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Original Article

Role of Pars Plana Vitrectomy with Internal Limiting Membrane Peel in Patients of Refractory Diabetic Macular Edema

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Objective: To see the role of pars plana vitrectomy (PPV) with Internal Limiting Membrane (ILM) peel in patients of refractory diabetic macular edema in reducing central macular thickness.

Introduction: Diabetic macular edema (DME) is a major cause of visual morbidity in diabetic patients. Vitrectomy for DME has seemingly gained rapid, widespread acceptance but studies evaluating the efficacy of vitrectomy (with or without ILM peeling) have yielded conflicting results. The role of Internal Limiting Membrane (ILM) peeling in the treatment of DME is also controversial, and sufficient data to clarify its role have not yet been available.

Methodology: Pre-operatively, Central Macular Thickness (CMT) was measured with Optical Coherent Tomogram (OCT). OCT was performed with a standard protocol of 6mm radial scan centered at patient's fovea. All patients underwent 23G Pars plana Vitrectomy (PPV) by single surgeon. After completing vitrectomy and fluid-air exchange, ILM was stained with brilliant blue G for 4 to 5 minutes. ILM peeling was done in all twenty cases with iatrogenic macular hole formation in two cases and retinal bleeding in vitreous cavity in three cases. Patients were followed up till 3 months postoperative. Post-operatively central macular thickness was measured by OCT after one month and three months respectively.

Results: Preoperative mean CMT of patients was 439.35±103.82. At 1st month post-operative it was 266.00±81.51 and at 3rd month post-operative it was 254.00±85.32. The decrease in CMT post operatively at 3rd month is statistically significant.

Conclusion: Pars plana vitrectomy with ILM peel has significant role in reducing refractory diabetic macular edema.

Key words: Refractory Diabetic macular edema, Central macular thickness, Pars plana vitrectomy, Internal limiting membrane peel

Introduction:

Diabetic macular edema (DME) is leading cause of visual impairment in patients with diabetes mellitus (DM).Without treatment 50% patients of type 2 DM have been reported to suffer from decrease of visual acuity of at least two lines of snellen's chart within two years of diagnosis[1]. The incidence of DME is approximately 25% in type 1 DM and 20% in type 2 DM. Though the incidence of DME can be reduced by systemic control of hypertension and hyperglycemia but the treatment of DME is chiefly ophthalmic treatment[2,3].

DME is characterized by intraretinal swelling with variable amount of intraretinal hemorrhages and hard exudates. According to Early Treatment Diabetic Retinopathy Study (ETDRS), DME may be focal or diffused depending upon fundus fluorescein angiographic pattern of leakage. Focal DME is the result of specific leakage from aneurysm, while diffused DME is the result of disruptive inner blood retinal barrier. Refractory DME is defined as persistent diffused DME for at least three months proven on optical coherence tomography (OCT) and fundus fluorescein angiography (FFA) which does not decreases significantly after treated with at least three consecutive intra vitreal injection of 1.25 mg/ 0.05 ml bevacizumab (Avastin) one month apart[1,4].

Pathogenesis of refractory DME is multifactorial. Hyperglycemia, increased vascular endothelial growth factors (VEGF), taught posterior hyloid and vitreo-macular traction all play role in pathogenesis of refractory DME. Hyperglycemia leads to development and acceleration of advanced glycation end-products (AGEs). AGEs cause damage to pericytes, endothelial cells and promote leukostasis. AGEs also believe to promote mechanical damage in vitreo-retinal interface. Increased production of angiogenetic growth factors especially vascular endothelial growth factors (VEGF) and hyperglycemia causes disruption of inner blood retinal barrier and capillary leakage[4,5].

Nasrallah and associates found that posterior hyaloid attachment was more common in patients with persistent diffused DME than other patients of DME. Lewis and his team showed definite improvement in persistent diffused DME and best corrected visual acuity(BCVA) after pars plana vitrectomy in upto60% of cases[1,6]. It is proposed that PPV reduces the VEGFs levels in vitreal cavity due to early wash-off as compared to vitreous and eliminates cortical vitreous traction on macula. PPV also increases the tissue oxygenation of retina thus reduces retinal ischemia and VEGFs production[6].

Many studies showed that PPV with ILM peel has better anatomic results in reducing CMT but does not significantly improves best corrected visual acuity (BCVA) as compared to PPV alone. One postulated mechanism is that ILM peeling accelerates absorption of macular edema[7,8].

Objective:

The objective of this study is to see the role of Pars Plana Vitrectomy (PPV) with internal limiting membrane (ILM) peel in patients of refractory diabetic macular edema in reducing central macular thickness.

Material & Methods:

This prospective interventional study was conducted at Vitreo retina clinic, Department of Ophthalmology Mayo Hospital Lahore. Total 20 patients of DME were included in the study through non probability purposive sampling technique. Selection of these patients was done with the following inclusion and exclusion criteria. i.e. Diabetic patients (Type-1 & Type-2) with age 30-65 years, with either gender presenting with BCVA 6/60 or less on Snellen chart and refractory DME proven by OCT with central macular thickness > 300 microns were include in the study. Following patients were excluded who presented with active diabetic retinopathy with vitreous haemorrhage, patients of cataract or glaucoma, having history of previous vitreo-retinal surgery and any abnormality of vitreo retinal interface i.e. epiretinal membrane, vitreo-macular traction or vitreous opacification.

Operational Definition:

Refractory diabetic macular edema: It is defined as persistent diffuse diabetic macular edema proven by FFA of at least more than 250 microns. CMT measured by OCT which persists for at least three months duration despite injecting three injections of 1.25 mg/0.05 ml bevacuzimab (avastin) one month apart.

Central macular thickness: CMT was measured by spectral domain OCT with a standard protocol of 6mm radial scan centered at patient fixation point.

Data collection Procedure:

After approval from ethical board of COAVS, twenty patients of refractory diabetic macular edema were collected from vitreo retina clinic of COAVS/ Ophthalmology Department Mayo Hospital,. Pre-operatively, central macular thickness was measured with OCT. OCT was performed with a standard protocol of 6mm radial scan centered at patient's fovea. All patients underwent 23G PPV by single surgeon. PVD was induced by suction vacuum of vitrectomy cutter. After completing vitrectomy and fluid-air exchange, ILM was stained with brilliant blue G for 4 to 5 minutes. After staining, ILM was peeled with membrane peeling forceps. ILM peeling was done in all twenty cases with iatrogenic macular hole formation in two cases and retinal bleeding in vitreous cavity in

three cases. Silicon oil was injected in patients with vitreous haemorrhage and C3F8 gas was injected in patients with iatrogenic macular hole formation. All other patients were closed with air in vitreous cavity. Patients were followed up till 3 months postoperative. Post-operatively central macular thickness was measured by OCT after one month and three months respectively.

Data analysis:

Data entry and analysis was done by using SPSS 20. Quantitative variables (age and central macular thickness) were presented with mean±SD. Qualitative variables [Gender & side operated (Right or left)] was presented with frequency and percentages. Paired sample t-test/ Wilcoxon signed rank test was applied to see the central macular thickness before and after treatment [Pars plana vitrectomy (PPV) with internal limiting membrane (ILM) peel]. A p-value ≤0.05 was taken as significant.

Results:

In this study mean age of patients was 50.85±8.51 years (ranging from 32-65 years). Gender distribution of patients showed that there were 10(50%) male and 10(50%) female patients included in the study. Male to female ratio was 1:1. There were 11(55%) patients whose right eye and 9(45%) patient's left eye was operated. Preoperative mean CMT of patients was 439.35±103.82 (Ranging: 280-650). At 1st month post-operative it was 266.00±81.51 (ranging from 156--447) and at 3rd month post-operative it was 254.00±85.32 (ranging from 174--447) respectively. A statistically significant decrease was observed in mean CMT at 3rd month post operatively i.e. p-value=0.000. Decrease in CMT at 3rd month postoperative was 37.24%±32.24 respectively.

Table-1: Descriptive statistics for CMT at base line & at different follow up intervals

	Pre-operative	Post-Operative		% Decrease in CMT
	Base Line	1st Month	3rd Month	
CMT	439.35±103.82	266.0±81.51	254.00±85.32	- 37.24±32.24
Range	(280-650)	(156-447)	(174-447)	

p= 0.000

Note: (a): Wilcoxon signed Ranks Test was applied

Figure-1: Gender Distribution of Patient

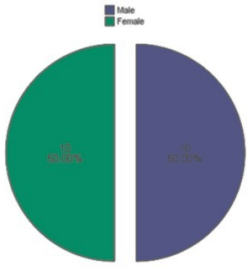
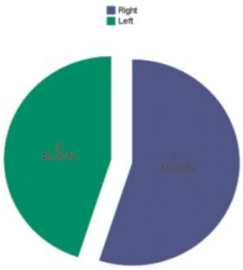


Figure-2: Eye Operated



Discussion:

Pars plana vitrectomy is another treatment modality reported to be useful in treating refractory DME. Several studies published in peer reviewed literature have shown that vitrectomy leads to a reduction of CMT in most cases and improvement of visual acuity in 43-69% of study eyes[1-3].

How PPV helps in resolving macular edema and improvement of vision is not entirely known, but it is postulated that increased macular blood flow in DME gets normalized after vitrectomy and increased retinal oxygenation through vitreal cavity, which leads to resolution of macular edema in diabetic eyes[4].

Another important decision when planning PPV is whether to remove ILM or not. Some studies have reported a beneficial effect of ILM removal in chronic DME where as others have reported no added advantage of ILM removal[5,6].

There are concerns for further photoreceptor damage in an already damaged macula by removing ILM. The reason of persistence of chronic edema and how ILM could improve outcomes in some patients remains unknown. The significant role of the ILM in the pathogenesis of persistent diffuse DME might be explained by stressing the importance of colloid and protein accumulation and retention in the retinal interstitial space. Furthermore, ILM removal may also have a beneficial effect in preventing postoperative epiretinal membrane formation by removing the scaffold for proliferating cells.

The role of ILM peeling in the treatment of DME is not well defined, and sufficient data to clarify its role have not been available. In this study it was observed that CMT significantly decreases after pars plana vitrectomy (PPV) with ILM peel in

patients of refractory diabetic macular edema at 3rd month post operative i.e. CMT (Preoperative): 493.35±103.82 and at 3rd Month(Post-operative): 254.00±85.32 respectively. (p=0.000) Mean decreases in CMT from preoperative till 3rd month post operative was -32.24±32.24% respectively.

Kristen I. Hartley reported that pars plana vitrectomy with ILM peeling was associated with an overall reduction in central macular thickness of 141µm at 3 months postoperative and 120µm at last follow-up[7].

Recently Seemant Raizada in his study reported that Post treatment decrease in CMT was more in PPV group as compared to that of intra-vitreal bevacizumab (IVB) group i.e. 161.36 vs. 108.45 respectively[8].

Patel et al, showed that PPV with ILM peeling produces reduction in central macular thickness as measured by optical coherence tomography (OCT), but there was minimal improvement in visual acuity[9].

Mohammad-Hossein Dehghan in his study reported that PPV with ILM peeling for persistent diffuse macular edema seems to reduce macular thickness i.e. Mean CMT at final examination was 315±95 µm, which was significantly less than its preoperative value of 467±107 µm (p=0.004)[10].

The rationale supporting the removal of ILM during vitrectomy is elimination of tractional forces at the vitreoretinal interface known to contribute to DME. Furthermore, the condensed vitreous pocket in the premacular area is strongly attached to the ILM, and thus, the induction of a PVD will only allow the anterior surface of the pocket to be released. ILM peeling would remove the posterior surface of the precortical vitreous pocket and would resolve the macular edema more efficiently. Internal limiting membrane is also known to serve as a scaffold for proliferating astrocytes. Thus, its removal may inhibit the re-proliferation of astrocytes on the retinal surface, avoiding the formation of the epiretinal membrane.

There is agreement in nearly all previous studies that PPV with ILM peeling significantly reduces macular thickness, although this is not exactly correlated with improvement in visual acuity[11-13].

Conclusion:

Pars plana vitrectomy with internal limiting membrane has significant role in reducing refractory diabetic macular edema.

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