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Early Foveal Pit Contour Recovery after Idiopathic Epiretinal Membrane Surgery as a Long-term Postoperative Visual Prognosis Factor

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Purpose: We investigated correlations between early foveal contour recovery after idiopathic epiretinal membrane (iERM) surgery and visual improvement.

Methods: We retrospectively reviewed the medical records of patients who had iERM surgery between June 2015 and June 2017. The patients were sorted into two groups (recovery and non-recovery groups) according to foveal changes within 1 month of surgery. We compared the best-corrected visual acuity (logarithm of the minimum angle of resolution) and central macular thickness (CMT) and their changes from the pre-operative state at 1, 2, 3, 6, and 12 months after surgery for the two groups. The pre-operative optical coherence tomography and fluorescein angiography features were also compared.

Results: A total of 43 patients were enrolled. There were 16 patients in the recovery group, and 27 patients in the non-recovery group. There was greater visual improvement in the recovery group at all time points compared to that in the non-recovery group. The differences were statistically significant at post-operative 2, 6, and 12 months ($p = 0.036$, $p = 0.023$, and $p = 0.008$, respectively). In addition, there were a significantly larger CMT reductions in the recovery group at all time points compared to that in the non-recovery group ($p = 0.006$, $p = 0.010$, $p < 0.001$, $p = 0.010$, and $p = 0.015$, respectively). Pre-operative inner retinal thickening on optical coherence tomography was significantly associated with foveal contour recovery.

Conclusions: During one year of follow-up, better visual improvement was observed in patients with early foveal pit contour recovery after iERM surgery.

Keywords: Epiretinal membrane; Fovea; Visual prognosis; Vitrectomy

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Introduction

Idiopathic epiretinal membrane (iERM) is a disease in which the fibrocellular proliferative membrane on the inner retinal surface causes symptoms such as visual loss and metamorphopsia [1,2]. Vitrectomy and epiretinal membrane (ERM) removal, with or without internal limiting membrane (ILM) peeling, are treatment options for iERM [3,4]. In approximately 70-90% of patients, surgery is successful, and the visual acuity (VA) improves. However, some patients show no improvement, or even a decrease in their post-operative VA [5-7]. Many studies have therefore investigated various factors that may predict the visual prognoses of patients after ERM surgery. Some of these factors include pre-operative VA, symptom duration, and the pre-operative status of the retinal layer [7-15].

Spectral domain optical coherence tomography (SD-OCT), which can detect minute retinal layer abnormalities, is a useful tool for evaluation of the ERM. There are several factors that can be evaluated using OCT that serve as good prognostic indicators of vision or metamorphopsia after ERM surgery [1,2,7-11,16-18]. These factors include central retinal thickness, disruption of the inner segment outer segment (IS/OS) junction of the photoreceptors, inner nuclear layer (INL) thickening, and some calculated indices based on the thickness or length of the inner retinal layers. In addition, post-operative restoration of the foveal inner retinal configuration has been reported as an indicator of the 1-year visual prognosis [19]. However, for analyses of these factors, time domain OCT is not appropriate, so SD-OCT is necessary for the determination of fine changes in the retinal layers and in the calculation of indices.

Among the patients who had ERM surgery, some showed definite normalization of the foveal pit contour during the early phase after surgery. Such recovery can be easily identified using OCT. We therefore determined whether post-operative foveal contour recovery was a prognostic factor in the visual prognosis after ERM surgery.

Materials and Methods

We reviewed the medical records of patients who underwent iERM surgery (vitrectomy and ERM removal, ILM peeling) between June 2015 and June 2017 at Kosin University Gos-

pel Hospital. Patients with diabetic retinopathy, retina vessel occlusion, uveitis or trauma history, a retinal break, or a history of vitrectomy surgery, all of which can cause secondary ERM, were excluded. Patients were also excluded if they were followed up for < 1 year, had ERM accompanying a macular hole (partial or full thickness), had a severe cataract (including nuclear sclerosis grade > 3, with severe cortical or posterior subcapsular opacity) before the surgery, or had complications of primary vitrectomy, including retinal detachment or vitreous hemorrhage.

Surgery was performed by two retina specialists (S.J.L, K.Y.N) using a 23-gauge vitrectomy (Accurus[®], Alcon Laboratories, Fort Worth, TX, USA). All patients underwent complete ERM removal with ILM peeling using indocyanine green (ICG) staining. The concentration of the ICG dye solution was 0.2% (2.0 mg/mL). At 10-15 seconds after injection, the ICG solution was removed. All cataract surgeries were performed during the iERM surgery in patients with phakic eyes. We used SD-OCT (Spectralis; Heidelberg Engineering, Heidelberg, Germany) for the pre- and post-operative examinations.

The patients were sorted into two groups (pit recovery and non-recovery groups) according to foveal changes within 1 month after ERM surgery (Fig. 1). Foveal pit contour recovery was defined as: 1) the pit notching to the level of the INL or more, in addition to 2) exposure of the central outer nuclear layer (ONL) to the retina surface within 1 month after surgery. Only patients who met both conditions were considered to exhibit recovery of the foveal contour. Despite small pit notching after surgery, if notching did not reach the level of the INL, or if the ONL was not exposed to the surface of the retina, the patient was classified into the non-recovery group (Fig. 2).

We compared the post-operative best-corrected visual acuity (BCVA; logarithm of the minimum angle of resolution [logMAR]) and central macular thickness (CMT) measurements between the two groups using OCT at 1, 2, 3, 6, and 12 months after surgery. We also compared the pre- to post-operative changes in BCVA (logMAR) and CMT at 1, 2, 3, 6, and 12 months after surgery between the two groups. All of these comparisons were only performed in pseudophakic eyes to minimize the lens effect on VA changes.

In addition, the pre-operative OCT features, including intraretinal cystic lesions, retinal folds, inner retinal thickening, vitreomacular traction, and IS/OS disruption, were com-

Figure 1. Group classifications: recovery group (A, B) and non-recovery group (C, D). Optical coherence tomography shows the pre-operative state (A, C) and the status at 1 month after epiretinal membrane surgery (B, D).

Figure 2. Definition of foveal pit contour recovery after epiretinal membrane surgery. (A, B) We assign patients showing a pit notched to the level of the inner nuclear layer (INL) or more and exposure of the central outer nuclear layer (ONL) to the retina surface to the recovery group. If notching did not reach the level of the INL (C), or if the ONL is not exposed to the surface of the retina (D), the patient is classified into the non-recovery group.

pared between the two groups. Cases in which the central ONL was not exposed to the retina surface were defined as

inner retina thickening. In addition, we determined leaking on fluorescein angiography (FA).

We used SPSS statistical software for Windows, version 20.0 (IBM Corp., Armonk, NY, USA) for all statistical analyses. The Mann-Whitney *U* test was used to assess the VA and CMT measurements and comparisons of their changes at each follow-up exam. Changes in VA and CMT over time in each group were analyzed by a repeated measures analysis of variance. The chi-squared test was used to analyze the baseline characteristics, and logistic regression analysis was used to evaluate factors associated with foveal contour recovery.

Results

A total of 43 eyes from 43 patients were enrolled. There were 16 patients in the recovery group, and 27 in the non-recovery group. There were two cases (7.4%) with foveal pit contour recovery at 3 months after ERM surgery among the patients who were originally placed in the non-recovery group. The baseline patient characteristics are shown in Table 1. There were no significant differences between the two groups.

The BCVA and CMT values after ERM surgery were compared between the recovery and non-recovery groups. The BCVA was better in the recovery group than in the non-recovery group at 1 year after surgery, but the difference was not statistically significant. During the follow-up period, the BCVA was significantly improved in both groups ($p = 0.001$ in both groups) and there was no significant difference

($p = 0.996$). The CMT was significantly lower in the recovery group at all time periods ($p < 0.001$). The CMT of both groups showed a significant reduction over time ($p < 0.001$ in both groups), and the degree of reduction was significantly higher in the recovery group ($p < 0.001$) (Table 2).

The VA improved in 79.1% (34/43 eyes) of patients by 12 months after ERM surgery. The VA change in BCVA after ERM surgery was better in the recovery group at all follow-up points when compared with the non-recovery group. These differences were statistically significant at 2, 6, and

Table 1. Preoperative baseline characteristics

Characteristic	Recovery group (n = 16)	Non-recovery group (n = 27)	p-value
Age (years)	67.7 ± 6.4	66.0 ± 8.2	0.421*
Sex (M:F)	5:11	7:20	0.737†
DM	8 (43.8)	5 (18.5)	0.092†
HTN	7 (43.8)	10 (37.0)	0.752†
Pseudophakia	3 (18.8)	8 (29.7)	0.494†
Preoperative VA (logMAR)	0.39 ± 0.18	0.29 ± 0.18	0.103*
Preoperative CMT (μm)	422.9 ± 47.1	457.9 ± 90.4	0.149*

Values are presented as mean ± standard deviation or number (%). DM = diabetes mellitus; HTN = hypertension; VA = visual acuity; logMAR = logarithm of the minimum angle of resolution; CMT = central macular thickness.

*Mann-Whitney *U* test; †chi-square test.

Table 2. Best-corrected visual acuity (logMAR) and central macular thickness after ERM surgery

Group	Time after ERM surgery						p-value*
	Preoperative	1 months	2 months	3 months	6 months	12 months	
BCVA (logMAR)							
Recovery group	0.39 ± 0.18	0.28 ± 0.15	0.20 ± 0.15	0.19 ± 0.14	0.16 ± 0.14	0.13 ± 0.14	0.996
Non-recovery group	0.29 ± 0.18	0.27 ± 0.19	0.24 ± 0.16	0.20 ± 0.16	0.17 ± 0.15	0.17 ± 0.15	
p-value†	0.103	0.817	0.408	0.979	0.928	0.257	
CMT (μm)							
Recovery group	422.9 ± 47.1	341.8 ± 68.1	321.3 ± 72.2	300.6 ± 56.4	300.8 ± 55.1	287.4 ± 57.7	<0.001†
Non-recovery group	457.9 ± 90.4	431.5 ± 56.5	413.9 ± 53.9	401.5 ± 43.6	393.7 ± 49.6	383.7 ± 52.0	
p-value†	0.149	<0.001†	<0.001†	<0.001†	<0.001†	<0.001†	

Values are presented as mean ± standard deviation.

BCVA = best-corrected; logMAR = logarithm of the minimum angle of resolution; ERM = epiretinal membrane; CMT = central macular thickness.

*Repeated measures analysis of variance; †Mann-Whitney *U* test; ‡significant differences.

12 months after ERM surgery ($p = 0.036$, $p = 0.023$, and $p = 0.008$, respectively). During the follow-up period, the BCVA change was significantly increased in both groups ($p < 0.001$ in the recovery group and $p = 0.002$ in the non-recovery group), and the degree of change was significantly higher in the recovery group ($p = 0.031$). The reduction in CMT was significantly larger in the recovery group at all time periods ($p = 0.006$, $p = 0.010$, $p < 0.001$, $p = 0.010$, and $p = 0.015$).

In both groups, the reduction in CMT showed a significant increase over time ($p = 0.008$ in the recovery group and $p < 0.001$ in the non-recovery group), and the degree of reduction was significantly higher in the recovery group ($p = 0.028$; Table 3, Fig. 3).

Cataract surgeries were performed at similar rates in both groups. However, VA can be affected by the pre-operative cataract grade, cataract, and ERM surgeries. We therefore

Table 3. Change of VA (logMAR) and central macular thickness from baseline after ERM surgery

Group	Time after ERM surgery					<i>p</i> -value [*]	
	1 months	2 months	3 months	6 months	12 months		
Δ VA (logMAR)							
Recovery group	-0.11 ± 0.22	-0.19 ± 0.22	-0.20 ± 0.19	-0.23 ± 0.18	-0.27 ± 0.21	<0.001 [†]	0.031 [‡]
Non-recovery group	-0.02 ± 0.15	-0.06 ± 0.19	-0.10 ± 0.17	-0.12 ± 0.15	-0.12 ± 0.14	0.002 [‡]	
<i>p</i> -value [†]	0.133	0.036 [‡]	0.093	0.023 [‡]	0.008 [‡]		
Δ CMT (μm)							
Recovery group	-81.1 ± 66.1	-101.7 ± 71.0	-122.4 ± 63.9	-122.2 ± 63.3	-135.6 ± 66.6	0.008 [‡]	0.028 [‡]
Non-recovery group	-36.4 ± 61.3	-54.1 ± 77.3	-66.4 ± 76.7	-74.2 ± 75.7	-84.2 ± 80.4	<0.001 [‡]	
<i>p</i> -value [†]	0.006 [‡]	0.010 [‡]	0.000 [‡]	0.010 [‡]	0.015 [‡]		

Values are presented as mean $\pm$ standard deviation.

VA = visual acuity; logMAR = logarithm of the minimum angle of resolution; ERM = epiretinal membrane; CMT = central macular thickness.

*Repeated measure analysis of variance; [†]Mann-Whitney U test; [‡]significant differences.

Figure 3. The visual acuity (VA) and central macular thickness (CMT) changes from pre- to post-operative times after epiretinal membrane surgery. (A) The post-operative improvement in VA is better in the recovery group at all follow-up periods than it is in the non-recovery group, with significant differences at 2, 6, and 12 months. (B) The reduction in CMT is significantly larger in the recovery group during the first post-operative 12 months than it is in the non-recovery group. m = month(s). * $p < 0.05$, error bars denote the mean standard deviation.

also analyzed the VA changes in pseudophakic eyes. There were three and eight pseudophakic eyes in the recovery and non-recovery groups, respectively. The VA improvement was better in the recovery group at all times. The differences were significant at 1, 2, 6, and 12 months after ERM surgery ($p = 0.038$, $p = 0.041$, $p = 0.040$, and $p = 0.040$, respectively).

We also analyzed the association between various factors, including baseline characteristics, pre-operative OCT, FA features, and foveal pit contour recovery. The preoperative OCT and FA features in both groups are described in Table 4.

Table 4. Association between OCT, FA features and foveal contour recovery

Various feature	Recovery group (n = 16)	Non-recovery group (n = 27)
Cystic lesions	8 (50.0)	3 (11.1)
Retinal folds	10 (62.5)	23 (85.2)
Inner retina thickening	1 (6.3)	17 (77.3)
VMT	2 (12.5)	2 (7.4)
IS/OS disruption	3 (18.8)	0
Leaking on FA	8 (50.0)	11 (40.7)

OCT = optical coherence tomography; FA = fluorescein angiography; VMT = vitreomacular traction; IS/OS = inner segment/outer segment.

Intraretinal cystic lesions, inner retinal thickening on OCT, and pre-operative BCVA were significantly associated with foveal contour recovery by univariate logistic regression analysis ($p = 0.009$, $p = 0.003$, and $p = 0.009$, respectively). That is, the rate of cases with cystic lesions was significantly higher in recovery group, on the other hand, the rate of inner retinal thickening was higher in non-recovery group. Pre-operative BCVA was significantly better in recovery group. However, by multivariate logistic regression analysis, only inner retinal thickening was significantly associated with foveal contour recovery ($p = 0.011$), and it was lower for the recovery group than the non-recovery group. Logistic regression analysis was not appropriate for IS/OS disruption because there was no IS/OS disruption in the non-recovery group, so IS/OS disruption was not included in this analysis (Table 5).

Discussion

There have been many reports regarding visual prognostic factors after iERM surgery. Pre-operative VA and symptom duration are well-known factors associated with the visual prognosis [7,20,21].

SD-OCT has been used in the diagnosis of ERM. Various

Table 5. Association between various factors including baseline characteristics, OCT, FA features and foveal contour recovery by logistic regression analysis

Factor	Univariate analyses			Multivariate analyses		
	B	OR (95% confidence interval)	p -value*	B	OR (95% confidence interval)	p -value†
Age	-0.031	0.970 (0.892, 1.054)	0.468			
VMT	0.58	1.786 (0.226, 14.099)	0.582			
Cystic lesion	2.079	8.000 (1.699, 37.672)	0.009‡	1.669	5.305 (0.806, 34.926)	0.083
Retinal fold	-1.238	0.290 (0.067, 1.257)	0.290			
IS/OS disruption [§]	21.934	3.3 x exp (9)	0.999			
Intraretinal thickening	-3.239	0.039 (0.004, 0.343)	0.003‡	-3.785	0.023 (0.001, 0.420)	0.011‡
FA leakage	0.167	1.182 (0.333, 4.195)	0.796			
Preop BCVA	-2.872	0.057 (0.002, 1.986)	0.009‡	-4.227	0.015 (0.000, 2.054)	0.094
Preop CMT	0.01	1.010 (0.999, 1.021)	0.084			

OCT = optical coherence tomography; FA = fluorescein angiography; OR = odds ratio; VMT = vitreomacular traction; IS/OS = inner segment/outer segment junction of the photoreceptors; BCVA = best-corrected visual acuity; CMT = central macular thickness.

*Univariate logistic regression analysis; †multivariate logistic regression analysis; ‡significant differences; §IS/OS disruption was not included in the logistic regression analysis because there was no IS/OS disruption case in the non-recovery group, so logistic regression analysis was not appropriate.

OCT features were studied as post-operative visual prognostic factors, and several studies have reported that photoreceptor disruption, as indicated by IS/OS disruption, is associated with a poor final VA [7-11]. Scheerlinck et al. [11] explained the mechanism of inner retina damage-like IS/OS disruption in the ERM, which is an inner retina disease. The traction forces on the inner retina can reach the photoreceptor layer via Müller cells, and vision is affected by anatomical damage to both the inner and outer retina [11].

Several features of the inner retina have been reported as prognostic factors in vision and metamorphopsia after ERM surgery. Okamoto et al. [1] reported that pre-operative INL thickness can predict post-operative metamorphopsia. Cho et al. [2] studied the correlation between the inner retinal irregularity index and post-operative visual outcomes. They defined this index as the length of the inferior border of the inner plexiform layer (IPL) by the length of the retinal pigment epithelium (measured within 3.0 mm from the Early Treatment Diabetic Retinopathy Study inner circle). This group used ImageJ software to measure the length. The index was found to be a good post-operative visual prognostic factor [2]. Yang et al. [19] measured each layer of the retina manually. The inner retinal layer thickness was defined as the sum of the thicknesses of the nerve fiber layer (NFL), ganglion cell complex (GCL), IPL, and INL. The thinning of the central inner retinal layer thickness after ERM surgery was correlated with post-operative visual outcome. These OCT factors may be a good indicator of visual function after ERM surgery. However, there remains the need for careful inspection of OCT and complex calculations using specific programs.

A prior study investigated the correlation between post-operative foveal changes and long-term VA after iERM surgery. Yang et al. [19] found that restoration of the post-operative foveal inner retinal configuration was well-correlated with visual outcomes after surgery. However, that study differed from ours in several ways. For example, that study only enrolled patients with pre-operative inner retinal thickening. Restoration of the inner retinal configuration in that study meant only thinning of the INL (NFL+GCL+IPL+INL) thickness (despite the maintenance of total foveal thickness), and not normalization of the shape of the foveal pit. In addition, manual measurement of each retinal layers was needed for the segmentation.

During follow-up after ERM surgery, we found that the foveal pit returned to its normal contour early after ERM sur-

gery in some patients, while it did not in others. We therefore assumed that this foveal change could serve as a long-term prognostic factor for visual outcomes. Although the BCVA was better in the recovery group than the non-recovery group at 1 year after surgery, the difference was not statistically significant. We also evaluated the association between early post-operative foveal pit contour recovery and visual improvement after ERM surgery. The results show that there was significantly greater VA improvement after ERM surgery in the foveal recovery group at 2, 6, and 12 months after surgery, when compared with the non-recovery group. The degree of improvement over the follow-up time was also significantly greater in the recovery group using a repeated measures analysis of variance. CMT reductions were significantly larger in the recovery group at all time points compared to that in the non-recovery group. Thus, the early foveal pit contour recovery within 1 month after ERM surgery may predict better visual improvement and larger CMT reduction compared to non-recovery group during long-term follow-up.

We also evaluated pre-operative factors, which were associated with foveal contour recovery. Although intraretinal cystic lesions, inner retinal thickening on OCT, and pre-operative BCVA were significantly associated with foveal contour recovery by univariate logistic regression analysis, inner retinal thickening was the only significant factor by multivariate logistic regression analysis.

The foveal contour change can be detected very easily on OCT, without the need for careful examination using high-resolution OCT. There is no need for manual measurements of the specific retinal layers, or complex calculations of the measured length. It is also easy to explain the prognosis to patients using OCT.

This study has several limitations. Its retrospective design introduced intrinsic bias. In addition, the sample size of eyes was small. It would be better to classify them into more groups for the analysis of correlations between foveal contour recovery and visual improvement. However, because of the small number of included cases, we had to simply compare the two groups. In addition, although we excluded patients with severe pre-operative cataracts in an attempt to minimize the effect of the lens, the number of pseudophakic eyes was too small to analyze the differences in VA changes between the two groups without influence from the pre-operative lens state. Overall, a prospective study with a larger sample of patients is needed to confirm our results.

In conclusion, the patients in the foveal recovery group had better VA improvement during 1 year of follow-up compared to those in the non-recovery group. Early foveal pit contour recovery may therefore be a useful visual prognostic factor after ERM surgery. It can be detected easily on OCT without careful inspections or complex calculations, and is helpful in explaining the long-term prognosis to patients.

Conflicts of Interest

The authors declare no conflicts of interest relevant to this article.

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