Thieme

Effect of Air Tamponade among Patients with Epiretinal Membranes and Intraretinal Cystoid Changes Undergoing Vitrectomy with Membrane Peeling – A Prospective Randomized Trial

Effekt der Lufttamponade bei Patienten mit epiretinalen Membranen und intraretinalen zystoiden Veränderungen nach Vitrektomie mit Membrane Peeling – eine prospektive randomisierte Studie

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ABSTRACT

Background The effect of air tamponade among patients undergoing vitrectomy with membrane peeling for removal of epiretinal membranes (ERM) is controversially discussed. The aim of the present study was to analyze differences in outcomes between air tamponade and balanced salt solution (BSS) in a study population with preoperative intraretinal cystoid changes.

Patients and Methods This randomized study included patients scheduled for pars plana vitrectomy with membrane peeling owing to ERM and intraretinal cystoid changes. Air tamponade or BSS at the end of surgery was applied according to preoperative randomization. Optical coherence tomography and best-corrected distance visual acuity (DCVA) measurements were performed before surgery, 5 days after surgery, and 3 months after surgery.

Results From 96 patients included, 85 eyes had full follow-up and could be included for analysis. Median improvement of DCVA was + 16 EDTRS letters (IQR: 8 to 22) among patients with BSS, while it was + 13 EDTRS letters (IQR: 8 to 17) among patients with air tamponade. There was a trend for better improvement of DCVA when BSS was left at the end of surgery, compared to air tamponade, but not reaching statistical significance.

Conclusions There were no statistically significant differences concerning resorption of preoperative intraretinal cystoid changes, improvement of visual acuity, and final DVCA between air tamponade and BSS.

ZUSAMMENFASSUNG

Hintergrund Die Auswirkungen der Lufttamponade bei Patienten nach Vitrektomie mit Membrane Peeling aufgrund von epiretinalen Membranen (ERM) werden kontrovers diskutiert. Ziel der Studie ist es, Unterschiede in den Ergebnissen zwischen Lufttamponade und „balanced salt solution“ (BSS) in einer Patientengruppe mit präoperativen intraretinalen zystoiden Veränderungen zu untersuchen.

Patienten und Methoden Diese randomisierte prospektive Studie inkludierte Patienten mit ERM und intraretinalen zystoiden Veränderungen, die zur Pars-plana-Vitrektomie mit Membrane Peeling vorgesehen waren. Lufttamponade oder BSS am Ende der Operation wurde entsprechend der Randomisierung durchgeführt. Optische Kohärenztomografie und Bestimmung des bestkorrigierten Fernvisus (DCVA) erfolgten präoperativ, 5 Tage und 3 Monate nach der Operation.

Resultate Von 96 in die Studie rekrutierten Patienten hatten 85 ein vollständiges „follow-up“ und konnten in die Analysen der Ergebnisse eingeschlossen werden. Die mediane Verbesserung des DCVA war + 16 ETDRS-Buchstaben (IQR: 8–22) bei Patienten mit BSS und + 13 ETDRS-Buchstaben (IQR: 8–17) bei Patienten mit Lufttamponade. Es zeigte sich ein Trend für eine stärkere Verbesserung des DCVA bei BSS verglichen zur Lufttamponade, jedoch nicht statistisch signifikant.

Schlussfolgerung Es zeigten sich keine statistisch signifikanten Unterschiede in Bezug auf Resorption der präoperativen intraretinalen zystoiden Veränderungen, Verbesserung des DCVA und des postoperativen DCVA zwischen BSS und Lufttamponade.

Introduction

Epiretinal membranes (ERM), a macular disorder leading to metamorphopsia and a decrease in visual acuity, is a rare finding among people under the age of 60 years, with prevalence rates of about 2 %, but increases to 12 to 20 % after the age of 70 years [1]. This is in accordance with other reports about ERM prevalence ranging between 1 and 28.9 % [2].

Studies examining ultrastructure and immunohistochemical properties of ERM outlined a role of hyalocytes and Müller cells in the development of ERM [3, 4], the first being located at the vitreal side of the internal limiting membrane (ILM) with a distance to the ILM of about 20–50 µm [5] and the second having the capability to migrate onto the retinal surface [6]. Both hyalocytes and Müller cells have the potential of transdifferentiation into cells with different characteristics [6, 7]. Among the cells found in ERM were also myofibroblasts, cells with contractile properties [4]. Preoperative retinal contraction, induced by tangential contraction of ERM, was reported to be positively associated with postoperative visual acuity improvement [8], whereas preoperative intraretinal cystoid changes did not significantly affect the potential for postoperative improvement of visual acuity compared to patients without [8]. Independent of that finding, preoperative intraretinal cystoid changes have been shown to significantly increase the risk for the presence of postoperative intraretinal cystoid changes [9], a factor with potential for lower final visual acuity, compared to patients without [10, 11]. The treatment of choice for ERM is vitrectomy with membrane peeling, in any case, as there is potential for improvement of visual acuity independent from the presence of preoperative intraretinal cystoid changes or retinal contraction. Nevertheless, it must be considered in presurgical planning, that disorders in the ellipsoid zone have been reported as correlating with poor visual recovery after surgery [12 – 19].

The use of air tamponade at the end of vitrectomy with membrane peeling, a common trend among vitreoretinal surgeons, is still controversially discussed. While Leitritz et al. reported a better postoperative foveal contour and a trend for better postoperative visual acuity for the group that received air tamponade at the end of surgery compared to balanced salt solution (BSS) [20], in our own previous studies, we did not find better postoperative visual acuity for air tamponade in study populations consisting of patients with and without preoperative intraretinal cystoid changes [9, 10]. As these results are somehow controversial, there is a rationale for examining the hypothesis of improved results due to the effect of tamponade among patients with preoperative existing intraretinal cystoid changes.

The aim of the present study was to analyze differences in outcomes between air tamponade and BSS in a study population scheduled for membrane peeling due to ERM with preoperative intraretinal cystoid changes, ranging from microcysts to intraretinal cystoid changes larger than microcysts.

Patients and Methods

This prospective randomized trial included patients scheduled for pars plana vitrectomy with membrane peeling for an ERM and intraretinal cystoid changes in the time period from 2017 to 2019 at the Department of Ophthalmology of the Hanusch Hospital in Vienna, Austria. Inclusion criteria for this analysis were: a) presence of an ERM with preoperative intraretinal cystoid changes, b) indication for membrane peeling defined as significant loss of vision and/or metamorphopsia due to the ERM, and c) written informed consent for study participation. Patients with macular edema caused by conditions other than ERM (such as choroidal neovascularization, diabetic macular edema, retinal vein occlusion, etc.) were excluded from the study. All research and measurements followed the tenets of the Declaration of Helsinki and were approved by the local ethics committee of the city of Vienna. Written informed consent was obtained from all patients in the study. Clinical trials registration: NCT 03457584.

After inclusion of patients into the study, randomization by minimization [21] was performed. To allocate patients to the air tamponade or BSS group (1 : 1), minimization criteria were preoperative intraretinal cystoid changes (microcysts defined as smaller than 100 micron/intraretinal cystoid changes larger than microcysts defined as 100 micron or larger), lens status (phakic/pseudophakic/planned phaco-vitrectomy), and best-corrected distance visual acuity (DCVA less than 35 letters/35 letters or more). Microcysts were defined as intraretinal cystoid changes with a maximum diameter smaller than 100 µm.

Surgery was performed with 23 G pars plana vitrectomy (23 G-ppv) and membrane peeling in all cases. To visualize the ERM and ILM, chromovitrectomy with a trypan blue and brilliant blue G-based dye was performed. The ERM was peeled using end gripping forceps, while ILM peeling was performed as a second step in cases where the retinal surface was still wrinkled after ERM peeling alone. During membrane peeling, continuous intraoperative optical coherence tomography (iOCT; Rescan 700, Carl Zeiss Meditec AG, Germany) assistance was used during the peeling procedure. The use of air tamponade at the end of surgery

was according to randomization. Only in cases where the need of a postoperative tamponade was indicated during surgery was randomization overruled. In case patients underwent air tamponade, fluid/air exchange with a complete air fill was done and postoperative face-down positioning for 24 hours was performed by the patients who were admitted overnight. Sclerotomies were checked for leakage at the end of surgery and sutured if needed (Vicryl 8–0, Johnson & Johnson Medical Limited, UK). OCT imaging of the macula was performed with a stand-alone spectral domain-OCT (SD-OCT) device (Cirrus HD-OCT, Carl Zeiss Meditec AG, Germany) before surgery, 5 days after surgery, and 3 months after surgery. All patients received nonsteroidal anti-inflammatory eye drops and steroidal eye drops during the first month after surgery.

Combined phacoemulsification with implantation of an intraocular lens and 23 G-ppv with membrane peeling was performed in cases with coexisting vision affecting cataracts. Need for cataract surgery was determined by a) grading of the cataract and comparison with the contralateral eye, and b) presurgical visual acuity. Due to randomization, the number of pseudophakic patients at the final visit (3 months after surgery) was comparable in both groups.

Intraretinal cystoid changes of the macula were diagnosed using OCT, and changes in retinal thickness in µm were assessed by OCT using the central subfield thickness of the macular thickness analysis with a diameter of 1 mm including the fovea. DCVA was measured preoperatively and at 3 months after surgery using EDTRS charts (Precision Vision, USA) at a distance of 4 meters by masked examiners.

Before inclusion into the study, patients eligible for the study were selected in cases where microcysts or intraretinal cystoid changes larger than microcysts could be detected in the preoperatively routine SD-OCT images (Spectralis OCT, Heidelberg Engineering, Germany) from our outpatient department. After patients gave informed consent for study participation, all study-related SD-OCT examinations were performed on the SD-OCT device in our study center (Cirrus HD-OCT, Carl Zeiss Meditec AG, Germany), including a baseline OCT before surgery. The SD-OCT in our study center is a device that is technically comparable to the iOCT (Rescan 700, Carl Zeiss Meditec AG) used for intraoperative assistance during membrane peeling. In case microcysts diagnosed during the prestudy screening (Spectralis OCT) were not found at the baseline examination (Cirrus HD-OCT), patients remained in the group with microcysts.

When planning the study, sample size calculation was performed under the following assumptions: a) effect of tamponade offers a hypothesis for better postsurgical results for the patients with ERM with preoperative intraretinal cystoid changes, and b) data used for sample size calculation showed a trend for better resorption of preoperative intraretinal cystoid changes among patients undergoing air tamponade at the end of surgery [10]. To avoid the sample size calculation being biased by a possible influence of phacoemulsification on resorption of preoperative intraretinal cystoid changes, only patients that were already pseudophakic before vitrectomy with membrane peeling were included into the calculation. The sample size calculation was performed using the software tool BiAS (epsilon Verlag, Germany) applying the chi-squared test, as the data was non-metric. Resorption of preoperative intraretinal cystoid changes could be seen among 7 of 23 patients in the group with air tamponade compared to 1 of 18 patients with BSS. This calculation resulted in a sample size of 44 cases for each group and we added 8 more patients to compensate for possible dropouts, resulting in 96 cases to be included into the study.

Statistical analysis was performed in a descriptive fashion for mean values, standard deviation, median, IQR, and range. All data were tested for normal distribution using the Shapiro-Wilk test and Kolmogorov-Smirnov test. In case of a normal distribution, the mean and standard deviation were calculated, and otherwise, median, IQR, and range. A t-test was used for normal distributed data, otherwise the Mann-Whitney U test was used. In cases of paired data, Wilcoxon matched pairs test was used, and for non-metric data, Fisher's exact test was used. Regression analysis was performed as a logistic regression analysis with elimination of factors with $p > 0.05$. A $p < 0.05$ was regarded to indicate significant differences between groups, and in case of significant outcomes for multiple tests, a Bonferroni test was applied, too. Statistical analysis was performed using the software tool BiAS (epsilon Verlag, Germany).

Results

From 96 eyes of 96 patients recruited for the study, 85 patients had complete follow-up and could be included into analysis of the results. The remaining patients decided not to participate at the follow-up examinations at 3 months after surgery, and therefore were excluded from analysis. Mean age of the patients included into the data analysis was 73 years ± 6 years, and among them were 46 females and 39 males, and 42 right eyes and 43 left ones. BSS was left at the end of surgery in 35 patients, 47 patients underwent air tamponade, and SF6 was applied in 3 patients (▶ **Table 1**).

The presence of idiopathic ERM (iERM) was diagnosed in 78 patients, and ERM with signs of a lamellar macular hole formation in 7 patients. Among patients with signs of a lamellar macular hole formation, three had signs of a pseudo-macular hole, three had signs of an ERM with foveoschisis, and one had signs of an atrophic lamellar macular hole. One of the patients with iERM needed a second surgery due to postoperative hemorrhage in the vitreous cavity and the patient with signs of an atrophic lamellar macular hole developed a full thickness macular hole and underwent a second surgery with pedicle ILM flap transposition, resulting in successful macular hole closure.

Randomization to BSS was overruled in five cases, three of them underwent endolaser treatment and air tamponade, and two of them underwent endolaser treatment and SF6 tamponade due to peripheral retinal breaks found during surgery. Randomization to air tamponade was overruled in one patient, who underwent endolaser treatment and SF6 tamponade due to peripheral retinal breaks, as well. Seven patients remained phakic without the need for cataract surgery, 31 patients were already pseudophakic before surgery, and in 47 patients, phaco-vitrectomy was performed.

▶ **Table 1** Demographic data of the patients.

Demographic Data	Number of Patients/Years
Mean age of patients	73 (± 6)
Gender	46 females, 39 males
Eye	42 right, 43 left
Indication for surgery	
▪ iERM	78
▪ ERM with sign of a lamellar macular hole	7
Air-tamponade/BSS/SF6	47 air, 35 BSS, 3 SF6
Lens status	7 phakic, 31 pseudophakic, 47 phaco-vitrectomy
Size of intraretinal cystoid changes	64 microcysts, 21 larger than microcysts

After exclusion of patients where randomization had to be overruled, patients with BSS had a median improvement of DCVA 3 months after surgery of + 16 EDTRS letters (IQR: 8 to 22, range: − 8 to 33) compared to patients that received air tamponade at the end of surgery, who had a median improvement of DCVA 3 months after surgery of + 13 EDTRS letters (IQR: 8 to 17, range: − 14 to 39). This difference between the groups was not statistically significant ($p = 0.182$, Mann-Whitney U test). Median final DCVA 3 months after surgery among patients with BSS was 50 EDTRS letters (IQR: 45 to 53, range: 30 to 60) compared patients with air tamponade with 48 EDTRS letters (IQR: 41 to 55, range: 5 to 58). This difference between the groups was not statistically significant ($p = 0.447$, Mann-Whitney U test). In both groups, postsurgical DCVA was significantly improved compared to presurgical DCVA (BSS: $p < 0.001$, air tamponade: $p < 0.001$, Wilcoxon matched pairs test). Detailed results of patients according to indication of surgery and size of intraretinal cystoid changes are listed in ▶ **Table 2**.

Intraretinal cystoid changes at the baseline OCT examination were predominantly present in the inner nuclear layer (68%), while presence in the outer nuclear layer (26%) and ganglion cell layer (7%) in most cases was additional to the presence in the inner nuclear layer. Intraretinal cystoid changes had the size of microcysts in 75% (n = 64) of patients, and larger than microcysts were found in 25% (n = 21) of patients (▶ **Fig. 1** and **2**). Median largest diameter of intraretinal cystoid changes at the preoperative baseline examination was 36 µm (IQR: 24 to 57; range: 14 to 94) for microcysts and 142 µm (IQR: 132 to 197; range: 104 to 426) for intraretinal cystoid changes larger than microcysts, indicating a significant difference between groups ($p < 0.001$, Mann-Whitney U test).

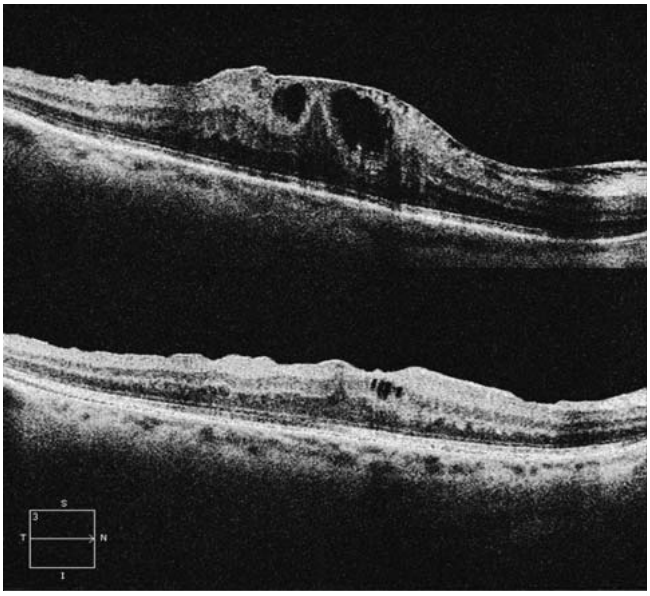
Resorption of intraretinal cystoid changes (microcysts or larger) among patients with iERM was seen in 58% (n = 45) of patients (▶ **Fig. 1**), while new postoperative intraretinal cystoid changes larger than microcysts (developed from preoperative microcysts) were present in 5% (n = 4) of patients 3 months after surgery. Patients with iERM that developed new postoperative intraretinal cystoid changes larger than microcysts had a significantly lower improvement of DCVA 3 months after surgery ($p = 0.001$, Mann-Whitney U test) and a trend for a lower final DCVA, although not reaching statistically significant levels ($p = 0.1$, Mann-Whitney U test). There were no statistically significant differences concerning resorption of intraretinal cystoid changes between patients with preoperative microcysts or preoperative intraretinal cystoid changes larger than microcysts ($p = 0.3$, Fisher's exact test). Among patients with ERM with signs of a lamellar macular hole formation, resorption of intraretinal cystoid changes occurred only in one patient (14%) that was allocated to the BSS group.

Fifty-one percent of patients (n = 43) underwent ERM and ILM peeling en bloc (the ILM was not actively peeled, but spontaneously together with the ERM), 36% (n = 31) underwent ERM peeling with additional ILM peeling as a second step, and 13% (n = 11) underwent ERM peeling alone. Furthermore, 15% (n = 13) had a

▶ **Table 2** An overview of the median improvement of DCVA and final DCVA for patients with air tamponade or BSS at the end of surgery (all patients, according to indications and size of intraretinal cystoid changes). Neither air tamponade nor BSS reached statistically significant levels (Mann-Whitney U test).

	Improvement of DCVA – air	Improvement of DCVA – BSS		Final DCVA – air	Final DCVA – BSS	
All patients	+ 13 letters, IQR 8 to 17	+ 16 letters, IQR 8 to 22	p = 0.2	48 letters, IQR 41 to 55	50 letters, IQR 45 to 53	p = 0.5
iERM patients (all)	+ 13 letters, IQR 9 to 17	+ 16 letters, IQR 10 to 23	p = 0.2	48 letters, IQR 42 to 55	50 letters, IQR 45 to 53	p = 0.4
▪ Preoperative microcysts (iERM)	+ 14 letters, IQR 10 to 17	+ 16 letters, IQR 8 to 21	p = 0.3	49 letters, IQR 43 to 55	50 letters, IQR 47 to 54	p = 0.6
▪ Preoperative intraretinal cystoid changes larger than microcysts (iERM)	+ 11 letters, IQR 6 to 16	+ 19 letters, IQR 10 to 25	p = 0.1	40 letters, IQR 15 to 48	45 letters, IQR 43 to 55	p = 0.2
ERM with signs of a lamellar macular hole	+ 6 letters, IQR − 14 to 10	+ 9 letters, IQR − 4 to 18	p = 0.6	50 letters, IQR 15 to 55	45 letters, IQR 39 to 54	p = 1.0

▶ **Fig. 1** Preoperative microcysts (upper panel) have the potential to disappear after surgery (lower panel).



▶ **Fig. 2** Preoperative intraretinal cystoid changes larger than microcysts (upper panel) showed a reduction in lesion size 3 months after surgery.

history of diabetes mellitus, but without diabetic macular edema. Logistic regression analysis (with the elimination of factors with $p > 0.05$ and 3 possible predictors) showed none of the selected predictors (air tamponade, ILM peeling, and presence of a diabetes mellitus) being a significant predictor for postsurgical resorption of intraretinal cystoid changes or postsurgical improvement of DCVA of 10 or more letters.

Discussion

Improvement of DCVA and final DCVA were not statistically significant different between patients receiving air tamponade or BSS at the end of surgery, but there was a trend for better improvement of DCVA in the group of patients with BSS.

ERM belongs to the three most frequent reasons for development of microcysts [22]. Preoperative intraretinal cystoid changes (microcysts or larger) occur in about 24 to 39% of patients with ERM [9, 23]. Besides possible mechanical reasons by traction on the tissue, induced by ERM contraction, oxidative stress and inflammatory mediators can lead to disturbed fluid transport of Müller cells, contributing to retinal edema [24].

Surgical removal of epiretinal membranes, and thereby relieving ERM caused traction on the retinal tissue, has the potential for improvement of visual acuity in a great majority of patients, and, furthermore, led to the resorption of intraretinal cystoid changes in more than half of our patients. The fact that resorption of intraretinal cystoid changes is possible after surgery confirms ERM to be one of the reasons for the development of intraretinal cystoid changes. Nevertheless, development of new postoperative intraretinal cystoid changes, described in 1 to 61% of patients undergoing vitrectomy with membrane peeling for iERM removal [11, 25–29], leaves speculations about postoperative inflammatory processes being the reason open. Effects on postoperative results of intraretinal cystoid changes were controversially discussed, as some authors reported new postoperative intraretinal cystoid changes not affecting postoperative visual acuity [25, 27–29], while others found intraretinal cystoid changes to be associated with reduced vision after surgery [11, 26]. In the present study, all included patients had intraretinal cystoid changes before surgery (microcysts or larger), therefore, we could only assess the conversion of microcysts to intraretinal cystoid changes larger than microcysts, with a somehow expected negative impact on postoperative visual acuity.

Patients with iERM and microcysts showed a trend for better improvement of DCVA and a statistically significant better final DCVA compared to patients with intraretinal cystoid changes larger than microcysts. Furthermore, resorption of preoperative intraretinal cystoid changes among patients with iERM was not significantly different between BSS and air tamponade.

Air tamponade at the end of surgery, which is quite commonly used by surgeons, did not provide any benefit for our patients that underwent 23 G-ppv with membrane peeling. Furthermore, there was even a trend for a slightly lower DCVA when air tamponade was applied. This is in accordance with our previous studies [9, 10, 30] in study populations where the presence or absence of intraretinal cystoid changes were not defined as exclusion criteria. In contrast to our results, Leitritz et al. [20] reported a trend for better postoperative visual acuity among patients with air tamponade, but it must be mentioned that that study was of a retrospective nature with possible bias concerning unequal distribution of lens status among groups, preferences of surgeons according to selection of tamponade, and unequal distribution of preoperative visual acuity and macular thickness. Additionally, it must be kept in mind when deciding for air tamponade, accumulation of inflammatory cytokines in the remaining fluid could also have a negative effect on intraretinal cystoid changes.

Unfortunately, the number of patients with complete follow-up was 85 and therefore, below the number of patients calculated during the sample size calculation (n = 88). Therefore, we performed a post hoc sample size calculation with the outcomes of iERM patients. For the parameter resorption of intraretinal cystoid changes after surgery between both groups and applying the chi-square test, the calculated sample size is 24581 cases for each group (power 80% and p = 0.05) and for the parameter differences in DCVA between both groups and applying the Mann-Whitney U test, the calculated sample size is 315 cases per group (power 80% and p = 0.05). For both parameters, the sample size is large – too large for a single study center – and indicates very small differences between groups. We, therefore, decided not to increase the number of patients to recruit for the study, as differences between air tamponade and BSS are very small, with comparable outcomes for patients with iERM.

A limitation of the present study is the small number of patients with ERM with signs of a lamellar macular hole formation, explained by the fact that more patients with iERM are undergoing surgery than patients with ERM with signs of a lamellar macular hole formation Therefore, we did not perform a detailed subgroup analysis among patients with ERM with signs of a lamellar macular hole formation. Furthermore, discrepancies in the presence of intraretinal cystoid changes with different SD-OCT devices occurred in the study. While it was known, when planning our trial, that there are differences in macular thickness measurements between the used devices [30, 31], we did not expect this for defining the occurrence of intraretinal cystoid changes. When planning the study, we decided to use a technically comparable OCT device (Cirrus HD-OCT, Carl Zeiss Meditec AG, Germany) to the routinely used iOCT (Rescan 700, Carl Zeiss Meditec AG, Germany), as we use this device for iOCT assistance during membrane peeling. Nevertheless, we checked eligibility for inclusion into the study on the preexisting OCT images from our outpatient department (Spectralis OCT, Heidelberg Engineering, Germany) to be in accordance with ethical standards performing study-related examinations only after written informed consent of patients.

Concluding, we did not find significant differences in resorption of preoperative intraretinal cystoid changes, improvement of visual acuity, and final DCVA between BSS and air tamponade after vitrectomy with membrane peeling for ERM removal.

Conflict of Interest

O. Findl is a scientific advisor for Alcon, Croma, Carl Zeiss Meditec AG and Merck, but has no personal interest in the products mentioned. All authors declare that they have no conflict of interest.

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