In addition, they reported involution, with reduced calibre and perfusion of neovascular fronds. Recurrence of fluorescein leakage was variable, but was seen as early as two weeks in one case.58 On the basis of the available evidence, surgery one to two weeks post-injection would seem to be optimal.

**Other Adjuvants**

A number of other adjuvant agents have been proposed. Although some have shown promise, their widespread adoption in clinical practice appears to be limited to date. They can be grouped into four main categories: pharmacological vitreolytics, aids to intra-operative removal of haemorrhage, suppressors of post-operative inflammation and suppressors of post-operative haemorrhage.

**Pharmacological Vitreolytics**

Traction associated with incomplete vitreoretinal separation and vitreoschisis are thought to be important to the pathophysiology of a number of retinal diseases, including PDR and cystoid macular oedema (CMO). Complete vitreous separation offers many potential advantages.59 First, surgery would be easier and safer, and in some cases even unnecessary. Second, the vitreous remnants often left after surgery act as a scaffold for subsequent cellular proliferation and would be removed. Third, the induction of posterior vitreous detachment (PVD) before onset of neovascularisation in PDR would avoid some of the complications of advanced disease. Finally, there is some evidence that removal of the vitreous improves retinal oxygenation, and it is possible that the same effect would be achieved by pharmacological vitreous liquefaction.4

Many pharmacological agents have been studied with the aim of aiding the separation of vitreous from the retina. Early trials of tissue plasminogen activator (tPA) given by intravitreal injection 15 minutes before diabetic vitrectomy failed to induce vitreoretinal separation.60 However, more promising results have been obtained using plasmin and the more stable recombinant microplasmin, which have both been shown to be capable of inducing PVD and may aid removal of the posterior hyaloid in TRD and CMO.61 This is the subject of the ongoing Microplasmin Intravitreal Administration in Patients with Vitreomacular Traction Scheduled for Vitrectomy (MIVI) trial. Other candidate agents include chondroitinase,50 dispase,62 hyaluronidase52 and combined plasmin with hyaluronidase.62

**Aids to Removal of Haemorrhage**

The removal of tenacious pre-retinal haemorrhage during vitrectomy surgery can be difficult, and several pharmacological agents have been suggested to aid this process. However, the literature is limited. A single case report describes a good result with heparin.64 Although tPA has been used more widely for this purpose,65 there are reports of retinal toxicity, and caution is advised.66

**Suppression of Post-operative Inflammation**

The role of thrombin is central to post-operative outcome in diabetic vitrectomy, where it may play both a beneficial role by suppressing post-operative haemorrhage and a deleterious role by promoting post-operative inflammation.

Formation of intraocular fibrin has been reported in approximately one-third of vitrectomies (the data include non-diabetic vitrectomy) and is severe in about 12% of cases, when it can be associated with pupil block glaucoma and reproliferation in PDR.6 Several pharmacological adjuvants have been suggested to suppress fibrin formation. tPA is a potent fibrinolytic, but its association with increased risk of intraocular haemorrhage and possible retinal toxicity suggest that it should be reserved for severe cases rather than prophylaxis.67 Furthermore, a dose of 10µg has been recommended,68 which is lower than the commonly used dose in clot lysis (typically 30–100µg). Unfractionated heparin has also been investigated, and although effective at reducing post-operative fibrin formation, it is associated with a mild increase in intra- and post-operative bleeding.
haemorrhage. Work on rabbits has produced promising results with the thrombin-specific inhibitor argatroban and the antithrombin agent recombinant hirudin. Here, levels of post-operative fibrin were reduced without increased risk of intra-operative or post-operative haemorrhage, but as yet we are not aware of any trials in human subjects. Currently, the weight of evidence would appear to support the use of low-molecular-weight heparin (LMWH). This has an equal antithrombotic effect, but with reduced haemorrhagic activity compared with unfractionated heparin. LMWH has been shown to be safe for intraocular use at doses of up to 6 units/ml of irrigating solution without increased risk of haemorrhage.

Suppression of Post-operative Haemorrhage

Several agents have been studied as potential suppressants of post-operative haemorrhage. A randomised trial of tranexamic acid showed no effect on incidence of post-operative haemorrhage, but more promising results have been obtained with aminocaproic acid. Although thrombin has been shown to reduce the risk of post-operative haemorrhage, its role in promoting post-operative fibrinous uveitis suggests the need for caution. Ultimately, it is possible that anti-VEGF agents may supersede other pharmacological adjuvants for the treatment of post-operative haemorrhage, although to our knowledge this has yet to be subject to a clinical trial.

Diabetic Vitrectomy, Lens Status and Phacoemulsification

Many patients who undergo PPV will either have pre-existing lens opacity or develop lens opacity soon after surgery. Rates of post-vitrectomy cataract of 66% have been reported after macular hole repair, 53% after epiretinal membrane peeling and 11.5–15% after diabetic vitrectomy. This probably reflects the effect of gas tamponade. However, Holekamp et al. have suggested that relative retinal ischaemia and lower oxygen tension in the anterior vitreous in diabetic retinopathy may reduce rates of cataract progression. It is known that older age is a significant risk factor for cataract progression after vitrectomy, regardless of the indication for surgery.

Combining vitrectomy with phacoemulsification and lens implantation offers several potential benefits. Intraoperatively, the removal of an opacified lens can improve visualisation of the posterior segment and allow more complete vitrectomy without the risk of lens touch. Post-operatively, the improved view can aid assessment of the posterior segment and make laser treatment easier. For the patient, removal of lens opacity can improve post-operative acuity and avoid the need for cataract surgery at a later date. However, combined surgery may have disadvantages, including longer operating time, corneal oedema impairing the surgical view, increased levels of anterior segment inflammation, risk of posterior synchiae and a risk of lens capture reported as high as 9% with phacoemulsification and gas tamponade.

Yorston et al. reported a 14.9% rate of combined cataract surgery and vitrectomy in their prospective study of 174 consecutive vitrectomies for diabetic retinopathy. Of the 67.9% who were phakic after surgery, only 11.5% required cataract extraction during a median follow-up period of eight months. Final visual outcomes appear to be comparable in combined surgery and sequential surgery, but are achieved more rapidly in a single procedure.

An increase in iris neovascularisation following cataract extraction without vitrectomy has been reported, suggesting that an intact iridolenticular complex may reduce exposure of the anterior chamber to vasoproliferative growth factors. However, when combined vitrectomy and phacoemulsification is performed this effect appears to be reversed, with a reduced rate of iris neovascularisation compared with vitrectomy alone.

Choice of Vitrectomy Gauge

Small-gauge vitrectomy has become increasingly popular in recent years, although its true benefits remain a subject of debate. Advocates of 25 and 23G systems point to reduced surgical time, improved fluidics, reduced patient discomfort and more rapid visual recovery. However, incidence of sclerotomy-related complications, such as hypotony, and an increased rate of endophthalmitis may be disadvantages compared with 20G surgery. Many of the early limitations of 25 and 23G surgery, such as instrument flexibility, poor illumination and low flow rates, have now been overcome.

Goldenberg and Hassan suggest that the choice of vitrectomy gauge should be matched to the indication for surgery and the experience of the surgeon. They recommend, for example, that 25G is appropriate for vitrectomy + ILM peeling for DMO, where scirrhus removal of the anterior vitreous is not required. They also advocate its use for pre-macular sub-hyaloid haemorrhage, non-clearing vitreous haemorrhage, ghost-cell glaucoma and TRD. Cases requiring scleral buckle or lensectomy were not considered suitable; neither were cases likely to require peripheral dissection, where 25G instrumentation might limit the ability to maximally rotate the globe. The 25 and 23G systems may offer a particular advantage in the removal of membranes, where the design of the ocutome cutting port is such that it sits 50% closer to the tip of the probe than in the 20G system. A recently published randomised controlled trial by Wickham et al. compares 25 with 20G vitrectomy for a variety of indications. Although less discomfort was reported in the 25G group, pain was not a prominent feature in either group and overall the authors found no significant advantage of 25G surgery. While it is clear that the quality of the new-generation 25 and 23G instruments has improved dramatically, and that almost every vitrectomy procedure can now be performed using small-gauge instruments, the drive to adopt this platform may owe more to the industry than to the limited randomised trial data.

Tamponade

In their series, Yorston et al. required tamponade in 48.8% of their 174 vitrectomies, of which air was used in 7.5%, sulphur hexafluoride (SF6) in 24.1%, octafluoropropane (C3F8) in 10.3% and silicone oil in 6.9%. The use of long-acting tamponade (C3F8 and silicone oil) was associated with a worse visual prognosis, which was attributed to the severity of the disease and the complexity of the surgery where long-acting tamponade was required.

The effectiveness of silicone oil in maintaining retinal tamponade and preventing hypotony is well recognised. A review of long-term silicone oil tamponade following primary diabetic vitrectomy by Shen and Yang showed good levels of anatomical success and functional stability, with significant complications being rare. Silicone oil may also lower the incidence of recurrent vitreous haemorrhage and iris neovascularisation. However, oil has a known association with reperfusion at the oil–retina interface that is attributed to a concentration of vasoproliferative growth factors under the oil. Reproliferation appears to be particularly problematic when pre-retinal haemorrhage is also trapped under the oil. We would
therefore conclude that silicone oil should be used selectively where there is a high risk of re-detachment, or where recurrent vitreous haemorrhage is anticipated.

Post-operative Vitreous Haemorrhage

Post-operative vitreous haemorrhage will affect approximately 75% of patients following diabetic vitrectomy.5 Usually this is mild, but as many as 17–30% of patients will experience significant recurrent post-operative vitreous haemorrhage.6 Wash-out rates are typically around 10–15%.7 Sources of blood include diffusion from residual clot in the peripheral vitreous and re-bleeds from neovascularisation at the posterior pole, vitreous base or close to sclerotectomy sites. The risk of proliferation has led some authors to advise prophylactic cryotherapy or endolaser to the anterior retina and sclerotomy sites.8,9 Yeh et al. reported a 37.5% risk of re-bleed following vitrectomy and endolaser compared with 11.5% in vitrectomy, endolaser and anterior cryotherapy. The rate was even lower with additional cryotherapy to the sclerotomy sites (4.3%).10 Thorough removal of the anterior vitreous is thought to be important in reducing the risk of haemorrhage by removing the scaffold for proliferation.11

Conclusions

Despite advances in surgical technique, instrumentation and adjuvant pharmacotherapy, it is important to remember that the principal determinant of post-operative visual acuity is retinal function. As PDR is associated with retinal ischaemia, visual outcome may be poor despite apparent anatomical success after surgery.

Improvements in the safety and outcome of vitrectomy have reduced the threshold for surgery, and are reflected in a trend towards earlier surgical intervention in diabetic retinopathy. The principal indications for surgery remain unchanged, but a growing body of evidence supports the role of vitrectomy in DMO in the presence of traction. The case for vitrectomy in the absence of traction is currently weak. The adoption of pharmacological adjuvants into clinical practice has been slow, but there is good evidence to suggest a role for anti-VEGFs in reducing intra- and post-operative haemorrhage, aiding membrane dissection, reducing macular oedema and reducing operating time. However, they may compromise physiological revascularisation and can cause progression of TRD. Timing of surgery after anti-VEGF injection lacks trial data, but one to two weeks post-injection seems to be optimal.

Rates of cataract formation following diabetic vitrectomy are lower than in other indications for vitrectomy surgery. However, combined cataract surgery and vitrectomy may reduce the risk of subsequent iris neovascularisation, and offers comparable visual outcomes from a single procedure compared with sequential surgery.

Despite a trend towards smaller-gauge vitrectomy surgery in recent years, generalisations over the choice of instrumentation gauge should be avoided. We would advise a pragmatic approach, matching the suitability of the case and the experience of the surgeon. Further evidence of the true benefits of small-gauge surgery is needed.

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**Posterior Segment**


