Vitrectomy for diabetic macular oedema

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Abstract

Aim To briefly review and discuss the literature on vitrectomy for diabetic macular oedema.

Methods Literature review.

Results There is a copious literature on the subject of vitrectomy for diabetic macular oedema (DMO). The most commonly hypothesised mechanism for the potential benefit of vitrectomy is relief of vitreomacular traction; however, both transvitreal oxygenation and improved growth factor diffusion away from the premacular retina have also been suggested to be potentially beneficial effects. Other systemic and local factors including duration of oedema, extent of ischaemia and exudation, and extent of laser may result in permanent photoreceptor and capillary damage, which precludes anatomical or visual benefit. Much of the literature on the subject of vitrectomy for DMO is retrospective and uncontrolled but strongly suggestive of a benefit in terms of improved acuity and reduced macular thickness following vitrectomy. There are five published small randomised controlled trials on this subject. Taken as a whole, these studies do not suggest a benefit from surgery. Selection of patients for surgery on the basis of OCT partial vitreomacular separation or clinical signs of traction such as an epiretinal membrane or taut thickened hyaloid has been reported to be associated with a modest improvement in prospective studies but this has not been subjected to controlled study.

Conclusion The evidence at present suggests that vitrectomy for DMO should be restricted to those with clinical or OCT signs of traction. *Eye* (2008) 22, 1337–1341; doi:10.1038/eye.2008.84; published online 25 April 2008

Keywords: vitrectomy; diabetic macular oedema; optical coherence tomography;

fluorescein angiography; ICG; posterior vitreous detachment

Introduction

Working with Schepens in 1998, Nazarallah *et al*¹ published the first data to suggest that the vitreous might play a role in the pathogenesis of diabetic macular oedema (DMO). They examined patients with diabetic retinopathy and found that DMO was present only in 20% of patients with a PVD compared to 55% in those with an attached hyaloid.

The second major landmark in the history of vitrectomy for DMO occurred in 1992 when Lewis *et al*² described 10 patients who underwent vitrectomy to remove a 'thickened taut glistening posterior hyaloid' (TTPH) in association with impaired vision and DMO. In 8 out of 10 patients, the acuity and macular thickening improved. The authors hypothesised in this pre-OCT era that the hyaloid was exerting tangential traction on the retinal surface, thereby inducing or exacerbating oedema and producing a shallow tractional retinal detachment as part of their clinical syndrome. In addition, they reported that vitrectomy with relief of this traction, resulted in reduction of oedema and visual improvement. (Following the invention of OCT, a group including Lewis imaged patients with DMO and a TTPH.³ They confirmed the previous predictions by demonstrating focal vitreoretinal traction associated with surrounding partial posterior hyaloid separation. Furthermore in eight patients, they reported the shallow tractional macular detachment previously predicted by Lewis.) The tractional cause and effect hypothesis advanced by this group is very attractive and appears to fit with the reported anatomical and visual success of vitrectomy in patients with a TTPH.^{3–7}

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The other paper that is frequently cited in the background to vitrectomy for DMO is a natural history study published by Hickichi *et al*⁸ in which they reported spontaneous resolution of DMO in 55% of eyes that developed a PVD during follow-up, compared with only 25% in those that did not.

Various mechanisms by which the vitreous may contribute to the formation of DMO have been postulated. These include vitreomacular traction, which may range from the taut thickened hyaloid described by Lewis *et al*^{2,3,9} through partial vitreomacular separation^{10,11} to microtraction resulting from an abnormal PVD resulting in posterior vitreoschisis and a persistent pre-macular vitreous adhesion.¹² Relief of traction is not the only postulated mechanism for improved structure and function after vitrectomy; Stefansson^{13,14} has long advocated that improved transvitreal oxygenation of the retina may be the causative mechanism. Others have suggested that removal of a growth factor reservoir in the pre-macular hyaloid is important.¹⁵ It is known that the diabetic vitreous is abnormal with enzyme-mediated vitreous collagen crosslinking and non-enzymatic glycation; with reduced permeability potentially increasing the concentration of a pre-macular growth factor soup.^{16–18}

There is now a copious literature on the subject of vitrectomy for DMO, which probably includes more than a thousand eyes^{2–4,6,7,9–11,15,19–44} (this list does not attempt to be exhaustive). Systematic interpretation of this literature is however very hard and the vast majority of these reports would be rejected from a structured systematic review. The reasons for this are that most studies are relatively small and retrospective with differing disease severity and inclusion criteria, variable and incomplete follow-up, and differing outcome measures.

Given the hypothesised importance of vitreomacular traction, few studies have classified their cases on the basis of OCT appearance. DMO is an extremely heterogeneous condition, with the reports describing surgery on patients with a taut thickened hyaloid,^{2,4,5,7} epiretinal membrane,^{11,43} and complete PVD formation.^{11,45} In a prospective study of the clinical and OCT features of 140 patients with DMO refractory to laser, we found a clinically and OCT normal hyaloid to be present in two-thirds.^{11,46}

Much of the early literature, although uncontrolled, concentrates on patients with DMO in the presence of a taut thickened posterior hyaloid and these reports all suggest benefit in terms of improved acuity and reduced macular thickening.^{2,4–7,23} This is however a rare clinical presentation occurring in just 4% of eyes in our prevalence study.⁴⁶

Other than macular traction, potentially important predictors of outcome include the duration of macular oedema, extent of previous laser, degree of macular ischaemia, and amount of exudation. Photoreceptor dysfunction following chronic oedema, laser photocoagulation-induced damage and the macular perfusion abnormalities found in diabetic eyes might all limit visual recovery despite resolution of oedema. Cataract formation and/or progression has not been routinely quantified. In addition, the surgery has varied in terms of inclusion of ILM peeling and, when performed, use of vital staining.

These important caveats notwithstanding most of the studies have suggested that vitrectomy is an impressively effective treatment in terms of improving macular thickening and visual acuity. As an illustration of this, we recently reviewed the results of 10 prospective studies, which in total included 178 eyes. The results suggest that vitrectomy may be beneficial in terms of visual recovery. 100/178 eyes (56.2%) demonstrated an acuity improvement of two or more lines at final follow-up.^{24,29,30,32,39,47–49} The proportion of eyes in these studies that improved by more than two lines ranged from 50 to 78%.

There are now six published randomised trials of vitrectomy for DMO, including one performed by our group.^{15,19,37,41,50,51} Our trial included 40 patients¹⁹ with an attached but otherwise normal posterior hyaloid (ie, no clinical traction or PVD), who were randomised to either more laser or vitrectomy with ILM peeling. We found no clinically or statistically significant difference in acuity or macular thickness reduction between the lasered control and vitrectomy groups at 12 months follow-up. There was also no significant change in either group between baseline and 1-year follow-up. Patel *et al*³⁴ and Kumar *et al*^{37,50} have also reported no benefit from similar RCTs, which respectively included 20 and 24 patients with an attached but clinically normal posterior hyaloid. Yanyali *et al*⁴¹ has however reported an RCT in which 10 patients with bilateral DMO were randomly assigned to vitrectomy on one eye and no treatment on the fellow eye with 12-month follow-up. There was a mean acuity improvement of just under 2 logMAR lines in the treatment group compared to a 1.5 logMAR line mean deterioration in the controls. In another paired-eye randomised trial of 12 patients by the same author, the eyes randomised to vitrectomy improved by 0.22 logMAR and 210 μ m from 0.75 logMAR and 439 μ m whereas the 12 fellow eyes randomised to laser improved by 0.10 logMAR and 29 μ m from 0.59 logMAR and 407 μ m respectively.⁵¹ The numbers in both of these trials are very small and the groups do not appear to be balanced at baseline in terms of acuity; however, statistically and clinically significant changes in acuity

were found in each study. In an RCT that included 56 eyes reported by Binder's group, 25 eyes were randomised to vitrectomy and 31 into the control group.¹⁵ This trial reported relatively subtle mean central macular thickness differences between the groups at the 6-month follow-up visit with a 20- μ m increase in the controls and a comparable decrease in the intervention group from a baseline of 560 μ m. In all, 32% of controls but only 12% of the intervention group worsened by 2 logMAR whereas 40% of those undergoing vitrectomy compared to 10% of control improved by the same increment. A fundamental principle of a randomised controlled trial is that the groups should differ only in terms of the intervention under scrutiny. The inclusion criteria allowed for patients with up to LOCS grade 3 cataract to be included and cataract surgery was performed on one-third of the intervention group on this basis, but none of the controls underwent such surgery. No allowance was made for this in the analysis. The inclusion criteria may also have selected for a group in whom OCT partial vitreomacular separation was present, as OCT evidence of an adherent hyaloid was an inclusion criterion. The omission of investigation into potential bias induced by the cataract surgery performed in one-third of the intervention group unfortunately casts significant doubt on the trial conclusions.

The importance of OCT imaging is increasingly being recognised and has now revolutionised the clinical analysis of the vitreomacular interface.^{10,11,52} OCT features suggesting vitreoretinal traction may occur in the absence of a clinical TTPH, which is anyway a clinically rare feature.^{11,46} From our prospective study of vitrectomy for DMO with systematic 1-year follow-up, we found that 15% (5/33) and 24% (8/33) respectively improved or deteriorated by 2 or more ETDRS logMAR lines. Patients were subdivided on the basis of their pre-operative OCT scan vitreoretinal interface appearance. The 22 patients who had no OCT macular traction had a respective mean VA deterioration of -0.11 logMAR and CMT improvement of -117 μ m. Overall, the 11 patients with vitreomacular traction (ie, TTPH, ERM, and/or OCT signs of traction) had an approximately 1 logMAR line improvement in acuity compared to a one-line deterioration in logMAR acuity in the 22 patients without any evidence of macular traction.¹¹

The findings of this study run parallel to those reported by Massin *et al*¹⁰ who suggested that the benefit of vitrectomy may be confined to patients with OCT signs suggestive of macular traction. They are however at odds with the other prospective data on this subject in which 56% of reported patients have improved by 2 or more logMAR or Snellen lines (*vs*). Included in these reports are the data recently reported by Recchia *et al*³⁹ in which only 2/11 patients had any OCT signs suggesting

macular traction but in which the mean acuity changed over 6 months from 20/352 to 20/119. In addition, Yanyali *et al*⁴² have recently reported a prospective series in which none of the 27 patients had OCT evidence of vitreomacular traction. They found a mean acuity improvement of just over 1 logMAR line and a 20% reduction of central macular thickness occurred in 80% of patients.

Where results have been compared, there appears to be little benefit or detriment from ILM peeling as part of the procedure.^{11,53}

At present, the jury appears to be out on the benefits of vitrectomy for DMO. Most retrospective and prospective uncontrolled studies have suggested that the surgery is beneficial and this is supported by two randomised trials, of which significant bias could be cast on the conclusions of one. Paradoxically, three other randomised trials and a number of other carefully conducted series have found no benefit. It has been suggested that the benefit may be confined to a subgroup of patients with vitreomacular traction evident on OCT; other studies, however, refute this. Hopefully, the evidence will become easier to interpret with the results of further studies such as those being performed by the Diabetic Retinopathy Clinical Research Network (www.drcr.net).

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