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Changes in the Ganglion Cell Complex after Inner Limiting Membrane Peeling for Epiretinal Membrane in Glaucoma Patients

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Background: Epiretinal membrane (ERM) is a disease that affects the vitreoretinal interface and causes metamorphopsia, anorthopia, and decreased visual acuity. In this study, ERM patients who underwent internal limiting membrane (ILM) peeling were classified as those with glaucoma (Group G) and a control group (Group C). Changes in ganglion cell complex (GCC) thickness were compared between these groups to investigate whether such changes had an effect on progression of glaucoma from structural change.

Methods: This was a retrospective, observational study that included 27 eyes of 27 patients. Group C included 22 eyes, and Group G included 5 eyes. Patients underwent ILM peeling, and cataract surgery was combined with vitrectomy for 16 phakic eyes; 2 phakic eyes and 9 aphakic eyes were treated only with vitrectomy. GCC thickness was measured preoperatively and at 2 weeks and 1, 3, and 6 months postoperatively, and these values and the rates of thinning were compared between the two groups.

Results: The mean age of patients was 66.7±12.8 years (range 30-84 years). There was no significant difference between groups in the thickness of the GCC or its rate of thinning after ILM peeling.

Conclusions: The present results suggest that this procedure does not cause structural exacerbation of glaucoma in glaucoma patients. Although further studies of the functional effects of ILM peeling are required, the present results suggest that there is no significant difference between the two groups.

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Key words: glaucoma, internal limiting membrane, peeling, ganglion cell complex, epiretinal membrane

Introduction

Epiretinal membrane (ERM) is a disease that affects the vitreoretinal interface, thereby causing metamorphopsia, anorthopia, and decreased visual acuity[1–3]. These symptoms are believed to occur when ganglion cells are damaged by ERM, which decreases retinal sensitivity and disrupts the alignment of visual cells[4–6]. There is no sex difference in the prevalence of ERM, but prevalence increases with age: from 2% in those aged <60 years to 12% in those aged ≥70 years. ERM often occurs in conjunction with retinal vein occlusion[1,7,8].

In recent years, internal limiting membrane (ILM) peeling has become standard during ERM surgery. Peeling the ILM rather than just the ERM alone reduces the rate of ERM recurrence[9]. Because the ILM is a colorless and transparent membrane, it is extremely difficult to detach, but Kadonosono *et al.* found that use of indocyanine green (ICG) to dye the ILM and make it visible enables it to be peeled safely and reliably[10]. Because ICG is retinotoxic, brilliant blue G (BBG) is now generally used as a safer alternative for dyeing the ILM[11]. ILM peeling completely removes the supraretinal cellular components, thereby releasing traction on the retina and improving its extensibility. The indications for ILM have been expanded from macular hole only to include conditions such as macular edema and ERM[1,12].

Because the ILM itself is a basement membrane bound to the ends of Muller cells, its removal can cause func-

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tional and mechanical damage to the retina[13], and ILM risks a gradual reduction in the thickness of the retina and ganglion cell complex (GCC)[14]. Glaucoma is a disease that causes retinal ganglion cell loss, and optical coherence tomography (OCT) scanning shows both the progress of the disease and reductions in the GCC and retinal nerve fiber layer (RNFL). Because the ILM is adjacent to the retinal ganglion cells, these nerve ganglion cells may be damaged by ILM peeling. Several studies have addressed the effect of ILM peeling on the RNFL, but no consensus has emerged[5,15–17]. In a meta-analysis of 16 studies of 1,286 eyes, Azuma *et al.* reported that addition of ILM peeling reduced ERM recurrence rate, with no effect on visual acuity or foveal thickness[18]. Ito *et al.* investigated the appearance of a dissociated optic nerve fiber layer (DONFL) and retinal function after ILM peeling and found that, although a DONFL appeared postoperatively, it had no effect on visual acuity or retinal sensitivity, suggesting that ILM peeling is effective and safe[19]. Tsuchiya *et al.* investigated changes in mean visual field sensitivity (MVFS) in glaucomatous eyes and reported that this tended to be exacerbated in glaucomatous eyes, whereas no change was observed in the eyes of a control group without glaucoma[20]. Different study methods have thus produced varying results concerning changes in retinal structure and the effect on retinal function. Further investigation is therefore required.

In this study, ERM patients who underwent ILM peeling were classified as a glaucoma (Group G) and control group (Group C), and change in GCC thickness was compared between these groups to determine whether changes had an effect on glaucoma progression caused by structural change.

Materials and Methods

Study design

This was a retrospective, observational study that adhered to the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board of the Nippon Medical School Hospital (approval number: 30-06-941). Patients who underwent ILM peeling and were observed for more than 6 months during the period from April 2013 through March 2018 were registered retrospectively using opt-out in our outpatient section. The study included 27 eyes of 27 patients (mean age 66.7±12.8 years); 22 eyes were classified as Group C and 5 eyes as Group G.

Inclusion and exclusion criteria

The study inclusion criteria included presence of a normal anterior segment and good-quality OCT images with retinal ERM. The exclusion criteria included severe ophthalmic disease, such as corneal dystrophy, degenerative retinal disease, macular degenerative disease, uveitis, and diabetic retinopathy, and any ophthalmic surgery during the previous 3 months. Eyes with indeterminate optic disc appearance were excluded from the study. Eight eyes with signs of retinal detachment or other retinal disease intraoperatively or postoperatively were also excluded.

Surgical procedures

Surgeries were performed by 3 surgeons (H.T., T.I., T.A.) using 25-gauge pars plana vitrectomy with the Stellaris PC (Bausch + Lomb, Rochester, NY, USA) or Constellation Vision System (Alcon Surgical, Fort Worth, TX, USA). Triamcinolone acetonide (TA; MaQaid, Wakamoto Pharmaceutical, Tokyo, Japan) was used to visualize the vitreous[21]. After cutting the core vitreous, TA was reinjected over the macula to grasp and peel the ERM with end-gripping forceps (Alcon Surgical). After removing the ERM, brilliant blue G (BBG; #0770 Sigma-Aldrich, St. Louis, MO, USA)-the use of which was approved by the Institutional Review Board of the Nippon Medical School Hospital (approval number: 2012-033)-was used for ILM staining. ILM peeling was performed with an extendible diamond dusted sweeper (Alcon Surgical) and end-gripping forceps (**Fig. 1**). Cataract surgery was combined with vitrectomy for 16 phakic eyes; 2 phakic eyes and 9 aphakic eyes were treated by vitrectomy only. Fluid-gas exchange (FGX) and intraocular gas tamponade with 20% SF6 were performed for all eyes with ERM in which intraoperative retinal breaks were found during a thorough peripheral vitreous shaving.

GCC thickness

The layer structure of the GCC comprises 3 layers: the nerve fiber layer (NFL), ganglion cell layer (GCL), and inner plexiform layer (IPL) (**Fig. 2**). The NFL around the fovea could not be measured by our OCT (RS-3000 Advance), but peripapillary NFL was measurable. Because this study was retrospective and investigated patients undergoing ERM surgery, no patient with glaucoma underwent peripapillary NFL measurement.

GCC thickness was measured preoperatively and at 2 weeks and 1, 3, and 6 months postoperatively, and these values and the rates of thinning were compared between the 2 groups. The thickness of the GCC in a 4.5-mm radius measured by OCT (RS-3000 Advance, NIDEK, Aichi, Japan) was compared preoperatively and postoperatively. Linear approximations were produced to compare rates

of thinning in each group in relation to preoperative thickness. Because the GCC is thinner in glaucomatous eyes, the changes in thickness at 1, 3, and 6 months postoperatively were measured with reference to GCC thickness at 2 weeks postoperatively.

Statistical analysis

In this experiment, means and SDs of the measurements were calculated for each group. Data were statistically analyzed by unpaired *t*-tests, with $p<0.05$ considered significant.

Results

Study population

This retrospective study analyzed 27 eyes of 27 patients: 22 eyes in the control group (Group C) and 5 in the glaucoma group (Group G). The mean age of the patients was 66.7 ± 12.8 years (range 30-84 years). Patient characteristics are shown in **Table 1**.

The mean thicknesses of the GCC preoperatively and postoperatively were compared in the 2 groups (**Table 2**, **Fig. 3a**). There was no significant difference in GCC thickness between Group C and Group G preoperatively or at 2 weeks or 1, 3, or 6 months postoperatively. As shown in **Figure 3b**, linear approximations of changes in GCC thickness were compared between the groups. The equation for the linear approximation was $y=-9.91x + 151.95$ for Group C and $y=-8.82x + 133.04$ for Group G; the slope was only slightly steeper for Group C. Because the GCC is thinner in glaucoma patients (**Fig. 4a**), the rate of thinning of the GCC at 1, 3, and 6 months postoperatively was evaluated in relation to the value at 2 weeks postoperatively (**Fig. 4b**). The rate of thinning of the GCC at 1, 3, and 6 months postoperatively was almost the same in Groups C and G. There was no significant difference between the 2 groups.

Discussion

Because the introduction of OCT has dramatically increased the diagnostic efficiency of ERM[3], few cases of

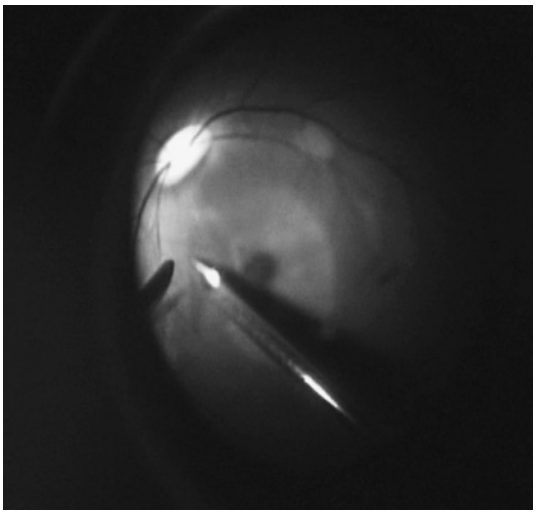

Fig. 1 Image of ILM peeling during surgery
ILM stained with BBG was peeled with end-gripping forceps.
ILM: internal limiting membrane, BBG: brilliant blue G

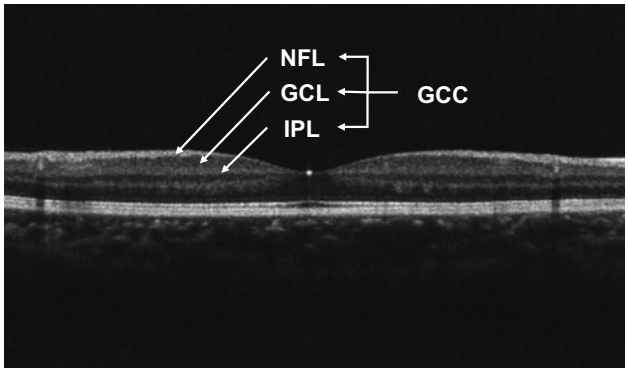

Fig. 2 The layer structure of the GCC
The layer structure of the GCC comprises three layers: the NFL, GCL, and IPL.
GCC: ganglion cell complex, NFL: nerve fiber layer, GCL: ganglion cell layer, IPL: inner plexiform layer.

Table 1 Demographic and ocular characteristics of control (Group C) and glaucoma (Group G) patients with ERM

Characteristic	Total (27)	Group C (22)	Group G (5)	*p* value
Male/Female	19/8	14/8	5/0	
Age (y)	67±12.8	67±10.5	64±20.6	0.57
Right/Left eye	16/11	14/8	2/3	
Visual acuity (log MAR)	–0.32±0.36	–0.29±0.38	–0.46±0.20	0.36
GCC thickness (μm)	143.5±28.7	147.6±28.9	125.8±21.9	0.13
FGX	6	5	1	
Combined cataract surgery	16	14	2	

ERM: Epithelial retinal membrane; GCC: Ganglion cell complex; FGX: Fluid gas exchange

Table 2 Change in GCC thickness in control (Group C) and glaucoma (Group G) patients

	Preop	2W	1M	3M	6M
Total GCC					
Group C (μm)	147.6±28.9	130.7±21.6	114.7±31.6	108.4±24.4	108.4±16.7
Group G (μm)	125.8±21.9	114.8±8.1	105.3±10.6	96±12.0	91.1±15.0
p value	0.13	0.32	0.62	0.41	0.14

GCC: Ganglion cell complex

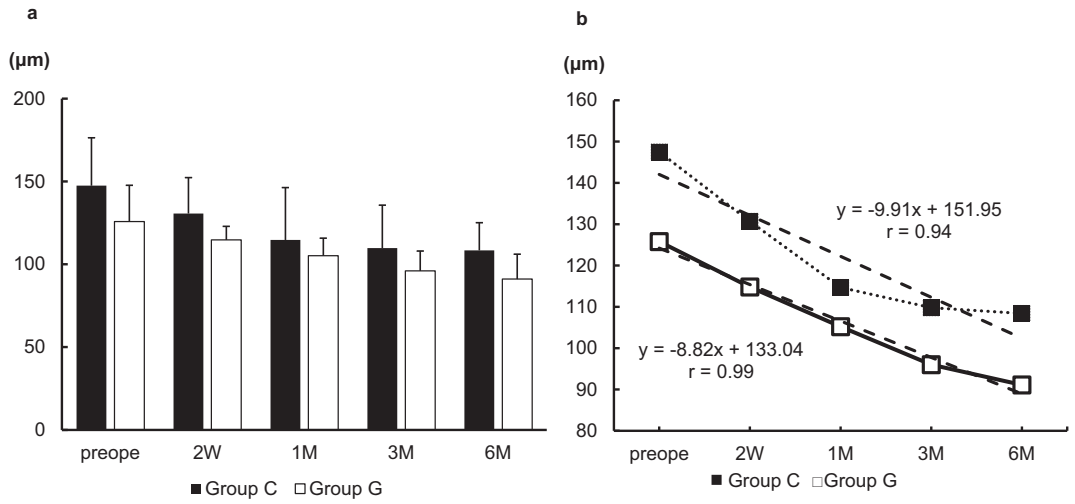

Fig. 3 Inner retinal layer thickness and thinning
(a) Comparison of mean preoperative and postoperative GCC thicknesses in Group C and Group G. There was no significant difference in GCC thickness between Group C and Group G (preope, p=0.12; 2W, p=0.32; 1M, p=0.62; 3M, p=0.41; 6M, p=0.14).
(b) Thinning of inner retinal layer
The slope of the linear approximation is greater in Group C than in Group G.

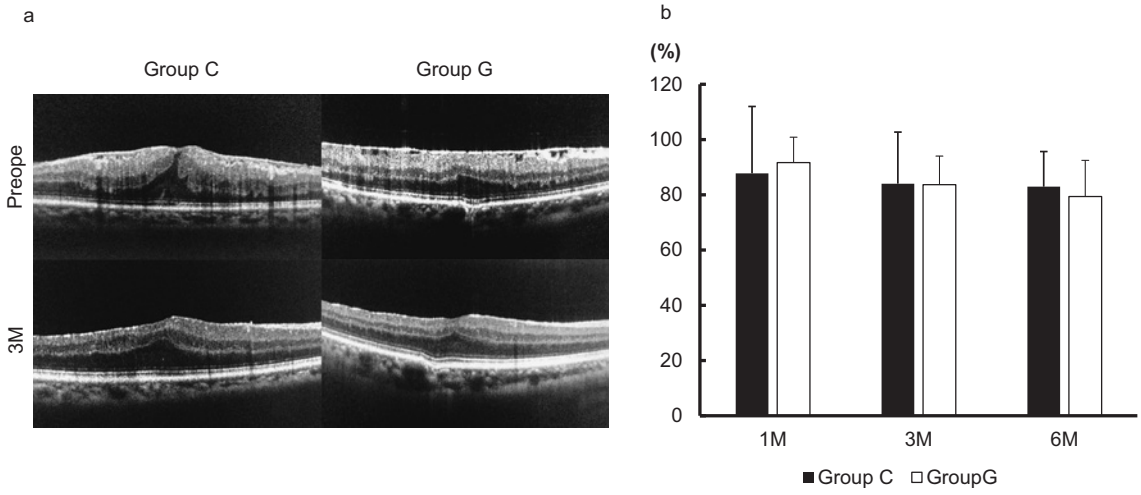

Fig. 4 OCT images and thinning of the GCC (with 2 weeks postoperatively as baseline)
(a) Typical OCT images of normal retina and preoperative and postoperative epiretinal membranes
The photographs show typical retinas preoperatively and at 3 months postoperatively in Group C and Group G.
(b) GCC thinning in Group C and Group G (with 2 weeks postoperatively as baseline). There was no significant difference in GCC thinning rate between Group C and Group G (1M, p=0.79; 3M, p=0.91; 6M, p=0.68).

ERM are now overlooked and prevalence has risen. ILM peeling is now widely used worldwide, but it has been suggested that removal of the ILM may damage the retina functionally and structurally[1,22,23]. However, previous studies found that although such damage was associated with the appearance of a DONFL it did not extend to problems with visual acuity, visual field, or electroretinography (ERG) findings, and changes in macular local ERG findings were slight[19,24,25]. In our hospital, functional assessment other than visual acuity was difficult because of the lack of testing devices to measure multifocal ERG, local macula ERG, and microperimetry.

In this study, the effect of ILM peeling on the macula, which is responsible for visual function, was investigated by comparing the postoperative rate of GCC thinning in relation to preoperative thickness in glaucoma patients. There was no significant difference between glaucoma patients and a control group in GCC thickness or its rate of thinning after ILM peeling. The present results suggest that, at a minimum, this procedure does not cause structural worsening of glaucoma in glaucoma patients.

No previous studies have evaluated the GCC but several have investigated changes in the RNFL. Reddy *et al.* reported that the RNFL decreased only in the lower quadrants[17], Kim *et al.* reported that it decreased only in the upper and lower quadrants[5], Balducci *et al.* reported that it decreased in the upper, lower, and temporal quadrants[15], and Lyssek-Boroń *et al.* reported that the decrease in RNFL was transient, with no subsequent decrease[16]. Existing evidence suggests that, even if a decrease in the RNFL does occur, it is only slight and does not indicate a major invasion in glaucoma patients. However, Tuchiya *et al.* reported that the MVFS is decreased by IML peeling in glaucoma patients only[20]; thus, future studies should perform preoperative and postoperative functional assessments of these patients.

In summary, as both ERM and glaucoma become more prevalent in an aging population, the number of patients with both conditions is expected to rise. Although further studies of the functional effects of ILM peeling are required, we found no significant difference between the 2 groups.

Conflict of Interest: The authors declare no conflict of interest.

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