

Long-term Follow-up of Indocyanine Green–Assisted Peeling of the Retinal Internal Limiting Membrane during Vitrectomy Surgery for Idiopathic Macular Hole Repair

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Objective: To determine the long-term efficacy of indocyanine green (ICG)–assisted retinal internal limiting membrane (ILM) peeling during macular hole repair.

Design: Retrospective, interventional, noncomparative case series.

Participants: One hundred twenty-one eyes of 114 patients with stage 2, 3, or 4 idiopathic macular holes that underwent ICG-assisted macular hole repair during the period of August 1999 to January 2003.

Intervention: All eyes underwent a pars plana vitrectomy, including peeling of the posterior cortical hyaloid when necessary. Indocyanine green dye (0.5%) was instilled over the macula, and after removal of the ICG, the retinal ILM was peeled. Medium- to long-acting gas tamponade was used in all cases, and all patients were asked to position themselves facedown for 1 to 2 weeks.

Main Outcome Measures: Long-term postoperative anatomic results, visual acuity (VA), and complications.

Results: Patients were observed postoperatively for an average of 26 months (range, 12–53). Anatomic closure of the macular hole was achieved in 118 eyes (98%) with a single surgery. Reoperation was successful at closing 2 of the 3 macular holes that did not close initially. One macular hole reopened 16 months after the original surgery, and the patient has not yet undergone further surgery. Visual acuity improved by ≥ 2 lines in 116 eyes (96%). Mean visual improvement after surgery was 6 lines (range, 0–14), and 96 eyes (79%) achieved a final VA of 20/50 or better. There were no intraoperative or postoperative complications attributed to the use of ICG.

Conclusions: Long-term follow-up of patients who underwent ICG-assisted ILM peeling for idiopathic macular hole repair demonstrates excellent anatomic and visual results. *Ophthalmology* 2004;111:2246–2253 © 2004 by the American Academy of Ophthalmology.

Retinal internal limiting membrane (ILM) peeling has been previously reported to be a useful adjunct to vitreoretinal surgery, and has been demonstrated to improve anatomic and visual outcomes after macular hole repair.^{1–11} Surgical peeling of the ILM can be technically challenging even for experienced vitreoretinal surgeons. Specific difficulties include initiating the ILM peel, visualization of the border

between peeled and unpeeled ILM, and determining the extent of the ILM peel.^{5,12–14}

We began working with indocyanine green (ICG) as a tool to visualize the retinal ILM early in 1999 and demonstrated ICG staining of retinal ILM in human cadaver eyes.¹⁵ Indocyanine green clearly facilitates ILM peeling, and many studies have reported success with the use of this technique.^{9,16–26} However, some basic science literature suggests the possibility of ICG toxicity,^{27–32} and some clinical reports have attributed complications and poor outcomes to the use of ICG.^{33–35}

Currently, ICG staining of the ILM for macular hole surgery remains a controversial topic. We previously reported our initial series of ICG-assisted ILM peeling during vitreous surgery for macular hole repair.¹⁶ To our knowledge, there have been no studies reporting the long-term results of ICG-assisted ILM peeling in a large series of macular hole repairs. Herein, we present long-term fol-

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low-up of 121 eyes in which ICG dye was used intraoperatively to assist ILM peeling for macular hole repair.

Materials and Methods

Patient Selection

Patients who presented to the retinal service at the Cincinnati Eye Institute with a stage 2, 3, or 4 idiopathic macular hole were considered for entry into our study. Inclusion criteria were an unequivocal stage 2, 3, or 4 idiopathic macular hole; a desire for surgery to attempt hole closure; and clinical follow-up of at least 1 year. Exclusion criteria included diabetic retinopathy and previous intraocular surgery, except for uneventful cataract extraction.

There were 16 eyes from our initial report of 24 eyes¹⁶ that met the inclusion criteria for this study. The follow-up duration in the initial report ranged from 23 to 195 days, whereas the follow-up of these same eyes in the current report ranged from 17 to 53 months.

Retrospective Power Calculations

For the purpose of performing retrospective power calculations, a severe adverse visual event was defined as a loss of ≥ 3 lines of visual acuity (VA) after surgery. Data analysis was performed using MEDLOG.³⁶ In this analysis, we used our 121 patients as the sample size and $\alpha = 0.05$ as our nominal significance level and then evaluated the probability of detecting true severe adverse event rates of 10%, 5%, and 1%.

Surgical Technique

The ICG was prepared as described previously.^{15,16,37} Briefly, a 25-mg vial of ICG dye (Akorn Inc., Buffalo Grove, IL) was reconstituted with 0.5 cm³ of sterile water. After the crystalline ICG was completely dissolved in the sterile water, 4.5 cm³ of balanced salt solution (BSS; Alcon Laboratories, Ft. Worth, TX) was added to the solution to attain a final ICG concentration of 0.5% and an osmolarity of 270 mOsm.

When appropriate, cataract extraction by phacoemulsification with posterior chamber intraocular lens (IOL) placement was performed to achieve media clarity. All eyes underwent a complete pars plana vitrectomy (PPV), including elevation and removal of the posterior hyaloid if still attached. Typically, to minimize trauma to the optic disc, we used only a very brief application of active suction, between 100 and 200 mmHg, before switching to a bent microvitrectomy blade to engage and separate the cortical gel. Indeed, one of us (MRP) does not use any active suction to elevate the hyaloid; instead, he initiates hyaloid elevation with a bent microvitrectomy blade.

Our initial protocol in 1999 used 0.2 to 0.4 ml of ICG solution, which was left in the BSS-filled vitreous cavity for 3 to 5 minutes. Shortly thereafter, we found that adequate ILM staining could be achieved by injection of 0.05 to 0.1 ml of ICG solution, followed by its removal within 30 seconds using active suction. We purposefully avoided injecting the ICG directly into the macular hole, and redirected or turned off the internal light pipe while the ICG was in the eye. The ILM peel was initiated with a bent microvitrectomy blade. Diamond-dusted intraocular forceps were used to complete the peel throughout the posterior pole (temporal edge of optic nerve to the temporal vascular arcades), as previously suggested.^{1,5,15} This was followed by a fluid-air exchange using a low pressure set (30 mmHg) and then placement of a medium- to long-acting gas. No attempt was made to evacuate fluid from the

macular hole directly. All patients were asked to position themselves facedown for 1 to 2 weeks. The type and concentration of intraocular gas, as well as the duration of postoperative prone positioning, were at the discretion of the vitreoretinal surgeon. Most commonly, we used a minimally expansive concentration of an intermediate duration gas (e.g., 22.5% to 25% sulfur hexafluoride) and asked patients to stay in a prone position for 4 to 6 days after surgery. Patients were examined on postoperative day 1, week 1, month 1, and month 3, and then semiannually thereafter. Fluorescein angiography was performed as described on all of the patients in the original study.¹⁶ As ICG-assisted ILM peeling became an acceptable standard of care, fluorescein angiography was no longer performed routinely, but was left to the discretion of the surgeon.

Initial surgical specimens were examined by both light and electron microscopy to verify the nature of the ICG-stained membrane peeled during surgery. As described previously, light and electron microscopy demonstrated unequivocally that the tissue stained by ICG and removed during peeling was retinal ILM.¹⁶

Data collected included preoperative best-corrected VA (BCVA) and postoperative BCVA at the most recent visit, duration and type of macular hole, anatomic outcome/closure of the macular hole, surgical or postoperative complications, and length of follow-up. Data were tabulated using Excel.³⁸ Snellen VA was determined using the Baylor Visual Acuity Tester (Medtronic-Solan Surgical Products, Jacksonville, FL).³⁹ Snellen VA was converted to a line score to record the number of lines gained or lost postoperatively, as previously described.¹⁶

Results

One hundred fourteen patients (121 eyes) with stage 2, 3, or 4 idiopathic macular holes were enrolled. The average age of the patients was 69 years (range, 51–85). Idiopathic stage 2 macular holes were present in 14 eyes (12%). Idiopathic stage 3 macular holes were present in 85 eyes (70%). Idiopathic stage 4 macular holes were present in 22 eyes (18%). The median reported macular hole duration was 3 months (range, 1–120). At the time of vitrectomy surgery, 29 eyes (24%) were pseudophakic, 56 eyes (46%) underwent concurrent cataract extraction, and 34 eyes (28%) were left phakic. Twenty-seven of the 34 eyes that were originally left phakic underwent subsequent cataract extraction during the follow-up period. Two eyes were aphakic at the time of macular hole surgery and underwent concomitant anterior chamber IOL implantation.

Initial surgical specimens were submitted for light and electron microscopy as reported previously.¹⁶ We did not identify cellular elements present on the retinal side of the ILM in our clinical specimens (Fig 1).

Postsurgical follow-up ranged from 12 to 53 months (mean, 26). Successful macular hole closure with a single surgery was achieved in 118 eyes (98%). Median preoperative VA was 20/100 (range, 20/40 to counting fingers). Median postoperative VA was 20/40 (range, 20/20–20/400). Final VA improved by ≥ 2 lines in 116 eyes (96%). No eye lost vision. Mean visual improvement after surgery was 6 lines (range, 0–14), and 96 eyes (79%) achieved a final VA of 20/50 or better. A scatterplot of the preoperative VA compared with the postoperative VA is demonstrated in Figure 2.

Only 3 macular holes in our series remained open after the primary surgery. Reoperation was successful at closing 2 of these 3 macular holes. During reoperation, ICG was utilized, and the absence of staining demonstrated that the ILM had been clearly removed within the temporal vascular arcades. However, these eyes were noted to have diaphanous epiretinal tissue around the



Figure 1. A transmission electron micrograph (original magnification, $\times 5800$) of peeled internal limiting membrane (ILM) demonstrates the characteristic smooth inner (vitreous) surface and the undulating or irregular outer (retinal) surface. Cellular elements were not observed on the retinal face of the ILM, but this magnification does not rule out traces of Müller cell membrane adherent to the ILM.

macular hole, which was removed with diamond-dusted forceps. The macular hole was closed in 2 eyes that were filled with silicone oil. One macular hole remained open in the eye that underwent reoperation and was filled with perfluoropropane. An additional macular hole that remained closed for 16 months after the initial surgery reopened and has not yet undergone reoperation.

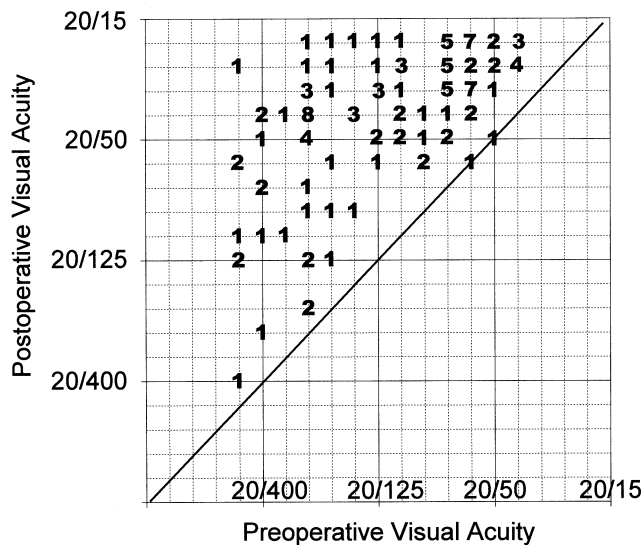


Figure 2. Scatterplot distribution of preoperative visual acuity (VA; x-axis) versus postoperative VA (y-axis). The actual number of eyes occurring at each point is displayed on the chart. The heavy diagonal line represents no change in VA. All points above the diagonal represent eyes that have gained ≥ 1 lines of VA.

During the study period, 14 eyes of 13 patients underwent ICG-assisted ILM peeling for macular hole surgery but did not complete 1 year of follow-up due to release to the referring physician, patient residence out of town, or attrition. One 75-year-old patient with preexisting coronary artery disease died of a myocardial infarction 14 weeks after surgery. The average follow-up of the patients in this group was 5 months (range, 1–10). Visual acuity improved by ≥ 2 lines in 11 of these 14 eyes. The average change in VA among this group was a gain of 4 lines (range, -1 to $+12$).

Besides the unrelated myocardial infarction, there were no adverse events detected among the patients who did not complete 1 year of follow-up. Indeed, among this group only 3 eyes did not gain ≥ 2 lines of VA. One of the 3 eyes followed for 7 months lost a single line of VA due to cataract progression. A second eye with only 2 months of follow-up had not changed from the preoperative VA of 20/50. The third eye had a macular hole that failed to close, and the patient did not follow-up beyond 1 month. The VA in this eye at the time of last examination had not changed from the preoperative VA of 20/200. If this eye had met our inclusion criteria, our anatomic success rate for primary closure would have dropped by $<1\%$.

Many of the elderly patients in this study were noted to have varying degrees of macular drusen, retinal pigment epithelium (RPE) mottling, and RPE atrophy before vitrectomy surgery with ICG-assisted ILM peeling. Only 2 eyes were identified in which macular RPE changes were first noted postoperatively. Macular RPE changes in 1 patient were noted preoperatively in the nonoperated eye, but not in the eye with the macular hole. After ICG-assisted ILM peeling, RPE changes were noted in both eyes, with the operated eye having more subfoveal atrophy than the nonoperated eye. Nonetheless, this eye gained 5 lines of VA. A second eye was also noted to have mild RPE changes after ICG-assisted ILM peeling. This eye gained 4 lines of VA.

Complications included iatrogenic peripheral retinal tears in 10 eyes (8%). Three of these retinal tears (2%) occurred postoperatively or went undetected at the time of surgery, resulting in retinal detachments (RDs) that were subsequently repaired. Additional complications included decentration of a previously placed posterior chamber IOL that required repositioning in 2 eyes as well as a postoperative recurrence of herpes simplex keratitis in 1 eye that was treated uneventfully. There were no intraoperative or postoperative complications attributed to the use of ICG in this series.

Retrospective power calculation analyses determined that our probability of detecting a severe adverse event with a 10% event rate was over 95%. In contrast, our probability of detecting an event with a 5% rate was between 50% and 80%. Given that our sample size was 121, our study did not have sufficient statistical power to detect a severe adverse event with a 1% rate.

An alternative approach for evaluating the power of our study to detect severe adverse event rates of a particular magnitude is the use of the $3/n$ rule.⁴⁰ This calculation provides the upper boundary of the 95% confidence limit for the actual frequency of severe adverse events in this population, given the lack of any such events in our 121 patients. According to this calculation, the upper boundary of the 95% confidence limit is 2.5%. Thus, by this rule a sample size of 300 would be required to have a reasonable probability of detecting adverse events that occur at a rate of 1%.

Discussion

The purpose of this study is to report our long-term experience and outcomes with intraoperative ICG-assisted peeling of the retinal ILM for macular hole repair. To minimize

the effects of confounding variables, we report herein only patients who met the selection criteria of unequivocal idiopathic stage 2, 3, or 4 macular holes; no diabetic retinopathy; and completion of at least 1 year of follow-up. As such, this article includes outcomes for some but not all of the patients reported in our original series.¹⁶ Our overall anatomic success rate and visual results compare favorably with the results of other reported series of macular hole repair.^{1-5,7-12,17,18,20,41-52} We found that with our technique, ICG-assisted ILM peeling provides excellent anatomic and VA results.

We recognize reports in the basic science literature suggesting the possibility of ICG toxicity to the retina and RPE. Experimental retinal and RPE toxicity was observed in a dose-dependent fashion when ICG was injected without removal into the vitreous cavity of rat eyes.²⁷ Dose-dependent toxicity has also been described with injection of ICG into the subretinal space of rabbit eyes.^{28,29} In addition, dose- and time-dependent toxicity has been observed when ICG was applied to cultured human retinal pigment epithelial cells.^{30,31,53}

It should be noted that experimental toxicity may not correlate exactly with actual clinical application of ICG, in which the intraoperative conditions are much different. Generally, in the clinical setting surgeons do not inject ICG into the vitreous cavity without removing it, nor do they intentionally inject ICG into the subretinal space. Nonetheless, Hirata et al described one case of accidental ICG injection into the subretinal space resulting in RPE atrophy at the site of the lesion.⁵⁴ The authors attributed RPE atrophy to the ICG in the subretinal space; however, it is well known that separation of the neurosensory retina from the RPE leads to atrophy and photoreceptor loss, whether it is due to subretinal ICG, fluorocarbons,⁵⁵ blood,⁵⁶ serous fluid,^{57,58} or even liquefied vitreous, as in RD.⁵⁹

Gandorfer et al described an interesting *ex vivo* system for evaluating the effect of ICG with and without illumination on human cadaveric eyes. Ten human donor eyes were hemisected, and a corneal trephine was passed through the vitreous gel and posterior pole, creating an artificial chamber into which 0.05 ml of 0.05% ICG was instilled in 8 of the 10 eyes. The dye was removed by irrigation after 1 minute. The macula was then illuminated for 3 minutes with wavelengths of 380 to 760, 380 to 620, or 620 to 760 nm. Two eyes were treated with ICG only, and 2 eyes were illuminated (380–760 nm) only. Light microscopy and electron microscopy were performed on specimens from the trephined macula and the untreated retina outside of the trephined area. They found that ICG instillation alone, even without illumination, induces ILM detachment and disruption of Müller cells. Furthermore, illumination of the ICG-stained ILM using wavelengths beyond 620 nm resulted in cellular damage to the inner retina.³²

Despite these experimental observations, there is notable laboratory experimentation to the contrary demonstrating that ICG does not produce histologic damage. Grisanti et al⁶⁰ examined 21 porcine eyes within 5 hours after enucleation. After hemisection and vitreous removal, different dosages of ICG were applied over the trephined macula.

They found that retinal exposure to ICG, even at high concentrations, followed by maximum power illumination for 3 minutes caused no histologically detectable damage. No microarchitectural disorganization or cellular disruption was observed. The vitreoretinal interface seemed unaffected. The authors concluded that the previously described damage to the inner retina of human donor eyes³² could not be found, even with higher doses of ICG in this porcine model. The authors suggest that species differences may contribute to these contradictory results, or that the degree of postmortem autolysis and the vitality of the tissue in human cadaveric donor eyes may explain the differences seen.⁶⁰ Alternatively, it is also possible that technical differences in the execution of the experiments might have led to differing results. Although Gandorfer et al's experiments were well planned, there were no sham operated eyes (eyes in which BSS was instilled into the artificial chamber, followed by irrigation). This raises the possibility that either the ICG instillation or the irrigation might have hydrodissected the ILM from the underlying retina. Indeed, if ICG instillation hydrodissected the ILM from the retina, the ICG solution would have had direct access to the retinal tissue, which might help to explain their reported photodynamic effects.

Furthermore, in our own cadaver experiments, 0.5% ICG solution was instilled and left to settle over the macula for 5 minutes. The posterior pole was continuously exposed to the operating microscope light for 1 to 2 hours. Histopathology of the posterior pole clearly demonstrated the border between the peeled and unpeeled ILMs. We observed no ILM detachment from the inner retina in the ICG-stained region, except for the area that was intentionally peeled. We did note postmortem autolysis histopathologically. Electron microscopy identified some cellular debris on the retinal side of the ILM, which we attribute to postmortem autolysis.¹⁵ However, the objective of this initial work was only to demonstrate that the ICG-stained membrane was truly retinal ILM. Thus, controls were not done to prove that the cellular debris seen was a result of postmortem autolysis.

Nakamura et al report the ultrastructural results of ICG-assisted ILM peeling in primate eyes. After PPV in 10 primate eyes, ICG-assisted ILM peeling was performed. Ultrastructural analysis revealed excised ILM associated with fragments of glial tissue. Mild damage and loss of Müller cell processes that were very similar to those of previously reported human ILM specimens both with⁶¹ and without ICG² were noted at the location of the ILM peel. Gradual recovery of the Müller cell processes was noted over the following 12 months; however, no ILM regeneration was noted.⁶²

Although this experiment approximates the clinical situation, there were no controls to demonstrate the effects of ILM peeling without ICG. Indeed, the authors attempted to peel the ILM without ICG but were unsuccessful due to "technical difficulties." Thus, the effect of ILM peeling alone cannot be distinguished from the effect of ICG-assisted ILM peeling in this primate model. It is encouraging to see regeneration of the damaged Müller cell processes. It is also interesting to note the absence of ILM regeneration,

which might explain the generally high success rate of macular hole closure after ILM peeling.

A few clinical reports attribute complications and poor outcomes to the use of ICG.^{33–35} The authors suggest that ICG-assisted ILM peeling results in poor VA outcomes, visual field (VF) defects, and RPE defects. We believe that our data regarding VA outcomes speak for themselves, and are commensurate with most of the published reports on ICG-assisted ILM peeling.^{9,17–21,23,24} It is not entirely clear why some authors have seen poor VA results.^{33–35} However, a short duration of follow-up as well as differences in surgical technique may explain some of the discrepancies. Furthermore, one group that observed poor outcomes with ICG-assisted ILM peeling suggested that a possible explanation might be that “the stained and therefore better visible ILM may be peeled off more aggressively than intended by the surgeon causing potential tractional forces and consecutive traumatic damage to the retina.”³⁴

The same group that has attributed poor VA outcomes to the use of ICG has also described the presence of significant amounts of cellular elements on the retinal side of the ILM after ICG-assisted ILM peeling.^{33,61} The etiology of these observed results is unclear, but it is conceivable that the reason for poor VA outcomes and the presence of cellular elements on the retinal face of the ILM might be one and the same: aggressive peeling of the well-visualized ILM.³⁴

During our initial clinical investigation of ICG-assisted ILM peeling, surgical specimens were sent for light and electron microscopy. Notably, these specimens were obtained during the period when we were using larger volumes (0.2–0.4 ml) of 0.5% ICG and allowing the solution to remain in the BSS-filled vitreous cavity for 3 to 5 minutes. Nonetheless, we did not identify cellular elements present on the retinal side of the ILM (Fig 1). Our findings corroborate those reported by others who also found no cellular elements on the retinal face of the ILM after ICG-assisted ILM peeling.^{18,25}

It should be kept in mind, however, that ILM is comprised primarily of the basement membrane derived from Müller cell footplates, and it is not surprising that ILM peeling might disrupt some of these footplates. Indeed, canals leading from the retinal surface through the ILM to the vitreal face were observed to contain degenerating Müller cell processes after ILM peeling long before the introduction of ICG.⁴ Cellular elements were not observed on the retinal face of the ILM, but this magnification does not rule out traces of Müller cell membrane adherent to the ILM or within ILM canals. Figure 1, however, clearly demonstrates the lack of gross cellular debris as described by Haritoglou et al³³ and Gandorfer et al.⁶¹

Regarding VF defects, it is well known that postoperative VF defects occur after PPV with fluid–air exchange.^{63–65} Indeed, VF defects have been reported after macular hole surgery whether or not the ILM is peeled.^{66–75} There are many proposed etiologies for the observed VF defects, including direct mechanical trauma to the optic nerve or nerve fiber layer, trauma resulting from fluid–air exchange, drying of the nerve fiber layer, and gas tampon-

ade.^{63–73,75} Clearly, VF defects after macular hole surgery are not a problem specific to ICG, or even to ILM peeling. One group compared the incidence of postoperative VF defects in 3 distinctly different types of vitreoretinal surgery. Yan et al examined the incidence of peripheral VF defects in 50 eyes after PPV for macular hole, subretinal neovascular membrane, and epiretinal membrane. They found VF defects in 19% of macular hole cases and 38% of the subretinal neovascular membrane cases. No patients who underwent epiretinal membrane peeling developed VF defects. Statistical analysis revealed that fluid–air exchange was the common denominator in all of the patients with a VF deficit. Only eyes that had fluid–air exchange developed VF defects. The authors suggested that trauma to the optic nerve during the fluid–air exchange may be responsible for the observed defects.⁶⁵ In addition, Hirata et al examined the occurrence of VF defects after macular hole repair in 100 eyes. The infusion cannula was placed either inferotemporally or inferonasally, and the air pressure was set at 50 mmHg or 30 mmHg. Eighteen eyes (18%) showed VF defects, and the defect was always located contralateral to the infusion cannula. Decreased air pressure reduced the incidence of VF defects from 24% to 4% ($P = 0.011$).⁶⁹ Fortunately, more recent reports have demonstrated that infusion with low air pressure and avoiding drying of the vitreous cavity—which are both part of our technique—result in a very low incidence (0%–1%) of peripheral VF defects.^{76,77} Visual field evaluation was not part of our outcome measures in this study. Nonetheless, our patients were questioned about subjective field defects, and none were reported.

Regarding postoperative RPE defects, we identified 2 eyes that were first noted to have macular RPE changes after ICG-assisted ILM peeling. However, RPE atrophy has been reported in the natural history of untreated macular holes,⁷⁸ after macular hole surgery without ILM peeling,^{79–85} after macular hole surgery with ILM peeling but without ICG,^{86,87} and after ICG-assisted ILM peeling.³⁵ Given our relatively low incidence of such postoperative changes and their description in the literature before the introduction of ICG, it seems likely that these changes may be related to patient-specific factors, rather than to the technique or the ICG itself.

Due to some experimental and clinical reports of ICG toxicity, it seems prudent to continue further investigation regarding the optimal technique for ILM staining. Perhaps a small dollop of viscoelastic material over the exposed RPE before the introduction of dye might limit access to the subretinal space, and thereby reduce the potential for toxicity. Perhaps the use of alternative stains such as infracyanine green or trypan blue may provide superior results relative to ICG.

It seems likely that ILM peeling and the intraoperative use of ICG will remain a controversial topic, with its opponents and proponents. We present our long-term experience with ICG-assisted ILM peeling for macular hole repair demonstrating excellent anatomic and visual outcomes. We conclude that, in our experience, ICG is a useful adjunct in vitreoretinal surgery for the closure of macular holes.

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