

Epiretinal membrane following pars plana vitrectomy for rhegmatogenous retinal detachment repair

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Abstract

• **AIM:** To determine the rate and possible contributors for post-pars plana vitrectomy (PPV) epiretinal membrane (ERM) in patients treated for rhegmatogenous retinal detachment (RRD).

• **METHODS:** This prospective, nonrandomized study comprised 47 consecutive patients (47 eyes) with acute RRD treated with 23 G post-PPV. All participants were followed prospectively for 6mo for the development of ERM using spectral domain optical coherence tomography. Preoperative and intraoperative data were collected by questionnaires to surgeons. Main outcome measure was the percentage of the ERM formation following post-PPV for RRD.

• **RESULTS:** ERM developed postoperatively in 23 eyes (48.9%), none necessitated surgical removal. There was a statistically significant difference between patients with and without ERM postoperatively in preoperative best corrected visual acuity (median logMAR 1.9 vs 0.3, respectively; $P=0.003$) rate of macula-off (69.6% vs 37.5%, respectively, $P=0.028$), and rate of ≥ 5 cryo-applications (55.6% and 18.8%, respectively, $P=0.039$). ERM developed mainly between the 1st and 3rd months of follow-up. Macula-off status increased the risk of ERM, with the odds ratio of 3.81 ($P=0.031$).

• **CONCLUSION:** ERM is a frequent post RRD finding, and its development is associated with macula-off RRD.

• **KEYWORDS:** epiretinal membrane; pars plana vitrectomy; rhegmatogenous retinal detachment; cryotherapy; macula-off

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INTRODUCTION

Primary rhegmatogenous retinal detachment (RRD) requires early surgical intervention to prevent loss of vision. Although the functional and anatomical success rates of pars plana vitrectomy (PPV) for the treatment of RRD are considered high^[1-2], late postoperative complications may occur, including the formation of an epiretinal membrane (ERM) and the development of proliferative vitreoretinopathy (PVR)^[3-4]. ERM, also known as cellophane membrane or macular pucker, principally consists of retinal pigment epithelial cells, hyalocytes, and retinal glia. It may be either idiopathic or secondary to a wide variety of conditions, including intraocular surgery^[5-9]. ERM formation following surgery for RRD may be asymptomatic, warranting follow-up alone. However, it may also distort the retina causing severe metamorphopsia or a clinically significant decrease in visual acuity, warranting further surgical intervention for membrane peel. PVR is characterized by the development of periretinal membranes which later contract to create retinal traction^[10]. Several authors have suggested that ERM following PPV^[11-13] may be considered an early stage of PVR^[10].

ERM has been reported to occur in 4%-8.5% of patients following successful scleral buckling procedure for primary RRD^[14-17]. Rates of 6%-13%^[5,16,18-19], more recently rising to as high as 21%^[20-21], have been reported following successful PPV. There is currently a paucity of large-scale prospective studies assessing possible contributors to the development of ERM after 23 G PPV for RRD. The aim of the present prospective study was to determine the rate and possible contributors for post-PPV ERM in patients treated for RRD in a large tertiary medical center.

SUBJECTS AND METHODS

Ethical Approval The study was conducted in accordance with the Declaration of Helsinki and was approved by the research Ethics Committee of Rabin Medical Center. All patients had been fully informed of the purpose and methods of the present study and provided written informed consent from themselves or their guardians.

A prospective, nonrandomized study design was used. The cohort included consecutive patients with acute primary RRD who underwent 23-gauge PPV in a single tertiary center. Exclusion criteria were PVR stage 3 and higher, diagnosis of ERM prior to surgery, giant retinal tear, and traumatic or non-RRD.

Pars Plana Vitrectomy Procedure PPV was performed by one of two surgeons using the Stellaris PC vitreoretinal surgical system (Bausch & Lomb Inc., Irvine, CA, USA) and the Resight fundus viewing system (Zeiss Meditech, Dublin, CA, USA). The method of retinopexy and type of tamponade were left to the surgeon's discretion. In all cases, either the presence of a posterior vitreous detachment was confirmed or, if it was not present, active aspiration was used to induce a separation.

Scleral depression was performed to identify all breaks. Particular care was taken to ensure all traction was relieved; this usually warranted excision of the anterior flap with the vitrector. Retinopexy was performed with cryotherapy or endolaser photocoagulation; the cryotherapy was performed until whitening covered the edges of the tear in smaller tears, and in larger tears two cryotherapy balls were applied to cover all the edges. Cryotherapy was not repeated twice on the same spot. The cryotherapy was performed under air or heavy liquid on an attached tear. For tamponade, nonexpansile mixtures of either perfluoropropane (C3F8) or sulfur hexafluoride (SF6) were used in the majority of cases. At the end of surgery, sclerotomies were routinely examined for leaks, and if their integrity was unclear, an absorbable suture was placed. After surgery, patients were instructed to maintain positioning for 5-7d to ensure the break was covered by the gas bubble. The use of heavy liquid to flatten the retina during surgery or to directly exchange air with drainage of fluid through the tear was left to the discretion of the surgeon.

Data Collection At completion of surgery, the surgeon filled out a detailed questionnaire covering the clinical features of the detachment, including documentation of macular involvement, number and position of retinal tears, and extent (in clock hours) of retinal detachment, as well as the course of surgery, including combination with phacoemulsification for cataract extraction, the use of perfluorocarbon liquid to flatten the retina, the type of tamponade chosen, and the use and number of applications of endolaser or cryo-coagulation. Surgical complications were documented. Demographic and background data on the patients were collected from the files.

Follow-up Examinations Patients were followed 1d, 1wk, and 1, 3, and 6mo after PPV. At each follow-up visit, best corrected visual acuity (BCVA) was assessed using Snellen charts followed by a detailed slit-lamp examination including dilated fundus examination. The diagnosis was confirmed with

spectral-domain optical coherence tomography (SD-OCT; Spectralis, Heidelberg Engineering, Heidelberg, Germany) at the 1-, 3-, and 6-month visits. The SD-OCT examinations were performed by a retina specialist blinded to the procedures performed during surgery. ERM formation was defined as the appearance of a hyper-reflective line internal to the inner limiting membrane on the SD-OCT scan. During the follow up time, all patients were treated with prednisolone 1% and ofloxacin eye drops applied four times daily to the operated eye starting the day after surgery and continued through the first post-operative month. The antibiotic treatment was then stopped, and the steroid drops were gradually tapered by a drop every week over the course of the second month, as commonly practiced.

Statistical Analysis Statistical analysis was performed using Statistica 10.0 (Statsoft, Tulsa, OK, USA). Snellen BCVA values were converted to the logarithm of the minimum angle of resolution (logMAR). Continuous variables were tested for normality using the Shapiro-Wilk test and presented as mean±standard deviation (SD) when normally distributed or as median (interquartile range) when non-normally distributed. Categorical variables were presented as counts and proportions. Patients with and without ERM were compared for continuous variables using Student's *t*-test or Mann-Whitney *U* test, and for proportions using Pearson's Chi-squared test or Fisher exact test. Backward stepwise multiple logistic regression analysis was performed to investigate the relationship between the method of retinopexy (cryocoagulation, laser photocoagulation, or both), macular status (on or off), tamponade agent used (silicon or gas) and the number of retinal tears (0-3 or 4+) with the formation of ERM. Two-tailed *P* values of less than 0.05 were considered statistically significant.

RESULTS

Of the 59 patients recruited for the study, 12 were excluded because they were lost to follow-up ($n=9$), died during the follow-up period ($n=2$), or had recurrent RRD due to PVR after the first surgery ($n=1$). The remaining 47 patients (47 eyes) were included in the statistical analysis.

ERM, either diagnosed or confirmed by SD-OCT, developed postoperatively in 23 eyes (48.9%). In no case was the ERM significant enough to necessitate surgical removal. The demographic and baseline features of the patients with and without ERM are detailed in Table 1.

On comparison of the two groups, the ERM group was found to have a significantly lower baseline mean BCVA [logMAR 1.9 (0.3-2.2) vs logMAR 0.3 (0.1-1.5), $P=0.003$] and a higher rate of macula-off (69.6% vs 37.5%, $P=0.028$). The ERM group also had a higher proportion of patients with 4 or more retinal tears (39.1% vs 16.7%), but the difference from the

Table 1 Demographics and baseline characteristics of the patients with and without ERM

Baseline characteristic	Groups		P
	ERM	Non-ERM	
No. of eyes	23	24	
Age (y), mean±SD	67.1±9.6	64.0±10.5	0.299 ^a
BCVA at diagnosis (logMAR), median (IQR)	1.9 (0.3-2.2)	0.3 (0.1-1.5)	0.003 ^b
Lens status, n (%)			0.181 ^c
Phakia	10 (43.5)	6 (25.0)	
Pseudophakia	13 (56.5)	18 (75.0) ^d	
Macula status, n (%)			0.028 ^c
On	7 (30.4)	15 (62.5)	
Off	16 (69.6)	9 (37.5)	
RRD extent (h), mean±SD	5.8±2.5	5.2±2.1	0.332 ^a
RRD location (quadrants)			0.970 ^c
Upper temporal	17 (73.9)	17 (70.8)	
Lower temporal	13 (56.5)	11 (45.8)	
Upper nasal	11 (47.8)	10 (41.7)	
Lower nasal	6 (26.1)	7 (29.2)	
No. of tears, n (%)			0.085 ^c
0-3	14 (60.9)	20 (83.3)	
≥4	9 (39.1)	4 (16.7)	

BCVA: Best corrected visual acuity; ERM: Epiretinal membrane; IQR: Interquartile range; RRD: Rhegmatogenous retinal detachment; SD: Standard deviation. ^aStudent's *t*-test; ^bMann-Whitney *U* test; ^cPearson's Chi-squared test; ^dIncluding one aphakic patient.

non-ERM group was not statistically significant ($P=0.085$). Other baseline variables were similar in the two groups, and no preoperative risk factors for the formation of ERM were identified. Overall, there was a predominance of upper temporal quadrant involvement in the RRD (73.9% in the ERM group and 70.8% in the non-ERM group).

The surgical and follow-up data of the ERM and non-ERM groups are detailed in Table 2. Significantly more patients in the ERM group received 5 or more cryo-applications (55.6% vs 18.8%, $P=0.039$). The ERM group also received more laser applications (1283±657 vs 948±427), but the between-group difference was not statistically significant ($P=0.122$). The two groups were similar for all other intraoperative variables, including the retinopexy method selected by the surgeon, the tamponade agent, use of heavy liquid, and performance of cataract surgery in combination with the RRD repair. At the end of the follow-up period, the BCVA was logMAR 0.2 (0.2-0.70) in the ERM group and logMAR 0.2 (0.10-0.5) in the non-ERM group ($P=0.65$). Figure 1 describes the change in BCVA from baseline to the end of follow-up in both groups. The course of ERM formation during follow-up is described in Figure 2.

In the majority of patients ($n=12$, 48.9% of the ERM group, 25.6% of the whole cohort), ERM developed between the first and third postoperative months; in only 5 patients (21.7%, 10.6%) was ERM evident already at one month.

Table 2 Surgical and follow-up data of the patients with and without ERM

Parameters	Groups		P
	ERM	Non-ERM	
No. of eyes	23	24	
Retinopexy, n (%)			0.516 ^c
Laser therapy	5 (21.7)	10 (41.7)	
Cryotherapy	9 (39.1)	8 (33.3)	
Both	9 (39.1)	6 (25.0)	
Laser applications, mean±SD	1283±657	948±427	0.122 ^a
360° laser applications			0.846 ^c
Yes	8 (34.8)	9 (37.5)	
No	15 (65.2)	15 (62.5)	
Cryo applications			0.039 ^d
1-4	8 (44.4)	13 (81.3)	
+5	10 (55.6)	3 (18.7)	
Tamponade, n (%)			0.348 ^c
Gas	20 (87.0)	23 (97)	
Silicone	3 (13.0)	1 (3.0)	
PFC, n (%)			0.671 ^c
Yes	6 (26.0)	5 (20.8)	
No	17 (74.0)	19 (79.2)	
Combined cataract surgery, n (%)			1.000 ^d
Yes	2 (8.7)	1 (4.2)	
No	21 (91.3)	23 (95.8)	
Final BCVA (logMAR), median (IQR)	0.2 (0.2-0.7)	0.2 (0.1-0.5)	0.65 ^b

BCVA: Best corrected visual acuity; ERM: Epiretinal membrane; IQR: Interquartile range; RRD: Rhegmatogenous retinal detachment; PFC: Perfluorocarbon; SD: Standard deviation. ^aStudent's *t*-test; ^bMann-Whitney *U* test; ^cPearson's Chi-squared test; ^dFisher exact test.

Table 3 Factors associated with risk of ERM

Independent variable	B	SE of B	P	Odds ratio	95%CI for odds ratio
Macular status, off	1.338	0.619	0.031	3.810	1.132-12.816
Constant	-0.762	0.458	0.096	0.467	N/A

B: Unstandardized coefficient; N/A: Not applicable; SE: Standard error. $\chi^2(1)=4.942, P<0.026$; Nagelkerke $R^2=0.133$; based on the final model of backward stepwise multiple logistic regression analysis. Independent variables: Method of retinopexy, cryocoagulation=0, laser photocoagulation=1, both=1; Macular status, on=0, off=1; Tamponade agent, silicon=0, gas=1; Number of retinal tears, 0-3 tears=0, 4+ tears=1.

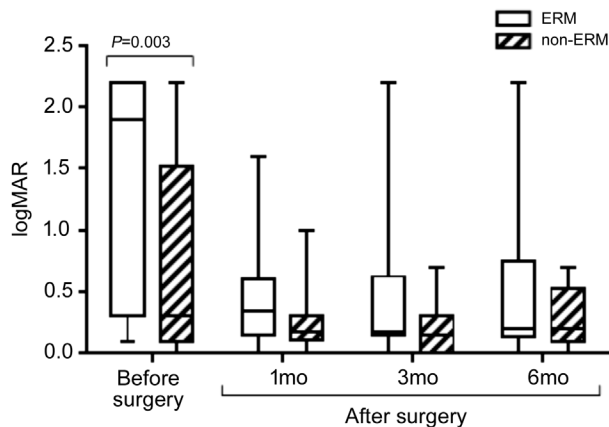


Figure 1 Box-and-whiskers plots of changes in BCVA during follow-up The boxes span the 25th to the 75th percentile; the whiskers span the lowest to the highest observations; and the line inside each box denotes the median. The figure shows the median BCVAs of the ERM and non-ERM groups prior to surgery and at every follow-up visit. BCVA was significantly worse in the ERM group prior to surgery. At each time point, the groups were compared using the Mann-Whitney *U* test.

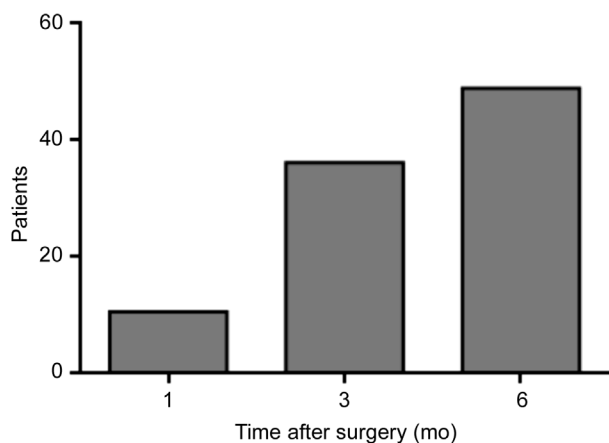


Figure 2 Proportion of patients with ERM during follow-up.

To further investigate the association between method of retinopexy, macular status, tamponade agent used and number of retinal tears with the formation of ERM, we performed a backward stepwise multiple logistic regression analysis. As shown in Table 3, only macular status was found significant in the final model.

Interpreting these data, the odds of ERM formation increases by a factor of 3.81 (95%CI 1.13-12.82, $P=0.031$) if the macula is off. The other variables are not associated with ERM formation.

DISCUSSION

Our study prospectively evaluated the incidence and potential contributors to the formation of ERM, as evaluated by SD-OCT, following 23 G PPV for primary RRD in phakic and pseudophakic eyes.

The incidence of ERM following PPV for RRD was 48.9%. Nevertheless, none of the patients with ERM required an internal limiting membrane (ILM) peel procedure during follow-up. The ERM had no adverse effect on BCVA. While we describe a statistically significant difference between patients with and without ERM postoperatively in preoperative BCVA, this may have been impacted by the lens status at presentation, however, we found no significant difference in the lens status between the ERM and non-ERM groups as stated in Table 1, and the lens status was not found to be a factor associated with ERM in multivariate analysis.

SD-OCT is the current gold standard method for ERM diagnosis. Its use has made it possible to identify cases of ERM that would otherwise be overlooked. We speculate that in the pre-SD-OCT era, the technological limitations of clinical examination or low-resolution time domain OCT may have led to an underdiagnosis of postoperative ERM formation^[5,12,16]. This is supported by two recent studies in which SD-OCT was used to evaluate the incidence of ERM formation following PPV for RRD with and without ILM peeling during the initial surgery^[21-22]. Both found a similar postoperative ERM incidence of 21%^[21-22], twice the rate cited in the earlier literature. However, both studies used a retrospective design and were therefore prone to recruitment bias. The even higher incidence in the present study might be attributable to the strict follow-up regimen. The performance of OCT in all patients at each check point, regardless of BCVA or visual symptoms, could have yielded a high rate of diagnosis of ERM, including many cases that were clinically nonsignificant. However, a direct comparison with previous studies is impractical owing to the major differences in study design, OCT equipment used, and exclusion criteria.

Several potential predisposing factors have been reported for the development of ERM in patients after surgery for RRD. These include preoperative macular detachment, vitreous hemorrhage (VH), low BCVA, and numerous or large equatorial retinal breaks^[5,15-17,22], intraoperative placement

of a high number of cryocoagulation spots; and lack of postoperative use of systemic steroids^[12]. In our study, none of the patients presented with VH. In concordance with some previous studies^[12,22] but not others^[5], the ERM group was characterized by significantly more cryocoagulation spots intraoperatively than the non-ERM group, which may possibly be attributable to an ensuing inflammatory reaction. The assumption that ERM is an early stage of PVR and that the development of PVR can be influenced by modifying the surgery-induced inflammatory reaction and disruption to the blood-retinal barrier was previously reported by Koerner *et al*^[12], based on a positive effect of postoperative steroids in reducing the early stages of PVR after RRD surgery. Interestingly, the number of cryocoagulation spots in their study was correlated to the percentage of eyes with ERM. This finding is in line with previous evidence of more frequent postoperative autoimmune reactions against retinal antigens in eyes after excessive cryocoagulation therapy^[23]. Some surgeons choose to use cryotherapy during RRD repair; it is reassuring that small amount of cryotherapy applications did not increase the risk of ERM formation. A possible explanation might be that the performance of cryotherapy under air prevents the dispersion of retinal pigment epithelium cells. The larger numbers of cryotherapy might have increased the risk for ERM formation due to increased inflammatory reaction or greater number of retinal tears that require more cryotherapy applications and more laser applications that were found to be also related to increased risk of ERM. In our study, the multiple logistic regression analysis, did not point at an association between cryotherapy, as the go-to method of retinopexy, and the development of ERM post-surgery. This, however, does not preclude the possible contribution of a high number of cryotherapy applications, to the development of ERM, as shown in Table 2.

Other possible contributors to the formation of ERM following PPV for RRD are the number, size, and location of retinal tears. This may be explained by the dispersion of retinal pigment epithelium cells through larger, peripheral, or more numerous retinal breaks, which later serve as a scaffold for ERM formation^[5]. In our study, the ERM group contained a larger proportion of patients with 4 or more retinal tears than the non-ERM group, in agreement with the results of Katira *et al*^[5] but not those of Nam and Kim^[20], although the difference between our groups did not reach statistical significance. Moreover, there were cases of ERM among our patients with RRD and macular involvement, as suggested by Rezar *et al*^[24]. We found no statistically significant differences in demographic parameters between the ERM and non-ERM groups, or in lens status at the time of surgery, retinopexy method selected by the surgeon, or tamponade agent. Intraoperative

considerations, such as performance of combined PPV and phacoemulsification or use of heavy liquid to flatten the retina, had no effect on the risk of ERM formation.

ILM peeling is not routinely done at our institution. Although ILM peeling has been suggested as a means to diminish ERM formation following PPV^[20-21], we found that it was not required in any of our patients during the 6-month follow-up after PPV owing to good visual acuity. This may suggest that routine ILM peeling has little clinical benefit in terms of avoiding complications of PPV for RRD.

The main limitations of our study are the relatively small sample size which prevented us from evaluating each possible contributor as an independent risk factor for the formation of ERM, and the short follow-up time which may have masked some late postoperative cases of ERM. Moreover, the prospective design of our study wherein patients with acute RRD were recruited at presentation did not allow for early, presurgery, clinical screening for ERM formation in the macula-off patients, which may have been one of the reasons for ERM overdiagnosis. It is, however, reassuring that the vast majority of the ERM group (78.7%) was diagnosed 1-6mo postoperatively, and in only 21.7% was ERM evident already at the one-month follow-up, indicating that most patients did not have ERM prior to surgery.

In summary, in the present single-center study, ERM formation occurred in nearly half the patients treated with 23 G PPV for primary RRD. This rate is higher than previously reported. The ERM group received more laser applications than the non-ERM group, but the difference was not statistically significant. A large number of cryocoagulation spots may pose a risk for ERM development although in a multiple logistic regression analysis this was not found to increase the risk of ERM. Yet, in cases in which there is a need for more extensive retinopexy, the surgeon might opt for laser treatment over cryotherapy. Macula off status was found to be independently associated with ERM formation. Larger scale prospective studies are needed to corroborate our data and determine which of the studied variables is an independent risk factor for postoperative ERM and PVR.

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