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# Ganglion Cell-Inner Plexiform Layer Thickness Changes After Internal Limiting Membran Peeling for Macular Hole Treatment

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## Abstract

This article's aim is to evaluate macular retinal ganglion cell-inner plexiform layer (GCIPL) thickness changes after Brilliant Blue G (BBG)-assisted internal limiting membrane (ILM) peeling for idiopathic macular hole treatment. Fifteen eyes of fifteen patients who underwent pars plana vitrectomy with ILM peeling were included in the study. Other eyes of the patients were included in the study as control group. BBG assisted ILM peeling performed in 15 eyes. Baseline and, postoperative 3<sup>rd</sup>, 6<sup>th</sup>, and 12<sup>th</sup> months' BCVA and GCIPL thicknesses were recorded. In the operation group, BCVA improvement ( $1.06 \pm 0.22$  to  $0.43 \pm 0.29$  logMar,  $p=0.0037$ ), inferotemporal and superotemporal GCIPL thickness decrease after surgery ( $76 \pm 2.3$  to  $65 \pm 4.84$ ,  $p=0.0044$ , and  $73 \pm 7.6$  to  $63 \pm 3.82$   $\mu\text{m}$ ,  $p=0.0166$ , respectively) were statistically significant. In the control group, there was no postoperative statistically significant change. Superotemporal and inferotemporal GCIPL thinning and BCVA improvement in operated eyes showed statistically significant difference comparing to control eyes ( $p=0.0128$ ,  $p=0.0024$ ,  $p=0.0029$  respectively). ILM peeling causes retinal morphological changes like irregularities and indentations on the inner surface of the retina, thickening of the nasal retina, temporal GCIPL thinning, and dissociated optic nerve fiber layer during the late postoperative period. GCIPL thinning, particularly in the temporal region, is a common finding after ILM peeling. This may be related to toxic effects of ILM dyes and mechanical trauma.

## 1. Introduction

Vitreo-macular interface diseases are a group of disorders including macular epiretinal membrane (ERM), vitreomacular traction (VMT), and idiopathic macular hole (IMH). Most of these pathologies occur as a result of tractional forces, on the other hand they themselves create tractional forces. IMH is a relatively common disorder affecting 7.8 persons per 100.000, per year [1]. It can lead to severe visual acuity (VA) deterioration to the levels of 0.1 or worse in a third of patients [2]. Vitreo-macular anterior-posterior and tangential tractional forces play a substantial role in the pathogenesis of IMH. A standard surgical intervention for IMH consists of pars plana vitrectomy (PPV), separation of

posterior hyaloid from retina, internal limiting membrane (ILM) peeling, and intravitreal gas injection. Surgical separation of posterior hyaloid from retina may be a sufficient procedure for small IMHs. However, the IMH closure rate without ILM peeling is 55%. If ILM peeling is added to procedure, closure rates up to 100% may be possible [3].

Although clinical results show benefit of ILM peeling, it has been a controversial issue whether or not to peel ILM during IMH or macular ERM surgery. We do not know very well about the necessity of ILM for internal retinal layers integrity and functionality after the surgery. Some morphological changes including thinning of internal retinal layers and dissociated optic nerve fiber layer (DONFL) have been reported to be associated with ILM peeling [4]. Vital dyes used for ILM peeling such as indocyanine green (ICG), trypan blue (TB), and brilliant blue (BB) may have potential adverse effects on retina and contribute to these postoperative changes with surgical trauma itself.

Time domain optical coherence tomography (TD-OCT) devices with lower resolution images were incapable of giving precise information about retinal layers. After the development of spectral domain optical coherence tomography (SD-OCT), it could be possible to achieve detailed images of retinal layers like inner segment-outer segment layer (IS/OS), external limiting membrane (ELM), and inner layers like nerve fiber layer (NFL) and ganglion cell-inner plexiform layer (GCIPL). SD-OCT can offer measurement of thickness of specific retinal layers. Zeiss HD-OCT 5000 (Carl Zeiss Meditec, Jena, Germany) has a software utility that can measure the GCIPL thickness in different sectors of macula. It can calculate average and minimal thickness of GCIPL. Essentially, this utility is designed for detecting ganglion cell loss in glaucoma patients; nevertheless it can give us useful information about macular changes after surgery.

There are different previous reports of ganglion cell layer thickness changes after IMH surgery; some show thinning of GCIPL, whereas others report no change. The different results may be due to different SD-OCT device measurement techniques or different toxic effects of different vital dyes used in the surgery. In the current study, we evaluated the GCIPL thickness changes with Zeiss HD-OCT after IMH surgery in which we used BB to visualize ILM.

## 2. Methods

### 2.1. Subjects

Fifteen eyes of fifteen patients who underwent pars plana vitrectomy with ILM peeling were included in the study. Other eyes of the patients were included in the study as control group. Patients were treated in Nisa Hospital and Inci Eye Hospital between January 2014 and May 2015. Patients were informed on the purpose of the treatments and possible complications, and a written informed consent was obtained

from all patients. The study was conducted in accordance to tenets of Declaration of Helsinki. Inclusion criterion was idiopathic macular full thickness or lamellar hole with best corrected visual acuity (BCVA)  $\leq 0.6$ . Exclusion criteria were active ocular or systemic infection, systemic collagen vascular disorders, uveitis, and such disorders which can affect GCIPL thickness as glaucoma, diabetic retinopathy, eyes with previous vitreoretinal surgery or retinal argon laser photocoagulation. BCVA and intraocular pressure (IOP) measurement, slit lamp anterior segment examination, dilated fundus examination, SD-OCT measurements were performed at the baseline examination. Macular OCT images were obtained with the 512 $\times$ 128 scan utility of Cirrus HD-OCT 5000 device. This utility performs 128 horizontal B-scans comprising 512 A-scans per B-scan over 1024 samples within a cube measuring 6  $\times$  6  $\times$  2 mm. The Cirrus HD-OCT has an axial resolution of approximately 5  $\mu$ m, transverse resolution of 15 $\mu$ m and a speed of 27,000 A-scans per second. The ganglion cell analysis (GCA) software utility, which is essentially designed for glaucoma progression analysis, measures the thickness of average and minimum the ganglion cell plus inner plexiform layers. The average and minimum thicknesses of the ganglion cell plus inner plexiform layers are measured in an elliptical annulus around the fovea in a sectorial fashion. Vertical inner and outer diameters are arranged as 0.5mm and 2.0mm, and horizontal inner and outer diameters are arranged as 0.6 and 2.4 mm, respectively. This utility has an automated measurement system and the only allowed manual intervention is to change the elliptical annulus' location as per to fovea. Measured area is divided into six sectors which are superior, superior temporal, inferior temporal, inferior, inferior nasal, and superior nasal. OCT measurements were performed by experienced clinical technicians. Eyes were dilated with Tropicamide 1% (Tropamid forte 1%, Bilim ilac, Istanbul, Turkey) and Phenylephrine 2.5%. (Mydrin 2.5%, Alcon Laboratories, Duluth, GA, United States) The follow-up was performed at 1<sup>st</sup>, 3<sup>rd</sup>, 6<sup>th</sup>, and 12<sup>th</sup> months of surgery with the measurement of BCVA, IOP, slit-lamp anterior segment and dilated fundus examinations, and with the Cirrus HD-OCT software utility of GCA and macular thickness analysis. At the 1<sup>st</sup> month BCVA measurements and OCT images were not taken into consideration because of C3F8 in the eye that did not resolve completely.

### 2.2. Surgery

Eyes were dilated with Tropicamide 1% and Phenylephrine 2.5% prior to surgery. Operations were performed under general anesthesia and aseptic conditions in the operating room. After periorbital skin and eyelashes had been disinfected with 10% povidone iodine, eyelids and lashes were covered with a sterile surgical drape. Lid speculum was inserted and then conjunctival sac was irrigated with 5% povidone iodine. If the patient had a cataract obscuring the view of posterior segment, then pars plana vitrectomy was performed after lens extraction with phacoemulsification and intraocular lens

implantation. Three 23 gauge pars plana vitrectomy trocars were inserted 3.5-4 mm from the limbus at the sites of inferotemporal, superotemporal and superonasal sclera. Infusion cannula was inserted to the inferotemporal trocar. BSS (Alcon Laboratories, Duluth, GA, United States) was used as infusion liquid. The active infusion pressure was set to 25 mmHg. Cut rate was set to 5000 cpm, and vacuum level to 400 mmHg for core vitrectomy. Vacuum level was decreased to 150 mmHg for peripheral vitrectomy, and vitrectomy mode was switched from core to shave mode. After core and peripheral vitrectomy posterior hyaloid membrane was peeled from the retina by active suction. (Constellation, Alcon, Fort Worth, TX, United States). BB was used for ILM staining. A volume of 0.1mL Brilliant Blue G (Brilliant Peel, Geuder, Heidelberg, Germany) at a concentration of 0.25mg/mL was injected over the posterior pole for 45 seconds. The ILM was grasped at the temporal quadrant and peeled off in an area of two disc diameter around the macular hole. After peripheral retinal examination to eliminate possible iatrogenic tears, fluid-air-C3F8 12% (Geuder, Heidelberg, Germany) exchange was performed. Sclerotomies were closed with 8.0 vycril (Ethicon, Cornelia, GA, United States) in case of leakage. After surgery, patients were asked to remain in a facedown position for at least one week.

### 2.3. Statistical Analysis

Patient charts were reviewed for demographic features, BCVA changes, and OCT measurements. BCVA data obtained with decimal charts was converted to logMar visual acuity system by calculating the negative logarithm of

decimal BCVA value. LogMar values were used for statistical analyses. Statplus Pro 5.9.8 software (Analysoft, Walnut, CA, United States) was used for statistical analyses. The differences of the baseline and postoperative values of the same group were analyzed with nonparametric Wilcoxon pairs test, and different groups were compared with Mann-Whitney U test. A two-tailed *P* value of  $\leq 0.05$  was considered to be significant.

### 3. Results

Fifteen eyes of 15 patients underwent macular hole surgery. Mean age was  $71.57 \pm 9.22$  years. Nine patients were female (60%), and six were male (40%). Non-operated eyes of the patients were accepted as control group. Eight eyes were pseudophagic in the operation group, and six in the control group ( $p=0.2918$ ). Macular hole stage was grade two in four eyes (27%), grade three in seven eyes (46%), and grade four in four eyes (27%) in operation group. Two eyes (13%) had grade one and one eye (7%) had grade two macular hole in control group ( $p=0.0611$ ). Baseline BCVA was  $1.06 \pm 0.22$  logMar in operation group, and  $0.14 \pm 0.14$  in control group. Two eyes had combined cataract surgery with IMH surgery in the operation group. All of the macular holes closed postoperatively. Inferior temporal and superior temporal sectors showed statistically significant postoperative thinning of GCIPL, whereas average GCIPL thickness had no significant change. BCVA had a significant improvement at 12<sup>th</sup> month. Baseline and postoperative GCIPL thickness and BCVA changes of operation group are shown in table 1.

**Table 1.** Baseline and postoperative GCIPL thickness and BCVA changes of operation group.

	Baseline	3 <sup>rd</sup> month	6 <sup>th</sup> month	12 <sup>th</sup> month	<i>P</i> value*
Average**	74±5.4	67±10.1	66±10.2	64±10.7	0.0945
Minimum**	52±13.9	45±9.36	45±11.2	44±15.7	0.5629
Superior**	77±10.5	69±8.75	66±9.85	65±17.6	0.2216
Superotemporal**	73±7.6	68±5.74	64±4.11	63±3.82	0.0166
Inferotemporal**	76±2.3	67±4.18	65±4.15	65±4.84	0.0044
Inferior**	83±11.4	64±8.77	64±10.42	65±17.7	0.1591
Inferonasal**	85±13.9	64±8.99	63±12.51	62±16.31	0.4731
Superonasal**	74±13.9	67±9.14	65±9.57	65±15.3	0.4560
BCVA (logMar)	1.06±0.22	0.57±0.25	0.45±0.21	0.43±0.29	0.0037

\*Comparison of baseline and and 12<sup>th</sup> month data.

\*\*GCIPL thickness (µm)

There wasn't any statistically significant GCIPL thickness and BCVA change in control group. Baseline and postoperative GCIPL thickness and BCVA changes of control group are shown in table 2.

**Table 2.** Baseline and postoperative GCIPL thickness and BCVA changes of control group.

	Baseline	3 <sup>rd</sup> month	6 <sup>th</sup> month	12 <sup>th</sup> month	<i>P</i> value*
Average**	79±5.3	77±5.1	78±5.8	79±5.5	0.8275
Minimum**	76±4.9	73±4.3	74±4.9	77±4.8	0.7489
Superior**	78±7.6	75±6.7	80±7.1	79±7.2	0.2419
Superotemporal**	77±4.8	79±4.9	75±5.4	77±4.4	0.3045
Inferotemporal**	79±5.5	78±5.9	78±5.9	78±5.9	0.7174
Inferior**	76±6.3	76±5.5	79±6.1	76±6.8	0.6455
Inferonasal**	80±3.3	80±4.3	81±2.9	81±3.2	0.4766
Superonasal**	82±4.7	80±6.8	80±5.7	81±5.8	0.5964
BCVA (logMar)	0.14±0.14	0.14±0.15	0.15±0.14	0.16±0.14	0.1877

\*Comparison of baseline and and 12<sup>th</sup> month data.  
 \*\*GCIPL thickness (µm)

Mean superotemporal and inferotemporal GCIPL thickness of operation group showed statistically significant thinning at 12<sup>th</sup> month compared to control group. Mean BCVA of operation group showed statistically significant improvement at 12<sup>th</sup> month compared to control group. (Table 3)

**Table 3.** Comparison of operation and control group in terms of BCVA and GCIPL thickness changes.

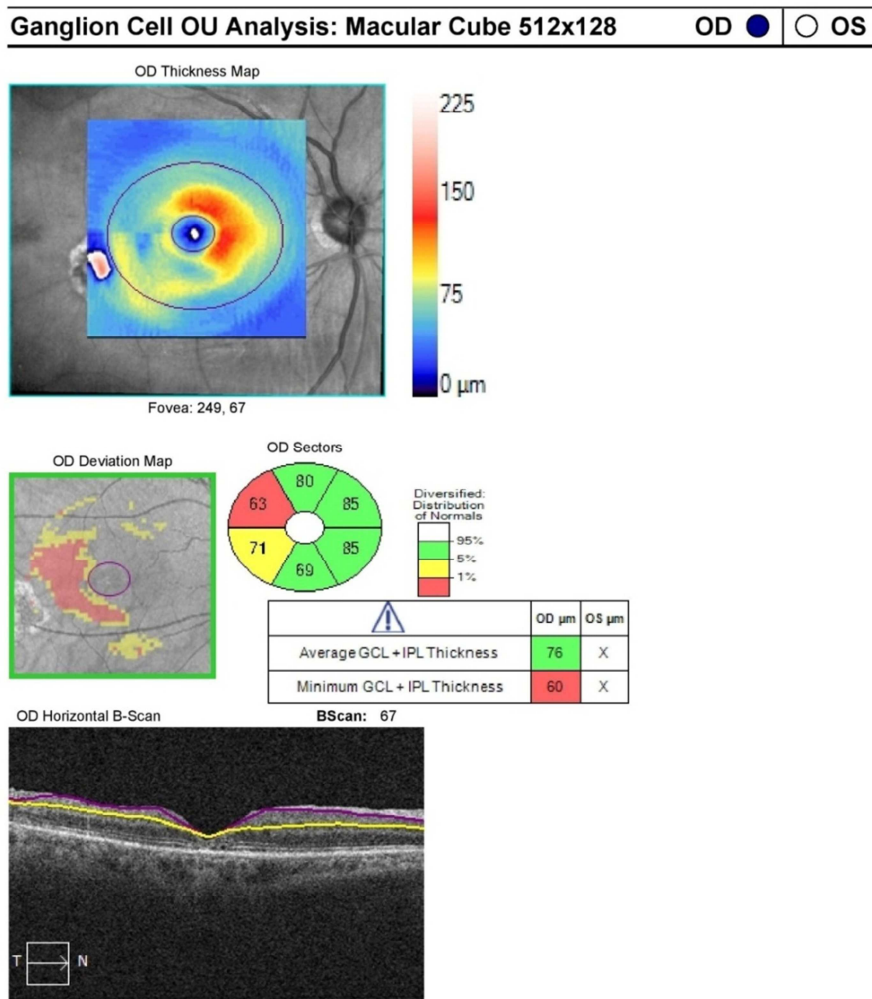
	Operation group	Control group	P value*
Average**	-9.9±9.1	-0.2±1.7	0.0990
Minimum**	-8±25.4	0.2±1.2	0.5539
Superior**	-12.2±16.8	0.8±1.2	0.1983
Superotemporal**	-10.8±5.4	0.6±1.0	0.0128
Inferotemporal**	-11±3.8	-0.4±2.1	0.0024
Inferior**	-10±11.6	-0.6±2.4	0.1813
Inferonasal**	-6.4±16.2	0.4±1.0	0.4484
Superonasal**	-9±21.8	-0.8±2.8	0.4964
BCVA (logMar)	0.62±0.21	-0.02±0.03	0.0029

\*Comparison of operation and control groups.  
 \*\*GCIPL thickness (µm) difference between 12<sup>th</sup> month and baseline, minus values represent thinning of GCIPL

A typical temporal GCIPL thinning after IMH surgery is shown in a figure 1.

Spearman rank correlation value between BCVA gain and average GGC thickness change was R=0,5 (p=0,391)

In the early postoperative period, three eyes showed transient posterior subcapsular cataract related to gas, and five eyes had transient intraocular pressure rise all of which were controlled with topical medication.



**Figure 1.** Inferotemporal and superotemporal GCIPL thinning at the 12<sup>th</sup> month of IMH surgery.

## 4. Discussion

The ILM is a membrane between the retina and the peripheral condensed vitreous gel. Internal expansions of Muller cells and a cuticular layer composed of collagen fibers, glycosaminoglycans, laminin, and fibronectin constitutes its structure [7]. ILM has approximately 10  $\mu\text{m}$  thickness. It has a smooth vitreal surface, and an irregular retinal surface. The retinal surface is composed of Muller cell footplates. ILM is constituted of an outer dense fibrillar meshwork and inner cuticular layer which is composed of loose net of fibrils. Outer layer is the Muller cells' basal membrane [8, 9, 10]. Muller cells support biomechanical integrity of retina by extending between ILM and ELM [11, 12]. Thus, Muller cells are the main component for the resistance to mechanical stimulation of the retina. The ILM is the basement membrane of Muller cells which can be surgically peeled of the retina. Its rigid structure provides a scaffold to contractile cells. Also, tangential and anterior-posterior traction forces influence retina over ILM's rigid structure. Thus, it plays an important role in vitreomacular interface diseases such as ERM, IMH, and VMT. Some authors noticed that traumatic ILM separation due to sub-ILM hemorrhage in Terson's syndrome did not cause glial proliferation and had a good visual prognosis [13, 14]. These experiences showed evidence that peeling the ILM might have a good visual outcome, and canalized the surgeons to remove the ILM to increase the elasticity of retina. Thus, they would be able to treat such diseases that are consequences of traction forces as IMH, ERM, and VMT [15]. After the introduction of surgical removal of the macular ILM, anatomic and functional success rates of the IMH treatment markedly improved [16-18]. Therefore, ILM removal has become a standard procedure for IMH treatment. Nevertheless, some morphological changes of retina after ILM peeling have been observed in the SD-OCT image sections. We do not know whether these morphological changes reflect a potentially progressive retinal damage. Toxic effect of the ILM dyes and mechanical trauma are mostly speculated factors responsible for these changes. Seo and Yu [19] reported average GCIPL thinning after ILM peeling with ICG. Temporal thinning was more prominent compared to other areas [19]. Balaiya et al. [20] reported significant decreased cell viability with ICG in cultured retinal ganglion cells and concluded that over 1.25 mg/ml and one minute exposure is toxic to retinal ganglion cells. Alfonso et al. [21] reported isolated temporal area thinning after ILM peeling with 0.25 mg/ml BBG over 30 seconds. In contrast to Seo's report [22] with ICG, average GCIPL thickness was spared with BBG. Ooi et al reported that intravitreal BBG is safe to rat's retina and a potential retinal toxicity is seen with ICG 0.05%. However, some recent reports showed not only temporal, also average thickness decrease with BBG [23]. In the presenting study, There was not a significant average GCIPL thinning. However, temporal area GCIPL thinning was significant. This finding is consistent with Alfonso's report. Not only the toxic effect of the dyes, also mechanical trauma to the retina may cause ganglion cell damage. Alfonso

concluded that, ILM peeling may cause a mechanical damage over the ganglion cell layer, which is "less" protected by the RNFL at the temporal area. On the other hand, ILM was usually grasped and peeled off from the temporal quadrant, which may contribute to the mechanical damage at this area [21]. GCIPL thinning did not accompany with VA decrease in this study. There was not a statistically significant correlation between BCVA changes and GCIPL thinning.

Other morphological changes reported after ILM peeling are the formation of irregularities and indentations on the inner surface of the retina, and the thickening of the nasal retina [16]. Other changes like the inner retinal dimpling, firstly called DONFL appearance, may be visible a few weeks after surgery in the SD-OCT images [24].

The current study has some limitations. First, limited case number can cause some statistical bias. Second, we do not know whether the morphological changes would cause a bad visual prognosis, so future studies with longer follow-up periods may be required.

## 5. Conclusion

ILM peeling causes such retinal morphological changes as irregularities and indentations on the inner surface of the retina, thickening of the nasal retina, temporal GCIPL thinning, and DONFL during the late postoperative period. GCIPL thinning, particularly in the temporal region, is a common finding after ILM peeling. This may be related to toxic effects of ILM dyes and mechanical trauma.

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