Published in final edited form as:

Retina. 2016 April ; 36(4): 727–732. doi:10.1097/IAE.0000000000000780.

Assessment of the Significance of Cystic Changes after Epiretinal Membrane Surgery with Internal Limiting Membrane Removal

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Abstract

Purpose—To assess the prevalence and significance of cystic changes after internal limiting membrane (ILM) peeling during epiretinal membrane (ERM) surgery.

Methods—A retrospective review was performed on 64 patients who underwent pars plana vitrectomy (PPV) with membranectomy for idiopathic ERM between January 2010 and January 2012 by a single physician. PPV alone (Group 1, n=32) or in combination with phacoemulsification (Group 2, n=32) were performed. Peeling of the ERM was assisted by triamcinolone, and ILM was peeled up to the vascular arcades with the aid of brilliant blue dye.

Results—In Group 1, BCVA in logMAR (Snellen) improved from 0.53 ± 0.29 (20/68) at baseline to 0.23 ± 0.22 (20/34) at 6-month follow-up ($p < 0.001$). Two cases (6.3%) developed new cystic changes within the inner nuclear layer (INL); however, there was no significant difference in BCVA at 6-months ($p = 0.475$). In Group 2, BCVA improved from 0.41 ± 0.17 (20/51) at baseline to 0.18 ± 0.15 (20/30) at 6-months ($p < 0.001$). Eight cases (25%) developed new INL cystic changes; however, there was no significant difference in BCVA at 6-months ($p = 0.894$).

Conclusions—Development of new INL cystic changes following ERM surgery may be a frequent finding, but in contrast to cystoid macular edema, does not appear to affect visual recovery and should be observed. The combination of PPV with cataract extraction may increase the risk of INL cystic changes.

Keywords

cysts; ERM; ILM; inner nuclear layer; OCT; optical coherence tomography; peel

Introduction

Idiopathic epiretinal membrane (ERM) is a glial proliferation over the internal limiting membrane (ILM) that frequently involves the macular area. ERM is related to loss of visual acuity, micropsia and metamorphopsia. Pars plana vitrectomy (PPV) and membrane peeling is the standard vitreoretinal surgery in cases of symptomatic ERM achieving good visual outcomes in most of the cases.¹ However the functional recovery is frequently incomplete and is directly related to both the baseline visual acuity and the duration of symptoms.² In the last few decades, different staining techniques (triamcinolone, indocyanine green, and brilliant blue) have been reported to facilitate membrane removal.³ Due to these dye-assisted improvements, ILM peeling is now often performed in addition to ERM removal.⁴ However, ILM peeling during ERM surgery is still controversial.³ Arguments against ILM peeling include possible mechanical trauma to the retinal nerve fiber layer⁵ and paracentral scotomas. There are also histopathologic and anatomical secondary changes, although these are usually subclinical.⁶⁻⁷ The arguments in favor of ILM peeling include a possible lower recurrence rate and a better anatomical restoration of the retinal striae.³

Spectral-domain optical coherence tomography (SD-OCT) has enabled physicians to better assess the retinal anatomy and it has become an essential technique in the diagnosis and follow-up of ERMs.⁴ The presence of retinal changes following ERM surgery has been reported by SD-OCT images. The most recent description of a novel postoperative sign is the presence of delayed cystic changes in the inner nuclear layer.⁸ The purpose of the present study is to assess the prevalence and functional significance of cystic changes after ILM peeling in ERM surgery analyzed by SD-OCT.

Methods

This non-randomized, retrospective, consecutive case series was performed on the charts of all patients who underwent vitrectomy surgery by a single surgeon (SC) for idiopathic unilateral ERM between January 2010 and January 2012. Patients with secondary causes of ERM such as diabetic retinopathy, retinal vein occlusion, vitreo-macular traction, high myopia, peripheral retinal tear or uveitis were excluded.

Best-corrected visual acuity (BCVA) measurements were collected at baseline and at 6-month follow-up and expressed as the logarithm of the minimum angle of resolution (logMAR) and Snellen visual acuity.

ERMs were analyzed by SD-OCT (HD-Cirrus; Carl Zeiss Meditec, Dublin, CA). SD-OCT scans were acquired using the macular cube 512 × 128 protocol based on the 6 × 6 mm data cube captured by 512 horizontal A-scans and 128 vertical B-scans. The minimum signal strength cut-off was set at 7/10. OCT images were analyzed at baseline and at 6-month follow-up and the same anatomic landmarks were used as reference points to ensure analysis of the same retinal areas. ERMs were classified into two grades (mild or severe). “Mild” ERM was defined as at most retinal folds and macular thickening with mild alteration of the macular cytoarchitecture. “Severe” ERM was defined as severe changes in the foveal contour with macular thickening and cystic spaces. We evaluated the status (normal,

disruption or cystic degeneration) of the ganglion cell layer (GCL), the inner and outer nuclear layers (INL and ONL), and the outer retina (photoreceptor-RPE complex: PR-RPE). Cystic degeneration was differentiated from cystoid macular edema (CME) through the use of the color-coded quantitative thickness map output of the OCT, since CME would result in increased macular thickness in contrast to cystic degeneration. The foveal central subfield thickness (CST) at baseline and at 6-month follow-up was also analyzed.

Standard 23-gauge (G) PPV either alone or in combination with phacoemulsification and intraocular lens implantation were performed. In combined cases, intraocular lens implantation took place prior to PPV. Patients were segregated into two groups in order to avoid any bias induced by the status of the lens. Group 1 included patients that underwent PPV alone. Group 2 included patients that underwent PPV in combination with phacoemulsification. Peeling of the ERM was assisted by 10 mg/mL intravitreal triamcinolone (Bristol-Myers Squibb Company, Canada). ILM was peeled up to the vascular arcades with the aid of brilliant blue dye 0.25%. Air tamponade was used in all cases at the end of the surgical procedure to provide internal tamponade of the non-sutured incisions. The patients were instructed to maintain a prone position for the day of surgery and the first postoperative day.

Results

Sixty-four patients with a mean age of 72.7 years [range: 59–90] were included. Thirty-two patients underwent PPV (Group 1, mean age 72.1 years, range: 59–86). Thirty-two patients underwent PPV in combination with phacoemulsification (Group 2, mean age 73.6 years, range: 61–90). In one case, there was a posterior capsule rupture during the phacoemulsification and the intraocular lens was placed in the sulcus without further complications.

Group 1

Functional analysis—Overall, BCVA in logMAR (Snellen) significantly improved from 0.53 ± 0.29 [range 0.2 to 1.3] (Snellen 20/68; range 20/30 to 20/400) at baseline to 0.23 ± 0.22 [range 0 to 0.7] (Snellen 20/34; range 20/20 to 20/100) at 6-month follow-up ($p < 0.001$, two-tailed t-test).

Tomographic morphologic analysis—At baseline, 13 eyes (40.6 %) showed mild ERM and 19 eyes (59.4 %) showed severe ERM. Baseline SD-OCT images showed a GCL that was graded as normal in 11 cases (34.4 %), disrupted in 18 cases (56.3 %) and cystic degeneration in 3 cases (9.4 %). The INL was normal in 10 cases (31.3 %), disrupted in 9 cases (28.1 %) and showed cystic degeneration in 13 cases (40.6 %). The ONL was normal in 16 cases (50 %), disrupted in 12 cases (37.5 %) and showed cystic degeneration in 4 cases (12.5 %). The PR-RPE layer was normal in 25 cases (78.1 %), disrupted in 7 cases (21.9 %) and no case showed cystic degeneration. All the baseline qualitative tomographic characteristics are summarized in Table 1.

At 6-month follow-up, SD-OCT images showed a GCL that was graded as normal in 27 cases (84.4 %), disrupted in 4 cases (12.5 %) and showed cystic degeneration in 1 case

(3.1 %). The INL was normal in 18 cases (56.3 %), disrupted in 4 cases (12.5 %) and showed cystic degeneration in 10 cases (31.3 %). The ONL was normal in 24 cases (75 %), disrupted in 5 cases (15.6 %) and showed cystic degeneration in 3 cases (9.4 %). The PR-RPE layer was normal in 21 cases (65.6 %), disrupted in 9 cases (28.1 %) and showed cystic degeneration in 2 cases (6.3 %). All the qualitative characteristics at 6-month follow-up are summarized in Table 1.

All cases with cystic changes in the GCL and ONL at 6-month follow-up also showed previous evidence of such changes at baseline SD-OCT. The incidence at baseline of cystic changes in the INL was 40.6 % and decreased to 31.3 % at 6-month follow-up. However, 2 cases (6.3 %) developed new cystic changes within the INL that were not present at baseline and therefore may be related to the surgical technique employed (Figure 1). A specific sub-analysis of the BCVA between these patients with new cystic changes and those without them evidenced no statistically significant differences neither at baseline ($p = 0.605$, two-tailed t-test) nor at 6-month follow-up ($p = 0.475$, two-tailed t-test).

Tomographic morphometric analysis—Overall, CST (microns) significantly improved ($p < 0.001$, two-tailed t-test) from 494.5 ± 83.6 [range 301 to 689] at baseline to 395.3 ± 75.0 [range 194 to 560] at 6-month follow-up. At baseline, CST values were significantly correlated with the classification of ERM based on OCT qualitative appearance ($p = 0.001$, two-tailed Pearson's correlation test).

Group 2

Functional analysis—Overall, BCVA in logMAR (Snellen) significantly improved from 0.41 ± 0.17 (range 0.1 to 0.9) (Snellen 20/51; range 20/25 to 20/150) at baseline to 0.18 ± 0.15 (range 0 to 0.5) (Snellen 20/30; range 20/20 to 20/60) at 6-month follow-up ($p < 0.001$, two-tailed t-test).

Morphometric analysis—At baseline, 18 eyes (56.2 %) showed mild ERM and 14 eyes (43.8 %) showed severe ERM. Baseline SD-OCT images showed a GCL that was graded as normal in 16 cases (50 %), disrupted in 15 cases (46.9 %) and showed cystic degeneration in 1 case (3.1 %). The INL was normal in 17 cases (53.1 %), disrupted in 8 cases (25 %) and showed cystic degeneration in 7 cases (21.9 %). The ONL was normal in 26 cases (81.3 %), disrupted in 4 cases (12.5 %) and showed cystic degeneration in 2 cases (6.3 %). The PR-RPE layer was normal in all cases. All the qualitative tomographic characteristics at baseline are summarized in Table 1.

At 6-month follow-up, SD-OCT images showed a GCL that was graded as normal in 31 cases (96.9 %), disrupted in 1 case (3.2 %) and no case showed cystic degeneration. The INL was normal in 19 cases (59.4 %), disrupted in none of the cases and cystic degeneration was observed in 13 cases (40.6 %). The ONL was normal in 30 cases (93.8 %), disrupted in none of the cases and showed cystic degeneration in 2 cases (6.3 %); the PR-RPE layer was normal in 27 cases (84.4 %), disrupted in one case (3.1 %) and showed cystic changes in 4 cases (12.5 %). All the qualitative tomographic characteristics at 6-month follow-up are summarized in Table 1.

On qualitative analysis, all cases with cystic changes in the GCL and ONL on 6-month follow-up also showed evidence of these changes on baseline SD-OCT (example in Figure 2). The incidence at baseline of cystic changes in the INL was 21.9 % and increased to 40.6 % at 6-month follow-up. However, 8 cases (25 %) developed new cystic changes within the INL that were not previously present at baseline and could therefore be related to the surgical technique employed (example in Figure 3), whereas other cases remained stable without development of cysts (example in Figure 4). A specific sub-analysis of the BCVA between these patients with new cystic changes and those without them evidenced no significant differences neither at baseline ($p = 0.149$, two-tailed t-test) nor at 6-month follow-up ($p = 0.894$, two-tailed t-test).

Tomographic morphometric analysis—Overall, CST (microns) significantly improved from 444.4 ± 98.7 [range 267 to 595] at baseline to 379.6 ± 57.3 [range 241 to 462] at 6-month follow-up ($p = 0.002$, two-tailed t-test). At baseline, CST values were significantly correlated with the classification of ERM based on OCT qualitative appearance ($p < 0.001$, two-tailed Pearson's correlation test).

Discussion

Visual outcomes following ERM surgery have been previously correlated with baseline BCVA, normal ellipsoid line and the recovery of the foveal contour.² Although there is growing evidence that ILM peeling may decrease the rate of recurrence compared with ERM peeling alone,³ the additional benefit of ILM peeling has not been proven and remains controversial.³

Different postoperative anatomic findings have been described after ILM peeling during ERM surgery. Differentiating between three common findings is beneficial in allowing prediction of which will typically remain subclinical versus affecting visual recovery. The first common finding is temporary swelling of the arcuate nerve fiber layer that may occur within 10 days after surgery and appears as three to five dark striae originating from the optic nerve head, best visualized with infrared and autofluorescence retinal imaging. This temporary swelling does not appear to preclude functional visual recovery.⁶ In contrast, CME may also occur and frequently affects postoperative visual improvement.⁹ CME is characterized on OCT by the presence of multiple round cystic spaces (circular and variable in size in OCT cross-sections) and can be found in any retinal layer; however, it is predominantly located in the outer retinal layers. In addition, CME induces an increase in retinal thickness, readily viewable on OCT color thickness maps. Recently, the presence of delayed, new-onset INL cystic changes following ERM surgery with ILM removal has been reported as a novel SD-OCT finding.⁸ It is characterized by more uniformly-sized, ellipsoidal cystic spaces, localized only in the inner nuclear layer in OCT cross-sections, that do not induce changes in the retinal thickness or influence the postoperative visual recovery.

The present study analyzes the functional influence of these INL cysts following ERM surgery with ILM removal. We differentiated cases presenting with cystic changes at baseline that were persistent during the follow-up from those who have developed new cystic changes within the INL. We found no significant differences in visual outcomes of

patients with these cystic changes and those without during our follow-up period. In addition, no significant differences in the morphometric characteristics (CST) of patients with cystic changes in the INL compared with those without. Our study is limited, however, by its uncontrolled, retrospective and nonrandomized nature.

INL cysts may arise from changes in Mueller cells, bipolar cells or horizontal cells that reside in this layer. It has been hypothesized that a response to late-onset Muller cell death or an alteration on the osmotic gradient across the retinal surface may cause these tomographic changes.⁸ They seem less likely to be related to stain or light toxicity since brilliant blue dye and the same intraoperative light intensity was uniformly used in all patients in our consecutive series, but only a subset of patients developed new INL cystic changes. Additionally, as pointed out by Sigler et al., although stain is generally applied diffusely over the entire macular area, cystic changes tend to be focal.⁸ The casual relationship between ILM peeling and INL cysts is unclear since these findings have not previously been reported in any other entities employing ILM peeling, and this was observed in only 10 out of 64 (15.6 %) of cases in the present study.

In summary, our results suggest that cystic changes in the INL do not appear to affect functional visual outcomes or significantly alter retinal thickness. The diagnosis of this new tomographic sign and its differentiation with cystoid macular edema must be assessed in the postoperative follow-up of patients following ERM surgery to avoid unnecessary treatment. Further studies are warranted in order to clarify the etiology of these histoarchitectural retinal changes and their long-term functional impact.

Acknowledgments

This publication was supported in part by an unrestricted award to the Harkness Eye Institute, Department of Ophthalmology, Columbia University College of Physicians and Surgeons from Research to Prevent Blindness and Career Development Awards from K08 Grant (QVH, 1 K08 EY023595, National Eye Institute, NIH), the Louis V. Gerstner Jr. Scholars Program (QVH), Research to Prevent Blindness (QVH), and the AR and JR Peacock Trusts (QVH).

References

1. Zhao F, Gandorfer A, Haritoglou C, et al. Epiretinal cell proliferation in macular pucker and vitreomacular traction syndrome: analysis of flat-mounted internal limiting membrane specimens. *Retina*. 2013; 33:77–88. [PubMed: 22914684]
2. Falkner-Radler CI, Glittenberg C, Hagen S, et al. Spectral-domain optical coherence tomography for monitoring epiretinal membrane surgery. *Ophthalmology*. 2010; 117:798–805. [PubMed: 20045567]
3. Chang S. Controversies regarding internal limiting membrane peeling in idiopathic epiretinal membrane and macular hole. *Retina*. 2012; 32:S200–3. [PubMed: 22929321]
4. Rispoli M, Le Rouic JF, Lesnoni G, et al. Retinal surface en face optical coherence tomography: a new imaging approach in epiretinal membrane surgery. *Retina*. 2012; 32:2070–6. [PubMed: 22842490]
5. Miura M, Elsner AE, Osako M, et al. Dissociated optic nerve fiber layer appearance after internal limiting membrane peeling for idiopathic macular hole. *Retina*. 2003; 23:561–3. [PubMed: 12972776]
6. Clark A, Balducci N, Pichi F, et al. Swelling of the arcuate nerve fiber layer after internal limiting membrane peeling. *Retina*. 2012; 32:1608–13. [PubMed: 22495325]

7. Tadayoni R, Paques M, Massin P, et al. Dissociated optic nerve fiber layer appearance of the fundus after idiopathic epiretinal membrane removal. *Ophthalmology*. 2001; 108:2279–83. [PubMed: 11733271]
8. Sigler EJ, Randolph JC, Charles S. Delayed onset inner nuclear layer cystic changes following internal limiting membrane removal for epimacular membrane. *Graefes Arch Clin Exp Ophthalmol*. 2013; 251:1679–85. [PubMed: 23306785]
9. Mylonas G, Sacu S, Deák G, et al. Macular edema following cataract surgery in eyes with previous 23-gauge vitrectomy and peeling of the internal limiting membrane. *Am J Ophthalmol*. 2013; 155:253–259. [PubMed: 23036567]

Summary Statement

Cystic changes following epiretinal membrane surgery and inner limiting membrane peeling are frequently encountered. The combination of pars plana vitrectomy with cataract extraction may increase the risk of cystic changes in the inner retina. We evaluate the prevalence of these histoarchitectural retinal changes and their functional impact.

Figure 1.

Color photograph (**A**) at baseline depicts vascular tortuosity with cellophane maculopathy. Best-corrected visual acuity (BCVA) was 20/80. Spectral-domain optical coherence tomography scan (SD-OCT, **B**) at baseline shows an advanced epiretinal membrane. Color photograph (**C**) and SD-OCT (**D**) taken 6 months after pars plana vitrectomy with removal of epiretinal membrane and internal limiting membrane shows complete resolution of the macular pucker. SD-OCT (**D**) also demonstrates a preserved foveal contour with slightly cystic changes in the inner nuclear layer (arrow). Final BCVA was 20/20.

Figure 2.

Spectral-domain optical coherence tomography scan (SD-OCT) at baseline (A) shows a mild epiretinal membrane. Best-correct visual acuity (BCVA) was 20/40. SD-OCT at 6 months (B) and 9 months (C) after pars plana vitrectomy with removal of epiretinal membrane and internal limiting membrane peeling combined with phacoemulsification with intraocular lens implant showed progressive cystic changes in the inner nuclear layer (arrows) with partial normalization of the foveal contour. Final BCVA was 20/20.

Figure 3. Spectral-domain optical coherence tomography scan (SD-OCT) at baseline (**A**) shows a severe epiretinal membrane. Best-corrected visual acuity (BCVA) at baseline was 20/80. SD-OCT taken 6 months (**B**) after pars plana vitrectomy with removal of epiretinal membrane and internal limiting membrane combined with phacoemulsification with intraocular lens implant showed improvement in foveal contour with cystic changes in the inner nuclear layer. Final BCVA was 20/30.

Figure 4.

Spectral-domain optical coherence tomography scan (SD-OCT) at baseline (**A**) shows a mild epiretinal membrane with a foveal cyst in the outer nuclear layer. Best-corrected visual acuity (BCVA) at baseline was 20/30. SD-OCT taken 6 months (**B**) after pars plana vitrectomy with removal of epiretinal membrane and internal limiting membrane combined with phacoemulsification with intraocular lens implant showed normalization of the foveal contour with no cystic changes. Final BCVA was 20/20.

Summary of the morphometric analysis by spectral-domain optical coherence tomography at baseline and 6 months after epiretinal membrane removal (M6). Data are displayed as total number of cases and as a percentage of those within the group sample (within parentheses).

Table 1

		Ganglion Cell Layer			Inner Nuclear Layer			Outer Nuclear Layer			Photoreceptors-RPE Layer		
		Normal	Disrupted	Cystic Degeneration	Normal	Disrupted	Cystic Degeneration	Normal	Disrupted	Cystic Degeneration	Normal	Disrupted	Cystic Degeneration
Group 1 (PPV)	Baseline	11 (34 %)	18 (56 %)	3 (9 %)	10 (31 %)	9 (28 %)	13 (41 %)	16 (50 %)	12 (38 %)	4 (13 %)	25 (78 %)	7 (22 %)	0
	M6	27 (84 %)	4 (13 %)	1 (3 %)	18 (56 %)	4 (13 %)	10 (31 %)	24 (75 %)	5 (16 %)	3 (9%)	21 (66 %)	9 (28 %)	2 (6 %)
Group 2 (PPV+Ph)	Baseline	16 (50 %)	15 (47 %)	1 (3 %)	17 (53 %)	8 (25 %)	7 (22 %)	26 (81 %)	4 (13 %)	2 (6%)	32 (100 %)	0	0
	M6	31 (97 %)	1 (3 %)	0	19 (59 %)	0	13 (41 %)	30 (94 %)	0	2 (6 %)	27 (84 %)	1 (3 %)	4 (13 %)

PPV = pars plana vitrectomy; Ph = phacoemulsification