Vitrectomy for Diffuse Refractory Diabetic Macular Edema Associated with a Taut Premacular Posterior Hyaloid

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Purpose: To evaluate the anatomic and visual results and complications of vitrectomy in eyes with diffuse refractory diabetic macular edema associated with a taut posterior hyaloid.

Methods: This prospective interventional case series was conducted on 25 eyes of 22 patients with diffuse refractory clinically significant diabetic macular edema, macular thickness greater than 250 µm on optic coherence tomography (OCT) and thickened posterior hyaloid. Best-corrected visual acuity (BCVA) and macular thickness measured by OCT were evaluated preoperatively and repeated 3 and 6 months postoperatively. Macular perfusion was evaluated by fluorescein angiography, pre- and six months postoperatively.

Results: Mean BCVA was 1.14±0.51 LogMAR, preoperatively which improved to 0.89±0.53 LogMAR six months postoperatively (P=0.005). Mean preoperative macular thickness was 506±121.9 µm which decreased to 318±90.5 µm, six months postoperatively (P=0.001).

Conclusion: Vitrectomy and removal of the posterior hyaloid membrane appears beneficial in eyes with diffuse diabetic macular edema unresponsive to laser therapy and a taut premacular posterior hyaloid.

INTRODUCTION

Macular edema is a major cause of visual impairment in diabetic patients. Diabetic macular edema (DME) develops in 29% of diabetic patients over a 20-year period after the onset of diabetes mellitus. Approximately half of these patients lose two or more lines of visual acuity within two years. Based on observations of the Early Treatment of Diabetic Retinopathy Study Group, laser photocoagulation can decrease the rate of moderate visual loss up to 50%, however visual improvement is uncommon (3-14.5%). Previous studies have reported unfavorable outcomes with laser treatment in diffuse diabetic macular edema. This fact has led investigators to seek alternative modalities for the management of DME such as vitrectomy.
and administration of steroids, protein kinase C inhibitors or vascular endothelial growth factor inhibitors by intravitreal injection.\(^7\)-\(^{10}\)

The pathogenesis of DME is not well known, however many several factors such as chronic hyperglycemia, insulin therapy, proteinuria, renal failure, heart failure, systemic hypertension (HTN) and panretinal photocoagulation (PRP) have been implicated.\(^{11}\)-\(^{18}\) For the first time, Schepens\(^{16}\) reported the role of the vitreous body in cystoid macular edema (CME). The higher prevalence of posterior vitreous detachment (PVD) in eyes without DME compared to those with DME and also spontaneous recovery of DME following development of PVD implicate the role of the vitreous in the pathogenesis of DME.\(^{13,16,17}\)

Lewis et al.\(^7\) first reported vitrectomy as an alternative treatment for diffuse DME associated with posterior hyaloid traction. It was used thereafter for the management of DME even in the absence of vitreomacular adhesion.\(^{18}\) Herein we report the visual and anatomical outcomes as well as complications of vitrectomy in a series of patients suffering from diffuse refractory DME associated with a taut premacular posterior hyaloid.

**METHODS**

This prospective interventional case series was conducted on diabetic patients referred to the vitreoretinal service at Farabi Eye Hospital, Tehran-Iran from January 2004 to January 2005 with clinically significant macular edema due to diabetes mellitus which was refractory to laser photocoagulation. Unresponsiveness to laser treatment was defined as no reduction in macular edema following at least two sessions of macular photocoagulation. All patients were provided with a thorough explanation of the study protocol as well as the risks and benefits of the proposed intervention and written informed consent was obtained from all participants before enrollment into the study.

Inclusion criteria were (1) diffuse DME; (2) at least two sessions of previous macular photocoagulation with no reduction in macular edema at least 4 months before; (3) diffuse leakage on fluorescein angiography (FA); (4) stable regressed proliferative diabetic retinopathy (PDR); and (5) vitreoretinal traction or thickened posterior hyaloid on optical coherence tomography (OCT). Exclusion criteria were (1) other causes of macular edema such as uveitis or retinal vascular occlusion; (2) epiretinal membrane; (3) fibrovascular proliferation resulting in macular detachment; (4) significant media opacity such as cataract or vitreous hemorrhage; (5) complete PVD; (6) history of glaucoma or intraocular pressure (IOP) >21 mmHg; and (7) history of vitrectomy.

Preoperative evaluation included determination of best-corrected visual acuity (BCVA), slitlamp biomicroscopy, applanation tonometry, vitreous biomicroscopic examination using a three-mirror contact lens, OCT for measuring retinal thickness and assessment of vitreous traction on the retina, FA, blood pressure (BP) measurements and blood chemistry including cholesterol, triglyceride and hemoglobin A1C.

All eyes underwent deep vitrectomy and were scheduled for follow up examinations 1 day, 1 week, and 1, 2, 3, 5, and 6 months postoperatively. OCT and hemoglobin A1C levels were repeated at months 3 and 6; FA was repeated at month 6. The effect of treatment was evaluated clinically, by OCT and FA.

BCVA was measured using Snellen E charts and converted to logarithm of minimum angle of resolution (LogMAR). Lens opacity was evaluated clinically and classified as cortical cataract (CC), nuclear sclerosis (NS), and posterior subcapsular cataract (PSC) graded in severity from 0 to 4+. HTN was defined as systolic BP \(\geq\) 160 mmHg or diastolic BP \(\geq\) 95 mmHg. The study data was analyzed using SPSS 12 software. Paired t test was used for comparison of mean values and Chi square test was used for comparison of frequency values, with level of significance set at 5%.

**Surgical Technique**

After core vitrectomy, PVD was induced followed by triamcinolone acetonide injection
into the vitreous cavity for better visualization and ensuring a complete PVD. Triamcinolone was removed as much as possible using a flute needle at the end of the procedure. No attempt was made to remove the internal limiting membrane and no laser therapy was performed. At the end of the operation funduscopy was performed to rule out iatrogenic retinal breaks, especially at the sclerotomy sites. After closure of the sclerotomies, a subconjunctival injection of 4 mg betamethasone and 20 mg gentamicin was given.

RESULTS

The study was performed on 25 eyes of 22 patients including 14 male and 8 female subjects with mean age of 58.1±6.0 (range 43-68) years. PRP had been performed for PDR in 12 eyes (48%); the remaining 13 eyes (52%) had non-proliferative diabetic retinopathy and had previously undergone only macular photocoagulation. None of the eyes had progressive active diabetic retinopathy at the time of vitrectomy. Eight eyes (32%) were pseudophakic.

Pre- and postoperative data are summarized in table 1. Macular thickness decreased by an average of 24.3% at month 3 (P= 0.006) and 37.2% at month 6 (P= 0.001). Overall, 95.6% of the eyes demonstrated reduction in macular thickness ranging from 21 to 490 µm on OCT six months postoperatively. Mean BCVA improved in 72%, 68%, and 65.2% and decreased in 8%, 12%, and 17.4% of the eyes after 1, 3, and 6 months, respectively. Visual improvement of 0.1 to 1.5 LogMAR (averagely 0.5 LogMAR) was seen in 65.2% of the eye after six months. Postoperative changes in mean IOP were not statistically significant. Only one eye developed IOP > 21 mmHg one month after the procedure which was controlled with topical medications.

The most prevalent pattern of macular edema based on preoperative OCT was sponge-like swelling of the retina (64%) followed by CME (56%) and serous retinal detachment (36%). All eyes had diffuse macular leakage on preoperative FA. Six months postoperatively FA revealed a decrease in leakage in 82% of the eyes.

There was no significant correlation between visual acuity and macular thickness, serum cholesterol or triglyceride, blood pressure and phakic condition (data not presented).

No intraoperative complication occurred. There were three cases (12%) of mild cataract development postoperatively with no need for extraction. One case of retinal detachment occurred one month postoperatively and one case of anterior ischemic optic neuropathy was observed three months after the operation.

**Table 1** Comparison of pre- and postvitrectomy laboratory tests

<table>
<thead>
<tr>
<th>Tests</th>
<th>Mean ± standard deviation (Range)</th>
<th>Preoperative</th>
<th>Month 3</th>
<th>Month 6</th>
<th>P1</th>
<th>P2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triglyceride (mg/dl)</td>
<td>174.6 ± 64.2 (95-266)</td>
<td>-</td>
<td>193.8 ± 76.3 (90-280)</td>
<td>-</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Cholesterol (mg/dl)</td>
<td>253 ± 63 (198-380)</td>
<td>-</td>
<td>147.8 ± 54.1 (190-340)</td>
<td>-</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Hb A1C (%)</td>
<td>8.9 ± 2.0 (4.9-11.0)</td>
<td>8.5 ± 2.3 (5.5-11.5)</td>
<td>8.6 ± 2.1 (5.6-11.7)</td>
<td>NS</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>BCVA (LogMAR)</td>
<td>1.14 ± 0.51 (2.6-0.2)</td>
<td>0.9 ± 0.46 (2.0-0.2)</td>
<td>0.89 ± 0.53 (2.6-0.2)</td>
<td>&lt;0.0001</td>
<td>&lt;0.005</td>
<td></td>
</tr>
<tr>
<td>Macular thickness (µm)</td>
<td>506 ± 121.9 (339-723)</td>
<td>383 ± 80.3 (280-490)</td>
<td>318.2 ± 90.5 (169-487)</td>
<td>0.006</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>IOP (mmHg)</td>
<td>15.3 ± 2.7 (10-20)</td>
<td>17.3 ± 3.5 (12-25)</td>
<td>15.8 ± 2.6 (12-21)</td>
<td>NS</td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>

Hb, hemoglobin; BCVA, best- corrected visual acuity; IOP, intraocular pressure; NS, non- significant

• Paired t test for comparing preoperative with third (P1) and sixth (P2) month values.

DISCUSSION

Diabetic macular edema results from intra- and subretinal accumulation of fluid due to break-down of the retinal pigment epithelium (RPE) barrier and increased vascular permeability. Retinal vascular leakage may be localized at the sites of microaneurysms or diffuse at the RPE/
blood-retinal barrier from hyperpermeable capillaries.5,6 Focal macular edema is better responsive to laser treatment, whereas the outcome of laser therapy in cases of diffuse macular edema is poor.3,19

Mediators such as VEGF and prostaglandins contribute to the pathogenesis of diffuse macular edema by changing vascular permeability.20,21 Yanoff et al15 suggested that intracytoplasmic swelling of Muller cells is the first histopathologic event in the process of macular edema followed later by extracellular fluid accumulation. Although retinal ischemia is the main factor in the pathogenesis of macular edema, the role of the vitreous body in this pathologic process was suggested for the first time by Schepens et al16 in 1984 who suggested that vitreous traction on the retina may contribute to development of macular edema. In a prospective study on patients with type II diabetes mellitus and DME including 22 cases with vitreomacular detachment and 60 cases with vitreomacular adhesion, Hikichi et al13 found that macular edema resolved spontaneously in 55% of the former group vs 25% of the latter group over a period of 6 months (P=0.01). They believed that in addition to vitreomacular traction, accumulation of several mediators in the macula may be the cause of persistent DME in eyes with vitreomacular adhesion. In a retrospective study, Nasrollah et al17 reported that 20% of eyes with DME versus 55% of eyes without DME had PVD.

Vitrectomy for management of DME was initially used in eyes with taut posterior hyaloid and vitreoretinal traction.7,8,22 Yamamoto et al23 categorized 30 eyes with DME into four groups based on presence of PVD and/or epimacular membranes and demonstrated that post-vitrectomy reduction in macular thickness and visual impairment does not depend on the condition of the posterior vitreous or existence of an epimacular membrane. Conversely, Massin et al24 believed that vitrectomy is effective in cases of DME with vitreoretinal traction.

The rationale for vitrectomy in DME is based on findings of different studies:

1) Lewis7 believed that anteroposterior vitreous traction results in superficial detachment of the macula; vitrectomy can relieve this traction and resolve the macular edema. However, Harbour8 believed that this traction is mainly tangential.

2) Vitrectomy can improve capillary blood flow in the macula which is directly associated with post-vitrectomy visual improvement.25

3) Increased post-vitrectomy fluid circulation in the vitreous results in delivery of more oxygen and nutrients from high-perfusion areas such as the ciliary body to ischemic areas of the retina. Increased oxygen concentration results in retinal vascular contraction and decreased edema.23,26

4) In eyes with epimacular membranes, accumulation of mediators such as VEGF and interleukin 6 (IL-6) in the membrane can increase macular edema, conversely removal of the membrane may help decrease the macular edema.23

5) Accumulation of mediators in the space between the retina and posterior vitreal surface aggravates macular edema. Vitrectomy can decrease the edema by eliminating this space.13,27

Grigorian et al28 reported post-vitrectomy visual improvement in 40-90% and partial or complete resolution of retinal edema in 70-100% of eyes with DME. Jahn et al29 reported visual improvement in 56%, decrease in macular edema in 74%, and decrease in leakage on FA in 81% of eyes in their series 6 months after vitrectomy. Harbour et al8 performed vitrectomy for management of DME in 10 eyes with thickened posterior vitreous membrane and found that 60% of the eyes achieved visual improvement.

There are also several studies on vitrectomy in eyes with DME without PVD or a taut posterior vitreous.27,30,31 Tachi and Ogino30 performed vitrectomy in 58 eyes with DME without PVD and reported decrease in macular edema in 98% and visual improvement in 53% 12 months after the operation. Post-vitrectomy visual improvement rate was reported from 47% to 86% in other studies23,25,32-34 In our series, mean visual improvement of 0.5 (range 0.1-1.5) LogMAR was achieved in 65.2% of eyes
after six months. We also found a decrease of 21-490 µm in macular thickness on OCT in 95.6% of the eyes and 37.2% reduction in mean macular thickness. Reduction in macular edema was reported between 45% and 98% in other studies.⁸,²²,³⁰ There was also a decrease in leakage on FA in our series six months postoperatively. It should be noted that we used intravitreal triamcinolone acetate during vitrectomy for better visualization and the improvement in visual acuity and macular thickness could be in part due to the effect of this steroid.

Reasons for incomplete anatomic and visual improvement in DME following vitrectomy are as follows:
1) Vitrectomy can eliminate only a number of factors related to macular edema such as vitreomacular traction, whereas other causes such as blood-retinal barrier abnormalities, systemic hypertension, heart failure, renal insufficiency, insulin usage and hyperglycemia still persist. Control of systemic factors, especially in the long term may be as important as vitrectomy.
2) Some pathologic changes resulting from prolonged macular edema are irreversible.
3) The length of follow up period affects the level of improvement: Tachi and Ogino⁴⁰ showed that macular edema improves over 6-12 months after vitrectomy. Therefore with longer follow up, the rates of improvement may differ significantly.
4) Complications of vitrectomy such as cataract progression and retinal detachment may adversely affect visual outcomes.

The rate of cataract progression in our series was 12%. Similar rates range from 10% to 58% depending on the length of follow up.⁷,⁸,²²,³⁰ One study has reported that the need for cataract surgery after vitrectomy for DME (15%) is less than other indications such as macular holes (53%) or epimacular membranes (66%).³⁵ Amino et al³¹ proposed vitrectomy combined with cataract extraction and intraocular lens implantation in DME because of the inevitable progression of cataracts after vitrectomy. Additionally, they believed that combined cataract surgery facilitates a more complete anterior vitrectomy which in turn prevents anterior fibrovascular proliferation. Relief of vitreous traction on the ciliary body may also decrease release of mediators from this site.²⁵

Pendergast¹⁸ reported post-vitrectomy complications in eyes with DME as follows: retinal tears (9.6%), epiretinal membrane (9%), retinal detachment, neovascular glaucoma and rubeosis iridis (each 1.9%). These complications did not occur in our series; we found 3 cases of cataract formation (12%) and one case of retinal detachment (4%). One eye developed anterior ischemic optic neuropathy which did not seem to be related to vitrectomy, because the fellow eye was also involved after some time.

Despite the limitations of the current series including small sample size, short follow up and lack of a control group, our findings demonstrated that vitrectomy could be an effective treatment modality for diffuse refractory DME, however our findings should be verified in a controlled clinical trial. At present we would suggest vitrectomy in eyes with diffuse DME unresponsive to laser treatment and a taut posterior hyaloid on OCT without significant macular ischemia.

REFERENCES