Biosketch

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Clinical Study

Predicting Visual Outcomes for Macula-Off Rhegmatogenous Retinal Detachment with Optical Coherence Tomography

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Purpose. We evaluated the ability of novel optical coherence tomography (OCT) parameters to predict postoperative best-corrected visual acuity (BCVA) in macula-off rhegmatogenous retinal detachment (RRD) eyes. *Methods.* We reviewed the medical records of 56 consecutive eyes with macula-off RRD. Clinical findings were analyzed including the relationship between preoperative OCT findings and 6-month postoperative BCVA. *Results.* Six-month postoperative BCVA was significantly correlated with preoperative findings including retinal height at the fovea, total and inner layer cross-sectional macular area within 2 mm of the fovea, and preoperative BCVA ($P < 0.001$, $P < 0.001$, $P = 0.001$, and $P < 0.001$, resp.). Multiple regression analysis revealed that the duration of macular detachment and total cross-sectional macular area were independent factors predicting 6-month postoperative BCVA ($P = 0.024$ and $P = 0.041$, resp.). *Conclusions.* Measuring preoperative total cross-sectional area of the macular layer within 2 mm of the fovea with OCT is a useful and objective way to predict postoperative visual outcome in eyes with macula-off RRD.

1. Introduction

Although remarkable progress has been achieved in the surgical treatment of eyes with rhegmatogenous retinal detachment (RRD), it is still difficult to predict postoperative visual outcomes when RRD includes a detached macula, known as macula-off RRD. Newly developed less-invasive surgical interventions, particularly 25-gauge microincision vitrectomy surgery (25GMIVS), have led to a very high initial reattachment rate for eyes with RRD, currently about 95% [1–5]. However, in eyes with macula-off RRD, degeneration of the photoreceptors in the detached area of the macula often prevents complete recovery of visual function and leads to central visual dysfunction, even after successful reattachment [5, 6].

Photoreceptor apoptosis has been reported to mainly occur within 3 days of RRD onset in experimental animal models [7, 8] and to induce the expression of various cytokines and chemokines [9, 10]. Clinically, many cases of macula-off RRD undergo postoperative atrophy of the outer macular layer after reattachment. Accordingly, a few reports have performed qualitative analysis of changes in the structure of the detached macular area represented in optical coherence tomography (OCT) images and have examined the potential role of such analysis in determining the postoperative visual prognosis of eyes with macula-off RRD [11, 12]. However, to the best of our knowledge, there are no current reports investigating the potential of quantitative OCT measurement parameters of the macula to serve as prognostic indicators of visual outcome.

We hypothesized that preoperative macular volume reflected photoreceptor apoptosis and could thus predict postoperative outcomes in eyes with macula-off RRD. In order to test this hypothesis, we developed new OCT parameters that could provide a suitable evaluation of the macular structure and then determined the relationship between these

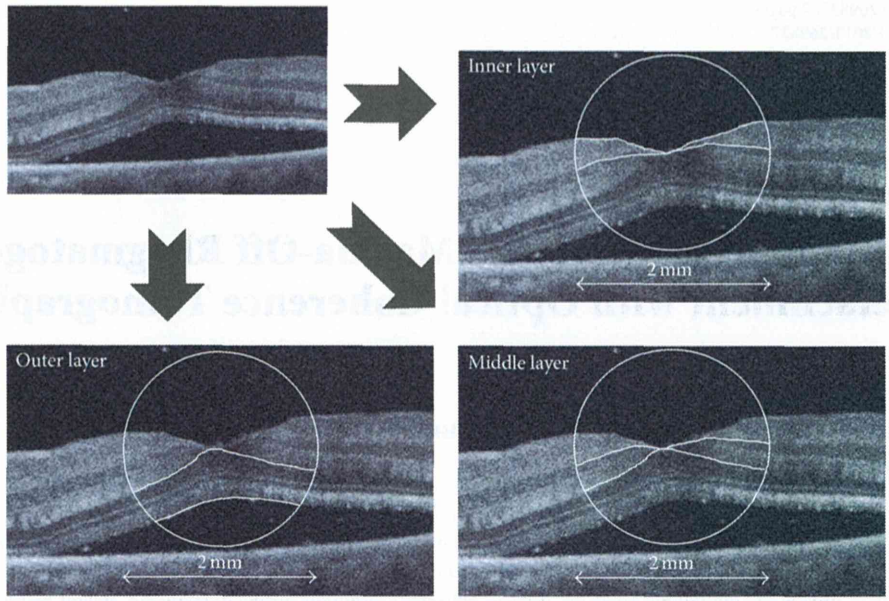

FIGURE 1: Preoperative optical coherence tomography (OCT) images. A circle with a diameter of 2 mm was manually centered at the foveal surface center of the detached macula in the OCT image. The macular area within the circle was divided into three sections: the inner layer (upper right: nerve fiber layer and ganglion cell layer), middle layer (lower right: inner plexiform layer and inner nuclear layer), and outer layer (lower left: outer plexiform layer and outer nuclear layer).

parameters and postoperative visual outcomes in macula-off RRD eyes.

2. Patient and Methods

2.1. Subjects. We performed a retrospective analysis of the medical records of 56 consecutive eyes with macula-off RRD that underwent surgical intervention with a 25-gauge trocar cannula system or scleral buckling from January 2011 to February 2014 at Tohoku University Hospital. Eyes were included only if complete reattachment of the RRD was achieved after initial surgery. Eyes were excluded if they had prior vitreoretinal surgery, proliferative retinopathy, retinal vascular disease, chorioretinal atrophy, or high myopia (more than −10 diopters), if we could not obtain clear preoperative OCT measurements due to a bullous RRD or vitreous opacity, or if a single OCT scan could not capture the detached fovea and the retinal pigment epithelium layer. After the purpose and procedures of the operation were explained, informed consent was obtained from all patients. The procedures conformed to the tenets of the Declaration of Helsinki, and the study was approved by the Institutional Review Board of Tohoku University Graduate School of Medicine.

2.2. Measurements of Clinical Findings. All patients underwent a complete ocular examination 6 months after surgery. Best-corrected visual acuity (BCVA) was measured preoperatively and 1 and 6 months postoperatively with the Landolt C visual acuity chart. Decimal acuity values were converted to logarithm of the minimal angle of resolution (log MAR) units. The detached macula was examined with spectral-domain (SD) OCT (Cirrus OCT, Carl Zeiss Meditec) in all patients preoperatively, and foveal thickness was also measured 1 and 6 months postoperatively. To evaluate the detached macula preoperatively, a 2 mm circle was manually centered on the surface of the fovea in a cross-sectional OCT macular image. The image of the macula within this circle was then manually segmented into three layers: the inner layer (nerve fiber layer and ganglion cell layer), middle layer (inner plexiform layer and inner nuclear layer), and outer layer (outer plexiform layer and outer nuclear layer) (Figure 1). All OCT images were horizontal scans. Postoperative foveal thickness was defined as the value in the central 1000 μm area and was automatically calculated by the onboard OCT software. Our analysis of preoperative OCT parameters included retinal detachment (RD) height (the vertical distance from the detached fovea to the retinal base) [12] and macular cross-sectional area within a 2 mm circle centered on the foveal surface center in the OCT image. Separate values were also recorded for cross-sectional area in three macular layers.

2.3. Statistical Analyses. All statistical analysis was performed with JMP software (Pro version 10.0.2, SAS Institute Japan Inc., Tokyo, Japan). The correlation of 6-month postoperative BCVA to preoperative characteristics and operative, visual, and anatomical outcomes was determined with Spearman's rank correlation coefficient. Significant differences between preoperative and 1- and 6-month postoperative BCVA were determined with the paired t-test. Independent variables affecting 6-month postoperative BCVA were determined

with multiple linear regression analysis. The significance level was set at $P < 0.05$.

3. Results

Table 1 shows the possible association of preoperative characteristics and operative, visual, and anatomical outcomes with 6-month postoperative BCVA in 56 eyes with RRD. Lens-sparing 25-gauge vitrectomy was performed in patients younger than 50 years. Cataract progression, which could have affected visual acuity, did not occur in any of these patients 6 months after surgery. Six-month postoperative BCVA was positively correlated with preoperative BCVA, 1-month postoperative BCVA, and preoperative RD height ($P < 0.001$, $P < 0.001$, and $P < 0.001$, resp.; Table 1 and Figure 2). Six-month postoperative BCVA was negatively correlated with 1-month postoperative foveal thickness and preoperative total and inner layer cross-sectional macular area ($P = 0.006$, $P < 0.001$, and $P = 0.001$, resp.; Table 1 and Figure 2). Six-month postoperative BCVA was significantly higher than preoperative BCVA and 1-month postoperative BCVA ($P < 0.001$ and $P < 0.001$, resp.). Multiple regression analysis revealed that the duration of the macular detachment and the total cross-sectional macular area were independent factors predicting 6-month postoperative BCVA ($P = 0.024$ and $P = 0.041$, resp.; Table 2).

Images of eyes representing good and poor visual outcomes after surgery for macula-off RRD are shown in Figure 3.

Table 1: Preoperative characteristics and operative, visual, and anatomical outcomes of 56 eyes with rhegmatogenous retinal detachment and their possible association with 6-month postoperative visual acuity.

		r	P value
Number of eyes	56	—	—
Age (years)	50.0 ± 19.8	0.09	0.524[a]
Sex (n, %)		—	0.557[b]
Male	38, 67.9%	—	—
Female	18, 32.1%	—	—
Spherical equivalent (diopter)	−3.15 ± 2.67	−0.01	0.950[a]
Duration of macular detachment (days)	33.3 ± 72.7	−0.09	0.565[a]
Procedure (n, %)		—	0.935[b]
PPV only	10, 17.7%	—	—
PPV with cataract surgery	27, 48.2%	—	—
Scleral buckling	19, 33.9%	—	—
Visual course (decimal VA)			
Preoperative	0.19 ± 0.27	0.48	<0.001[a]
1 M postoperative	0.53 ± 0.51	0.82	<0.001[a]
6 M postoperative	0.69 ± 0.55	—	—
Pre-op OCT findings			
RD height (mm)	1.45 ± 0.87	0.47	<0.001[a]
Total macular area (mm^2)	1.05 ± 0.16	−0.44	<0.001[a]
Outer layer macular area (mm^2)	0.62 ± 0.13	−0.17	0.221[a]
Middle layer macular area (mm^2)	0.19 ± 0.06	−0.04	0.759[a]
Inner layer macular area (mm^2)	0.23 ± 0.08	−0.43	0.001[a]
Post-op OCT findings			
1 M postoperative FT (μm)	269.9 ± 79.7	−0.37	0.006[a]
6 M postoperative FT (μm)	255.4 ± 35.7	−0.24	0.096[a]

FT = foveal thickness, OCT = optical coherence tomography, PPV = pars plana vitrectomy, RD = retinal detachment, and VA = visual acuity.
[a]Spearman's correlation coefficient by rank test, [b]unpaired t-test.

4. Discussion

We set out to evaluate the potential of newly developed OCT parameters to predict postoperative BCVA in macula-off RRD eyes. We found that 6-month postoperative BCVA was significantly correlated with RD height at the fovea and with the total and inner cross-sectional area of the macular layer within 2 mm of the fovea, as well as with preoperative BCVA. Furthermore, multiple regression analysis revealed that the duration of the macular detachment and the total cross-sectional macular area were independent factors predicting 6-month postoperative BCVA.

Surgeons cannot easily predict postoperative visual outcomes in cases of RRD, and even after successful RRD surgery, many patients only regain a poor level of postoperative visual function. This often causes patients to experience preoperative anxiety. Our results confirmed existing data showing that the duration of the macular detachment was associated with postoperative visual outcome, although the usefulness of this parameter is limited, because it depends on the memory of the patient and their cooperation and therefore cannot always be reliably known [13–15]. Though there are many existing reports showing that early postoperative OCT macular findings are associated with final visual function [16–25], there are only a few reports examining preoperative structural changes in the macula using up-to-date SD-OCT imaging of the detachment and the association of these changes with visual outcomes [11, 12]. These studies found that qualitatively measured preoperative characteristics of RRD eyes, such as intraretinal separation and outer layer undulation, were associated with a higher postoperative incidence of disruption to the photoreceptor inner/outer segment junction and the presence of external limiting membranes, causes of poor visual outcomes. Qualitative measurements are, however, subjective and prone to error, creating the need for quantitative methods to measure the detached macula with OCT, in order to find prognostic indicators of final visual outcome in RRD eyes.

The pathogenesis of poor visual outcomes in RRD is related to photoreceptor cell death [7–10], suggesting that the number of surviving retinal cells in the fovea should be the ideal prognostic indicator of final visual outcome. The three-dimensional (3D) volume of the macula, which is measureable by recent advanced OCT techniques, is closely associated with the number of surviving cells but would only be feasible to measure in young patients with flat RRD. In patients with bullous RRD, the detached macula is unstable and shifts its position in the vitreous faster than the scanning

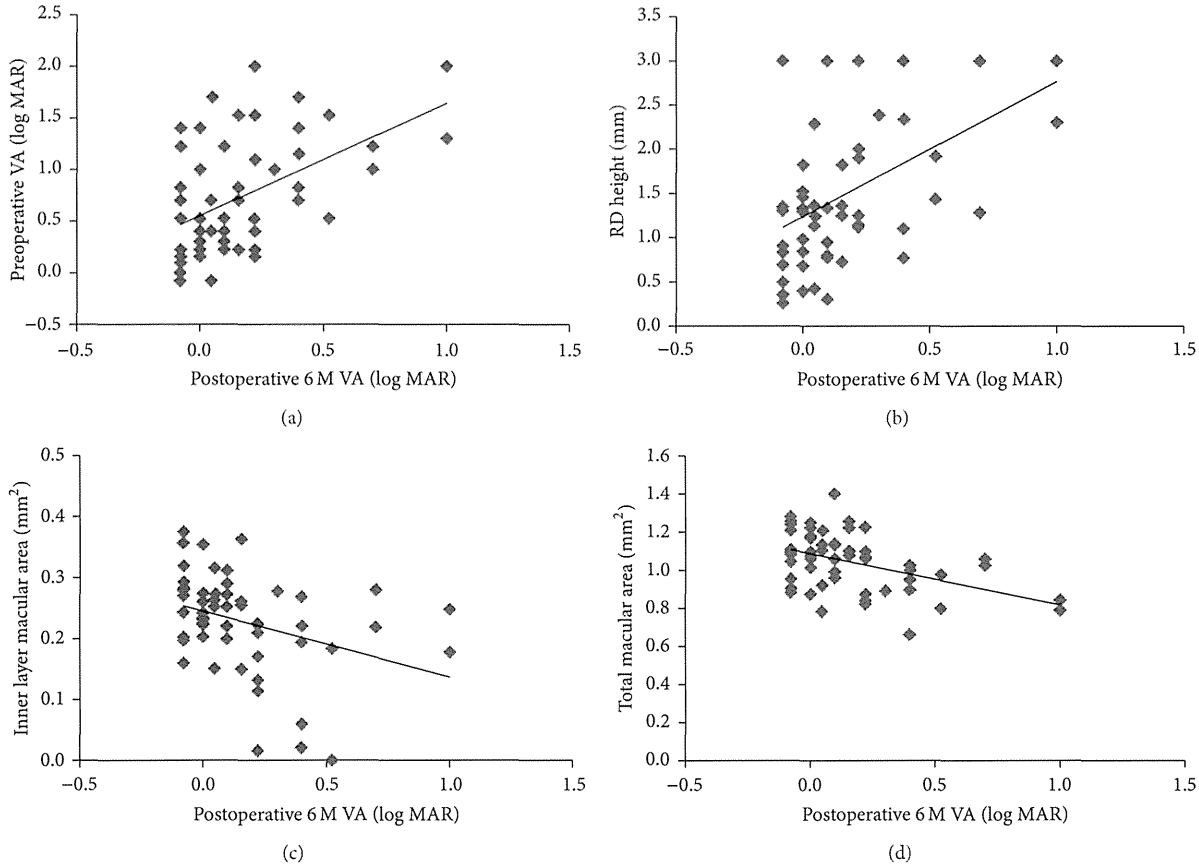

FIGURE 2: Correlation of preoperative clinical findings to 6-month postoperative best-corrected visual acuity (BCVA). There was a positive correlation between preoperative and 6-month postoperative BCVA ((a); $r = 0.48$, $P < 0.001$). There was also a positive correlation between retinal detachment height and 6-month postoperative BCVA ((b); $r = 0.47$, $P < 0.001$). There was a negative correlation between the cross-sectional area of the inner macular layer and 6-month postoperative BCVA ((c); $r = -0.43$, $P = 0.001$). There was also a negative correlation between total macular cross-sectional area and 6-month postoperative BCVA ((d); $r = -0.44$, $P < 0.001$).

TABLE 2: Multiple regression analysis for independent factors contributing to 6 M postoperative VA.

Dependent	Variable Independent		β	P value
Postoperative VA	Age		0.041	0.784
	Duration of macular detachment		0.869	0.024
	Preoperative VA		0.188	0.249
	Preoperative OCT findings	RD height	0.212	0.203
		Total macular area	−0.511	0.041
		Outer layer macular area	0.334	0.180
		Middle layer macular area	0.267	0.156

VA = visual acuity, OCT = optical coherent tomography, RD = retinal detachment, and β = standard partial regression coefficient.

speed of existing 3D OCT devices, making it impossible to evaluate foveal volume in these eyes. To overcome this technical difficulty, we used two-dimensional OCT to measure the cross-sectional area of the macular layer in a 2 mm circle centered on the fovea and investigated its potential as an indicator of final BCVA. We developed this measurement parameter after observing that the detached section of the macula is not straight or flat in OCT images but instead lies obliquely across the image plane. Conventionally measuring cross-sectional area in a square or rectangle horizontal to the choroid would thus tend to overestimate foveal thickness. By contrast, measurements of cross-sectional area in a 2 mm circle centered on the fovea (which is about 1 mm in diameter) should be reliable regardless of the orientation or position

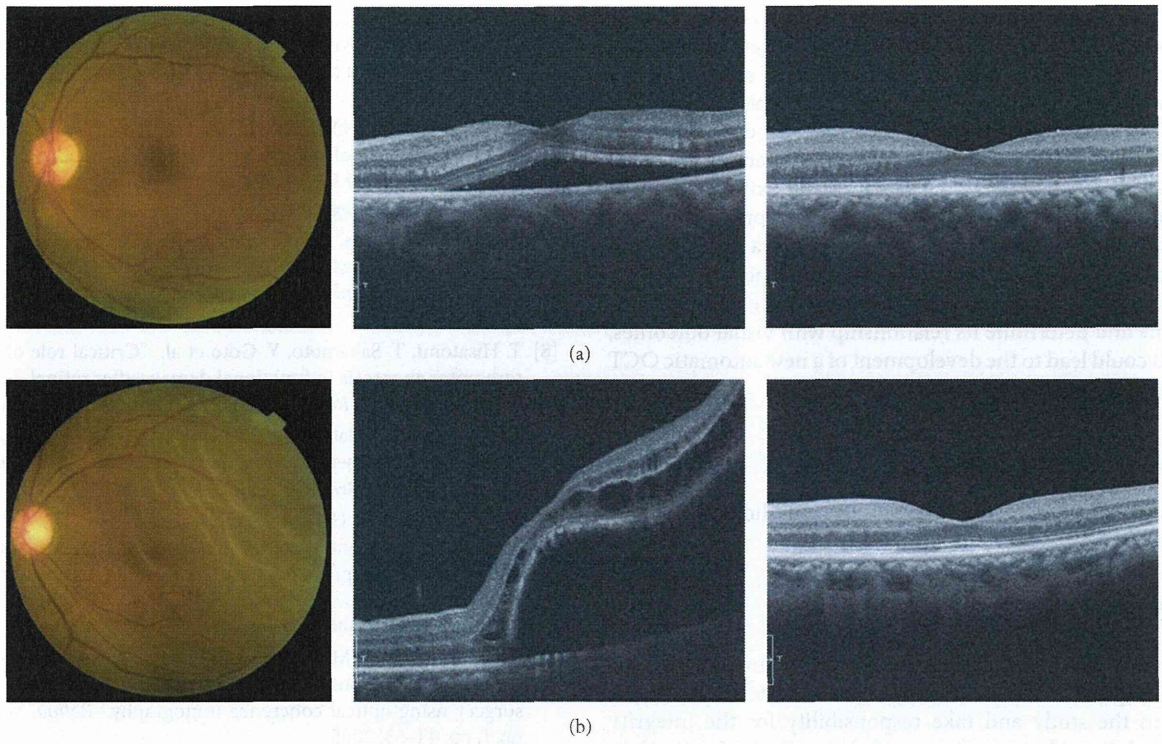

FIGURE 3: Representative eyes with good and poor visual outcomes after surgery for macula-off rhegmatogenous retinal detachment. (a) 65-year-old woman (preoperative decimal visual acuity: 0.7) with a good visual outcome (postoperative decimal visual acuity: 1.2). (b) 60-year-old woman (preoperative decimal visual acuity: 0.3) with a poor visual outcome (postoperative decimal visual acuity: 0.3). Preoperative photographs of the fundus, preoperative optical coherence tomography (OCT) images, and postoperative OCT images are shown on the left, center, and right, respectively. Preoperative foveal area was relatively thinner in the case with a poor outcome than in the case with a good outcome.

of the detachment. A circular area larger than 2 mm would begin to lose reliability, as it would be more influenced by intraretinal edema, bending, or severe undulation of the detachment. Thus, we believe that it is most reasonable to adopt the cross-sectional area of the macular layer within 2 mm of the fovea as an indicator of macular health.

This study showed that RD height at the fovea, a measurement parameter used in a number of earlier studies, was associated with postoperative BCVA in a single regression analysis, confirming earlier reports [11, 12]. This is an understandable result, as when the distance between the retinal pigment epithelium and the photoreceptors increases, the foveal cones receive less oxygenation and nutrition from the choroid and photoreceptor cell degeneration increases. However, multiple regression analysis revealed that it was not an independent factor predicting 6-month postoperative BCVA ($P = 0.203$). The cause of this discrepancy is unclear but may have been related to the instability of RD height, particularly in bullous RRD and particularly in older eyes, because the detached macula can more easily shift its position in the vitreous. It is difficult to accurately and reproducibly evaluate RD height in such eyes, leading us to speculate that preoperative RD height cannot be considered a reliable predictor of postoperative visual function in eyes with macula-off RRD.

Limitations of this study included a relatively short follow-up time of 6 months, a relatively small sample size (about 60), and the omission of postoperative functional findings from standard automated perimetry or focal electroretinography. Additionally, although bullous RRD eyes are often seen in the clinic, the method described here cannot be used to predict postoperative outcomes in cases when OCT scans do not show the macula. Furthermore, to prevent bias in the results, it was necessary to omit the inner macular layer in the cross-sectional image from our multiple regression analysis, because the total and inner layer values were not independent, both being OCT findings and being closely correlated with 6-month postoperative BCVA. At first, we hypothesized that visual outcome would be associated with the area of the outer macular layer, as this contains the outer nuclear layer and the photoreceptor cells, but this hypothesis was not borne out by the data. It is unclear why this was so, but it may have been related to the susceptibility of the outer layer to intraretinal edema or undulation, which makes it difficult to obtain accurate measurements. Nevertheless, we believe our results show that simple OCT measurement of total cross-sectional area within 2 mm of the fovea is currently the most useful and objective way to predict postoperative visual outcomes in eyes with macula-off RRD, at least until technology to quickly evaluate

macular volume in three dimensions becomes available for use in eyes with detached maculas. The usefulness of the measurement method described here would also be greatly enhanced by an OCT program to automatically measure cross-sectional macular area in eyes with macula-off RRD.

In conclusion, OCT measurement of preoperative total cross-sectional area of the macular layer within 2 mm of the fovea is a useful and objective way to predict postoperative visual outcomes in eyes with macula-off RRD and was closely correlated with 6-month postoperative BCVA. Further investigation is needed to measure the macular volume and determine its relationship with visual outcomes, which could lead to the development of a new automatic OCT program.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Authors' Contribution

The principal investigator, Dr. Noriyuki Suzuki, and the coinvestigator, Dr. Naoko Aizawa, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the analysis. Involved in the design and conduct of the study were Hiroshi Kunikata and Toru Nakazawa; collection, management, analysis, and interpretation of the data Noriyuki Suzuki, Hiroshi Kunikata, and Naoko Aizawa; drafting of the paper Hiroshi Kunikata; and review or approval of the paper Hiroshi Kunikata, Toshiaki Abe, and Toru Nakazawa. All authors read and approved the final paper.

Acknowledgments

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Clinical Study

25-Gauge Microincision Vitrectomy to Treat Vitreoretinal Disease in Glaucomatous Eyes after Trabeculectomy

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Purpose. To determine the feasibility of using 25-gauge microincision vitrectomy surgery (25GMIVS) to treat vitreoretinal disease in glaucomatous eyes which have previously undergone trabeculectomy (TLE). *Methods.* A consecutive, interventional case series. We performed 25GMIVS in 15 glaucomatous eyes that had undergone TLE. Follow-up period was 11.5 months. *Results.* 25GMIVS was successfully used and led to improvement in visual acuity ($P < 0.01$). We performed 25GMIVS for proliferative diabetic retinopathy with neovascular glaucoma in 53% of eyes (8 of 15). Although 3 eyes needed further TLE following 25GMIVS, final IOP was below 21 mmHg in all eyes except one eye (93%) and was comparable to pre-25GMIVS IOP ($P = 0.20$) without an increase in the number of glaucoma medications ($P = 0.14$). *Conclusions.* 25GMIVS is a feasible treatment for vitreoretinal disease in eyes with preexisting TLE, effective in both significantly improving BCVA and preserving the filtering bleb, while not excluding further glaucoma surgery.

1. Introduction

Trabeculectomy (TLE) is a procedure most often performed when drug-based therapies for glaucoma have been ineffective. It can effectively reduce intraocular pressure (IOP) over the long term [1–3], but can lead to problems if further severe retinal diseases requiring vitrectomy arise. This is particularly the case for conventional 20-gauge par planar vitrectomy (20GPPV), because that procedure requires suturing and a conjunctival incision, which can disrupt the ocular surface and lead to impairment of the filtering bleb [4]. Furthermore, 20GPPV can make future or unanticipated filtering surgery more difficult as it causes conjunctival-scleral adhesion in multiple quadrants. It would thus be desirable to establish an alternative vitrectomy technique that has a lower risk of causing filtering bleb failure and does not exclude further glaucoma surgery.

Twenty-five-gauge microincision vitrectomy surgery (25GMIVS) was first reported in 2002, and this procedure is now commonly used worldwide [5–15]. One of the advantages of this technique is that intraoperative suturing is not needed, which reduces postoperative ocular pain and discomfort in patients. Furthermore, 25GMIVS allows earlier postoperative visual improvement than 20GPPV and does not induce significant changes in the corneal topography or optical quality of the cornea [16–20]. Although 25GMIVS does have limitations [21–23], we believe that because it is sutureless, it is the best choice to treat retinal disease in eyes with preexisting TLE and can best preserve the filtering bleb. However, to the best of our knowledge, using the PubMed search system, there are no reports discussing or evaluating the use of 25GMIVS to treat retinal diseases in glaucomatous eyes after TLE, except one case report of familial amyloid polyneuropathy (FAP) [24].

Thus, the purpose of this study was to determine the feasibility of using 25GMIVS to treat vitreoretinal disease in glaucomatous eyes that have undergone TLE.

2. Patients and Methods

2.1. Participants. This was a retrospective, consecutive, interventional case series performed at a single center. Fifteen consecutive post-TLE eyes of 15 patients with retinal diseases who underwent 25GMIVS were studied. The inclusion criterion was any retinal vitreous disease causing visual dysfunction in eyes that had previously undergone TLE, (meaning the eyes already had a filtering bleb). The exclusion criteria were prior scleral buckling, prior trauma, and a follow-up period of less than 3 months. The preoperative demographics and postoperative courses of the patients are shown in Table 1. All of the surgeries were performed at the Surgical Retina Service of Tohoku University Hospital from October 2008 to May 2012. All 25GMIVS procedures were performed by a single surgeon (H.K.). After the purpose and procedures of the operation were explained, informed consent was obtained from all patients. This study conformed to the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board of the School of Medicine, Tohoku University.

2.2. Surgical Procedures. All surgeries were performed under retrobulbar anesthesia using the oblique sclerotomy technique and were performed using the Accurus Vitrectomy System (Alcon Laboratories; Fort Worth, Texas, USA). First, an infusion cannula was inserted through the inferotemporal sclera followed by the insertion of two cannulas through superotemporal and superonasal sites. The insertion point of the cannulas was shifted as necessary to avoid disturbing the conjunctiva adjacent to the filtering bleb. Next, a 2.4 mm superotemporal corneal incision was made, followed by phacoemulsification, aspiration (PEA), and intraocular lens (IOL) implantation before the vitrectomy, if the eye had a cataract. After resecting the vitreal core, 4 mg of triamcinolone acetonide (TA; Kenacort-A, Bristol-Meyers Squibb, Tokyo, Japan) was injected into the vitreous cavity to determine if a posterior vitreous detachment (PVD) was present. If a PVD was not present, we created one with a 25-gauge cutter. After shaving the peripheral gel, the proliferative membrane was removed, and fluid air exchange and endophotocoagulation were performed if needed. The exact surgical procedures varied according to the type of vitreoretinal disease. Additional TLE was also performed under retrobulbar anesthesia, with a fornix-based conjunctival flap. A half-thickness 4.0 by 4.0 mm rectangular scleral flap was made in the superior area. Mitomycin C (MMC) was used with a concentration of 0.04% and an exposure time of 5 minutes. The area was irrigated thoroughly with 200 mL of balanced salt solution. Trabeculectomy was then performed, followed by peripheral iridectomy. The scleral flap and conjunctiva were closed with a 10-0 nylon suture. Postoperatively, antibiotics and corticosteroids were injected subconjunctivally.

2.3. Measurements of Clinical Findings. We evaluated best-corrected visual acuity (BCVA), IOP, number of glaucoma medications, intraoperative subconjunctival hemorrhage, intraoperative suturing at the sclerotomy site, and additional TLE (after 25GMIVS). BCVA was measured using the Landolt C visual acuity chart, and the decimal BCVA was converted to logarithm of the minimal angle of resolution (LogMAR) units for statistical analysis. Success of the 25GMIVS procedure was defined as improvement or maintenance of BCVA and maintenance of IOP $\leq$21 mmHg with the use of topical glaucoma medication, with no need for additional TLE. The procedure was recorded as a failure if there was a decrease in BCVA, additional TLE was required, or IOP could not be maintained $\leq$21 mmHg with the use of topical glaucoma medication.

2.4. Statistical Analysis. The data are presented as the mean $\pm$ standard deviation. The significance of the difference between the pre-25GMIVS BCVA and final BCVA in logMAR units was determined by the single tailed paired t-test. For the statistical analysis, "count fingers" visual acuity was set as 2.0 logMAR units, and "hand motion" acuity was set as 3.0 logMAR units. The significance of the difference in IOP before TLE, after TLE, and after 25GMIVS was determined by the Friedman test, and the significance of the difference between the IOP after TLE and after 25GMIVS was determined by the Scheffe's test. The significance of the difference in the pre-25GMIVS number of glaucoma medications and the final number was also determined by the two tailed paired t-test. A P value of less than 0.05 was considered to be statistically significant.

3. Results

A summary of the patients' characteristics and pre-25GMIVS course is shown in Table 1. There were 8 men and 7 women with a mean age of 57.4 $\pm$ 13.2 years. The type of glaucoma originally requiring TLE included neovascular glaucoma (NVG, 8 eyes; 53%), open angle glaucoma (2 eyes; 13%), malignant glaucoma (2 eyes; 13%), traumatic glaucoma (1 eye), uveitis-associated secondary glaucoma (1 eye), and developmental glaucoma (1 eye). Vitreoretinal diseases in eyes with preexisting-TLE treated with 25GMIVS in our study included proliferative diabetic retinopathy (PDR, 7 eyes; 47%) (Figure 1), malignant glaucoma (2 eyes; 13%), rhegmatogenous retinal detachment (1 eye) (Figure 2), branch retinal vein occlusion (1 eye), macular hole (1 eye), dislocated intraocular lens (1 eye), endophthalmitis (1 eye), and choroidal hemorrhage (1 eye). The mean period between the original TLE procedure and 25GMIVS was 25.3 $\pm$ 29.7 months, with a range of 0.3 to 105 months. All blebs were located in the upper quadrants. Prior to TLE, vitrectomy had been performed in 3 eyes (20%) with PDR. Before 25GMIVS, intravitreal injection of bevacizumab (IVB) was performed in 4 eyes (27%) with NVG, but after 25GMIVS it was not necessary. There were 9 eyes (60%) with pseudophakia before 25GMIVS.

Table 1: Characteristics and pre-25-gauge microincision vitrectomy course of 15 glaucomatous eyes.

Patient no./sex/age, yrs	Eye	Type of glaucoma	Pre-25GMIVS retinal disease	Period of 25GMIVS after TLE (M)	Site of bleb	Pre-TLE vitrectomy	Pre-25GMIVS IVB	Pre-25GMIVS pseudophakia
1/M/45	L	Trauma	RRD	4	Upper temporal	N	N	Y
2/M/58	L	NVG	BRVO/VH	30	Upper nasal	N	N	N
3/M/62	R	NVG	PDR/VH	48	Upper temporal	N	Y	Y
4/F/60	L	NVG	PDR/TRD	36	Upper nasal	N	Y	N
5/M/68	L	NVG	PDR/VH	10	Upper nasal	Y	Y	Y
6/F/62	L	Uveitis	MH	55	Upper nasal	N	N	Y
7/F/44	R	NVG	PDR/VH/CD	0.5	Upper	N	Y	Y
8/F/83	R	Malignant glaucoma	Malignant glaucoma	1	Upper nasal	N	N	Y
9/F/33	L	Developmental glaucoma	Lens luxation	105	Upper nasal	N	N	N
10/M/52	R	POAG	Endophthalmitis	0.3	Upper temporal	N	N	N
11/M/59	R	POAG	ERM	50	Upper temporal and nasal	N	N	N
12/M/61	R	NVG	PDR/VH	25	Upper temporal	Y	N	Y
13/F/56	R	NVG	PDR	7	Upper temporal	Y	N	Y
14/F/77	L	Malignant glaucoma	Choroidal hemorrhage	1	Upper temporal	N	N	Y
15/M/41	R	NVG	PDR/VH	6	Upper nasal	N	N	N
Mean 57.4		NVG 53%	PDR 47%	25.3		20%	27%	60%

25GMIVS: 25-gauge microincision vitrectomy surgery; TLE: trabeculectomy; IVB: intravitreal injections of bevacizumab; NVG: neovascular glaucoma; TRD: tractional retinal detachment; RRD: rhegmatogenous retinal detachment; BRVO: branch retinal vein occlusion; PDR: proliferative diabetic retinopathy; VH: vitreous hemorrhage; MH: macular hole; ERM: epiretinal membrane; POAG: primary open angle glaucoma; CD: choroidal detachment.

A summary of the patients' characteristics and post-25GMIVS course is shown in Table 2. PEA, IOL, and 25GMIVS were performed together in 4 eyes (27%), and 25GMIVS was performed by itself in 11 eyes (73%). None of the eyes required suturing of the 25-gauge sclerotomy site at the end of the initial surgery except one (7%) that had undergone vitrectomy before TLE. The mean operative time was 38.3 ± 16.3 minutes. The mean decimal pre-25GMIVS BCVA and final BCVA were 0.05 and 0.3, respectively. Final BCVA in logMAR units was significantly better than the pre-25GMIVS BCVA ($P = 0.01$). Pre-TLE IOP, pre-25GMIVS IOP, and final IOP were 36.0, 11.9, and 15.7 mmHg, respectively. There were significant IOP differences pre-TLE, pre-25GMIVS, and post-25GMIVS ($P < 0.001$), but no significant difference between the pre-25GMIVS IOP and final IOP ($P = 0.20$). There was no difference in the pre-25GMIVS and final number of glaucoma medications ($P = 0.14$). Subconjunctival hemorrhage occurred in 5 eyes (33%); however, in 3 of these eyes, there was no hemorrhage invasion into the filtering bleb. Four eyes (27%) had intraocular pressure >20.0 mmHg after 25GMIVS, and 3 of these eyes needed additional TLE. It should be mentioned that this additional TLE was a technically simple procedure, because 25GMIVS had been performed without any sutures. Vitreoretinal diseases in all 15 eyes with preexisting TLE were successfully treated with 25GMIVS. We achieved success with 25GMIVS in 10 cases (67%) and did not observe surgical complications, such as bacterial endophthalmitis, associated with either TLE or 25GMIVS in any of the cases. The mean follow-up period was 11.5 ± 7.7 months with a range of 6 to 34 months.

4. Discussion

We set out to evaluate the feasibility of using 25GMIVS to treat vitreoretinal disease in glaucomatous eyes that had undergone TLE. The most common vitreoretinal disease in eyes with preexisting TLE we treated with this technique was PDR complicated by NVG (in almost 50% of cases). In spite of the relatively high incidence of such a severe disease, mean BCVA improved significantly after 25GMIVS. Additionally, although 3 eyes needed further TLE following our 25GMIVS procedure, the final measurement of IOP was statistically

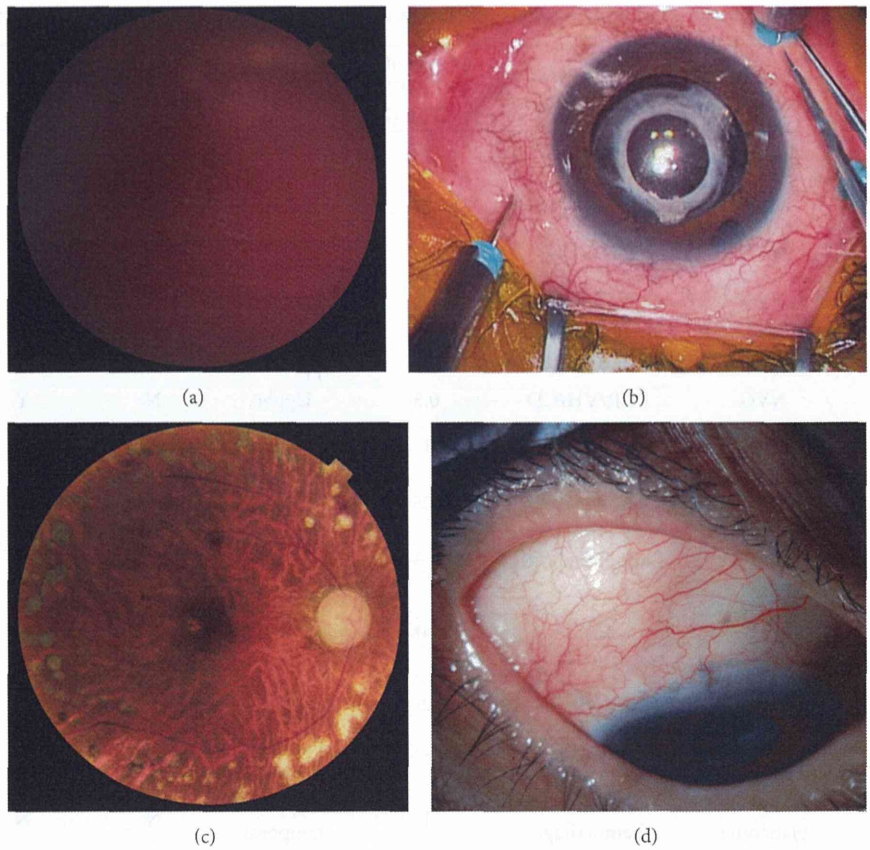

FIGURE 1: Representative example of proliferative diabetic retinopathy (PDR) complicated by neovascular glaucoma (NVG) (Patient 12; see Table 1). Fundus, anterior segment, and intraoperative photographs of the eye of a 61-year-old man with PDR/NVG. The eye underwent 25-gauge microincision vitrectomy surgery (25GMIVS) after trabeculectomy. (a) Preoperative photograph of the fundus. We could not visualize the posterior fundus due to vitreous hemorrhage (VH). (b) Intraoperative photograph of the anterior segment. 25GMIVS was being performed with 3 ports. The insertion placement of the cannulas was shifted to avoid disturbing the subconjunctival hemorrhage of the filtering bleb in the upper temporal region. (c) Postoperative photograph of the fundus. The VH has been removed and the retinal surface can be seen clearly. (d) One-day postoperative photograph of the anterior segment. There was no subconjunctival hemorrhage, including the filtering bleb, in the upper temporal region.

comparable to IOP before 25GMIVS, without an increase in the number of glaucoma medications. Furthermore, because of our use of sutureless 25GMIVS, the additional TLE procedure itself, following 25GMIVS, was not more difficult than a standard TLE procedure.

Our results confirm existing data that, in about one-third of cases, eyes will develop elevated pressure if they undergo vitrectomy after TLE [4]. About 30% of our case series had IOP ≥20.0 mmHg following 25GMIVS, and 3 cases needed additional TLE. In the 3 eyes with types of glaucoma other than NVG, IOP was maintained ≤21 mmHg after 25GMIVS and further TLE was not necessary. In almost 50% of post-TLE eyes we treated with 25GMIVS, however, PDR with NVG was present (Thompson et al; 13% of eyes had PDR) [4]. Our final result for IOP control could thus be considered reasonably successful, given that NVG is known to be generally refractory to conventional TLE with MMC. Specific prognostic factors for surgical failure have been reported to be young age, previous vitrectomy, and, when PDR is present, a fellow eye with NVG [25]. An alternative technique to effectively reduce elevated IOP in eyes with NVG is vitrectomy and complete pan-retinal photocoagulation combined with TLE [26, 27]. Our results, which also support a single existing case report on 25GMIVS for a FAP eye with a filtering bleb, show that 25GMIVS has the potential to become the treatment of choice for vitrectomy in glaucomatous eyes that have already undergone TLE [24]. Additionally, our study now shows that there is no hypotony (IOP < 5.0 mmHg) after 25GMIVS. Thompson et al. reported that IOP outcomes after 20GPPV were rather variable; one-third of eyes in that study developed hypotony, one-third developed elevated pressure, and one-third maintained bleb function [4]. The cause of this discrepancy with our results is unclear, but we speculate that one reason was the high retinal reattachment rate that results from 25GMIVS. The hypotonic eyes from the earlier report included some with persistent retinal detachments following vitrectomy [4]. Additionally, we also believe that the smaller gauge required less infusion

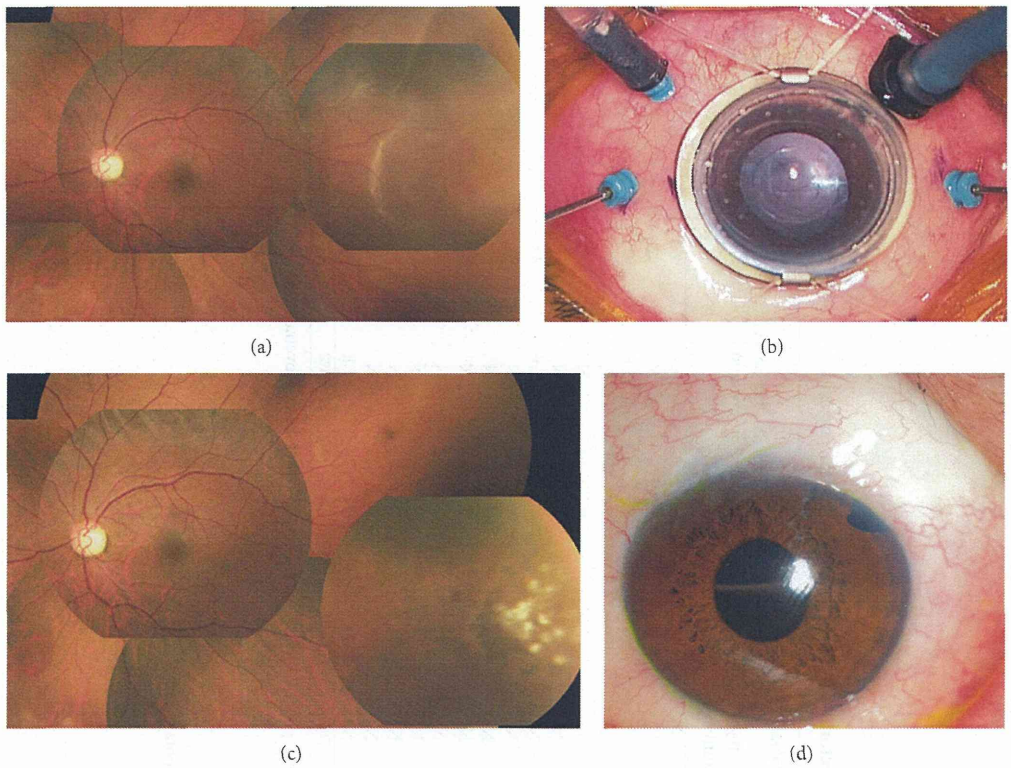

FIGURE 2: Representative example of rhegmatogenous retinal detachment (RRD) (Patient 1; see Table 1). Fundus, anterior segment, and intraoperative photographs of the eye of a 45-year-old man with RRD. The eye underwent 25-gauge microincision vitrectomy surgery (25GMIVS) after trabeculectomy. (a) Preoperative photograph of the fundus. There was focal retinal detachment with a peripheral retinal tear. (b) Intraoperative photograph of the anterior segment. 25GMIVS was being performed with 4 ports. The insertion placement of the cannulas was shifted to avoid disturbing the subconjunctival hemorrhage of the filtering bleb in the upper temporal region. (c) Postoperative photograph of the fundus. Retinal reattachment was achieved with 25GMIVS. The white retinal scars of endophotocoagulation can be seen. (d) One-day postoperative photograph of the anterior segment. There was no subconjunctival hemorrhage, including the filtering bleb, in the upper temporal region. An air-fluid level line of intraocular gas tamponade can be seen through the pupil.

of balanced solution during the procedure and had less of a negative intraoperative effect on the ciliary bodies, which have the important role of producing the intraocular aqueous humor.

We speculate that subconjunctival hemorrhage during 25GMIVS affects the preexisting filtering bleb. Many earlier reports have demonstrated the advantages and disadvantages of using autologous blood injection to treat overfiltering or leaking blebs after glaucoma surgery [28–33]. Thus, the sutureless nature of 25GMIVS, which prevents intraoperative subconjunctival hemorrhage from flowing into preexisting bleb, could be a great benefit for the treatment of vitreoretinal disease in eyes with preexisting TLE. We also believe that 25GMIVS can prevent conjunctival adhesion, thereby preserving an existing filtering bleb and clearing the way for additional glaucoma surgery. Subconjunctival hemorrhage after 25GMIVS occurred in about 30% of our cases, with consequent additional glaucoma surgery (about 20%). We thus find it highly advisable to avoid disrupting conjunctival vessels when creating a 25-gauge sclerotomy in glaucomatous eyes that have undergone TLE. The prognostic factors for surgical failure of TLE with MMC in vitrectomized eyes have been reported to be high preoperative IOP and NVG [34]. As stated above, we had 3 NVG patients undergo additional TLE following 25GMIVS, and we were able to achieve a final reduction in IOP in all 3 eyes. We believe that one reason for our success in such severe cases was the conjunctiva's good condition following the sutureless 25GMIVS procedure, in contrast with the earlier report on vitrectomy for NVG, in which a conventional 20GPPV procedure was used. The good condition of the conjunctiva after 25GMIVS might also make it possible to implant recently introduced glaucoma drainage devices, which can aid in the management of complicated glaucoma such as NVG. The need for suturing of a 25-gauge sclerotomy at the end of the 25GMIVS procedure in one vitrectomized eye (patient 5) due to high leakage leads us to believe that vitrectomy can be difficult to perform multiple times without any scleral suturing. In addition, it is difficult to perform IVB in vitrectomized eyes with NVG (patients 5, 12, and 13), because, as has already been demonstrated, injected bevacizumab is quickly washed away from a vitrectomized eye [35]. However, there is one report demonstrating that IVB before TLE might further improve the surgical success rate for NVG in previously vitrectomized eyes [36].

Table 2: Characteristics and post-25-gauge microincision vitrectomy course of 15 posttrabeculectomy eyes.

Patient no./ sex/age (y)	Decimal VA course		IOP (mmHg) course			Number of glaucoma medications		25GMIVS			Post-25GMIVS hyposphagma	Post-25GMIVS interventions	Followup (M)	Post-25GMIVS time before failure	Post-25GMIVS success
	Pre-25GMIVS	Final	Pre-TLE IOP	Pre-25GMIVS	Final	Pre-25GMIVS	Final	Combined cataract surgery	Port suturing	Operative time (min)					
1/M/45	1.2	1.2	29	9	9	0	0	N	N	41	N	N	12	—	Y
2/M/58	HM	0.8	35	15	15	0	2	Y	N	17	N	N	6	—	Y
3/M/62	CF	0.01	36	7	19	3	2	N	N	35	N	TLE	9	0.5	N
4/F/60	0.02	0.03	46	21	26	1	4	Y	N	56	Y	N	6	4	N
5/M/68	HM	1.2	37	11	10	0	0	N	Y	41	Y	N	8	—	Y
6/F/62	0.9	1.2	38	7	7	0	0	N	N	22	N	N	6	—	Y
7/F/44	CF	0.2	56	16	19	0	4	N	N	45	Y	TLE	13	8	N
8/F/83	1	1.2	30	30	13	3	0	N	N	25	N	N	12	—	Y
9/F/33	0.15	0.9	32	12	20	0	0	Y	N	74	N	N	9	—	Y
10/M/52	HM	0.7	16	7	16	3	4	N	N	26	Y	N	34	—	Y
11/M/59	0.6	0.6	19	10	15	0	2	Y	N	26	N	N	6	—	Y
12/M/61	HM	0.6	30	9	16	1	2	N	N	22	N	N	23	—	Y
13/F/56	HM	NLP	49	9	18	3	3	N	N	35	N	N	13	13	N
14/F/77	HM	0.08	32	10	17	3	3	N	N	59	Y	N	7	—	Y
15/M/41	0.03	HM	55	6	16	1	2	N	N	50	N	TLE	8	1	N
Mean 57.4	0.05	0.3	36.0 mmHg	11.9	15.7	1.2	1.9	27%	7%	38.3	33%	20%	11.5		67%

25GMIVS: 25-gauge microincision vitrectomy surgery; IOP: intraocular pressure; VA: visual acuity; IOP: intraocular pressure; TLE: trabeculectomy; HM: hand movement; CF: counting fingers; NLP: no light perception.

$P < 0.01$; Wilcoxon signed-ranks test; pre-25GMIVS VA versus final VA.

$P < 0.001$; Friedman test for 3 groups: pre-TLE IOP, pre-25GMIVS IOP and final IOP.

$P = 0.50$; Scheffe's test; pre-25GMIVS IOP versus final IOP.

$P = 0.67$; Wilcoxon signed-ranks test; pre-25GMIVS number of glaucoma medications versus final number of glaucoma medications.

There were limitations to our study, including the retrospective nature of the analysis, a short follow-up period, and a small number of patients. We did not discuss filtering bleb function in detail because our study included eyes with blebs whose function before 25GMIVS was doubtful (these eyes continued to need glaucoma medication after TLE). Furthermore, we did not compare 25GMIVS and 20GPPV. A comparative, prospective study in post-TLE eyes would provide valuable insights into the relative value of these techniques but is impossible due to ethical considerations, making an experimental analysis using an animal model perhaps the most useful approach for such a future study. Nevertheless, as post-TLE eyes that require glaucoma medication for IOP control before vitrectomy are commonly observed clinically and indeed comprised about 50% of the cases in our study, we believe that this is a valuable study of a useful treatment for post-TLE eyes with various retinal conditions. Further investigation is needed to evaluate postoperative visual quality and complications in the late postoperative period before a final determination can be made of the efficacy of this procedure.

In conclusion, 25GMIVS is technique that can feasibly be used to treat vitreoretinal disease in glaucomatous eyes that have undergone TLE. Regardless of a high incidence of PDR with NVG in our case series, we were able to achieve good final results for BCVA and IOP with 25GMIVS, without increasing the number of glaucoma medications. Though there were a few cases that needed additional TLE following 25GMIVS, the additional TLE procedure was not more technically difficult than usual, because of the good condition of the conjunctiva after sutureless 25GMIVS. Our results showed that 25GMIVS was effective in preserving the filtering bleb and the other quadrant conjunctiva in eyes with glaucoma and did not exclude further surgical intervention for this disease.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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A Platform for Controlled Dual-Drug Delivery to the Retina: Protective Effects against Light-Induced Retinal Damage in Rats

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Retinal diseases such as glaucoma, age-related macular (AMD) degeneration, and retinitis pigmentosa (RP) are among the most common causes of visual impairment worldwide.[1] Retinal degenerations from progressive loss of photoreceptor or retinal ganglion cells are largely responsible for vision loss.[2–4] Multiple drugs have been used to treat patients with ocular diseases, such as glaucoma[5,6] and to suppress choroidal neovascularization in patients with AMD.[7] Generally, a better therapeutic efficacy to slow the progression of retinal degeneration can be obtained when using two or more, compared with therapy using a single drug.

One of the risk factor for the onset and/or progression of AMD is excessive light exposure, which leads to reactive oxygen species (ROS) generation and intracellular $Ca^{2\pm}$ influx,[8,9] resulting in photoreceptor degeneration.[10,11] Thus, in this study, edaravone (EDV), a potent-free radical scavenger,[11] and unoprostone isopropyl (UNO), a large conductance $Ca^{2\pm}$ activated $K^{\pm}$ channels activator,[12,13] were used as potential therapeutics and retinal neuroprotection by controlled transscleral co-delivery of the two drugs using a polymeric device was tested.

We previously developed a polymeric device that can release multiple compounds at independently controlled release rates.[14] The device comprises a microfabricated reservoir, a controlled-release cover, and formulations made of photopolymerized tri(ethyleneglycol)dimethacrylate (TEGDM) and poly(ethyleneglycol)dimethacrylate (PEGDM). The release rate of each compound is controlled by varying the PEGDM/TEGDM ratio in its formulation and in the cover. The device is designed to deliver drugs via the transsceleral route, which is less invasive compared to intravitreal injections[15] and more bioavailable compared to topical eye drops.[16,17] Thus, we investigated the fabrication of the device that contains different formulations of EDV and UNO and evaluated the protective effects of this device against light-induced retinal damage in rats.

First, we investigated the controlled release of EDV and UNO using this polymeric system. The drugs were pelletized with P60 (PEGDM/TEGDM prepolymer mixture ratios of 60%/40%), loaded in the reservoir, and sealed with covers having various PEGDM/TEGDM proportions. The release of both EDV (**Figure 1**a) and UNO (Figure 1b) can be tuned by changing the ratio of PEGDM/TEGDM in the cover, and the release rate was almost constant in the covered devices. The release of both EDV and UNO was dependent on the PEGDM/TEGDM ratio and the release rate decreased with a decreasing PEGDM ratio in the cover (Figure 1c,d). A pure TEGDM (P0) cover was impermeable to EDV and UNO. Both of the devices without a cover showed a rapid burst-like release. The release rates estimated from the gradient curve for P60-, P40-, P20-, and P0-covered EDV-DDSs were 6.28, 2.80, 0.82, and 0 μg per day, respectively. In turn, the release rates for P60-, P40-, P20-, and P0-covered UNO–DDSs were 1.10, 0.48, 0.16, and 0 μg per day, respectively. The ability to control the release of drugs from the device is based on the swelling of the PEGDM/TEGDM polymer.[14] The polymer made of short chains of TEGDM is likely to be compact, allowing no penetration of drugs. On the other hand, long chains of PEGDM may result in a greater tendency to swell, facilitating permeation of small molecules

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