Surgical management of Diabetic Macular Edema

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ABSTRACT

Diabetic retinopathy is a leading cause of vision loss among those of working age and diabetic macular edema (DME) is a common cause of vision loss among those with diabetes mellitus (DM).[1,2] In the Early Treatment of Diabetic Retinopathy Study (ETDRS), the 3-year risk of moderate visual loss (a decrease of three lines or more on a logarithmic visual acuity (VA) chart) among untreated eyes with DME involving or threatening the central macula was 32%.[3] The pathogenesis of DME is multifactorial, predominantly involving retinal vascular hyperpermeability and other alterations in the retinal microenvironment. Mechanical causes at the vitreoretinal interface, however, are believed to contribute in select patients.[4-7] There are a number of ophthalmic treatments, including focal and grid laser, Intravitreal injection of anti-vascular endothelial growth factor (anti-VEGF) agents, and Intravitreal injection of corticosteroids. Surgical interventions, including vitrectomy with possible peeling of the internal limiting membrane (ILM), have also been used.[8-11] Our aim in this article is to review the surgical options for managing DME, more specifically in patients with vitreoretinal interface problems.

Key words: diabetic macular edema, intravitreal injection, anti-VEGF, corticosteroids, vitrectomy.

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TREATMENT OPTIONS FOR DME

Treatment options for DME include medical management and ophthalmic interventions, both non-surgical and surgical. Medical management focused on glycemic and hypertensive control reduces the onset and progression of diabetic retinopathy in both type 1 and type 2 DM.[12] The ETDRS showed that macular laser reduced the risk of visual loss by 50%. However, only 3% of patients had improved by >3 lines of vision by the end of the study.[3] Other treatments for DME include steroids, such as fluocinolone, dexamethasone, and triamcinolone.[8-10] Intravitreal injection of anti-VEGF agents, such as pegatanib, bevacizumab, ranibizumab, and VEGF Trap, has become a mainstay of treatment.[11]

In spite of these treatments, procedures targeting the posterior hyaloid in select DME cases have become increasingly recognized. In 1988, Nasrallah et al. observed a lower incidence of posterior vitreous detachment in eyes with DME compared with eyes without edema.[13] Later, Lewis et al in 1992 reported resolution of macular edema in 80% of cases after vitrectomy for DME associated with posterior hyaloidal traction.[6] Following these results, various

groups have reported results of vitrecto Diabetic retinopathy is a leading cause of vision loss among those of working age and diabetic macular edema (DME) is a common cause of vision loss among those with diabetes mellitus (DM).[1,2] In the Early Treatment of Diabetic Retinopathy Study (ETDRS), the 3-year risk of moderate visual loss (a decrease of three lines or more on a logarithmic visual acuity (VA) chart) among untreated eyes with DME involving or threatening the central macula was 32%.[3] The pathogenesis of DME is multifactorial, predominantly involving retinal vascular hyperpermeability and other alterations in the retinal microenvironment. Mechanical causes at the vitreoretinal interface, however, are believed to contribute in select patients.[4-7] There are a number of ophthalmic treatments, including focal and grid laser, Intravitreal injection of anti-vascular endothelial growth factor (anti-VEGF) agents, and Intravitreal injection of corticosteroids. Surgical interventions, including vitrectomy with possible peeling of the internal limiting membrane (ILM), have also been used.[8-11] Our aim in this article is to review the surgical options for managing DME, more specifically in patients with vitreoretinal interface problems.

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RATIONALE FOR SURGICAL INTERVENTION

The vitreous has been implicated as a cause of DME due to several mechanical and physiologic mechanisms, all of which lead to increased vascular permeability. Vitrectomy aims at removal of vitreous traction, including anterior-posterior, oblique, and tangential, which relieves traction on Muller cells that result in cell hypertrophy, proliferation, and vascular leakage.[14,15] Traction can also result in RPE changes and distortion of intraretinal vessels. This can result in loss of apposition between the retina and RPE pump and ultimately vascular leakage and disturbances of macular microcirculation.[16-18] Vitrectomy would also suppress the release of inflammatory cytokines, such as basic fibroblast growth factor, induced by mechanical stresses on these same cells. [19] As the vitreous can act as a sink, vitrectomy can help to remove growth factors such as VEGF, interleukin-6 (IL-6), platelet-derived growth factor (PDGF) that are secreted in diabetic retinopathy and can promote macular edema.[20-22] Finally, vitrectomy increases vitreous cavity oxygen tension and oxygenation of the posterior segment.[23-28] Supporting this line of reasoning, Nasrallah et al observed in 1988 a lower incidence of posterior vitreous detachment (PVD) in eyes with DME compared with eyes without edema.[13] As mentioned above, Lewis et al described encouraging results after vitrectomy in diabetic eyes with macular edema.[6] Additionally, spontaneous resolution of edema in 55% of eyes with posterior vitreous separation, compared with 25% of eyes with or without incomplete PVD, was observed by Hikichi et al in 1997.[29]

As an adjunct to vitrectomy, peeling of the epiretinal membrane (ERM) and ILM has been recommended in select cases of DME. If present, ERM peeling can help to remove traction. In cases of DME, the ILM may thicken due to an increased content of extracellular matrices and cellular proliferation on the vitreous surface. This can lead to decreased water movement between the vitreous and retina, build-up of proteins in the interstitial space, decreased diffusion of proteins to the vitreous space, and macular

edema.[30,31] Removal of this thickened ILM eliminates a possible barrier to cytokines and oxygen.[32,33] It can also help to ensure complete removal of residual cortical vitreous.[30,34] Tangential traction exerted by the ILM can also be removed. Finally, ILM peeling can ensure complete removal of epiretinal cells and may limit postoperative ERM formation by removing scaffold for proliferating cells.[35] Taken together, ILM and/or ERM peeling can serve as useful adjuncts to vitrectomy for select cases of DME.

ILM PEELING

Peeling of the ILM has been proposed as a helpful adjuvant to vitrectomy for DME. This procedure has been thought to relieve macular traction by the vitreous, prevent the development of secondary epimacular membrane and eliminating the scaffold for astrocyte reproliferation.[36] Results from the literature, however, are mixed. Kamura et al evaluated 34 DME eyes treated with ILM peeling during vitrectomy compared to eyes treated with vitrectomy alone and found that VA improved significantly after vitrectomy regardless of ILM peeling and without a significant difference between the groups.[37] Bahadir et al examined 17 DME eyes treated with ILM peeling during vitrectomy compared to eyes treated with vitrectomy alone and found a significant improvement in postoperative VA in both groups but no difference between them.[38] Rosenblatt et al reviewed 26 eyes with refractory DME (unresponsive to two laser treatments) without traction that were treated with vitrectomy and ILM peel. There was a statistically significant improvement of mean VA (50% of eyes gained at least two lines of VA) and mean foveal thickness (311 μm from 575 μm).[39] Patel et al evaluated 10 eyes with diffuse DME refractory to laser which were treated with vitrectomy and ILM peeling compared to a vitrectomy alone control, finding the ILM peeling was associated with a significant improvement in foveal thickness and macular volume postoperatively but no change in VA was seen.[40] Recchia et al examined 10 patients after vitrectomy and ILM removal with diffuse DME refractory to laser finding both improvement in central macular thickness and VA.[41] Finally, Yanyali et al treated 12 DME eyes with vitrectomy and ILM peel compared to controls treated with laser in this prospective study, finding a significant improvement in mean foveal thickness and VA in the surgical group but not in the laser group.[42] In the later study, Yanyali et al reviewed 27 DME eyes that underwent vitrectomy with ILM, finding a significant decrease in foveal thickness and improvement in VA.[43] In summary, most of these studies report an additive benefit to ILM peeling in conjunction to vitrectomy although several did not find this benefit. Restoration of foveal anatomy was more common than improvement in VA. Actual practice of ILM peeling for diffuse DME appears mixed as 54% of surgeons in the DCRC Vitrectomy Study elected to peel the ILM.[44]

In order to better understand how ILM peeling improves foveal contour and may improve VA in DME, several studies have thoroughly investigated changes in pathology and imaging. Gentile et al described 2 cases of diffuse DME after vitrectomy and were found to have a taut ILM after undergoing ILM peeling, macular edema and VA improved. A segment of the ILM was analyzed with immunostaining and revealed an inner monolayer of cytokeratin-positive (retinal pigment epithelial (RPE) cells) and/or glial fibrillary acidic protein-positive cells with smooth muscle actin (SMA) immunoreactivity. As SMA suggests myofibroblastic differentiation and the contractile ability of the RPE and glial cells, these changes likely caused tangential traction which was relieved by ILM peeling.[45] This tangential traction that can be exerted by the ILM was also imaged in Abe et al. They performed a retrospective case series of 26 DME eyes imaged with SD-OCT to identify both traction seen on tomography and fine folds seen on 3D imaging. After IML peeling, the fine folds resolved, even in those eyes without traction on tomography. Surgically obtained specimens confirmed that the fine folds involved the ILM.[46] This suggests that ILM peeling can help resolve tangential traction in DME, even when not obvious on standard tomography.

PROGNOSTIC FACTORS

Multiple prognostic factors for favorable outcomes after vitrectomy for DME have been identified. A strong correlation exists between preoperative and postoperative VA. In their study of 55 eyes with DME that underwent vitrectomy with stripping of a taut hyaloid, Pendergast et al found that eyes with preoperative BCVA of 20/200 or less tended to respond less favorably to vitrectomy than eyes lacking those characteristics. The group of eyes with

preoperative BCVA of 20/100 or better improved by a median of 60% compared to 18% for eyes with VA or 20/200 or worse at baseline. Additionally, those eyes with macular ischemia postoperatively had worse final VA and tended to show less improvement.[7] Perhaps due to this strong correlation between preoperative and postoperative VA, early surgical intervention is often associated with better outcomes. In their study on 10 DME patients who underwent vitrectomy for a taut posterior hyaloid, Harbour et al found that the 3 eyes with rapid deterioration of vision from DME followed by prompt surgical intervention (less than 1 month) experienced the most improvement in final BCVA.[47]

Additional studies have used OCT to delineate prognostic factors for DME and surgical intervention. Disruption of the IS/OS junction is associated with worse VA in DME patients. Maheshwary et al used SD-OCT in 62 eyes with DME found a statistically significant correlation between percentage disruption of the IS/OS junction and VA.[48] Additionally, Chhablani et al found that external limiting membrane (ELM) integrity correlate with postoperative outcome. In their study of 34 eyes with resistant DME treated with vitrectomy, they found that each percentage increase of ELM integrity there was a 0.13 letter gain in vision.[49] Finally, Nishijma et al indentified hyperreflective foci in outer retina predictive of photoreceptor damage and poor vision. In their study of 32 eyes undergoing vitrectomy for DME, they found that VA was significantly better in eyes without hyperreflective foci than in those with hyperreflective foci postoperatively.[50] These prognostic factors serve as markers for damage to macular photoreceptors, which would limit visual potential after surgery.

Additionally, longer axial length has been found to be associated with better outcomes after vitrectomy. In Wakabayashi et al, 51 eyes with DME underwent vitrectomy. They found that a significant negative correlation was observed between postoperative VA and axial length.[51] Finally, better glycemic control correlates with better outcomes. Yamada et al examined 44 diabetic eyes underwent vitrectomy with ILM peeling for DME and found that the postoperative OCT macular thickness was significantly thicker when there was a higher glycosylated hemoglobin. They also found postoperative BCVA was significantly lower in patients without any diabetic treatment prior to the diagnosis of diabetic retinopathy.[52] These studies suggest that there are retinal, ocular and systemic factors that can help identify patients who could benefit from surgical intervention for DME.

SUMMARY

When vitrectomy is performed for select cases of DME, there are typically favorable anatomic results but unfortunately more limited visual results. As the studies discussed here show, foveal thickness usually decreases postoperatively by 100-250 μm on OCT. This is often a greater than 50% reduction of retina thickening. However, this does not translate to significant visual results. VA usually improves 5 to 15 letters postoperatively but may worsen. This limited improvement in VA is not unexpected given that vitrectomy is often performed for refractory DME cases with long-standing edema with irreversible macular damage. However, this could possibly be due to delayed surgical intervention.

When DME cases are characterized by vitreoretinal interface problems, the utility of vitrectomy in select cases becomes clearer. Vitrectomy has been shown to be beneficial in most DME cases without a PVD, where a taut hyaloid or vitreomacular traction is present. It is indicated in select cases where the posterior hyaloid is attached, even if no observable traction. When separation of the posterior hyaloid has occurred, vitrectomy can be beneficial in select cases where an ERM is present but is only occasionally indicated when an ERM is absent.

In summary, eyes with observable vitreous and/or epiretinal traction are most likely to improve after vitrectomy. Eyes with refractory edema and no observable traction, however, are less likely to improve. Improvement in retinal thickening is often more impressive than improvement in VA. As a strong correlation exists between preoperative and postoperative VA, early surgical intervention is often associated with better outcomes.

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