

EDITORIAL

Indocyanine Green–Assisted Macular Hole Surgery: Too Pioneering?

J. SEBAG, MD, FACS, FRCOPHTH

FEW STORIES TO COME OUT OF THE OLD WEST HAVE captured the imagination of the American people more than the tale of the Donner Party, who in the winter of 1846 suffered great hardships high in the Sierra Nevada. With time, the ordeals of the Donner Party passed into history and legend, but their pioneering spirit lived on in the hearts and minds of vitreoretinal surgeons living and working in the area of the Donner Pass in Sacramento, California. Neil Kelly was among the first to attempt the surgical repair of macular holes. With his partner Rob Wendell he reported a relatively high success rate in the cure of a condition previously considered beyond repair.¹ Since that time, surgical techniques have improved and success rates have increased. However, it appears that recent developments in the treatment of macular holes, may be jeopardizing previous successes.

The pathogenesis of macular holes is not well understood. It is likely that macular holes represent a heterogeneous group of conditions with a common final pathway and similar clinical manifestation. In the vast majority of cases, however, the posterior vitreous cortex (PVC) plays an important role in the pathogenesis of macular holes. This structure, which is the peripheral shell of the vitreous body, contains a high density of collagen fibrils and hyalocytes, mononuclear histiocytes that could be critical, albeit to date overlooked, participants in the pathogenesis of macular holes. Whether the PVC exerts anteroposterior traction, tangential traction, or both is difficult to determine in the absence of an experimental animal model.

The pioneering procedures first reported by Kelly and Wendell¹ were based upon the hypothesis that the PVC is important, and the surgical approach was designed to remove this tissue from the macula. In an attempt to increase the rate of macular hole closure, some surgeons grew more aggressive and sought to excise the internal limiting lamina (ILL), perhaps believing that this tissue

contributed to pathophysiology. While they might be right in some instances, particularly cases that fail conventional (without ILL peeling) macular hole surgery, the most likely explanation for the increased rate of macular hole closure following peeling of the ILL is that this deeper plane of dissection guarantees removal of the entire posterior vitreous cortex. Indeed, vitreoschisis, the splitting of the posterior vitreous cortex that is known to occur in proliferative diabetic vitreoretinopathy,² myopic macular holes,³ and very likely other vitreoretinopathies,⁴ can often go unrecognized resulting in persistent adherence of the outer layer of the posterior vitreous cortex and failed macular hole surgery.

Internal limiting lamina is in part the basement membrane of Mueller cells, and as such is firmly adherent to these critical cells in retinal neurophysiology. Removal of the entire ILL cannot be done without disrupting Mueller cells (Figure 1) and the nerve fiber layer.⁵ Indeed, focal macular ERG studies⁶ demonstrated b-wave abnormalities that did not improve after macular hole surgery with ILL peeling, as compared to controls without ILL peeling. The only reasonable explanation why surgeons are able to remove the ILL, if indeed the tissue being removed is truly the ILL and not just the outer wall of a vitreoschisis cavity, without adversely impacting visual acuity, is that not all of this layer is being excised. One hypothesis is that there is distinct electron dense layer and an electron lucent layer at the vitreoretinal interface. Another hypothesis⁷ is that the ILL is a multilaminar structure containing a lamina rara interna, lamina densa, and lamina rara externa. If the plane of dissection leaves the lamina rara interna intact, Mueller cells will be relatively undisturbed and will likely restore ILL integrity by resynthesizing the missing laminae. Visual outcomes are predictably good.

More recently, intravitreal indocyanine green (ICG) dye has been employed to facilitate identification of the posterior vitreous cortex and purportedly the ILL so as to dissect these tissue planes more completely. Like the first attempts at macular hole surgery, this innovation was introduced into clinical practice without the benefit of experimental investigation to assure efficacy and safety. Whereas the absence of an animal model of macular holes

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From the Doheny Eye Institute, University of Southern California, California.

Inquiries to J. Sebag, MD, VMRI Institute, 7677 Center Ave, Suite 400, Huntington Beach, CA 92647; fax: (714) 901-7770; e-mail: jsebag@vmrinstitute.com

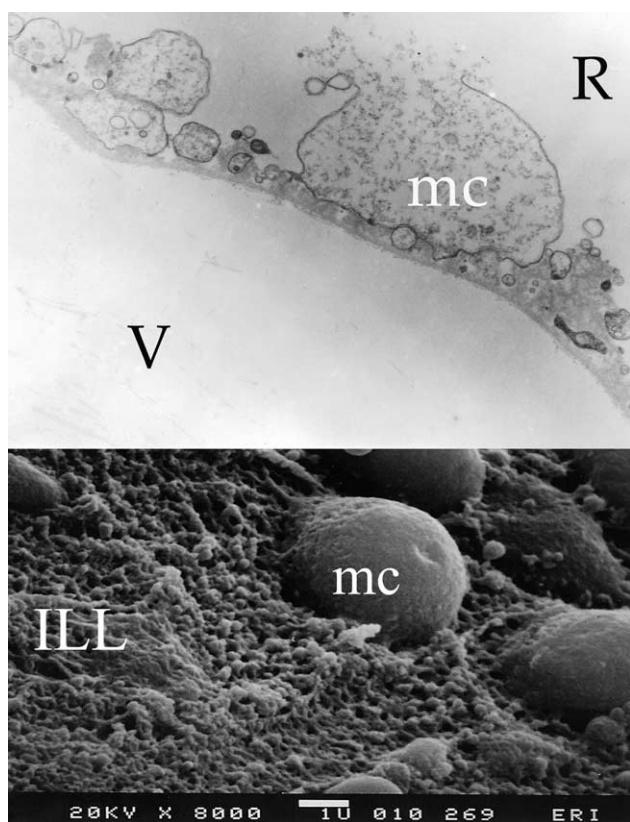


FIGURE 1. Ruptured vitreoretinal interface. Removal of the sclera and choroid, and dissection of the retina (R) off the vitreous (V) in a 14-year-old boy resulted in rupture of the Mueller cell with persistent attachment of the foot plate of the cell (mc) to the internal limiting lamina (ILL). Owing to the firm vitreoretinal adhesion in this young patient, the ILL remained adherent to the posterior vitreous cortex. The photograph above is a transmission electron micrograph (original magnification $\times 21,300$). The photograph below is a scanning electron micrograph showing the anterior portion of a Mueller cell (mc) adherent to the ILL. (Photographs are modified from Sebag J. Age-related differences in the human vitreo-retinal interface. *Arch Ophthalmol* 1991;109:966–971.)

makes this approach understandable in the surgical arena, it would have been relatively easy to test ICG for any untoward effects upon the retina or retinal pigment epithelium prior to its use during macular hole surgery. It appears from previous studies and an important new report in this issue of *THE JOURNAL* that, in this instance, the pioneering spirit may be deleterious to patients.

The December 2002 issue of *THE JOURNAL* contained a report⁸ out of Munich, Germany, that described a series of 20 patients who underwent macular hole surgery with intravitreal ICG. In spite of a high rate of hole closure, there was no improvement in visual acuity. Histologic analysis of ICG-stained tissue specimens revealed Mueller cell plasma membranes and other undetermined retinal structures adherent to the retinal side (posterior aspect) of the excised tissue. The authors concluded that the use of

ICG resulted in a deeper plane of dissection and untoward effects. Another possible reason for no improvement in visual acuity is dye toxicity, either immediate or long-term. Indeed, there have been reports⁹ of persistent optic disc and macular fluorescence due to ICG months after surgery, as well as findings of dye toxicity to the retinal pigment epithelium.¹⁰

In this issue of *THE JOURNAL*, Ando reports his experience with three different techniques of macular hole surgery in a consecutive series of patients. In 48 eyes undergoing conventional macular hole surgery and 21 eyes undergoing macular hole surgery with ILL peeling, the closure rate, as determined by optical coherence tomography (OCT), was 85% and there was statistically significant improvement in visual acuity by an average of 50%. In 28 eyes, ICG was used to assist ILL peeling. In spite of 100% hole closure, the mean logMAR visual acuity postoperatively was not improved (0.691, in comparison with the preoperative level of 0.767; $P = .342$). The advantages of this study are that a single surgeon performed all operations, eliminating individual variability, similar to a previous series of cases,¹¹ and that a more objective outcome measure than ophthalmoscopy was employed to establish hole closure, ie, OCT.

The major disadvantages are that the study population was not large and the study was retrospective. The former aspect is somewhat of a concern insofar as the small number of subjects in each sub-group could amplify the importance of small differences, such as the higher incidence of preoperative visual acuity greater than 20/50 in the group who underwent ICG-assisted ILL peeling (7 of 28, 25%) as compared with the group who had ILL peeling without ICG (1 of 21, 4.8%). There was, however, no significant difference preoperatively between the group who underwent ICG-assisted peeling and the group with no ILL peeling (visual acuity greater than 20/50 in 9 of 47, 19%). Furthermore, the latter group of patients did improve postoperatively (incidence of visual acuity greater than 20/50 increased to 25 of 47, 52%), whereas patients with ICG-assisted ILL peeling did not improve in this category (postoperative visual acuity greater than 20/50 in 7 of 25, 25%).

It is not clear why some studies¹¹ support these findings, whereas others¹² have not found similar results. There may be differences in the dose of ICG employed, both in terms of the concentration injected as well as variations in the local concentration delivered to the target tissue, eg, injecting under air as opposed to into an entirely aqueous milieu, and thus there could be varying amounts of dye toxicity. Perhaps dye toxicity is only relevant when the plane of dissection is deep. In the absence of pertinent experimental data, these and other questions are open to conjecture. What remains clear, however, is that the pioneering spirit of the Donner Party is no longer an appropriate guiding principle for the treatment of these patients. A randomized, controlled trial of the use of ICG

and other agents, such as Trypan Blue,¹³ is warranted prior to continued widespread use of this technique in macular hole surgery. This clinical trial should also assess whether there is truly a need for ILL peeling at all.

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