Evaluation of the Effect of Peroperative Bevacizumab on Anatomical and Functional Outcomes in Epiretinal Membrane Cases Secondary to Diabetes Mellitus

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ABSTRACT

Purpose: To evaluate the effect of peroperative intravitreal bevacizumab (IVB) addition on anatomical and functional outcomes in the secondary epiretinal membrane (ERM) peeling surgery in eyes with a diagnosis of proliferative diabetic retinopathy (PDR).

Materials and Methods: Patients who had previously received laser photocoagulation and anti-vascular endothelial growth factor (VEGF) treatments for PDR had extensive macular thickening/loss of foveal depression with ERM and underwent ERM peeling surgery were included. Surgeries were classified according to the use of IVB. Changes in best-corrected visual acuity (BCVA) and central macular thickness (CMT) were compared.

Results: While IVB was applied to 9 eyes of 9 patients with a mean age of 65.8 years at the end of the surgery, IVB was not applied to 13 eyes of 13 patients with a mean age of 66.2 years. The mean BCVA was 0.78 and 0.72 logMAR preoperatively, 0.40 and 0.47 at postoperative 1st month, and 0.38 and 0.43 logMAR at postoperative 3rd month in IVB and control groups respectively. Mean BCVA change favored the IVB group, but the difference was not significant. The mean CMT was 417.53 and 397.6 µm preoperatively, 341.23 and 361.63 at postoperative 1st-month, and 312.34 and 341.37 µm at postoperative 3rd-month in IVB and control groups respectively. The change of CMT was found to be significantly higher in the IVB group in both the 1st-month (P=0.009) and 3rd-month (P=0.019).

Discussion: Increased VEGF load due to PDR and traction due to ERM may be responsible for cases of macular thickening accompanied by ERM. It has been observed that the addition of IVB at the end of the surgery may have a positive effect on anatomical and functional results by targeting both possible etiopathogeneses.

Keywords: Bevacizumab, Diabetic retinopathy, Macular surgery, Secondary epiretinal membrane.

INTRODUCTION

First described by Iwanoff in 1865, the epiretinal membrane (ERM) is an avascular, translucent formation arising from fibrocellular proliferation on the inner surface of the retina.[1] Its cellular component consists mostly of glial cells, retinal pigment epithelial cells, and myofibroblasts.[2] ERM can cause loss of the normal anatomy of the retina and functional complaints such as metamorphopsia, micropsia, monocular diplopia, and decreased visual acuity.[3]

ERM is classified as idiopathic or secondary according to the presence of pathology that initiates its formation.[4] A proliferating fibroglial component causes idiopathic ERM after a break in the inner limiting membrane (ILM) that occurs during posterior vitreous detachment. Secondary ERM can develop from retinal vascular pathologies such as diabetic retinopathy (DR) and retinal vein occlusion, an existing ocular pathology such as uveitis, or after ocular treatments such as vitreoretinal surgery and argon laser photocoagulation.[5]

Several chemokines, cytokines, and growth factors are reported to be upregulated in the vitreous eyes with proliferative diabetic retinopathy (PDR).[6] Growth factors, especially vascular endothelial growth factor (VEGF), immunological components, and laser photocoagulation therapy, may cause secondary ERM development in an eye with a history of PDR. Similarly, upregulated VEGF and

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receptors are reported in cells in vascular and avascular ERM formations secondary to DR.[7, 8]

Epiretinal membrane peeling (MP) has become a well-established procedure for treating ERM, with high reported rates of visual improvement.[9] The most common cause that may endanger the visual outcome following a successful ERM surgery is macular edema after vitrectomy, which has been reported as high as 47%[10], and it is possible to be encountered in ERM cases secondary to diabetes. A recent meta-analysis reported that the addition of an intraoperative dexamethasone implant in eyes underwent vitrectomy for ERM provided better visual and anatomical results at 3 months compared to ERM vitrectomy without an implant.[11] However, there is no report in the literature regarding intraoperative anti-VEGF administration at the end of ERM surgery.

Therefore, we aimed to compare the effect of intravitreal bevacizumab (IVB) supplementation applied at the end of surgery on early anatomical and functional outcomes in patients with ERM secondary to diabetes mellitus who had a diagnosis of PDR and stabilized with argon laser photocoagulation and anti-VEGF treatments but cause foveal contour loss/visual complaints.

MATERIALS AND METHODS

Study design

This retrospective comparative study included patients scheduled for pars plana vitrectomy (PPV) with MP due to ERM cases secondary to PDR at Kayseri City Training and Research Hospital. This study adhered to the Declaration of Helsinki's tenents and was approved by the Kayseri City Training and Research Hospital Ethics Committees (approval number: 151074054).

Chart Review

We reviewed the medical records of patients who underwent PPV and MP surgery for ERM secondary to diabetes between June 2017 and 2021, from patients with stabilized retinopathy who had previously received argon laser photocoagulation and intravitreal treatments for PDR. Patients who had MP surgery due to ERM secondary to PDR that disrupted the fovea contour caused visual complaints, and had follow-ups longer than postoperative 3 months were evaluated. It was obtained from the surgical records whether or not an IVB injection was performed at the end of the operation. Accordingly, 22 eyes of 22 patients were included in the final analysis.

Secondary ERM formations were diagnosed clinically by funduscopy and visualized by spectral domain-optical coherence tomography (SD-OCT, Spectralis HRA OCT; Heidelberg Engineering, Heidelberg, Germany). On the SD-OCT images, secondary ERM was defined as a diffuse or focally attached hyperreflective band anterior to the neurosensory retina. Patients who underwent surgery for secondary ERM were evaluated according to Govetto et al.'s OCT-based ERM staging system, and patients with stage 2 and above in whom foveal depression disappeared were included in the study.[12] Fundus fluorescein angiography (FFA, Carl Zeiss Meditec AG, Jena, Germany) imaging of the patients in the last 3 months before surgery was evaluated to detect the presence of neovascularization and/or retinal ischemic areas requiring treatment. Patients without a recent FFA image were not included in the study.

Best-corrected visual acuity (BCVA) was evaluated with ETDRS charts. Patients with ERM secondary to PDR, treated with panretinal argon laser photocoagulation and anti-VEGF intravitreal injections, without active retinopathy but with continuing visual complaints such as diffuse retinal thickening and/or metamorphopsia/micropsia were included in the study.

Primary ERM, macular oedema caused by other retinal pathologies (retinal vascular occlusion, age-related macular degeneration, uveitis), tractional retinal detachment secondary to PDR, recent (within 3 months) intraocular surgery, or previous vitreoretinal surgery were the exclusion criteria.

SD-OCT was performed preoperatively and at 1st-month and 3rd-month postoperatively to document central macular thickness (CMT). Similarly, BCVA was evaluated preoperatively, at 1st- and 3rd-month postoperatively. The CMT analysis was performed within a 1 mm diameter circle centered on the fovea. In the present study, all of the imaging was performed by the same experienced nurse (SE), which provides data standardization for retrospective research. We evaluated the macula using a 6x6 mm square macular cube protocol. Both the anatomical and visual acuity evaluations were performed by the other retina specialist (NB), who was masked and did not know whether IVB was used in the patients' operation. Subsequently, the operating surgeon performed the anatomical and functional comparisons of the two surgical groups using the medical data recorded in the patients' files. The surgical procedure is described below.

Surgical Technique

Surgery was performed in a standardized fashion, with a 25-gauge 3-port pars plana vitrectomy (Constellation Vision System; Alcon Inc.) was performed in all patients. In the phakic patients, since all patients were over 50 years old and had at least early-stage cataracts, phacoemulsification and intraocular lens implantation were performed in the same surgical setting. Firstly, a core vitrectomy was performed, and posterior hyaloid (PH) was removed with the help of 0.1 mL (4 mg) triamcinolone acetonide (Kenacort-A; 40 mg/mL; Bristol-Myers Squibb). After removing PH, brilliant blue G and trypan blue-based dye (Membrane Blue-Dual; DORC-Dutch Ophthalmic Research Center) was injected to enhance the visualization of the ERM and ILM before their removal. Operations were performed with the help of the nitinol flex loop (NFL). An edge of the flap was created by NFL, and the uplifting end of the membrane was caught by forceps and peeled off. In the case of flap loss, the new flap creation attempt was achieved with the NFL again. MP was performed in a circumferential pattern for an average of 2 disk diameters around the foveal area, and attempts were made typically temporal to the macula. After removing the ERM, ILM peeling was performed in all patients with secondary staining. After fluid-air exchange (FAX), sclerotomies were checked and sutured if needed at the end of the surgery. All procedures were performed by a single surgeon (CO). Due to the change in the insurance system in January 2019 and the ease of access to bevacizumab, 1.25 mg/0.05 ml bevacizumab was added to the surgeries performed after this date, and no additional criteria or bias was found in patient selection. The patients were classified into two groups according to the use of IVB at the end of the operation.

Outcome Measures

The effect of IVB administration on CMT and BCVA improvement at 1 month and 3 months postoperatively was investigated. The change in CMT was determined by the difference between preoperative and postoperative 1st-month and 3rd-month in the 1 mm central retinal circle.

STATISTICAL ANALYSIS

SPSS for Windows version 22.0 (SPSS Inc., Chicago, IL, USA) was used for data analysis. Mean and standard deviations were calculated for quantitative variables. Frequencies and percentages were calculated for categorical variables. The difference between preoperative and postoperative at 1st and 3rd-month visits in CMT and BCVA within the same group was compared with the Wilcoxon-Signed rank test. Preoperative CMT, BCVA, and the change in CMT and BCVA at follow-up visits were compared between the groups using the Mann-Whitney U test. P <0.05 was considered to be statistically significant.

RESULTS

Twenty-two eyes of 22 patients who underwent MP surgery for secondary ERM due to PDR were studied. Of the patients included in the study, 9 (40.9%) were male, and 13 (59.1%) were female, with a mean age of 66 ± 5.13 years. At the end of the operation, IVB was applied to 9 eyes (40.9%), while IVB was not applied to 13 eyes (59.1%). Patients were followed up for 4.7 ± 0.7 months (4.4 months in the IVB group vs. 4.8 months in the control group, P> 0.05). In the same session, simultaneous cataract surgery was performed in all phakic eyes (IVB group: 44.4% vs. control group: 46.1%, P> 0.05). There were no significant differences in patient age, gender, CMT, BCVA, and the number of past intravitreal anti-VEGF injections between the two groups in the preoperative period (Table 1).

Comparison of anatomical and functional outcomes

An overview of the CMT and BCVA changes following surgery is detailed in Table 2. Examining the central macula, the mean CMT was 417.53 ± 40.39 µm at preoperatively, 341.23 ± 51.17 µm at postoperative 1st-month (preoperative vs. 1st-month p=0.001), and 312.34 ± 44.62 µm at postoperative 3rd-month (preoperative vs. 3rd-month $p<0.001$) in the IVB group vs. 397.62 ± 53.72 µm at preoperatively, 361.63 ± 40.49 µm at postoperative 1st-month (preoperative vs. 1st-month p=0.027), and 341.37 ±

Table 1. *Baseline characteristics of the surgery groups.*

Parameter	IVB	Control	P
Age (year)	65.8 ± 5.01	66.2 ± 5.26	0.353†
Gender (female/male)	5/4	5/8	0.231*
Laterality (R/L)	5/4	6/7	0.376*
Follow up duration (month)	4.4±0.54	4.8±0.83	0.286†
Phakic eyes	4/9	6/13	0.429*
Preperative mean BCVA (logMAR)	0.78 ± 0.19	0.72 ± 0.18	0.376†
CMT (µm)	417.53 ± 40.39	397.62 ± 53.72	0.462†
Past intravitreal anti-VEGF injections	5.89±2.25	6.34±1.79	0.473†

BCVA; best corrected visual acuity, CMT; central macular thickness, VEGF; vascular endothelial growth factor
† Mann-Whitney U test, *Chi-square test

48.93 µm at postoperative 3rd-month (preoperative vs. 3rd-month *p*=0.019) in the control group. The average CMT thickness reduction was significantly higher in the IVB group in the postoperative 1st-month (76.3 µm vs. 35.99 µm, *p*= 0.009) and postoperative 3rd-month (105.1 µm vs. 56.25 µm, *p*= 0.019)

In the preoperative period, the mean BCVA was 0.78 ± 0.19 and 0.72 ± 0.18 logMAR in the IVB and control groups, respectively. No significant difference was observed between preoperative BCVA in the two surgery groups (*p*= 0.067). In both surgery groups, the VA improved significantly. The mean BCVA improved to 0.40 ± 0.08 logMAR in the IVB and 0.47 ± 0.16 logMAR in the control group at the postoperative 1st-month visit (*p*=0.109). The mean BCVA improved to 0.38 ± 0.12 logMAR in the IVB and 0.43 ± 0.26 logMAR in the control group at postoperative 3rd-month visit (*p*=0.186). Although the increase in BCVA was higher in the postoperative 1st-month and postoperative 3rd-month in the IVB group, this difference was not significant (Table 2).

Simultaneous phacovitrectomy was performed on 4 eyes (44.4%) in the IVB group and 6 eyes (46.1%) in the control group. When we evaluated the patients who underwent phacoemulsification combined surgery as the groups that received and did not receive IVB, we analyzed 4 (combined surgery) and 5 (PPV alone) eyes in the IVB group and 6 (combined surgery) and 7 (PPV alone) eyes in the group without IVB, but we did not find any significant difference in terms of visual gain or anatomical improvement between groups (p>0.05). When the two groups were evaluated together whether combined phacoemulsification surgery impacted CMT and BCVA changes, no significant difference was observed between vitrectomy surgery and phacovitrectomy surgery in terms of VA improvement (p=0.204) or CMT decrease (p=0.191).

In the early postoperative period, intraocular pressure (IOP) increase was observed in five eyes (22.7%), which was controlled by medical treatment, and surgery was not needed. Complications such as hypotonia, retinal tear, retinal detachment, vitreous hemorrhage, ERM recurrence, or endophthalmitis were not encountered in the postoperative period.

DISCUSSION

In this study, we compared the effect of IVB addition at the end of the surgery on anatomical and functional recovery in patients who underwent surgery for ERM secondary to PDR.

While the migration and proliferation of glial cells in the retina due to ILM rupture and the formation of a basis that may lead to cell proliferation of the vitreous cortex remaining in the posterior precortical vitreous pocket are held responsible for the development of idiopathic ERM; it is thought that cytokines and growth factors (VEGF, etc..) released into the vitreous cavity due to retinal ischemia seen in PDR may be responsible for the development of secondary ERM.[13] The presence of macrophages, fibroblasts, and collagen fibrils in addition to glial cells and hyalocytes, the presence of more cells compared to idiopathic ERM[14], the fact that some of the cells are composed of endothelial cells forming microvascular spaces, and expression of proliferation and adhesion markers such as Ki-67 and CD 34 support this hypothesis.[15]

DR can progress to the proliferative stage, which can lead to permanent vision loss, with the effect of VEGF and similar growth factors secreted from ischemic retinal areas unless timely and adequate treatment is applied. Increased VEGF expression in response to tissue ischemia and hypoxia from retinal non-perfusion areas results in macular edema and fibrovascular proliferation. While panretinal photocoagulation (PRP) prevents the continuation of

Table 2. *Comparison of central macular thickness and the mean best corrected visual acuity changes before and after surgeries according to groups.*

		IVB applied group	Control group	P value of the mean CMT change†	P value of the mean BCVA change†
	Preoperative	417.53 ± 40.39	397.62 ± 53.72	0.462	
CMT um	Postoperative 1st month	341.23 ± 51.17	361.63 ± 40.49	**0.009**	
	Postoperative 3rd month	312.34 ± 44.62	341.37 ± 48.93	**0.019**	
BCVA logMAR	Preoperative	0.78 ± 0.19	0.72 ± 0.18		0.376
	Postoperative 1st month	0.40 ± 0.08	0.47 ± 0.16		0.109
	Postoperative 3rd month	0.38 ± 0.12	0.43 ± 0.26		0.186

CMT; central macular thickness, BCVA; best corrected visual acuity. † Mann-Whitney U test

VEGF production from ischemic areas in an eye that has reached the PDR stage, intravitreal anti-VEGF agents reduce the VEGF load in the vitreous and are effective in preventing PDR-related complications and improvement of vision.[16] Therefore, in our study, we thought that it would be advantageous to suppress VEGF, which may continue to be produced from retinal tissues and contribute to the development of macular edema/retinal cystic formations, by applying an anti-VEGF agent at the end of the surgery. Both hyperglycaemia, ischaemia, inflammatory cytokines/growth factors (TGF-β) accompanying PDR and argon laser photocoagulation treatment may play a role in the development of secondary ERM.[17]

The treatment of secondary ERM that causes foveal distortion and/or visual disturbances such as micropsia, metamorphopsia, monocular diplopia, and decreased visual acuity is surgical, and spontaneous separation of these membranes is rare.[18, 19] There are many reports in the literature regarding the safety and effectiveness of idiopathic and secondary ERM surgery.[11, 20, 21]

It has been reported that the ILM of patients with diabetes may contribute to the development of simultaneous diabetic macular edema/diffuse macular thickening, as it expresses higher collagen, fibronectin and laminin, is thicker, and contains VEGF and interleukin 6 receptors.[22, 23] Besides, higher VEGF levels in the vitreous of PDR eyes also contribute to increased vascular permeability. The eyes included in our study had diffuse retinal thickening (mean preoperative CMT: 417.53 µm in the IVB group, 397.62 µm in the control group) with an ERM that disrupted the foveal contour, despite previous treatment with an argon laser and intravitreal anti-VEGF agents. The presence of VEGF and VEGF receptors (VEGFR1 and VEGFR2) in cells in ERMs and ERM suggests that VEGF may be an autocrine/paracrine stimulant that may contribute to the progression of ERM.[24] Studies have been reported that triamcinolone acetonide and dexamethasone implant given as an intravitreal injection at the end of the surgery can accelerate the resorption of intraretinal oedema and the improvement in visual acuity, rather than waiting for intraretinal oedema to resolve spontaneously after ERM peeling, and this has been explained as facilitating fluid reabsorption by decreasing VEGF production.[25, 26] It is reported in the literature that dexamethasone implant can be safely injected intraoperatively in PPV surgery performed for ERM.[27] In a meta-analysis examining the effects of intravitreal dexamethasone implant addition to ERM surgery, it was reported that the addition of intraoperative dexamethasone implant provided a better visual outcome at 3 months and a better anatomical outcome with a faster reduction of macular thickness compared to ERM vitrectomy without the implant.[11] However, to the best of our knowledge, no study has been reported comparing the effects of anti-VEGF addition on anatomical and functional recovery after PPV surgery for ERM secondary to diabetes. Therefore, we investigated the effects of adding an antagonist of the VEGF molecule, which is known to have a direct role in pathogenesis, on the results. It was observed that anatomical recovery was faster in the postoperative 1st- and 3rd-month in eyes with IVB addition, and the decrease in CMT was significantly higher compared to the control group. Although the vision improvement was higher in the IVB group, this difference was not significant between the groups. However, visual improvement in a short time after surgery was remarkable for both groups.

It is known that vitreoretinal surgery accelerates cataract progression in phakic eyes, and simultaneous cataract surgery provides faster and permanent visual rehabilitation.[28] 44.4% of the IVB group and 46.1% of the control group were phakic. All of them were over 50 years of age and had at least early-stage cataracts. Therefore, combined surgery was performed on all phakic eyes, even in mild cataracts, and the effect of cataract progression on visual recovery was controlled in the postoperative period. Also, no difference was observed between the vitrectomy surgery and phacovitrectomy surgery groups regarding postoperative VA improvement and decrease in CMT. The point that should be considered is that the inflammation created by combined surgery can make a difference in CMT reduction. However, the phakic eye and combined surgery rates were similar between the two groups, suggesting that they would have similar effects on anatomical recovery.

It was observed that anatomical recovery was faster and the foveal contour improved faster in the IVB group in the 1st- and 3rd-month postoperatively, CMT reduction was significantly better, and intraretinal cystic formations were less common in eyes that underwent IVB during the 3rd-month follow-up period (Figure 1 and 2). Visual acuity improved significantly in both groups in the postoperative period, but the improvement was similar in both groups, and the anatomical superiority of the IVB group was not significantly reflected in functional recovery. The fact that possible problems with optic nerve and macular blood supply may affect functional recovery in eyes with PDR accompanied by ischemia may explain these anatomical and functional discrepancies. Any anti-VEGF agent could be used at the end of the surgery; we administered IVB to the patients because of ease to access in operating room conditions.

One of the shortcomings of this study is the short follow-up period. However, at a follow-up period of bevacizumab well above the half-life in the vitrectomized eye, additional

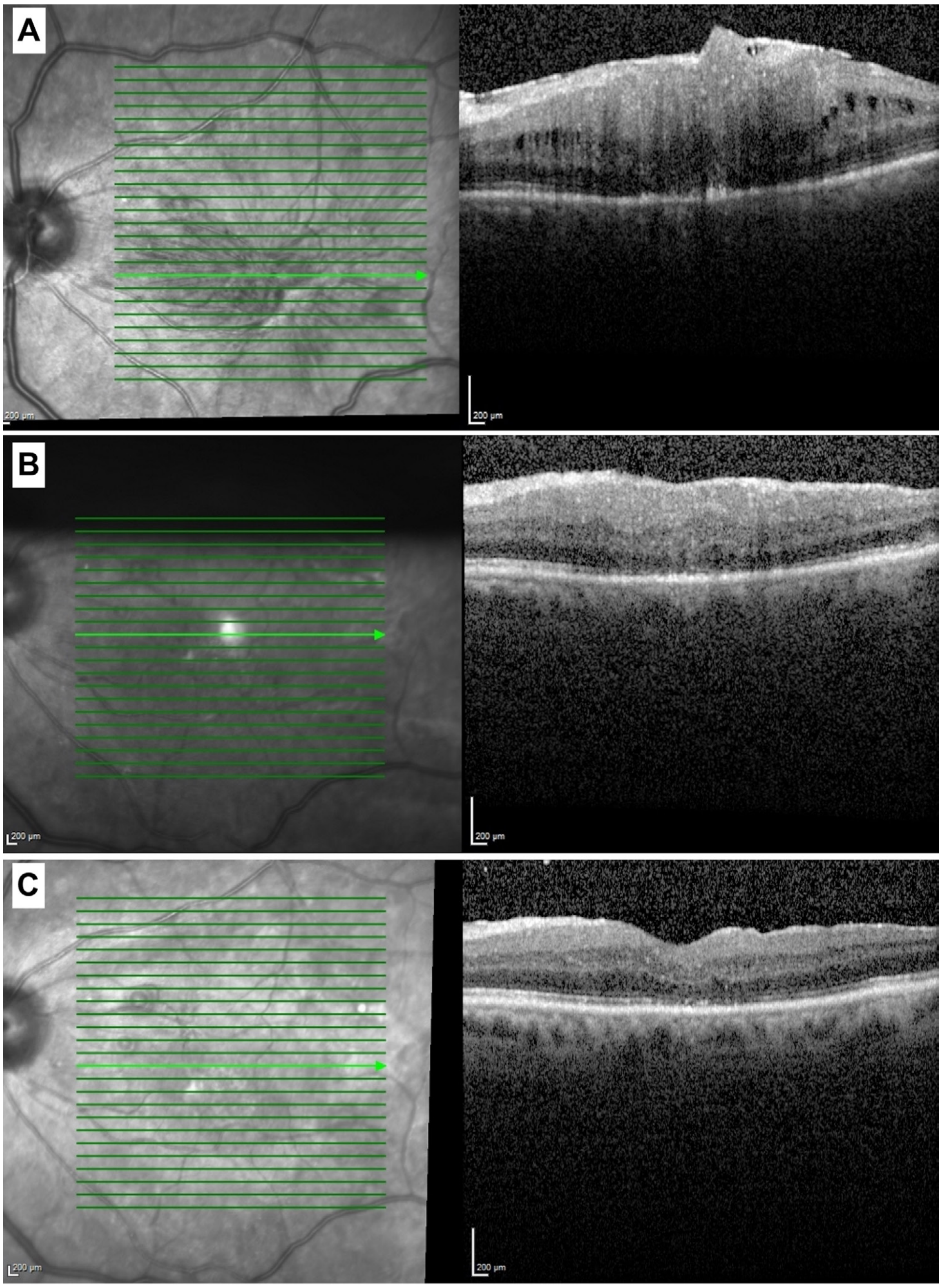

Figure 1: *Preoperative and postoperative optical coherence tomography images of intravitreal bevacizumab added to secondary epiretinal membrane peeling surgery. It is observed that IVB accelerates the formation of the foveal contour and reduces intraretinal cyst formations.*

anti-VEGF may be needed, and postoperative anti-VEGF activity may be in question instead of an intraoperative anti-VEGF activity. It should also be kept in mind that with longer follow-up periods, ERM recurrences may develop, and anatomical/functional results may be affected. The non-randomized character and a limited number of patients can be considered as another limitation. In addition, if the numbers of patients were larger, the effect of confounding factors such as phacoemulsification could be statistically more strongly evaluated. However, it should be kept in mind that the number of patients with a history of PDR who underwent secondary ERM surgery without tractional retinal detachment is considerably less compared to the idiopathic ERM patient group. One of the advantages of this study is that, to our knowledge, it is the first study to compare the effects of intraoperative IVB use for secondary ERM surgery.

In conclusion, it can be stated that ERM surgery secondary to PDR is a safe and effective procedure that provides foveal contour formation and improves vision and macular

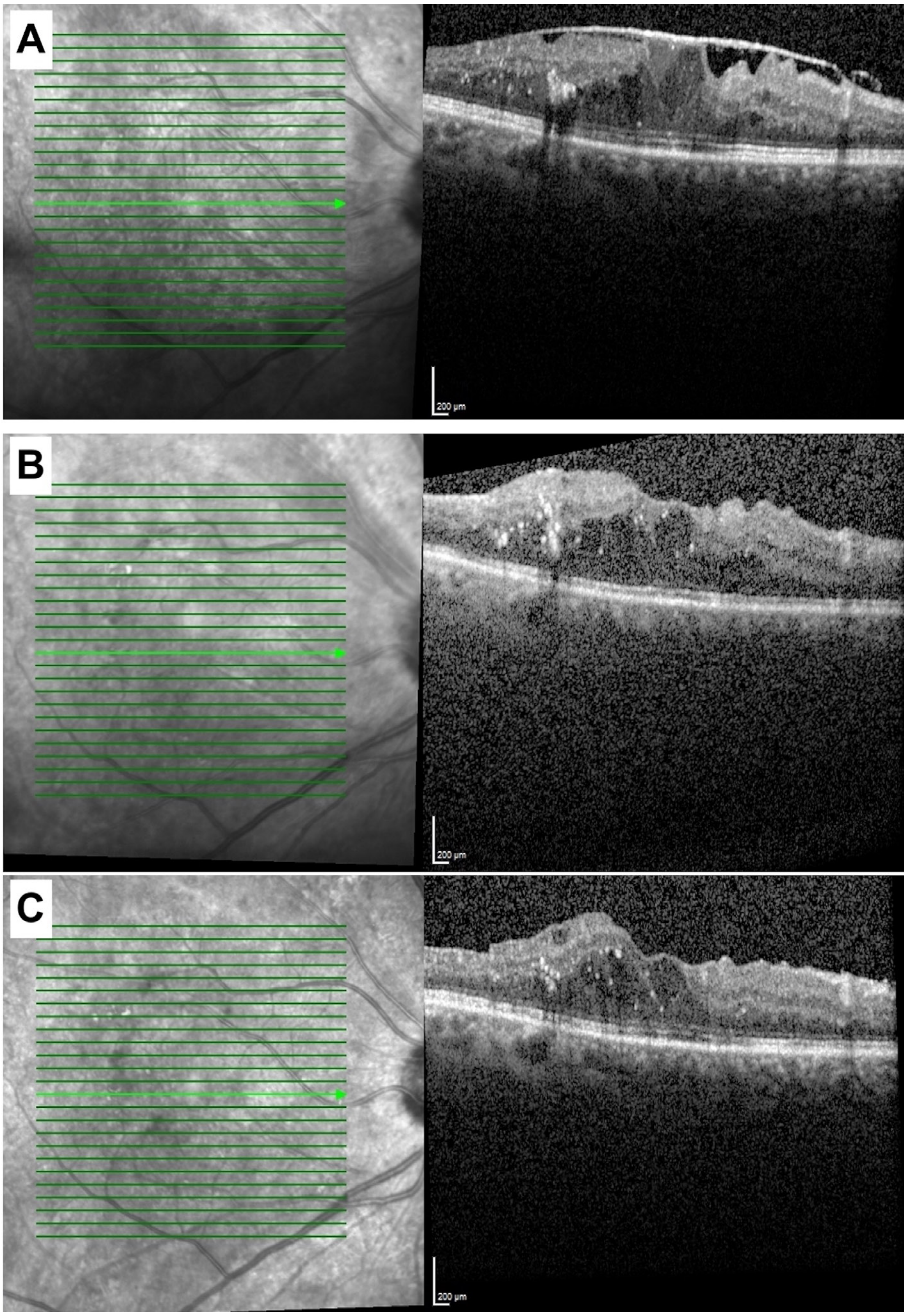

Figure 2: *Preoperative and postoperative optical coherence tomography images of an eye underwent secondary epiretinal membrane peeling surgery without intravitreal bevacizumab.*

thickness. With the clarification that growth factors, especially VEGF and various cytokines, are involved in the pathogenesis of secondary ERM formation, it can be thought that the use of intraoperative anti-VEGF agents may accelerate anatomical recovery and contribute to functional improvement.

DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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