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Original Article

Evaluation of Factors Affecting Epiretinal Membrane Surgery Outcomes

Burak Erden,[1] Ziya Kapran[2]

[1]Retina Department, University of Health Sciences Okmeydani Training and Research Hospital, Istanbul, Turkey
[2]NeoRetina, Private Clinic, Istanbul, Turkey

Abstract

Objectives: The aim of this study was to evaluate several factors affecting the outcome of epiretinal membrane (ERM) surgery.

Methods: The data of a total of 41 eyes of 40 patients (20 female, 20 male) who underwent pars plana vitrectomy (PPV) and epiretinal membrane (ERM) peeling with/without internal limiting membrane (ILM) peeling between November 2001 and October 2005 at Beyoğlu Eye Training and Research Hospital with a minimum follow-up of 6 months were included in this retrospective study. The patients' best corrected visual acuity (BCVA; Snellen) and the biomicroscopic, funduscopic, and optical coherence tomography (OCT) findings measured preoperatively and at month 1,3,6, and a final visit were recorded. The surgical technique (partial 25-gauge vs 20-gauge), ILM peeling, intraoperative dyes, and the etiology of the ERM were evaluated as separate factors in the surgical outcome. Intraoperative, peroperative, and postoperative complications were assessed and compared.

Results: The mean age of the study group participants was 63.56±14.96 years. The mean BCVA had increased from 0.28±0.149 to 0.35±0.24 Snellen lines (p=0.028) at the 6-month visit. In all, 18 of 41 eyes (43.9%) had gained ≥2 Snellen lines at the final visit. Cataract progression was detected in 17 cases (54.8%) of phakic eyes. The incidence of ERM recurrence was significantly greater in the ILM Intact group (37% vs 0%) than in the ILM Peeled group (p=0.009). There was no significant difference in anatomical or functional outcome between the partial 25-gauge and 20-gauge PPV techniques.

Conclusion: ILM peeling significantly reduced ERM recurrence. Follow-up observations indicated that cataract progression was the primary factor limiting visual gain.

Keywords: Epiretinal membrane, internal limiting membrane, surgical dyes.

Introduction

Epiretinal membrane (ERM) formation is a unique clinical entity in vitreoretinal research. It was first described by Ivanoff (1) in 1865, and the first surgical treatment was introduced by Machemer in 1978 (2). Clarkson et al. (3) found an ERM prevalence of 5.5% in a large series examining enucleation (n=388) and autopsy (n=1612) material. The authors histologically evaluated 168 cases of preretinal membrane and found that the majority of cellular proliferation was of glial origin. This cell distribution has been confirmed by more recent studies using modern immunohistochemical methods. Yan et al. (4) analyzed the expression of progenitor cell markers (Sox2, Nestin, and Pax2) in idiopathic and non-idiopathic ERM specimens of different etiologies to examine the origins of proliferative cells and concluded that glial cells in ERMs are unique, and that some of these glial-like cells can proliferate and co-express progenitor cell markers. The histological research exploring the origin and etiology of ERMs

Address for correspondence: Burak Erden, MD. Saglik Universitesi Okmeydani Egitim ve Arastirma Hastanesi, Retina Bolumu, Istanbul, Turkey
Phone: +90 533 688 18 56 **E-mail:** drburakerden@gmail.com

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has generally postulated that development is secondary to Müller cell activation following posterior vitreous detachment and internal limiting membrane (ILM) damage in idiopathic cases (5) or due to glial cell proliferation secondary to trauma (6).

In the last decade, ILM peeling following ERM removal has been widely discussed. Morris et al. (7) were the first to intentionally remove the ILM during macular surgery in eyes with hemorrhagic macular cysts secondary to Terson syndrome and they reported a successful clinical outcome. Since then, ILM peeling has become a popular technique in macular surgery, including both macular hole (MH) and ERM cases. Many surgeons have preferred to use ILM peeling in an attempt to diminish the possibility of future ERM recurrence and to encourage a greater resolution of retinal folds (8, 9). Although ILM peeling has generally been accepted as a fundamental step in MH repair, its current role in ERM surgery remains controversial. The principal argument in favor of ILM peeling has been that the ILM may serve as a scaffold for cellular proliferation and removal is required for complete removal of ERM and inhibiting future recurrence (10). On the other hand, stripping the ILM has damaged the Müller cell footplates, consequently leading to complications, such as microscotomas (11), eccentric MHs (12), and retinal dimpling associated with retinal nerve fiber damage (13). The current study was a comparison of the functional and anatomical outcomes of ILM peeling (ILM Peeled and ILM Intact groups).

Visualization has been always a crucial part of vitreoretinal surgery. Without the use of surgical dyes, evaluation of ILM location and integrity is not reliable. Carpentier et al. (14) demonstrated in a prospective study of 98 ERM cases that brilliant blue (BB) dye was important to the ability to define the ILM. Triamcinolone acetonide (TA) has been used to visualize the posterior vitreous, the ERM, and even ILM staining. Indocyanine green (ICG) was first used by Kadonosono et al. (15) to selectively stain the ILM in MH surgery, but several subsequent studies have demonstrated toxic effects on foveal function (16). Its role as an ERM dye has now largely been replaced by the relatively safer BB or trypan blue (TB), which is well known to have an affinity for cellular tissue. At the time this study was conducted, TA, ICG, and TB were the most popular surgical dyes and the results of these 3 different staining methods were compared.

Methods

The data of 41 eyes of 40 patients (20 male, 20 female; mean age: 63.56±14.96 years) who underwent pars plana vitrectomy (PPV) for ERM removal at Beyoğlu Eye Research and Training Hospital between November 2001 and October 2005 were used in this retrospective study. The exclusion criteria included the presence of proliferative diabetic retinopathy, a follow-up of fewer than 6 months, and a history of prior PPV surgery. The patient records were reviewed and ophthalmological examination findings of best corrected visual acuity (BCVA; Snellen), intraocular pressure (IOP; Goldmann applanation tonometry), and biomicroscopic and funduscopic data, as well as the etiology of the ERM, optical coherence tomography (OCT) findings, and details of the surgical technique (20-gauge/partial 25-gauge), intraoperative tamponade, and dyes used were recorded. Three sclerotomies were performed using a 20-gauge system and surgical instruments, including forceps. Two sclerotomy sites were prepared using a 2-step, 25-gauge trocar system. The infusion sclerotomy site was positioned inferotemporally in the conventional 20-gauge procedure; however, the partial 25-gauge approach allowed the surgeon to use 25-gauge surgical instruments, such as end-gripping or asymmetric endoforceps.

The preretinal membrane was classified by the vitreoretinal surgeons as idiopathic or secondary ERM according to the patients' ocular history, and the red-free funduscopy and OCT findings. The ERMs were grouped in 3 categories according to the Gass classification. OCT examinations (Stratus; Carl Zeiss Meditech AG, Jena, Germany) were performed preoperatively, and at the third and sixth month. ERM recurrence was defined as clinically significant when there was visual impairment that could be detected in the foveal area via OCT and funduscopy. Written, informed consent was obtained from the participants before all interventional procedures. Due to the retrospective nature of this study an ethical committee approval was weaved but the study was conducted according to the tenets of the Declaration of Helsinki. For inter- and intra-group comparisons, the Student's t-test (paired and independent) was applied. Pearson correlation and repeated measure tests were used for analytical purposes. IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp., Armonk, NY, USA) was used to perform the statistical analysis. A p value <0.05 was considered statistically significant.

Results

Baseline Characteristics

The data of 41 eyes of 40 patients (20 male, 20 female; mean age: 63.56±14.96 years) were included in this retrospective study. The most common preoperative complaint was visual impairment, recorded in 38 cases (92.7%), followed by metamorphopsia in 5 cases (12.2%). The mean duration of pre-existing visual loss was 31.22±59.52 months. The majority of the eyes in the study population (31 eyes, 75.6 %) were phakic, while 8 eyes were pseudophakic, and 2 eyes had aphakia. The mean IOP was 15.49±2.02 mmHg according to

Goldmann applanation tonometry measurements recorded at the last preoperative visit.

Preretinal membranes of different stages were detected in the contralateral eyes of 12 patients (30%), but in only 1 case was bilateral surgical removal indicated. The etiological classification of the ERMs indicated that while in 25 eyes no ocular or systemic etiological disease was identified (60.9% idiopathic ERM), another etiological cause was found in 16 cases (39.1% secondary ERM). In the secondary ERM subgroup, 2 eyes had a history of retinal detachment surgery, 3 cases had non-proliferative diabetic retinopathy, 3 cases had undergone argon laser photocoagulation, 10 eyes had a history of cataract surgery, 4 patients had a history of non-penetrating ocular trauma, and retinal vein occlusion was detected in 2 eyes with fluorescein angiography. Using the Gass classification system, 8 cases were grouped as Stage 1, 29 as Stage 2, and 4 as Stage 3.

Functional Results

Visual gain in Snellen lines was defined as functional success. The overall preoperative mean BCVA of the total study group increased from 0.28±0.149 to 0.25±0.2 lines (1 month), to 0.31±0.23 lines (3 months; $p<0.05$), 0.3±0.22 lines (6 months), and 0.35±0.24 lines (1 year; $p=0.012$) (Fig. 1). The main cause of visual decline at the sixth month visit was nuclear cataract progression. A myopic shift of -0.61 diopters was observed in the phakic subgroup, and the 10 phakic eyes (24.3%) underwent phacoemulsification and bag-in-the-lens implantation of an intraocular lens after the sixth month visit (mean: 11.6 months postoperatively). The comparison of final visual gain between these 10 cases and the rest of the phakic study population (0.147 vs 0.037 lines) revealed a statistically significant difference ($p=0.001$).

Effect of Surgical Dyes on Functional Outcome

The most preferred ERM staining dyes in our study population were TB (n=14) and triamcinolone acetonide (TA; n=12). In 15 cases, no surgical dye was needed (No Dye) for ERM visualization. The TB and No Dye group postoperative final visual gain values (0.26 vs 0.25 lines) were comparable and significantly superior to the outcome of the TA subgroup ($p=0.02$) (Fig. 2).

In cases of ILM peeling (n=25), indocyanine green (ICG) was applied in 12 eyes to visualize the ILM, TB was used in 10 cases, and in 3 eyes, TA was selected by the surgeon. When surgical dyes and final visual outcomes were evaluated, The TB subgroup visual gain was determined to be superior (0.075 vs 0.13 lines; $p=0.037$) to the functional improvement achieved in the ICG subgroup (Fig. 3). The TA subgroup could not be statistically analyzed due to the small number of cases.

Effect of Surgical Technique

This case series consisted of 41 eyes operated on by 6 different surgeons. While the majority of the operations (n=28) were performed by the most experienced vitreoretinal sur-

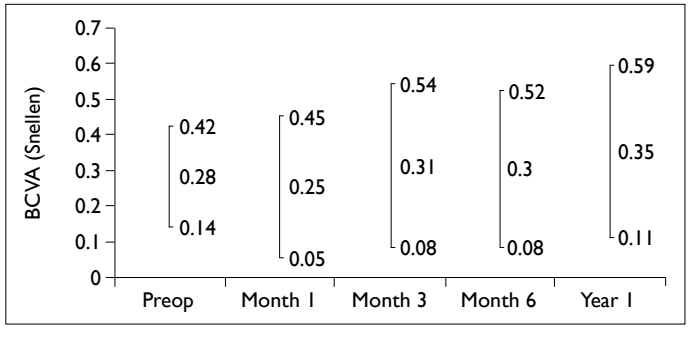

Figure 1. Best corrected visual acuity (BCVA) change over 1 year of follow-up. A visual decline secondary to cataract progression was detected at the 6-month visit following cataract surgery. In 10 eyes, the mean BCVA had increased at the 1-year visit.

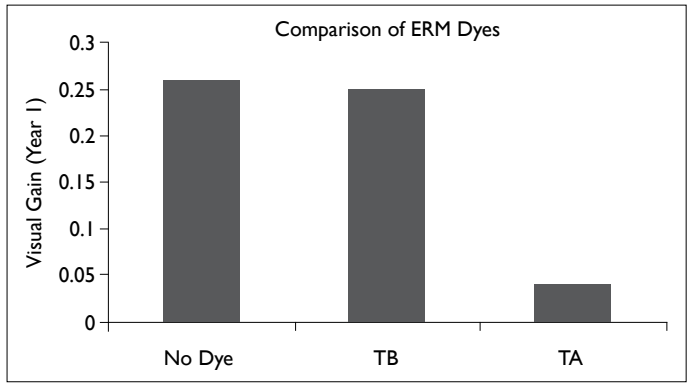

Figure 2. Visual gain seen in Snellen lines at the final 1-year visit was comparable in the No-dye and TB subgroups, and was significantly superior to the TA subgroup ($p=0.02$).
ERM: Epiretinal membrane; TA: triamcinolone acetonide; TB: trypan blue.

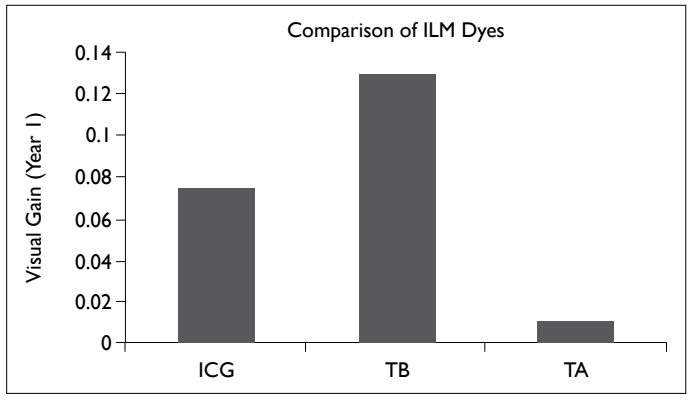

Figure 3. In ILM staining, the visual gain in the TB (n=11) subgroup was significantly better ($p=0.037$) than that of the ICG (n=12) subgroup. TA was preferred in only 3 eyes.
ICG: Indocyanine green; ILM: internal limiting membrane; TA: triamcinolone acetonide; TB: trypan blue.

geon (VRS), the rest of the operations was distributed by the vitreoretinal surgeons as follows: VRS No. 2: 6 cases, VRS No. 3: 3 cases, VRS No. 4: 2 cases, VRS No. 5 and No. 6: 1 case each. The mean visual gain in the total study group at the final visit was evaluated according to each VRS and the result suggested superior results for VRS No. 1; however, this finding could not be analyzed statistically due to the asymmetrical distribution of the surgeries (Fig. 4).

Twelve patients in the study group were operated on using a partial 25-gauge transconjunctival sutureless vitrectomy (TSV) system to allow for the use of 25-gauge surgical instruments in the ERM removal. In 29 cases, a conventional 3-port, 20-gauge PPV was used. The comparison of visual gain results of the entire study group according to the system applied revealed no significant difference (0.08 vs 0.01 lines). In the pseudophakic subgroup, although statistically insignificant (p=0.07) the 20-gauge PPV visual gain was better than that of the partial TSV cases (0.21 vs 0.15 lines).

In 30 of 41 cases, an intraoperative gas tamponade (12 nonexpansile sulfur hexafluoride, 4 nonexpansile perfluoropropane, 14 air) was applied at the end of the surgery according to the surgeon's decision. In 11 cases, no tamponade was used. The visual gain comparison between the No Tamponade and Gas Tamponade subgroups of the total study population showed no statistically significant difference (0.073 vs 0.076 lines). In the pseudophakic group; however, the best results were achieved in the air tamponade subgroup (p<0.01) (Fig. 5).

In 25 cases (61%), the ILM was peeled by the surgeon using different dyes and end-gripping forceps with a maculorhexis technique. When the visual gain in the total study group at the final visit was compared between the ILM Peeled and ILM Intact subgroups, no statistical significance was found (0.09 vs 0.047 lines; p=0.08). In the pseudophakic subgroup, however, the final visual gain was significantly better in the ILM Peeled group (0.21 vs 0.16 lines; p=0.03) (Fig. 6).

Anatomical Results

Effect of Surgical Dyes on Anatomical Outcome

The mean central macular thickness (CMT) of the total study group decreased significantly from a preoperative measurement of 443.59±99.88 µm to 355.38±40.21 µm (Month 1), 353.24±79.89 µm (Month 3), 321.11±45.32 µm (Month 6), and finally 311.68±67.45 µm (Year 1) (p=0.001) (Fig. 7). When the 3 different ERM dye subgroups were compared for anatomical gain in terms of the final CMT reduction, the greatest reduction was seen in the TB subgroup (n=14; 104.42±99.95 µm), though it was not statistically insignificant (Fig. 7). The mean CMT reduction was 93.18±69.21 µm in the No Dye subgroup (n=15) and 71.9±66.64 µm in the TA subgroup (n=12).

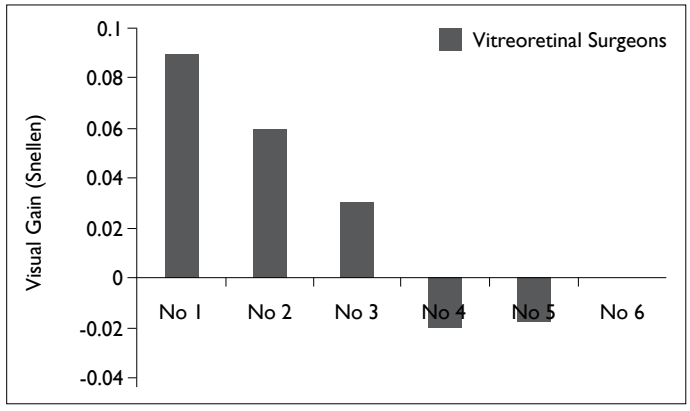

Figure 4. The visual gain results at the final visit demonstrated a positive correlation between surgical experience and better functional outcomes.

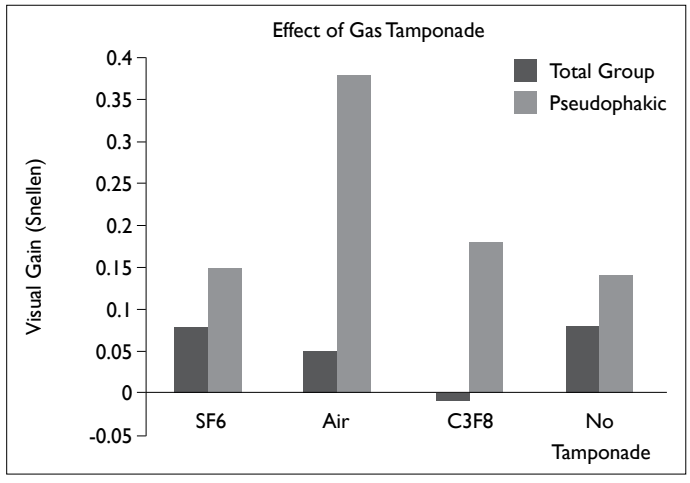

Figure 5. Evaluation of the functional outcome at the final visit according to the intraoperative tamponade revealed a significant superiority of an air tamponade.

C3F8: Perfluoropropane; SF6: sulfurhexafluoride.

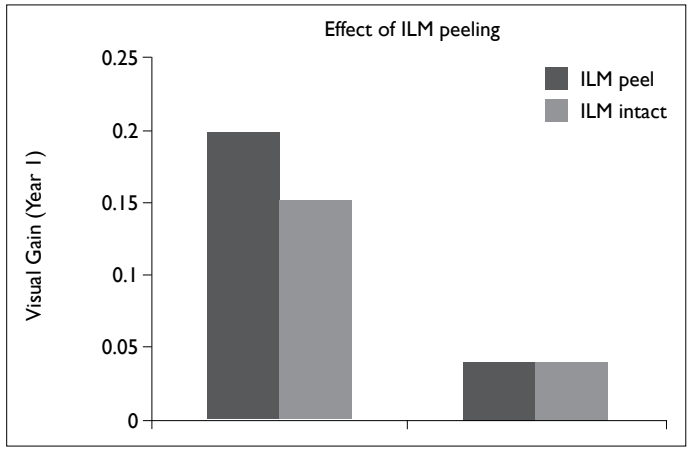

Figure 6. The increase in BCVA at the final visit (Year 1) was highest in the ILM-Peeled, pseudophakic subgroup.

BCVA: Best corrected visual acuity; ILM: internal limiting membrane.

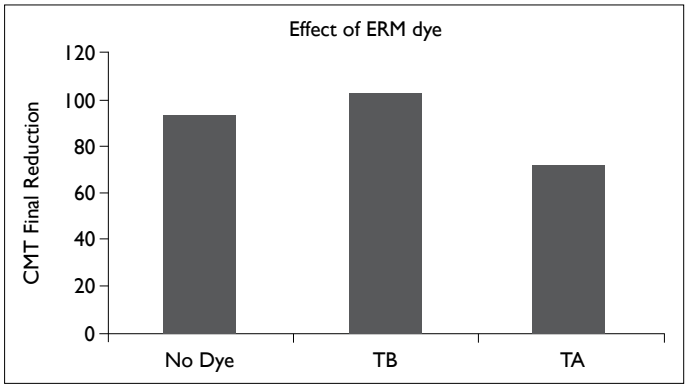

Figure 7. TB staining demonstrated an insignificant superiority in the comparison of anatomical gain by ERM dye subgroup.
CMT: Central macular thickness; ERM: epiretinal membrane; TA: triamcinolone acetonide; TB: trypan blue.

Effect of ILM Peeling on Anatomical Outcome

The CMT reduction analysis of the ILM Peeled (n=25) and ILM Intact (n=16) groups revealed similar final outcomes (98.23±25.4 μm vs 89.12±24.3 μm; p=0.34). The ERM recurrence was detected with red-free funduscopy in 13 eyes (31.7%) at a mean of 6.3 months. In 6 cases, preretinal recurrence (all in the ILM Intact group) occurred in the foveal area and could also be detected on OCT scans. Four of these 6 instances were defined as a clinically significant ERM recurrence limiting patient vision. In 7 cases, perifoveal ERM recurrence was detected with funduscopy (ILM Peeled: n=3; ILM Intact: n=4). In the ILM Peeled group, however, no foveal recurrence of ERM was encountered as of the 1-year follow-up. The final foveal ERM recurrence rate (0% vs 37.5%) was statistically different in favor of the ILM Peeled group.

Discussion

The established treatment of ERMs has been surgical removal since Machemer performed the first surgical intervention (2), although there have been some reports of spontaneous separation of ERMs, particularly in young individuals (17). With the introduction of modern technologies in vitreoretinal surgery, several strategies have been discussed, including the application of various surgical dyes and ILM peeling. This discussion of "to peel or not to peel" the ILM has proponents on both sides. The ILM consists of Müllerian cell footplates and to peel such a membrane can have negative consequences on the Müllerian infrastructure of the retina, but even histopathological reports differ in the correlation between the ratio of ILM fragments in surgically removed ERMs and the clinical outcome. While Sivalingham et al. (18) concluded that the presence of long fragments of ILM in ERM specimens was correlated with a poorer visual outcome, Bovey et al. (19) reported better visual outcomes and fewer recurrences in cases of long ILM fragments, and Gaudric et al. (20) did not find any correlation between the ratio of ILM remnants and visual improvement. We did not have the opportunity to evaluate the ILM fragments of our ERM specimens; however, the best visual outcome at the end of 1 year of follow-up was observed in the pseudophakic ILM Peeled subgroup. We concluded that this finding was mainly related to the high ratio of phakic patients at the baseline of our study group and cataract progression, particularly after the 6th month visit, rather than a positive effect of ILM peeling. The major significant difference in our study was the anatomical success in terms of foveal ERM recurrence (36% vs 0%). Similar anatomical results in the literature support the idea of ILM peeling to minimize ERM recurrences. Recent meta-analyses (21, 22) have clearly demonstrated the inhibiting effect of ILM peeling on ERM recurrence. Numerous reports, however, also point to microperimetric scotomas induced by ILM peeling associated with surgical trauma. Research published by Ripandelli et al. (23) and Deltour et al. (24) used microperimetry to demonstrate a larger number of microscotomata and a slower recovery in retinal sensitivity in the ILM peeling group. Additionally, there are also reports that have showed that ILM-intact eyes had a greater postoperative proportional decrease in CMT than ILM-peeled cases (9). This finding might be associated with postoperative swelling of the inner retina following the ILM removal. We, too, found no significant difference between groups in the mean CMT reduction at the final visit. Since there was no obvious positive effect of ILM peeling, either functional or in anatomical results, other than a low ERM recurrence rate, we believe ILM peeling should be applied as needed for each individual case.

The successful removal of ERMs usually results in a good clinical outcome and significant visual improvement. Wong et al. (25) reported that in their series of 123 consecutive eyes, more than 80% demonstrated an improvement in visual acuity of ≥2 lines. The mean postoperative visual acuity was 20/40, and the mean improvement was 3 lines. Our mean visual gain was limited to 0.07 Snellen lines, partially due to the nuclear cataract progression in the phakic patients. A secondary reason was probably a long preliminary duration of visual decline (31.22±59.52 months), leading to a lower baseline BCVA (mean: 0.28 lines). Preoperative visual acuity has been defined as the most decisive prognostic indicator of surgical outcome (26), alongside other factors, such as the presence of cystoid macular edema or thicker membranes and preoperative fluorescein leakage (27, 28). In our opinion, the chronic nature of the ERMs in our study group resulted in a somewhat limited functional improvement.

The surgical dye used in some cases to visualize the ERM and the ILM is a crucial element. Our anatomical results showed a statistically insignificant but clear superior-

ity of TB as an ERM dye compared with TA or no dye. TB has a high affinity for cellular structures, making it ideal for ERM staining and enabling the surgeon to perform a complete removal of preretinal membranes (29), which leads to better anatomical outcomes. Compared with ICG and TA, TB demonstrated better functional results in ILM staining in our study. This finding was not surprising, since Rodrigues et al. (16) concluded in their meta-analysis that functional results were poorer when ICG was used to stain the ILM. Due to its safety and staining ability, BB is currently the most frequently applied surgical dye in ILM staining, particularly outside the USA. Azuma et al. (30) demonstrated in a recent meta-analysis that BB resulted in better visual outcomes in MH surgery, compared to ICG.

The best visual result seen among intraocular gas tamponade subgroups in our cohort was found in the pseudophakic air tamponade subgroup at the final visit. The significant difference observed might be associated with known potential consequences of gas tamponades. Both intraocular tamponade gases studied can induce cataract progression in phakic eyes (31), and intraocular pressure changes may occur, despite a non-expanding concentration, which may lead to irreversible damage to the retinal nerve fibers. Thus, we recommend the use of air as a short-term intraocular tamponade for faster visual rehabilitation and safety in ERM cases, unless a longer-acting tamponade agent is indicated in a particular case.

In 12 members of our study group a partial 25-gauge PPV technique was preferred, while a classic 20-gauge approach was applied in the remainder of the group. The time period of the study reflects the introduction of a 25-gauge system at our facility. Partial 25-gauge sclerotomies enabled surgeons to use 25-gauge instruments in ERM and ILM peeling procedures. Kadosono et al. (32) compared 20-gauge and 25-gauge these systems in ERM surgery and found that 25-gauge vitrectomy demonstrated significantly greater gains at an early postoperative visit (Month 1), however, the final functional improvement did not differ at month 6. The comparison of our functional results revealed no difference between the 2 gauge systems. The degree of surgical experience had an apparent positive effect on visual outcomes in our study group, although a statistical conclusion could not be drawn due to multiple intraoperative parameters.

In conclusion, ERM surgery is a safe and effective treatment method of treating this clinical entity. We recommend TB as the vital dye for ERM staining and air as the short-term intraocular tamponade of choice, based on our findings. Long-standing visual impairment and the chronicity of the disease may limit functional improvement; earlier surgical interventions may be advisable. Nuclear cataract progression is a significant postoperative, vision-limiting factor, therefore, combined surgery might be a logical choice in phakic patients. Although ILM peeling is still debatable, it was observed to reduce ERM recurrence significantly, and so the decision to pursue a surgical approach should be made for each individual.

Disclosures

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Involved in design and conduct of the study (BE, ZK); preparation and review of the study (BE, ZK); data collection (BE); and statistical analysis (BE).

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