• Clinical Research •

The impact of macular surgery in different grades of epiretinal membrane

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Abstract

• AIM: To assess the impact of macular surgery on the functional and anatomic outcomes of the patients in different grades of epiretinal membrane (ERM).

• METHODS: Seventy-one eyes of 71 patients who underwent 23-gauge transconjunctival sutureless pars plana vitrectomy for primary isolated ERM were evaluated in this study.

• RESULTS: There were 38 females (53.5%) and 33 males (46.5%). The average age of the patients was 68.1y (range 42-89y). Mean follow up period was 14mo (range 6-26mo). The cases were divided into two subgroups of cellophane maculopathy (CM) and macular pucker (MP). An improvement was observed in the postoperative best-corrected visual acuity (BCVA), as well as a decrement in central foveal thickness (CFT) in both groups (both of these being statistically significant; *P*=0.001). In comparison between two groups, it was found that there was a significant improvement on BCVA and CFT in CM group than MP group (*P*=0.01). Furthermore, the postoperative fundus findings regarding RPE alterations and macular edema were significantly higher in MP group when compared to the CM group (*P*=0.01).

• CONCLUSION: ERM and internal limiting membrane peeling surgery can lead to a significant reduction of CFT and visual improvements in idiopathic ERM. A long-term ERM persistence will cause unrecoverable retinal damage and visual loss.

• **KEYWORDS:** cellophane maculopathy; epiretinal membrane; internal limiting membrane peeling; macular pucker; membrane peeling; vitrectomy

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INTRODUCTION

Abnormalities of the vitreomacular interface (VMI) are involved in the pathogenesis of several macular conditions such as idiopathic epiretinal membrane (ERM), vitreomacular traction syndrome, and primary macular holes. Anomaly in posterior vitreous detachment (PVD) has been considered as a cardinal factor in the pathogenesis of idiopathic ERM[1]. Abnormal attachments are detected between the vitreous and retina in VMI diseases. Traction on the retina causes changes in the retinal anatomy and subsequently results in loss of vision[1]. Traction maculopathies classify based on their anatomic and pathologic differences[2]. Macular traction may be anterior/posterior like in vitreomacular traction syndrome. Also this traction may be tangential as in cellophane maculopathy (CM), macular pucker (MP), and macular hole. Tangential traction in inner retina may cause to CM. Besides, tangential traction in full thickness retina may trigger MP. Traction on the macula causes gradual anatomical and functional deterioration proportional to traction forces and their duration of action[3]. Gass[3] has proposed a classification schema for ERM. In this classification translucent membranes not associated with retinal distortion are Grade 0 (CM). The membranes causing disorganized wrinkling of the inner retina are Grade 1 (crinkled CM). Also the opaque membranes causing full-thickness retinal distortion are Grade 2 (MP)[3]. The progression of ERM from CM to MP can be considered as a fibrotic process because of the pathological findings including an increased excetral cellular matrix (ECM) protein deposition and the membrane contraction in which myofibroblasts play a crucial role[4].

The vitreoretinal alterations that characterize these conditions are often subtle and 'difficult-to-distinguish' on the biomicroscopic examination[1]. By providing a high resolution cross-sectional image of the retina and vitreoretinal interface, optical coherence tomography (OCT) can supply additional valuable information not visible on biomicroscopy. Moreover, OCT can provide a more objective means to monitor the natural history and therapeutic response of these conditions[1]. OCT has become a powerful tool in the evaluation of those conditions.

The aim of this study is to evaluate the impact of macular surgery on the functional and anatomic outcomes of the patients in different grades of ERM.

SUBJECTS AND METHODS

We prospectively evaluated 71 eyes of 71 patients with primary isolated ERM diseases between 2012 and 2016. The study was conducted by the Ophthalmology Department at the tertiary referral hospital, after obtaining institutional review board and ethics committee approval (The Ethical Committee of Koru Hospital) and informed consents were taken from all of the participants. The study procedures were performed in accordance with the ethical standards of the Declaration of Helsinki. This study was performed with standard 23-gauge three-port pars plana vitrectomy (TSPPV). Subjects who had any kind of medication, who had smoking and drinking habits, or who had history of systemic and ocular disease were not included in the study. None of the patients had a history of diabetes mellitus, hypertension, connective tissue diseases, malignancies, or other systemic disorder, nor had any undergone prior vitreoretinal surgery ocular trauma, and any corneal pathology.

The complete ophthalmologic examination including best-corrected visual acuity (BCVA), intraocular pressure (IOP) with applanation tonometry, slit-lamp biomicroscopy, and dilated fundus examination was performed before the surgical intervention. BCVA was measured by using the Snellen chart. Snellen values were converted to the logMAR for statistical analysis. The IOP was measured with the Goldmann applanation tonometer. The VMI changes were evaluated by using spectral-domain optical coherence tomography (SD-OCT). A SD-OCT volume scan (20×20 with 49 horizontal sections, ART 15) including en face images and macular mapping image obtained with HRA2 (Heidelberg Retina Angiograph-Optical Coherence Tomography, Heidelberg Engineering, Heidelberg, Germany) of the macula was performed. Follow-up examinations were performed at day 1, week 1, and months 1, 3, 6, and 12 postoperatively. Patients were separated into two groups according to the findings of clinical ophtalmologic examination and OCT. The first group included 44 eyes with tangential traction in inner retina (CM) that called Grade 1 (crinkled CM) according to Gass classification. The second group included 27 eyes with tangential traction in full thickness retina that called Grade 2 (MP) according to Gass classification. Grade 0 CM cases were not operated. The difference between two groups was determined according to the OCT images. All surgeries were performed by the same surgeon (Batman C). The OCTs were examined by a retina specialist (Citirik M) who was masked to the patient and visual acuity outcomes. Retinal architecture and central foveal thickness (CFT) measurement were evaluated with the OCT.

All cases were phakic and had primary isolated ERM. All surgeries were performed under local anesthesia. The 23-gauge Constellation System (Alcon Laboratories, Fort Worth, TX, USA) was used in all cases. The technique including the insertion of a cannula, using a bevelled trocar, following displacement of the conjunctiva to purposefully misalign the conjunctival and scleral incisions with oblique entries was used in every case. Transscleral cannulas were inserted through the pars plana. In cases with mild and moderate cataract, phacoemulsification (PE) and intraocular lens (IOL) implantation was performed before vitrectomy through a 2.2 mm clear corneal incision. Hydrophobic acrylic monofocal IOLs (Acrysof IQ SN60WF; Alcon Laboratories Inc.) were inserted to the capsular bag in all cases and stromal hydration was applied to the corneal wound. After removal of the posterior hyaloid membrane and vitreous traction, all cases underwent core vitrectomy. Macula was stained with Brilliant Blue G (BBG; Dorc International, Zuidland, The Netherlands) in all cases. Valved sclerostomy ports were used and fluid-air exchange was performed prior the staining. After 60s, the dye was aspirated by using the vitrectomy probe. The internal limiting membrane (ILM) was peeled using a pinch technique with Grieshaber DSP 23-G end-gripping forceps (Schaffhausen, Switzerland) and a peel radius of approximately two disc diameters. In case of incomplete staining of the ILM with adherent pre-ILM tissue, a normally stained area of ILM was selected and the peeling was initiated from there. The ILM were hence peeled en bloc, without the need for a second peel. Air-fluid exchange was performed followed by air-sulphur hexaflouride exchange in all cases. Finally, the inferotemporal cannula and infusion line were removed, followed by the repositioning and inspection of the conjunctiva.

Differences between the two groups for retinal thickness parameters and visual acuity were evaluated using independent samples *t*-test analysis. Differences between the pre-op and post-op values in each group for retinal thickness parameters and visual acuity were evaluated using paired test analysis. The level of significance was set at <0.05. All statistical analyses of the study were performed by using SPSS for Windows (SPSS Inc., Chicago, IL, USA) software.

RESULTS

The clinical research was performed on 71 eyes of 71 patients diagnosed as primary isolated ERM diseases. There were 38 females (53.5%) and 33 males (46.5%), with a mean age of (mean±SD) 68.5±8.2y (range 42-89y). Mean follow up period was 14mo (6-26mo). In all cases, no intraoperative complications occurred including vitreous prolapsus, bleeding in sclerotomy site, and contact to lens. Through the follow-up visit, none of the 71 eyes developed endophthalmitis. None of the eyes developed recurrent macular ERM at the final visit.

We divided our series into two subgroups of CM and MP. Table 1 shows the baseline characteristics of all of the subjects in groups A and B. There were no statistically significant differences between 2 groups in terms of age (P=0.2) and female/male ratio (P=0.3).

Table 1 Characteristics of patients in CM group and MP group

Parameters	CM group (*n*=44 eyes)	MP group (*n*=27 eyes)	*P*
Gender (F:M)	24/20	14/13	0.3
Mean age (a)	65.3±10.1 (42-74)	72.5±8.9 (49-89)	0.2
Mean follow-up (mo)	13.8	14.3	0.4
Vitrectomy combined with phacoemulsification	30	19	0.7
Vitrectomy alone	14	8	0.6
Preop. logMAR BCVA (Snellen equivalent)	0.47 (20/60)	1 (20/200)	0.001
Postop. logMAR BCVA (Snellen equivalent)	0.14 (20/28)	0.39 (20/50)	0.001
Preop. CFT	405.79±53.34	469.51±97.82	0.48
Postop. CFT	294.95±43.90	307.70±42.89	0.5
Presence of defects of the photoreceptor IS/OS junction (ellipsoid zone)	5	10	0.0001
Presence of defects of the ELM	4	6	0.003
Postop. 6th month retinal pigment epithelium alterations	5	6	0.018
Postop. 6th month macular edema	2	6	0.0001

CM: Cellophane maculopathy; MP: Macular pucker; BCVA: Best-corrected visual acuity; CFT: Central foveal thickness; ELM: External limiting membrane; IS/OS: Inner and outer segment.

In the CM group, the mean preoperative BCVA was 20/60 (range 20/400-20/28). Mean overall postoperative BCVA was 20/28 (range 20/60-20/20) on sixth months. Statistically significant improvement in BCVA was established at the 6th month visits compared to the preoperative BCVA (*P*=0.001). The mean preoperative IOP was 15 mm Hg (range 10-16 mm Hg). The IOP of all eyes remained in normal limits at 6th month of postoperative period (range 10-20 mm Hg). There were no statistically significant changes in IOP during the postoperative period (*P*>0.05). Thirty eyes of 44 cases (68.2%) underwent 23-gauge vitrectomy combined with PE, and 23-gauge vitrectomy alone was performed in 14 eyes of 44 cases. The CFT was reduced from a preoperative value of 405.79±53.34 μm to a postoperative value of 294.95±43.90 μm (*P*=0.0001; Figure 1). Presence of photoreceptor layer defects analyzed with SD-OCT. In CM group, defects of the photoreceptor inner and outer segment (IS/OS) junction (ellipsoid zone) were seen in 11.3% (5 of 44) of eyes, and defects of external limiting membrane (ELM) in 9% (4 of 44) of eyes. Dilated fundus examination of the 44 eyes at the postoperative 6th month showed retinal pigment epithelium (RPE) alterations in 5 eyes (11.3%) and macular edema in 2 cases (4.5%).

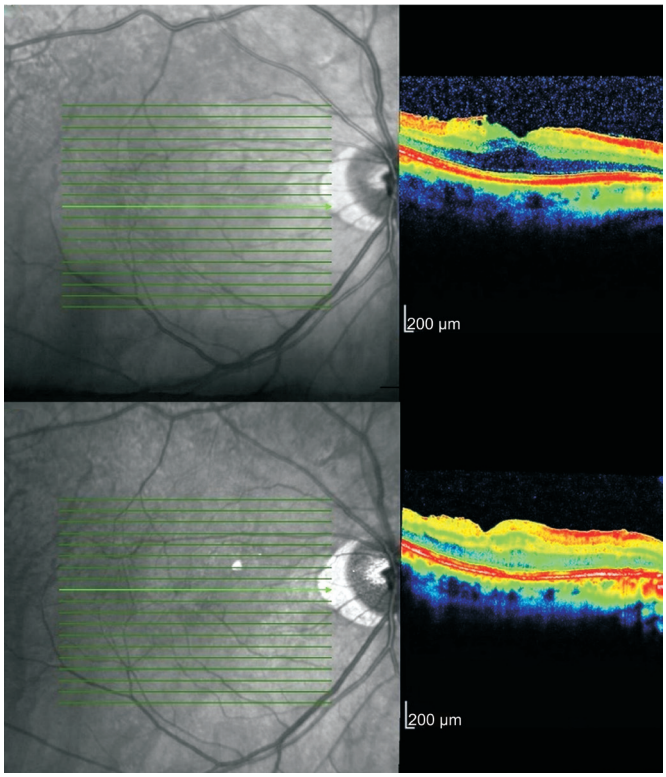

Figure 1 Preoperative and the third month postoperative OCT image in patient with CM.

In the MP group, the mean preoperative BCVA was 20/200 (range 20/800-20/30). Mean overall postoperative BCVA was 20/50 (range 20/200-20/25) on sixth month. Statistically significant improvement in BCVA was established at the 6th month visits compared to the preoperative BCVA (*P*=0.001). The mean preoperative IOP was 14 mm Hg (range 10-18 mm Hg). The IOP of all eyes remained in normal limits at 6th month of postoperative period (range 11-19 mm Hg). There were no statistically significant changes in IOP during the postoperative period (*P*>0.05). Nineteen eyes of 27 cases (70.3%) underwent 23-gauge vitrectomy combined with PE, and 23-gauge vitrectomy alone was performed in 8 eyes of 27 cases. The CFT was reduced from a preoperative value of 469.51±97.82 μm to a postoperative value of 307.70±42.89 μm (*P*=0.0001; Figure 2). Presence of photoreceptor layer defects analyzed with SD-OCT. In MP group, defects of the photoreceptor IS/OS junction (ellipsoid zone) were seen in 37% (10 of 27) of eyes, and defects of ELM in 22.2% (6 of 27) of eyes. Dilated fundus examination of the 27 eyes at the postoperative 6th month showed RPE alterations in 6 eyes (22.2%) and macular edema in 6 cases (22.2%).

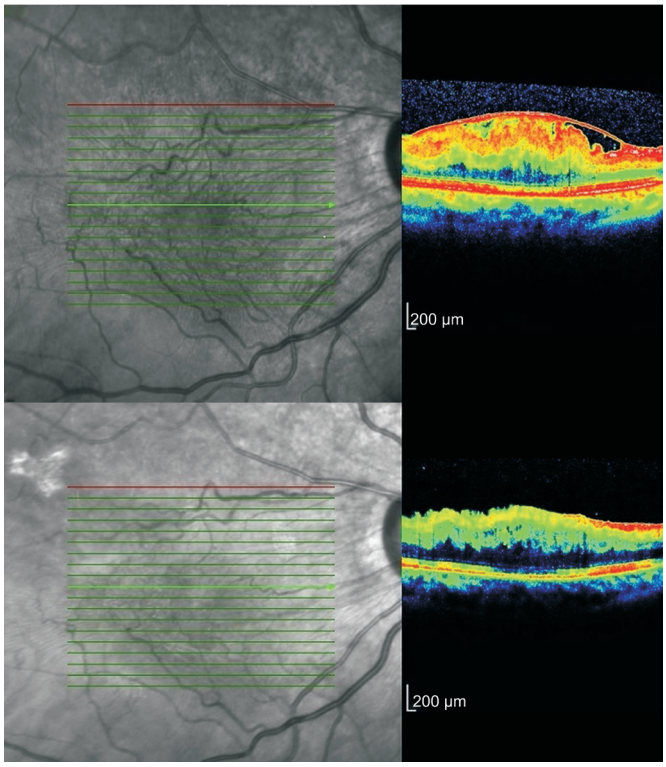

Figure 2 Preoperative and the third month postoperative OCT image in patient with MP.

There was a statistically significant difference between the two groups regarding the improvement in BCVA on 6th month (*P*=0.001). Also, There was a significant difference in the CFT at 6th month between the two groups (*P*=0.001). The mean duration of visual symptoms (that is, visual loss and/or metamorphopsia) was 13mo (±6.28mo) for CM and 22.16mo (±8.08mo) for MP group. There was a significant difference in the duration time of the study groups (*P*=0.001). Comparing the rate of photoreceptor defects in CM and MP at baseline, defects of the IS/OS were significantly more frequent in eyes with MP (37%) than in eyes with CM (11.3%) (*P*=0.0001). Defects of the ELM were seen in 22.2% of eyes with MP and in 9% of eyes with CM (*P*=0.003). Furthermore, the postoperative fundus findings regarding the RPE alterations (*P*=0.018) and macular edema (*P*=0.0001) were significantly higher in the MP group when compared to the CM group.

DISCUSSION

PVD is the result of a complex and inevitable set of events that occurs as the eye ages[1]. When the tractional vitreous pull due to loss of vitreous volume with vitreus liquefaction and weakening of attachments occur asynchronously, an anomalous PVD is developed which can lead to VMI diseases[5]. PVD, commonly associated with idiopathic ERM, may precipitate the formation of ERM by causing defects in the ILM[5]. It is thought that glial cells, which have direct access to the inner surface of the retina through breaks in the ILM, may proliferate or undergo transformation into other cell types to form ERM[6]. The cells in this collagenous layer may proliferate and ultimately contribute to traction at the retinal surface[7]. ERMs may contain myofibroblasts which may exhibit their contractile properties in the clinical feature of prominent retinal striae[4]. According to density and contractility of epiretinal cell proliferation, surface wrinkling CM referring to a thin, glistening membrane with superficial retinal folds and MP is associated with a dense membrane with full thickness retinal distortion[8-9]. CM and MP correspond to different stages of the same pathology[10]. The difference between the various stages has been noted in terms of the type of collagen and the thickness: collagen type VI characterizes cellophane membrane, which is the thinnest; types I and II characterize epiretinal fibrosis, while type IV and laminin are ubiquitous[10]. Kritzenberger *et al*[11] declared that macular reflex fibrils are thin in CM, while fibers are thick in MP.

It has been shown consistently by many studies that degree of outer retinal layer disruption (IS/OS) changes is correlated with visual outcomes in ERM[12]. Gupta *et al*[13] used combined OCT/scanning laser ophthalmoscopy (SLO) to evaluate 44 consecutive eyes with ERM. Of the patients evaluated, 20 out of 44 exhibited multiple foci of contracture within the ERM. They divided ERM into subdivisions as “simple puckers” and “complex puckers”. Complex puckers had a higher rate of macular thickening than simple puckers. In present study, we prospectively evaluated 71 eyes of 71 patients with primary isolated ERM. All the eyes underwent core vitrectomy, removal of the posterior hyaloid membrane, and peeling of ILM. In CM group, defects of the photoreceptor IS/OS junction (ellipsoid zone) were seen in 11.3% of eyes, and defects of ELM in 9% of eyes. In MP group, defects of the photoreceptor inner and outer segment (IS/OS) junction (ellipsoid zone) were seen in 37% of eyes, and defects of ELM in 22.2% of eyes. We found statistically significant differences between two groups in terms of defects of the photoreceptor IS/OS junction (*P*=0.0001) and defects of ELM (*P*=0.003).

Vitrectomy surgery for idiopathic ERM peeling is an effective procedure that has been shown to improve BCVA in 75%-85% of cases[14]. Park *et al*[15] evaluated 44 patients with MP, who underwent PPV and removal of epimacular membrane with/without ILM peeling. BCVA improved in 19 of 24 eyes without ILM peeling and in 20 of 20 eyes with ILM peeling. At the final visit 21% of eyes without ILM peeling showed evidence of recurrent MP or persistent contraction of the ILM and the retinal vessels. None of the eyes with ILM peeling had evidence of a recurrent MP[14]. In our study, ERM and ILM peeling were performed. Recurrent macular ERM were not observed at the final visit. A statistically significant difference was determined between pre- and post-operative BCVA values (*P*=0.001).

Advances in the instrumentation and technique in both vitrectomy and PE now allow combining these procedures for

the management of ERMs accompanied by visually-significant cataracts[16]. ERM is a disease related to aging; some eyes have concurrent idiopathic ERM and cataracts, making vitrectomy surgery more difficult related to blurred media. For this reason, ERM is probably one of the most popular indications in combined surgery[16]. Dugas *et al*[17] reported no statistical differences between the BCVA improvement in combined and consecutive surgeries groups, but BCVA recovery was quicker in the combined surgery group. We preferred performing combined surgery in cases with mild and moderate cataract to gain clear surgical visualization. Posterior chamber IOL were implanted at the end to avoid any interference at peeling surgery. In present study, 68.2% of CM cases and 70.3% of MP cases underwent 23-gauge vitrectomy combined with PE. There was no significant difference between the two groups regarding combined surgery (P=0.7).

CM is the early stage of the ERM formation and MP mostly has more counter contracting force towards the vitreous chamber and is more tightly attached to the vitreous cortex[18]. There are several different definitions about the classification and severity of ERM[19]. The Gass's classification is one of that. Gass[3] proposed a classification for ERM: Grade 0: CM; Grade 1: crinkled CM; Grade 2: MP. Our study composed from patients with Grade 1 and Grade 2. Hwang *et al*[20] described an OCT-based idiopathic ERM classification based on foveal morphology. They subdivided fovea-attached ERM into three groups. Based on this classification; Group 1A is ERM with outer retinal thickening and minimal increase in the inner retinal thickness. Group 1B is ERM with more exaggerated tenting of the outer retinal layer in the foveal area and slightly thickened inner retinal layer. Configuration of inner retinal layer is distorted by centripetal and anteroposterior tractional forces due to ERM. Group 1C is ERM with prominent inner retinal thickening, with inward tenting of the outer retinal reflectivity in the foveal area[19-20]. According to this classification our cases consist of Group 1B and Group 1C.

Many prognostic factors for the visual outcome after ERM surgery have been investigated and duration of the symptoms, preoperative BCVA, and the IS/OS junction are known as the most significant factors[21]. Most of the previous studies have demonstrated good functional results with ERM and ILM peeling[14-18]. There is only limited number of studies mainly focusing on tangential traction in inner retina and full retina thickness[18]. Lee *et al*[18] reported mean CFT of CM and MP groups demonstrated significant reduction at final follow-up. In their study, mean final BCVA reached significant improvement in MP group, but no significant alterations was observed in CM group. We can speculate that better BCVA and less CFT level of CM patients may cause these results. In the current study, 71 cases were enrolled in a prospective observational study with a mean follow up period of 14mo. Cases were classified into 2 major groups, CM and MP. Measuring BCVA in eyes with CM and MP underwent peeling of ILM with BBG staining revealed improvement in postoperative follow up compared to preoperative BCVA. Statistically significant improvement in BCVA was established at the 6th month visits compared to the preoperative BCVA (P=0.01). Furthermore, there was a significant difference between the two groups regarding the change in BCVA on 6th month (P=0.001). Additionally, the postoperative fundus findings regarding RPE alterations and macular edema were significantly higher in MP group when compared to the CM group (P<0.05). Postoperative macular edema observed in just cases underwent 23-gauge vitrectomy combined with PE in both groups. We speculate that this situation may relate with additional cataract extraction surgery.

In conclusion, the present study shows that ERM and ILM peeling surgery can lead to a significant reduction of CFT and visual improvements in idiopathic ERM. Tangential traction in inner retina seen in CM may cause reversible changes of the retinal structure and may gradually recover after the surgery. However, mechanical traction induced by the MP may be irreversible even after successful removal of the ERM. A long-term ERM persistence will cause unrecoverable retinal damage and visual loss. This study also indicated that the CM seems to provide better surgical outcome compared with MP. It is hoped that future prospective clinical studies on this important surgical topic would shed further light and additional clinical perspectives.

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