

Vitrectomy in Diabetic Retinopathy

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Abstract

Pars plana vitrectomy (PPV) is integral to the management of late complications in diabetic retinopathy. As a greater understanding of the pathophysiology of diabetic eye disease has developed, so the role of PPV has evolved. This article reviews the current indications for PPV in diabetes (vitreous haemorrhage, tractional retinal detachment and combined rhegmatogenous and tractional retinal detachment) and the evidence for potential future applications, such as in diabetic macular oedema. The role of pharmacological adjuncts, such as anti-vascular endothelial growth factor (VEGF) agents, to reduce intraocular complications, improve success rates and minimise post-operative complications is examined. Drug-induced vitreolysis as a tool in achieving complete vitreoretinal separation, thus reducing progression of diabetic retinopathy, is discussed. It has already become routine practice for endolaser photocoagulation to be employed during PPV and, in the future, vitreolytic and antiproliferative agents may also be important as adjuncts to achieve good outcomes.

Keywords

Diabetic retinopathy, pars plana vitrectomy

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The first successful pars plana vitrectomy (PPV) was performed in 1970 in an eye with vitreous haemorrhage secondary to diabetes-related changes.¹ Since then, advances in instrumentation such as wide-angled viewing systems, smaller instruments, the use of heavy liquids and more sophisticated software have enabled the role of PPV in diabetic eyes to evolve, and it is now integral to managing late complications of diabetic eye disease.

The indications for vitrectomy in the Early Treatment Diabetic Retinopathy Study (ETDRS)² in 1987, where 5.6% of all 3,711 enrolled patients underwent vitrectomy, were either vitreous haemorrhage (VH) or retinal detachment with or without VH. Today, PPV is used for VH, tractional retinal detachment (TRD), combined tractional rhegmatogenous retinal detachment (TRRD) and, in some cases, where tractional abnormalities may contribute to diabetic macular oedema.

Pars Plana Vitrectomy in Diabetic Eye Disease

The ETDRS was the first large randomised, controlled trial looking at vitrectomy as an intervention for proliferative diabetic retinopathy (PDR). Of the 243 eyes undergoing vitrectomy, 47.5% achieved visual acuity (VA) of 20/100 or better compared with only 6.2% pre-operatively. Although today's success rates are much higher, this demonstrated a clear benefit of PPV in a previously blinding condition.

Vitreous Haemorrhage

Despite advances in the management of and screening for diabetes, a significant proportion of patients develop severe ocular complications, usually related to proliferative disease. VH originates from new blood vessels, which develop in response to growth factors

released from ischaemic retina. These tend to proliferate from the vascular arcades along the inner surface of the retina or into the substance of the gel, using its collagen matrix as a scaffold. Traction on vessels at the vitreoretinal interface following posterior vitreous detachment (PVD) causes rupture, resulting in haemorrhage into the gel or the subhyaloid space. Pan-retinal photocoagulation (PRP) results in regression of new vessels and peri-vascular fibrosis, which may anchor the vitreous. Continued tractional forces can disrupt these vessels, causing recurrent haemorrhage, so vitrectomy can still be indicated in otherwise quiescent retinopathy. As well as directly reducing vision, blood that persists in the vitreous or subhyaloid space may lose pigment over time, giving rise to ghost cells, which impede trabecular aqueous outflow and raise intraocular pressure.

In the Diabetic Retinopathy Vitrectomy Study (DRVS),³ 616 eyes with a recent onset of severe VH of at least one month's duration and VA of 5/200 and below were randomised to undergo either early vitrectomy or deferral for one year. The percentage of eyes achieving VA of 10/15 or better was significantly higher in the early vitrectomy group throughout the four-year follow-up period. The greatest benefit was in patients with type 1 diabetes of less than 20 years' duration, where there was a sustained significant visual advantage over the deferral group throughout the four years. However, there was also an increased number of patients in all diabetic sub-groups who developed no perception of light (NPL) vision in the early-treatment group. This may reflect, at least in part, surgical complications associated with earlier vitrectomy techniques and instrumentation. An early improvement in vision to at least 10/50 in the early vitrectomy group was shown in all diabetes types, suggesting that in

patients where only one eye is affected early vitrectomy is likely to be of functional benefit, although this may be for a limited period in some diabetes types.

Although this study is the largest to date looking at vitrectomy in diabetic eye disease, it is limited by the absence of retinal photocoagulation, which is now in widespread use either pre- or intraoperatively and is recognised as the only definitive way to permanently treat retinal ischaemia. The most important indication for vitrectomy in diabetic vitreous haemorrhage is to allow application of PRP to the retina, usually intraoperatively, if adequate PRP has not been performed previously.^{4,5} The widespread use of PRP in severe non-proliferative diabetic retinopathy (NPDR) and PDR under ETDRS treatment guidelines, along with systemic management of blood glucose and other risk factors, has had a significant impact in preventing early progression of diabetic retinopathy to proliferative disease with a poor prognosis. More recent studies have confirmed the advantage of early vitrectomy combined with intraoperative PRP in type 1 diabetes,⁶ and have also suggested a benefit in patients where there is severe progressive proliferative disease in the fellow eye.^{7,8}

Simple VH often clears without intervention, the route being anteriorly through the zonules and via the aqueous outflow pathways. Its patency is indicated by red blood cells in the anterior chamber. Failure of this pathway may be due to anterior neovascularisation or retained haemorrhage with subsequent fibrosis at the vitreous base, blocking access to the zonules. Peripheral laser capsulotomy has been used to encourage anterior clearance in eyes where vitreous haemorrhage is slow to clear.⁹

Intraocular fibrin formation may complicate an otherwise successful vitrectomy by reducing clearance of recurrent bleeds through the anterior chamber and causing pupillary block glaucoma. It may also provide a scaffold for fibrovascular proliferation. The use of intraoperative adjuncts, such as low-molecular-weight heparin and 5-fluorouracil (5FU),¹⁰ has been shown to be useful in reducing post-operative fibrin formation.

Tractional Retinal Detachment

Contraction of fibrovascular membranes combined with abnormal vitreoretinal adhesions gives rise to TRD and macular heterotopia, which develops slowly, most commonly beginning over the arcades. The success of vitrectomy for TRD varies according to the location, extent and duration of detachment. Increasing age and the presence of anterior segment neovascularisation have been shown to indicate a poorer prognosis.¹¹

Peripheral TRD without VH may be left untreated if the fovea is not threatened by progression. Long-standing macular heterotopia confers a poor prognostic outcome, but vitrectomy in progressive disease with recently reduced vision can achieve good functional and anatomical results.^{12,13} Studies have reported improved VA in about 75% of eyes with vitrectomy with or without silicone oil;¹³ however, many factors influence visual outcome, making it difficult to predict.¹⁴ Visual prognosis is poor in eyes with tractional macular detachment even if anatomical improvement is achieved, and is even more limited in long-standing macular detachments.^{12,13} For this reason, patients with any degree of treated new vessels or TRD should be monitored appropriately and surgical intervention applied in cases where macular detachment with reducing vision is present or

likely to occur. The most important predictors of poor visual outcome are poor pre-operative vision, presence of iris neovascularisation and macular detachment.^{11,15}

Combined Tractional and Rhegmatogenous Retinal Detachment

TRD may be complicated by retinal breaks alongside fibrovascular retinal adhesions. VA can be improved in up to 70% of eyes with this scenario.¹⁶ The location and extent of detachment will influence the outcome, with macular detachment being a poor prognostic factor. One study noted a higher detection rate of retinal breaks intraoperatively rather than pre-operatively.¹⁷ The development of proliferative vitreoretinopathy in response to growth factors released from exposed retinal pigment epithelium (RPE) makes surgery difficult as it adds tangential retinal traction to existing anteroposterior forces and the fibrous membranes are difficult to dissect from a mobile retina. Silicone oil is frequently employed in this group, often for long-term tamponade; while anatomical success may therefore be higher, pre-operative VA is still the best predictor of visual outcome.¹⁶⁻¹⁸

The principles of surgery for TRD and TRRD are removal of VH, vitreous base clearance, removal of tractional fibrovascular membranes and adhesions by delamination, segmentation and *en bloc* dissection techniques. Dissection using perflourocarbon has been described as a useful technique for diabetic membranes.¹⁹ Silicone oil tamponade may provide anatomical and functional stability,¹⁸ and may be necessary as a long-term adjunct in eyes with severe proliferative disease with complex membranes.

Vitreotomy for TRD is often complicated by intraoperative VH from active new vessels and recurrent haemorrhage from persisting or recurrent new vessels. The frequency and degree of these complications has been shown to be significantly reduced by pre-treatment with intravitreal anti-vascular endothelial growth factor (VEGF) agents one week prior to vitrectomy.^{20,21} This has held true in procedures where silicone oil tamponade has been required, although this may carry a slightly higher risk of sub-retinal bleeding.²² The rapid progression of TRD has been observed in a few patients after injection with intravitreal bevacizumab.²¹ Long-acting intraocular gas, with and without intravitreal bevacizumab, has also been shown to reduce post-operative bleeding, but may accelerate cataract formation.^{23,24}

Diabetic Macular Oedema

Diabetic maculopathy in the presence of vitreous interface disease in the form of epiretinal membranes and/or a taut posterior hyaloid, which gives rise to vitreomacular traction, may be improved by PPV.²⁵ The evidence for improvement in macular oedema with no evidence of macular traction refractive to repeated grid laser is more conflicting. Cytokines, which may promote vascular permeability, are present in the retina and the vitreous in diabetic eye disease. Unlike at the peripheral retina, ablation of ischaemic tissue cannot be applied at the macula to reduce production of these cytokines. Vitrectomy, with or without internal limiting membrane (ILM) peeling, facilitates diffusion of these agents away from the retina and removes the vitreous reservoir. Along with improved oxygenation, this may improve the failing integrity of the retinal vascular endothelium, reducing retinal oedema.

At least one study reports a significant increase in VA in patients with oedema refractive to argon laser treatment after vitrectomy and ILM

peel,²⁶ but others suggest that a reduction in macular volume and physiological function may occur without a consistent increase in VA^{27,28} and that there is no benefit over performing standard macular photocoagulation.²⁹ It has been pointed out that improvement in VA may be compromised by potential complications such as cataract, vitreous haemorrhage and raised intraocular pressure. These inconsistencies may arise because of differences between studies in baseline vision and the amount of previous laser treatment. The degree of macular ischaemia and the presence of active proliferative retinopathy, and thus a different profile of vitreous cytokines, may also have an effect. There appears to be some value in PPV for persistent macular oedema without tractional abnormalities, but further studies are required to clearly establish which sub-groups would benefit the most.

Vitreotomy and Cataract Surgery

In the early days of vitrectomy, concurrent removal of the lens was associated with a high incidence of anterior segment neovascularisation,³⁰ which led to a tendency to spare the lens. This was thought to be due to disruption of the anterior hyaloid face and breach of the zonules, allowing previously contained neovascular growth factors access to the anterior chamber. Application of endolaser photocoagulation to the peripheral retina has become routine and, consequently, the rates of anterior segment neovascularisation following PPV, with or without lens extraction, have become extremely low.³⁰ Since cataract development is accelerated by vitrectomy, it is often appropriate to perform cataract surgery in conjunction with PPV, particularly as subsequent cataract surgery may be technically more difficult due to intraoperative anterior chamber depth fluctuation. In addition, the lens may limit peripheral retinal and vitreous access and the view may be sub-optimal.

Vitreolysis

Anomalous PVD occurs when liquefaction of the vitreous gel and dehiscence of the posterior hyaloid from the ILM are not concurrent.³¹ It has been shown that partial PVD promotes progression of PDR and other vitreoretinal interface disease,³² while the presence of a complete PVD reduces vulnerability to developing PDR. At the macula, anomalous PVD gives rise to vitreoschisis³³ with vitreomacular traction.

The alteration of fluid currents within the diabetic vitreous as a result of abnormal liquefaction may also affect its nutritional role.^{31,34} A promising future intervention to prevent the onset of PDR in susceptible or high-risk eyes is pharmacological vitreolysis,³⁵ in which drugs rather than surgery are used to induce a complete PVD, with a cleaner separation of vitreous components from the ILM. In diabetic animal studies, a combination of hyaluronidase and plasmin can successfully induce a complete PVD without retinal toxicity,³⁶ as can various other agents, such as chondroitinase and recombinant microplasmin.³⁵ Enzymatic-assisted PPV has been performed in human *post mortem* eyes by injecting tissue plasminogen activator (TPA) to generate plasmin prior to surgery, and this has been shown to reduce the amount of vitreous remaining adherent to the ILM after surgery compared with conventional PPV.³⁷ This chemically induced PVD may increase oxygen levels in the vitreous and, by this route, improve retinal oxygenation.³⁸ The potential use of vitrectomy augmented by pharmacological vitreolysis to reduce the development of PDR requires further research.

Conclusion

The role of vitrectomy in diabetic eye disease has become central in stabilising or improving vision in late complications that were previously considered to be blinding conditions. As the understanding of biochemical interactions between the vitreous and its surrounding structures increases, new and adjunctive therapies to improve vitreous separation and reduce the adverse effects of ischaemia are likely to develop.³² The widespread use of PRP to effectively reduce retinal and anterior segment ischaemia and associated blinding complications has been essential in exposing the potential applications of vitrectomy in diabetes. A growing appreciation of the physiological and anatomical sequelae of PPV will no doubt continue to guide improvements in the treatment of a potentially devastating disease. ■



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