THE EFFECT OF INTERNAL LIMITING MEMBRANE REMOVAL AND INDOCYANINE GREEN ON THE SUCCESS OF MACULAR HOLE SURGERY

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ABSTRACT

Purpose: To compare the anatomic and functional results of 3 different epimacular dissection techniques on macular hole surgery.

Methods: Vitrectomy was performed in 123 eyes for macular hole in a retrospective, consecutive case series by one surgeon. The surgical technique was identical except for the method of epimacular dissection, which was performed using 1 of 3 techniques sequentially. The first group of 29 eyes had abrasion of the macula with a sharp pick (epiretinal dissection [ERD]), the second group of 32 eyes had partial or complete removal of the internal limiting membrane (ILM), without ILM staining. The third group of 62 eyes had complete removal of the ILM using indocyanine green (ICG) to stain the ILM.

Results: The mean preoperative visual acuity was 20/125 -2 in the ERD and ILM groups and 20/160 -2 in the ICG groups (P = .167). Long-term successful closure of the macular hole was achieved with one operation in 22 of 29 ERD eyes (75.9%), 31 of 32 ILM eyes (96.7%), and 62 of 62 ICG eyes (100%). The mean visual acuity at 3 months was 20/63 +2 (ERD), 20/80 (ILM), and 20/125 (ICG) (P < .001), with significantly poorer visual acuity in the ICG group. The final visual acuity (mean, 2.27 years) was 20/63 +1 (ERD), 20/50 -2 (ILM), and 20/80 -1 (ICG, P = .073), with no significant differences in mean visual acuity, visual acuity gain, gain of ≥3 lines, or percentage ≥20/40.

Conclusions: Removal of the ILM decreases persistent and recurrent macular holes. ICG staining and complete removal of the ILM slows the rate of visual recovery but does not appear to have any long-term deleterious effect on the results of macular hole surgery.

Trans Am Ophthalmol Soc 2007;105:198-206

INTRODUCTION

Macular hole surgery has become a common treatment for idiopathic macular holes, and refinement of techniques has improved the success rate of surgery with fewer complications. The procedure typically consists of a pars plana vitrectomy, removal of the posterior hyaloid, and fluid-air or fluid-gas exchange with some period of prone positioning following surgery. A number of surgical technique variations have been used to attempt to improve anatomic success (closure of the macular hole) and functional success (improved visual acuity). Some studies have suggested that removal of the internal limiting membrane (ILM) is helpful in improving the percentage of eyes that achieve closure of the macular hole.[1-6] In contrast, one study found no improvement in macular hole surgery when the ILM was peeled.[7] There is controversy about whether the ILM should be stained with indocyanine green (ICG) or other agents, such as trypan blue. Staining the ILM improves the ability to completely remove the ILM and usually decreases the operative time needed to remove the ILM during vitrectomy. Some studies have found that ICG-assisted removal of the ILM improves results,[8,9] whereas other have found that ICG makes no difference.[3,10-15] Some studies have found that ICG has a negative effect on the results of macular hole surgery.[16-19] A recent randomized study found no significant differences in visual acuity comparing ICG with trypan blue.[20] The effect of removing ILM and staining ILM with ICG was evaluated in the following study.

METHODS

The results of macular hole surgery were evaluated in a retrospective, consecutive case series of 123 eyes that underwent surgery between 1994 and 2005 to examine the effect of epimacular dissection or removal of the ILM on the results of surgery. The study was performed in the author's practice and was in conformity with the Declaration of Helsinki, US federal, and HIPAA guidelines, although no institutional review board approval was requested. The diagnosis of a macular hole was made by the surgeon and confirmed by fluorescein angiography in earlier operated eyes in the series and by optical coherence tomography in the later operated eyes in the series. All patients were treated by a single surgeon (J.T.T.) using 1 of 3 techniques for epimacular dissection. The techniques were used sequentially such that the surgeon used the same technique on all eyes until he switched to a different technique. Prior to the onset of the study, the surgeon had performed over 100 macular hole surgeries, so the results do not appear due primarily to a "learning effect" for performing macular hole surgery. The remaining aspects of the surgeries were identical.

Patients were eligible if they had a primary idiopathic or traumatic macular hole with symptoms of blurred vision of 2 years or less. Eyes with other significant macular diseases such as diabetic retinopathy or prior vitrectomy were excluded. The preoperative data collected included patient age, approximate age of the macular hole, macular hole stage (confirmed intraoperatively), preoperative lens opacities using the LOCS II grading system,[21] visual acuity measured on a Snellen chart with current correction, and intraocular pressures. Patients were examined postoperatively at 1 day, 1 to 2 weeks, 6 weeks, 3 months, 6 months, 12 months, and variable times following 12 months. Additional postoperative visits were performed as necessary. Results of a standard ophthalmologic examination including current corrected Snellen visual acuity, status of the macular hole, cataract grade using the LOCS II system, intraocular pressures, and any postoperative complications were also recorded.

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The primary outcome variables were complete macular hole closure and visual acuity at 3 months, 12 months, and the final examination following 12 months. Categorical variables were compared using chi-square tests, and numerical variables were compared using *t* tests or analysis of variance with post hoc testing for multiple comparisons, when appropriate.

SURGICAL TECHNIQUE

The basic surgical technique included a pars plana vitrectomy using a 20-gauge vitrectomy system in all eyes with removal of the posterior hyaloid. Active aspiration with the vitrectomy probe or a vacuum cleaner needle was used to create the posterior vitreous detachment in eyes with stage 2 and 3 macular holes. The vitreous was removed in the periphery as far as could be safely reached to allow a large gas bubble fill. This was followed by 1 of 3 epimacular dissection techniques The first technique, called epiretinal dissection (ERD), consisted of abrasion of the perimacular retina using a bent microvitreoretinal blade or bent sharp 20-gauge needle in 29 eyes. The sharp tip was used to scratch around the macular hole, typically around the border of the cuff of neurosensory retinal detachment surrounding the macular holes, but the edge of the macular hole itself was avoided. Petechial hemorrhages often formed during the macular abrasion, but forceps were not used to remove any ILM.

The second technique was ILM removal, where vitreoretinal forceps were used to pinch and lift the ILM around the macular hole in 32 eyes. The goal was to remove the ILM completely surrounding the macular hole. Confirmation of ILM removal was primarily determined by the presence of a pale edema in the perimacular retina where the ILM had been successfully removed. This allowed the "edge" of the removed ILM to be identified in some eyes so further removal could be performed. It was often difficult to verify complete removal of the ILM, since the ILM was not stained.

The third technique was called the ICG technique, because ICG was used to stain the ILM and remove all of the perimacular ILM. The use of ICG to stain the ILM represents a common off-label use of ICG. The ILM was stained by performing a fluid-air exchange and placing 1 or 2 drops of 0.5 mg/mL ICG over the macular hole. The ICG was left for about 60 seconds, and then the air was replaced with fluid and the ICG was lavaged from the eye over several minutes until the vitreous fluid was no longer stained green. Removal of the ILM was started usually by grasping the ILM with flat-tipped vitreoretinal forceps and lifting the ILM until a break in the ILM developed. The edge of the ILM was grasped with the forceps and peeled circumferentially around the macular hole for a distance of at least 3 disc diameters. Occasionally, a sharp microvitreoretinal blade was used to create a small nick in the ILM to lift an edge to grasp with the forceps. Rarely would ILM removal extend beyond the temporal vascular arcades. A fluid-air exchange was then performed, and residual intravitreal fluid was again aspirated about 5 minutes after the initial fluid-air exchange to try to obtain a complete gas fill. Later in the series, eyes had preplacement of the sclerotomy sutures prior to the fluid-air exchange to allow rapid closure to try to prevent dehydration injury to the nerve fiber layer, which has been associated with postoperative visual field defects.[22-27]

All eyes received a 16% perfluoropropane bubble, and about 50 mL of 16% perfluoropropane was lavaged through the eye to ensure the correct gas concentration. Patients were placed immediately prone in the operating room after dressing the eye and remained prone full-time for 14 days. Patients were instructed to sleep prone for a total of 6 weeks. The intraocular gas bubbles absorbed by 6 to 8 weeks following surgery.

RESULTS

The baseline characteristics of the three groups (ERD, ILM, and ICG) were similar and are given in the Table. Visual acuity was slightly worse in the ICG group, but this difference was not statistically significant. The ILM group had a significantly shorter duration of the macular hole ($P = .032$), and the time of the final examination was significantly greater for the ERD and ILM groups, which had surgery before the ICG group ($P < .001$).

The macular hole was closed at 3 months in 26 of 29 eyes (89.7%) in the ERD group, 31 of 32 eyes (96.9%) in the ILM group, and 61 of 62 eyes (98.4%) in the ICG group (Figure 1). The one open macular hole in the ICG group closed spontaneously between 3 and 6 months. There were 3 persistent macular holes in the ERD group, and 4 additional macular holes recurred following initial successful closure at various times during follow-up. A second macular hole surgery was performed in 6 of 7 ERD eyes with persistent or recurrent macular holes, and the holes were closed at the final examination in 27 of 29 eyes (93.1%). Of the remaining open holes, 1 patient refused surgery and the other eye had 2 surgeries with unsuccessful closure, possibly due to severe cystoid macular edema that developed following cataract surgery.

There was 1 persistent macular hole (3.1%) in the ILM group and 1 additional macular hole (3.1%) reopened between the 1-year and final examination. Both eyes had 1 additional surgery with successful closure of the macular holes for a final closure rate of 32 of 32 eyes (100%) All eyes in the ICG group maintained closure of the macular hole with no recurrent macular holes, for a final closure rate of 62 of 62 eyes (100%). Figure 2 presents the cumulative macular hole closure rates, defined as the percentage of eyes with closure of the macular hole with 1 surgery throughout the entire follow-up period.

The mean visual acuities at 3 months, 1 year, and the final examination are plotted in Figure 3. Visual acuity improved significantly more in eyes in the ERD and ILM groups at 3 months compared to the ICG group ($P < .001$ comparing the ERD to ICG group, and $P = .036$ comparing the ILM to ICG group). There were no statistically significant differences in the visual acuities between the 3 groups at the 1-year or final examination. Eyes in the ERD and ILM groups showed improvement at 3 months compared to preoperatively, with some decline at 1 year due to nuclear sclerotic cataracts in most phakic eyes and further improvement at the final examination when over two-thirds of eyes were pseudophakic. The eyes in the ICG group did not show as much improvement at 3 months but did show gradual improvement at the 1-year and final examinations.

Figure 4 presents the mean change in visual acuity by the number of Snellen lines (1 Snellen line = 0.1 logMAR unit). Again, the ERD eyes showed the greatest improvement at 3 months, which was significantly better than the ICG group (*P* = .004). The mean visual acuity improvements were similar by the 1-year and final examinations (+3.6 lines for ERD, +3.9 lines for ILM, and +3.2 lines for ICG groups).

TABLE. BASELINE CHARACTERISTICS OF THE THREE GROUPS THAT UNDERWENT MACULAR HOLE SURGERY

CHARACTERISTIC	ERD GROUP (n=29)	ILM GROUP* (n=32)	ICG GROUP† (n=62)	*P* VALUE (ANOVA)
Mean age, yr	69.99	70.34	66.97	.299
Mean preoperative visual acuity	20/125 -2	20/125 -2	20/160 -2	.167
Age of the macular hole, mo	7.11	3.11	6.42	.032
Macular hole stage				
Stage 2	4 eyes (13.8%)	12 eyes (37.5%)	15 eyes (24.2%)	
Stage 3	18 eyes (62.1%)	17 eyes (53.1%)	28 eyes (45.2%)	
Stage 4	7 eyes (24.1%)	3 eyes (9.4%)	19 eyes (30.6%)	
Number of phakic eyes	20/29 eyes (69%)	29/32 eyes (90.6%)	45/62 eyes (72.6%)	
Nuclear sclerosis score	0.73	0.63	0.54	.180
Posterior subcapsular cataract score	0	.02	.02	.084
Intraocular pressure	16.21	15.38	15.11	.394
Time to final examination, yr	2.97	3.04	1.54	<.001

ERD, epiretinal dissection; ICG, indocyanine green; ILM, internal limiting membrane.
*ILM removal without ICG.
†Complete ILM removal using ICG.

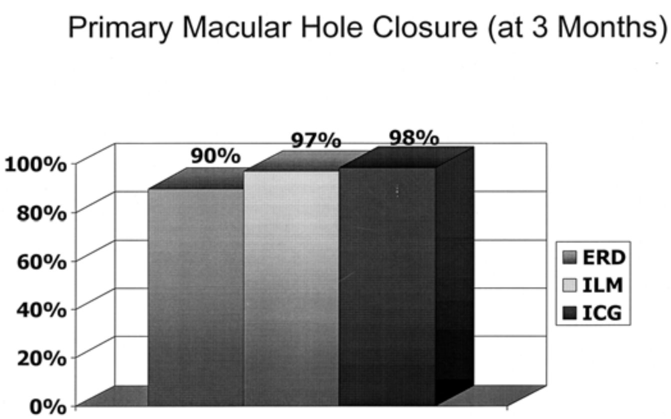

FIGURE 1

Macular hole closure at 3 months. Closure was successful in a higher percentage of eyes where the ILM was removed (ILM and ICG groups) compared to eyes where the ILM was not removed (ERD group), although the differences were not statistically significant. ERD, epiretinal dissection; ICG, indocyanine green; ILM, internal limiting membrane.

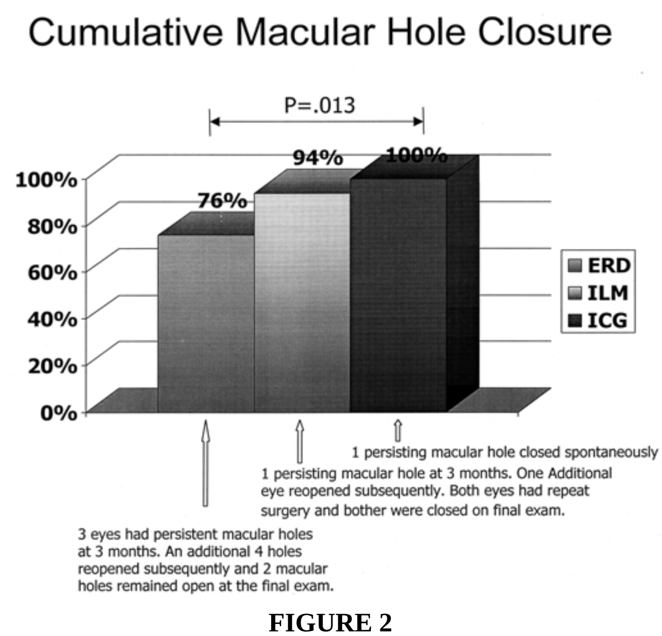

FIGURE 2

Cumulative macular hole closure rate. This is the percentage of eyes that had long-term closure of the macular hole with one operation. Eyes with persistent and recurrent macular hole months or years later were subtracted from the total. ILM removal resulted in a significantly better closure rate than eyes where the ILM was not removed (ERD group). ERD, epiretinal dissection; ICG, indocyanine green; ILM, internal limiting membrane.

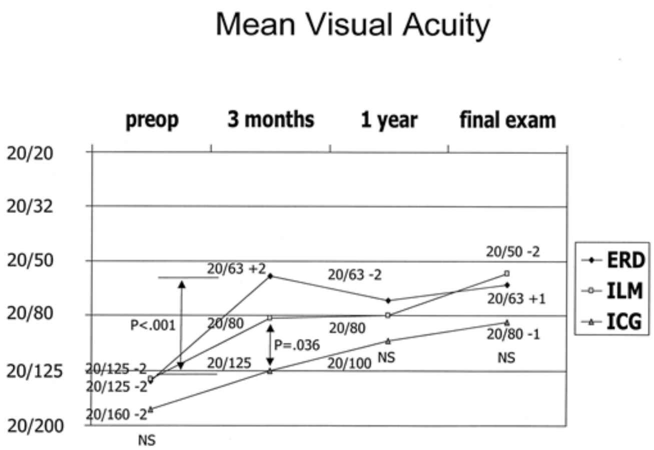

FIGURE 3

Mean visual acuities for the 3 groups plotted over time. Eyes in the ERD only group (without removal of the ILM) had significantly more improvement at 3 months compared to both groups where the ILM was removed, despite a lower rate of successful closure. The visual acuity tended to decrease some at 1 year primarily due to cataract progression in phakic eyes. The visual acuities were similar at the final examination with no statistically significant differences between the eyes where ILM was removed (ILM and ICG groups) compared to eyes where the ILM was not removed (ERD group). ERD, epiretinal dissection; ICG, indocyanine green; ILM, internal limiting membrane.

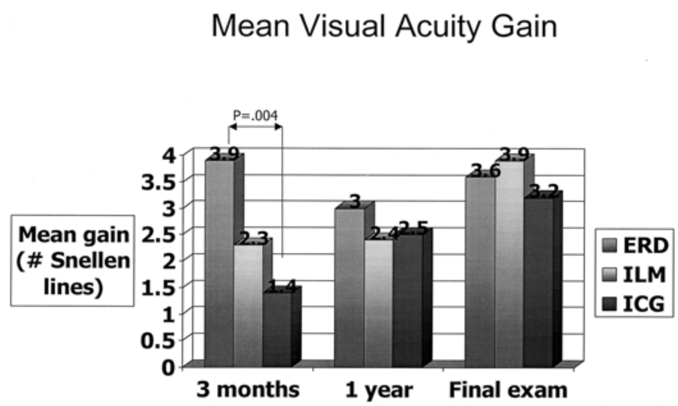

FIGURE 4

Mean visual acuity gain. Gain was higher in the eyes without removal of ILM at 3 months compared to the other 2 groups, although the visual acuity gain was similar at the final examination in all 3 groups. ERD, epiretinal dissection; ICG, indocyanine green; ILM, internal limiting membrane.

Figure 5 shows the percentage of eyes that gained at least 0.3 logMAR unit (3 or more Snellen lines) in the ERD, ILM, and ICG groups. The ERD eyes again showed a statistically significant improvement at 3 months (20/29 eyes, or 69%, compared to 23/62 eyes, or 37%; P = .007). There were no statistically significant differences at the 1-year or final examinations.

Other visual parameters (Figure 6) showed similar trends with a higher percentage of eyes in the ERD group attaining a visual acuity of 20/40 or better at 3 months (10/29 eyes [35%]) compared to the ILM (5/32 eyes [16%]) and ICG (3/62 eyes [5%]) groups. The difference between the ERD and ICG groups was significant (P = .0004), whereas the difference between the ILM and ICG groups did not reach statistical significance (P = .12). The percentage of eyes that were 20/40 or better at the 1-year and final examinations was similar in the 3 groups (11/29 [38%] of ERD, 11/32 [34%] of ILM, and 18/62 [29%] of ICG groups, with no significant differences between the 3 groups).

COMPLICATIONS

One eye in the ERD group developed a peripheral rhegmatogenous retinal detachment (with an attached macula), for an 0.8% incidence of retinal detachment in 123 eyes. One eye in the ICG group developed a presumed bacterial scleritis at the location of one of the sclerotomy sites 3 months following surgery, which responded to topical antibiotics. There were no other serious complications, such as infectious endophthalmitis or recognized macular ICG toxicity, in the ICG group. Intraocular pressure became transiently elevated in some eyes immediately following surgery, but all eyes had an intraocular pressure of less than 25 mm Hg by the 3-month, 1-year, and final examinations. Progression of nuclear sclerotic cataracts was expected in phakic patients, and all patients over age 50 years showed increased nuclear sclerosis. The mean nuclear sclerosis scores at 3 months were 0.96 in the ERD group, 1.027 in the ILM group, and 0.84 in the ICG group. The mean nuclear sclerosis scores at 1 year were 2.0 in the ERD group, 2.17 in the ILM group, and 1.38 in the ICG group. Cataracts had been removed in an additional 4 eyes (13.8%) in the ERD group, 11 eyes (34.4%) in the ILM group, and 17 eyes (27.4%) in the ICG group at 1 year. The mean nuclear sclerosis scores at the final examination were 1.94 in the ERD group, 2.31 in the ILM group, and 1.25 in the ICG group. Cataracts had been removed in an additional 7 eyes (24.1%) in the ERD group, 9 eyes (28.1%) in the ILM group, and 9 eyes (14.5%) in the ICG group between 1 year and the final examination. Only 9 of 29 eyes (31%) in the ERD group, 8 of 32 eyes (25%) in the ILM group, and 11 of 62 eyes (17.7%) in the ICG group were still phakic at the final examination.

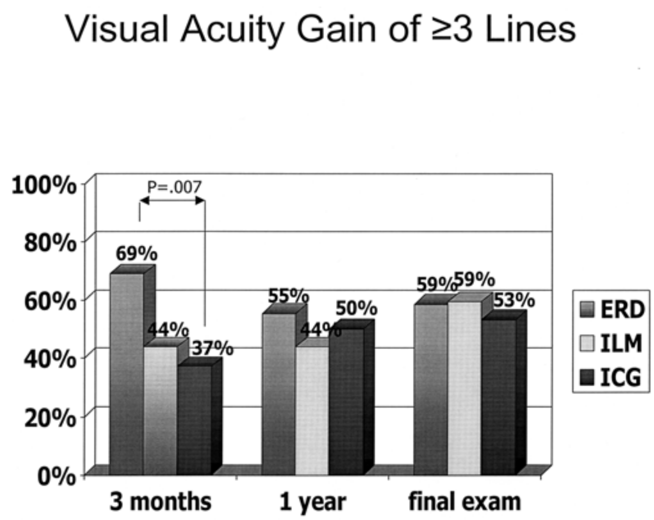

FIGURE 5

The percentage of eyes that gained 3 or more Snellen lines. Gain was significantly higher in eyes where the ILM was not removed at 3 months, but was very similar at the final examination. ERD, epiretinal dissection; ICG, indocyanine green; ILM, internal limiting membrane.

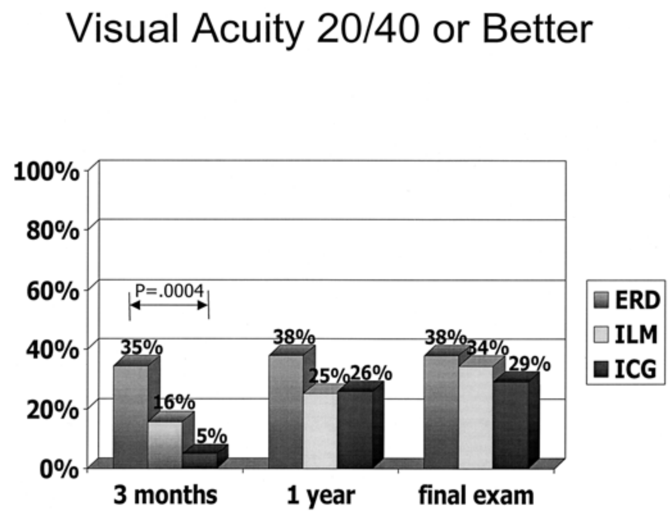

FIGURE 6

Percentage of eyes that attained a visual acuity of 20/40 or better. Percentage was significantly higher in eyes where the ILM was not removed at 3 months, but the percentage of eyes with 20/40 or better visual acuity was very similar at the final examination with no significant differences. ERD, epiretinal dissection; ICG, indocyanine green; ILM, internal limiting membrane.

DISCUSSION

The success of macular hole surgery has improved over the past 20 years with refinements in surgical techniques to achieve a higher likelihood of closing the macular hole and improving visual acuity compared to early studies. Some of the early innovators of macular hole surgery, such as Kelly and Wendel, advocated removal of what they described as cortical vitreous strands from the perimacular retina before the fluid-air exchange to help release any traction from residual cortical vitreous.[28] Their technique resulted in limited dissection around the edges of the macular hole, usually with forceps. The success rate for closing macular hole was 73% in their early series,[28] so they and other surgeons attempted to refine their surgical technique to achieve macular hole closure and visual acuity improvement in a larger percentage of eyes.

Adjuvants such as transforming growth factor β2, plasma, serum, and platelet lysate were used extensively in the 1990s to try to improve the results of macular hole surgery, but the use of adjuvants has largely been abandoned. Some surgeons began to experiment with removal of the ILM, and the first large series was reported by Brooks.[1] He was able to close the macular holes in 116 of 116 eyes (100%) with ILM peeling vs 36 of 44 eyes (82%) without ILM peeling, with a statistically significant improvement by removing the ILM. He also noted that ILM peeling seemed most beneficial in eyes with larger macular holes. Most recent studies have confirmed that ILM removal improves the results of macular hole surgery,[1-6] and one study that found no improvement had a sample size of only 22 eyes.[7]

The role of ICG staining of the ILM is more controversial where some studies found a benefit (or at least no harm) while other found evidence of toxic effects, resulting in poorer visual acuity or increased central scotomas. This suggests that the concentration of ICG, the way it is used to stain the ILM around the macular hole, and how completely the ICG is removed may have a role in potentiating or avoiding the harmful effects of ICG. Lochhead[8] found improved results with ICG staining of the ILM compared to ILM removal without ICG use. Studies by Slaughter,[10] Rivett,[11] Husson-Danan,[12] Mavrofrides,[13] Kumagai,[14] Villota-Deleu,[29] Rufer,[30] Oficjalska-Mlynczak,[31] and Ullern[32] found no significant differences between macular hole surgery with and without use of ICG to peel the ILM. Studies by Ando,[16] Gass,[17] Yamashita,[18] Ferencz,[19] Brasil,[33] and Tsuiki[34] have reported that ICG impairs the results of macular hole surgery. Ando reported a follow-up study using a lower concentration of .05% ICG and found no toxicity[15] compared to his earlier study, though.[16]

ICG can cause macular toxicity, as was noted with early ILM staining techniques for macular holes that used unfiltered ICG.[35] The technique by which ICG is used may influence whether ICG toxicity occurs in an individual eye, although some eyes may be more susceptible to ICG toxicity. The present study attempted to minimize the amount of ICG in the vitreous cavity by staining only the ILM around the macular hole with 1 or 2 drops of ICG in an air-filled eye. The ICG was positioned over the macular hole by rotating the eye as necessary. Once the perimacular ILM was stained, the ICG was lavaged from the eye. ICG can be excluded from entering the subretinal space through the macular hole by placing a perfluorocarbon bubble over the macular hole before ICG is placed into the eye .[36] This technique is especially helpful when the macular hole is associated with a retinal detachment.

Two published studies compared ILM removal using ICG or trypan blue. Lee[37] found no significant differences between macular hole closure, but postoperative visual acuities were significantly better in the eyes treated with trypan blue. A study by Beutel[38] found no statistically significant difference between visual acuity in eyes treated with ICG vs trypan blue, but visual improvement was somewhat better (not significant though) with trypan blue with fewer central scotomas. The higher success rate of closing small macular holes without ILM removal has caused Tadayoni[39] to advocate ILM removal only in macular holes over 400 µm.

The current study has several limitations inherent in a retrospective, nonrandomized study. One limitation was a smaller sample size in eyes without ILM peeling and eyes with ILM peeling without ICG, compared to removal of the ILM using ICG. Because the series was a consecutive series, little selection bias would be expected, since the same technique was used in all eyes with macular holes until a new technique was adopted. All other features of the macular hole surgery were identical, such as the surgeon, gauge of the vitrectomy system (20-gauge), intraocular gas tamponade (16% C_3F_8), and prone positioning (2 weeks). Another limitation is that visual acuities were taken using current correction rather than refracted visual acuities using a standardized ETDRS visual acuity chart and refraction. A third limitation is that cataracts were not removed in all phakic eyes by the last follow-up visit. The author believes that the study limitations would not likely change the primary findings of the study, though.

This study found no long-term deleterious effect of ICG on the results of macular hole surgery, but the short-term visual acuity recovery was delayed in eyes treated with ICG and also somewhat delayed in eyes with ILM removal, without use of ICG. This suggests that complete removal of the ILM slows the visual recovery, especially if ICG is used, but ILM removal results in a higher long-term macular hole closure rate. The delayed visual recovery in ICG eyes may be due to ICG itself or more complete removal of the ILM. Terasaki and associates[40] found delayed recovery in the macular b-wave 6 months following surgery in eyes with ILM removal, even when ICG was not used to peel the ILM. The slowed visual recovery can explain some of the discrepancies between studies that found differing results in macular holes treated with ICG-assisted ILM removal compared to eyes where ICG was not used. Studies that showed poorer results with ICG had visual acuities reported at varying times following surgery, so some of the visual results with ICG may have improved with longer follow-up. Internal limiting membrane removal with ICG in phakic eyes often results in decreased vision until after cataract surgery, since progressing cataracts decrease visual acuity by the time the macula has recovered from ICG-assisted ILM removal. The long-term results with and without use of ICG appear relatively equivalent, although eyes without ILM removal will have a higher probability of requiring reoperation for persistent or recurrent macular holes. The study suggests that excellent results can be obtained with removal of the ILM using ICG, but the use of ICG may not be necessary in all eyes with macular holes. It may be difficult to identify which macular holes require ILM removal preoperatively. Surgeons are reluctant to abandon a technique for macular hole surgery with ILM removal, which ensures close to a 100% rate of successful macular hole closure. Patients are also often reluctant to agree to a second surgery if the first operation was not successful, so closure of the macular hole with 1 surgery is very desirable.

Trypan blue has been offered as an alternative staining agent for macular hole surgery, but visualization of the ILM with trypan blue is substantially poorer than ILM staining with ICG. Triamcinolone particles can be dusted on the macula to identify where ILM has been removed, but triamcinolone does not stain ILM and allow easy identification of the edges of ILM. Further studies will hopefully identify other dyes that stain the ILM better than trypan blue but that allow more rapid visual recovery than ICG.

ACKNOWLEDGMENTS

Funding/Support: None

Financial Disclosures: None

Author Contributions: The author designed the study, collected, analyzed, and interpreted the data, as well as prepared the manuscript.

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PEER DISCUSSION

DR DENNIS P. HAN: Dr Thompson presented a consecutive, retrospective, surgical case series of 123 eyes that underwent macular hole surgery between 1994 and 2005. His findings verify previous studies showing that internal limiting membrane (ILM) peeling results in fewer reoperations for persistent or recurrent holes. However, he found that ILM peeling did not significantly improve visual outcome, contradicting numerous previous studies.[1] He also found that no significant worsening of outcome seemed to occur with the use of indocyanine green (ICG). This is currently a topic of much debate.[2]

The main strength of this study is that it involved a single surgeon in a highly technical procedure. Its weaknesses include its nonrandomized design, lack of protocol refracted visual acuity measurement, and perhaps underpowered statistics.

Important baseline factors differed between the groups, such as the initial visual acuity and the type, stage, and duration of the macular hole. The study included traumatic holes, which carry different prognoses from idiopathic holes, and are not distinguished from the others. Also, relative to the ICG group, the ILM group had a statistically shorter duration of macular hole (3.1 vs 6.4 months), and fewer stage 4 holes (9.4% vs 30.6%). Indeed, the ILM group had a slightly better visual result than the ICG group, probably because it had a better prognosis at the start. What is surprising is that the epiretinal dissection (ERD) group had final visual acuity results about as good as any of the other groups, despite having a lower hole closure rate. How might this be?

Aside from differing baseline factors, retinal or retinal pigment epithelial toxicity from ICG deserves mention. Such has been reported to occur at concentrations as low as 0.1%.[3] A concentration of half of that was used in the current study, but following fluid-air exchange, that can increase its effective concentration at the retinal surface. It is notable that the ICG group had the slowest rate of visual recovery of the study eyes and the worst visual outcome, in spite of a 100% hole closure rate. Could subtle ICG toxicity have limited visual recovery?

Finally, Dr Thompson's study might be underpowered to detect small differences in outcome between the treatment groups. Standard deviations for visual acuity results were not given, so that the magnitude of differences required to assign significance cannot be calculated. Nevertheless, the mean change in acuity differed between groups by no more than 0.7 lines, suggesting that differences, if any, may not be clinically meaningful.

In summary, Dr Thompson's study shows that lower reoperation rates can be obtained with ILM removal, but that removal may not be essential for good outcomes. He should be congratulated for contributing to our knowledge of macular hole surgery.

ACKNOWLEDGMENTS

Funding/Support: Research to Prevent Blindness, Inc.
Financial Disclosures: None.

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DR. JERRY SEBAG: I have no conflicts of interest. There is a fundamental flaw regarding the widely held opinion of the structure of internal limiting lamina of the retina. This is considered as one entity by many, but in fact it is a multilaminar in nature. If the entire internal limiting laminar were removed, two consequences would occur. First, the lamina would scroll up due to its internal elasticity and secondly, visual acuity would worsen, due to damage of Mueller cells that are intimately associated with it. I believe that the increased success rates of macular hole surgery that we have all experienced is the direct result of using ICG or other dyes. This technique permits more aggressive dissection and removal of the truly pathogenic tissue, the outer layer of the posterior vitreoschisis cavity, in my opinion. If you dissect farther into the retina you guarantee removal of that tissue, and if you do not, then you would need to implicate the internal limiting lamina as part of the pathophysiology in this disease. Are you saying that the internal limiting membrane is part of the disease or do you agree with the statement that its removal and at least partially, the innermost layer, the lamina rara interna of the lamina layer of the internal limiting lamina guarantees removal of the outer layer of the vitreous and thereby increases the closure rate?

DR. GEORGE O. WARING, III: No conflicts. I work 23 mm away from the retina. John, I have two questions. The first has to do with visual acuity testing. We spend a great deal of effort precisely measuring the best corrected and uncorrected visual acuity after refractive surgery and you are trying to do the same thing in these three different groups. What visual acuity chart did you use? How did you compute lines of visual acuity since you give credit for all the letters that they read? For example, if a patient correctly identifies two targets or letters on one line, one on another, three on the next, and so forth and how did you compute lines of vision?

Finally, I would like to ask an important general question: what cutoff should we use for judging a change in vision? If one agrees that a change of one line is normal biological variability, and that the minimal standard for anterior segment change is two lines, why is a three line change used as a cutoff point for determining clinically meaningful improvement as I have heard at this meeting. Could you comment on that point? The concentration of ICG you used ICG, 0.5 mg/mL, if I read it correctly, is toxic to the corneal endothelium, because we use these dyes to stain the anterior lens capsule for the removal of dense cataracts.

DR. TRAVIS A. MEREDITH: No conflicts. I have been following this literature for fifteen years and it is very difficult to use vision as an endpoint when you are comparing different series. There are so many confounding variables, such as the entry vision, size of the hole, duration of follow-up, and the occurrence cataract that make it difficult to compare one series with another. I consider a report from the Bascom Palmer Eye Institute as the gold standard. They followed patients who had best corrected vision measured three years after surgery and waited until all patients had undergone cataract extraction. They reported that visual acuity improved between the second and third year and the final visual acuities were remarkably good, in the range of 20/32. I think it would be extremely important to get all these patients back at three years for follow-up after cataract extraction. By performing standard protocol refractions, the authors could then tell us what the visual acuities are when ICG has been used and ILM peeling, and we could compare those results with the previous literature.

DR. HANS E. GROSSNIKLAUS: Thank you for that nice paper. Were any of the tissues removed during surgery examined histologically or ultrastructurally to confirm the presence of the internal limiting membrane and possible portions of Mueller footplates, and preretinal cellular proliferations?

DR. JOHN T. THOMPSON: I like to thank Dennis Han for his comments. They really helped to expand the discussion. I do not have any direct comments to challenge anything. One of the reasons that I found ILM peeling with ICG attractive, at least in my hands, is that it gives a hundred percent success. One of the problems with patients whose first intervention fails to close the hole or that opens subsequently, is that it sometimes is very difficult to ask those patients to agree to another surgical procedure. Even though the eyes with epiretinal dissection group did well, this was because I reoperated and then closed all the holes. If we would had left the holes open and not performed the epiretinal dissection group, they would not have as done well visually. We need to develop a technique that gives us very high success without sacrificing visual acuity. Regarding the comments of Jerry Sebag, it is hard to know why peeling the ILM improves the likelihood of surgical success, even though the literature suggests that it does. I think that his theory, that the procedure removes residual cortical vitreous from the eye, could be the case. I believe that patients with macular holes actually have very fine epiretinal membranes, and I am not just talking about old stage 4 holes. When I did not remove the epiretinal membrane, it caused traction at the edge of the macular hole. These membranes are not clinically visible, but can cause traction that explains why the hole did not close. I believe that by removing the internal limiting membrane you also remove any epiretinal membrane and the outer cortical vitreous. In essence, the surgery produces a small wound and encourages wound repair. Remember from the studies of Frangieh and Dick Green that a glial plug that closes the macular hole. What better way to create a glial plug than to stimulate a little bit of proliferation by peeling the ILM? I believe that this is comparable to freshening up the edges of a wound to stimulate wound closure after a general surgical procedure. I believe that we are producing a tiny wound that encourages closure of the macular hole.

Regarding the comments of George Waring about measuring visual acuity, this is the problem we face. You know what good visual acuity is and you are absolutely right in stating this is an imperfect system of measurement. The projector chart was used for determining visual acuity in all the patients with their current spectacle correction. The Snellen visual acuities, such as 20/70-2, were converted to a log MAR scale, and then calculations were used with the log MAR scale values. How many lines of visual acuity gain or loss are clinically significant? In the retina community we really believe the standard is three lines or more. Visual acuity can vary by one or two lines from time to time. The comments of Travis Meredith regarding the Bascom Palmer Eye Institute series are interesting. I would like to follow all patients and measure vision acuities after cataract surgery; however, some of them have already been lost to follow-up. In a recent study Ingrid Scott reported the visual acuities of patients after macular hole surgery with a minimum of five year follow-up. Many of these patients had participated in a an earlier study by Bill Smiddy to determine the efficacy of transforming growth factor beta (TGF-beta) on macular hole surgery. The results were amazingly good and many patients continued to improve years later. The surgery is a worthwhile surgery. In reference to Dr. Grossniklaus question, the ILM was not submitted for histopathology but other studies have shown glial cells and presumed fragments of Mueller cells attached to the ILM fragments.