Vitrectomy with Internal Limiting Membrane Peeling versus No Peeling for Idiopathic Full-Thickness Macular Hole

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Objective: To determine whether internal limiting membrane (ILM) peeling improves anatomic and functional outcomes of full-thickness macular hole (FTMH) surgery when compared with the no-peeling technique.

Design: Systematic review and individual participant data (IPD) meta-analysis undertaken under the auspices of the Cochrane Eyes and Vision Group. Only randomized controlled trials (RCTs) were included.

Participants and Controls: Patients with idiopathic stage 2, 3, and 4 FTMH undergoing vitrectomy with or without ILM peeling.

Intervention: Macular hole surgery, including vitrectomy and gas endotamponade with or without ILM peeling.

Main Outcome Measures: Primary outcome was best-corrected distance visual acuity (BCdVA) at 6 months postoperatively. Secondary outcomes were BCdVA at 3 and 12 months; best-corrected near visual acuity (BCnVA) at 3, 6, and 12 months; primary (after a single surgery) and final (after >1 surgery) macular hole closure; need for additional surgical interventions; intraoperative and postoperative complications; patient-reported outcomes (PROs) (EuroQol-5D and Vision Function Questionnaire-25 scores at 6 months); and cost-effectiveness.

Results: Four RCTs were identified and included in the review. All RCTs were included in the meta-analysis; IPD were obtained from 3 of the 4 RCTs. No evidence of a difference in BCdVA at 6 months was detected (mean difference, −0.04; 95% confidence interval [CI], −0.12 to 0.03; $P = 0.27$); however, there was evidence of a difference in BCdVA at 3 months favoring ILM peeling (mean difference, −0.09; 95% CI, −0.17 to −0.02; $P = 0.02$). There was evidence of an effect favoring ILM peeling with regard to primary (odds ratio [OR], 9.27; 95% CI, 4.98−17.24; $P < 0.00001$) and final macular hole closure (OR, 3.99; 95% CI, 1.63−9.75; $P = 0.02$) and less requirement for additional surgery (OR, 0.11; 95% CI, 0.05−0.23; $P < 0.00001$), with no evidence of a difference between groups with regard to intraoperative or postoperative complications or PROs. The ILM peeling was found to be highly cost-effective.

Conclusions: Available evidence supports ILM peeling as the treatment of choice for patients with idiopathic stage 2, 3, and 4 FTMH. *Ophthalmology 2014;121:649-655 © 2014 by the American Academy of Ophthalmology.*

Several preoperative, intraoperative, and postoperative factors seem to influence anatomic and functional success rates of macular hole surgery.[1,2] One of these is the maneuver of peeling the internal limiting membrane (ILM) of the retina at the time of the surgery.[3,4] Peeling the ILM of the retina was introduced in macular hole surgery in an attempt to improve anatomic and functional outcomes of the procedure.[5] Several observational studies suggested a benefit of peeling the ILM (revised by Abdelkader and Lois[6]). The rationale for ILM peeling is to relieve tractional forces occurring around the fovea and ensure that any epiretinal tissue that could cause foveal traction, including epiretinal membranes, is removed.[7,8]

Although pars plana vitrectomy is accepted as the mainstay of treatment for full-thickness macular holes (FTMHs), the additional use of ILM peeling has remained a matter of debate for many years. Some surgeons reserve this maneuver to treat large or long-standing holes, whereas others use it routinely in all cases. Evidence is required to ascertain the benefits and potential detrimental effects of ILM peeling[9–11] and to determine which patients may benefit the most from this surgical maneuver. On this basis, this study aimed at determining whether ILM peeling improves functional and anatomic 4 of macular hole surgery when compared with the no peeling counterpart and exploring the impact of different parameters, such as presenting vision and stage/size of the hole and duration of symptoms, in the success of the surgery.

Methods

We undertook a systematic review and meta-analysis using individual participant data (IPD) under the auspices of the Cochrane Eyes and Vision Group.[12]

Inclusion Criteria

Only randomized controlled trials (RCTs) evaluating ILM peeling versus no ILM peeling in idiopathic FTMH surgery were included

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in this study. Full-thickness macular holes of stages 2, 3, and 4 were included, with no restrictions on participant age, sex, or ethnicity. Studies of secondary macular holes (traumatic or myopic) or lamellar holes were excluded.

Search Strategy

The following databases were searched: Cochrane Central Register of Controlled Trials, part of the Cochrane Library (www.thecochranelibrary.com, accessed February 25, 2013), Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid MEDLINE Daily, Ovid OLDMEDLINE (January 1950 to February 2013), EMBASE (January 1980 to February 2013), Latin American and Caribbean Literature on Health Sciences (January 1982 to February 2013), the metaRegister of Controlled Trials (www.controlled-trials.com, accessed February 25, 2013), ClinicalTrials.gov (www.clinicaltrials.gov, accessed February 25, 2013), and the World Health Organization International Clinical Trials Registry Platform (www.who.int/ictrp/search/en, accessed February 25, 2013). Proceedings for the following conferences were searched: American Academy of Ophthalmology, Annual Meeting of the American Society of Retina Specialists, Annual Meeting of the Retina Society, Congress of the Asia-Pacific Academy of Ophthalmology, European Association for Vision and Eye Research Annual Congress, European Vitreoretinal Society Annual Meeting, International Vitreoretinal Meeting, Association for Research in Vision and Ophthalmology (ARVO), and World Ophthalmology Congress. No language restrictions were used in the electronic searches for trials. Reference lists of the studies included in the review were searched for information about other eligible studies on ILM peeling in macular hole surgery and, if found, included. Principal investigators of identified trials were contacted for details, when required.

Risk of Bias

Two review authors (K.S.C. and N.L.) independently assessed all titles found by electronic and manual searches; studies included were assessed for methodological quality. Three authors (K.S.C., N.L., and N.W.S.) independently assessed the studies using the Cochrane Collaboration's "Risk of Bias" tool, which assesses sources of systematic bias according to the guidelines in chapter 8 of the Cochrane Handbook for Systematic Reviews of Intervention.[13] The criteria used for this were selection bias, performance and detection bias, attrition bias, and reporting bias.

Outcome Measures

Anonymized IPD were sought from each trial. From each trial, the following data were extracted: demographics; duration of the macular hole; stage (based on Gass classification)[14,15] and size of the macular hole; lens status (phakic, pseudophakic, aphakic); baseline distance and near visual acuity (VA) (logarithm of the minimum angle of resolution); surgical details (including whether cataract/lens extraction and intraocular lens implantation were undertaken before or at the time of macular hole surgery, primary capsulotomy, ILM peeling, epiretinal membrane peeling, type of dye used, type of gas used); days of posturing facedown postoperatively; postoperative macular hole status (open with or without subretinal fluid around it and closed) after a single (primary anatomic closure) or further surgery (final anatomic closure); postoperative distance and near VA at 3, 6, and 12 months (logarithm of the minimum angle of resolution); intraoperative and postoperative complications; number of additional surgical interventions and type; patient-reported outcomes (PROs); and cost-effectiveness of the procedures.

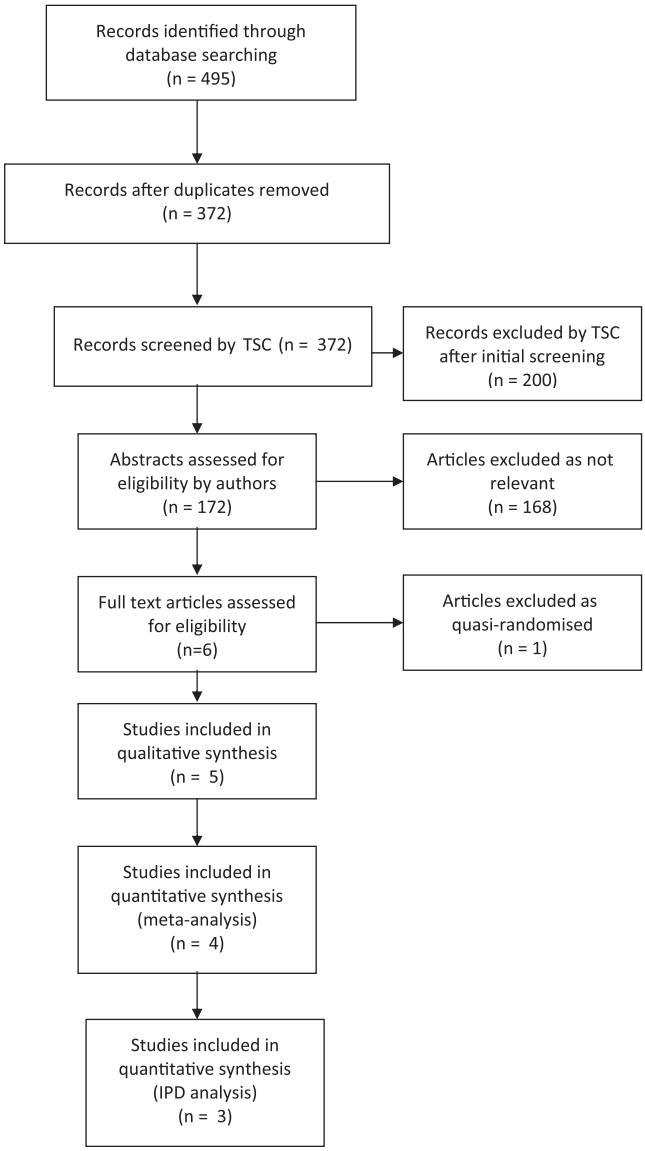

Figure 1. PRISMA diagram of search for inclusion in the review, meta-analysis, and IPD analysis. IPD = individual participant data; TSC = Trials Search Coordinator.

The primary outcome was distance VA at 6 months postoperatively. Secondary outcomes included distance and near VA at 3 and 12 months postoperatively; near VA at 6 months postoperatively; primary and final macular hole closure (defined as complete apposition of the macular hole after a single surgery or after >1 surgery, respectively); additional surgical interventions; PROs, based on the scores of the EuroQol (EQ)-5D and Vision Function Questionnaire (VFQ)-25 at 6 months postoperatively; intraoperative and postoperative complications; and cost-effectiveness of the intervention.

Statistical Methods

Where IPD were received, each dataset was recoded into a standard format for analysis. Each study was then analyzed separately, and appropriate summary data were derived for inclusion in each meta-analysis. Where IPD were not available, published data were included if appropriate.

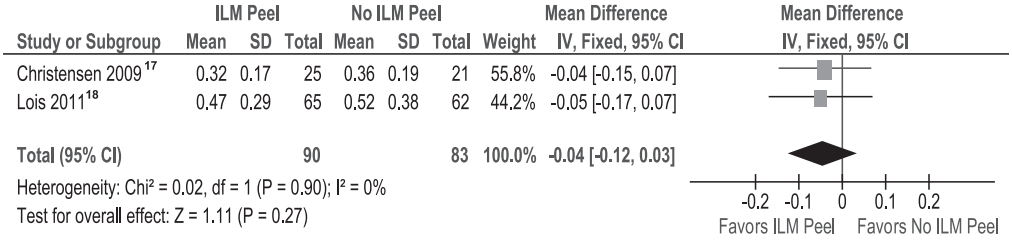

Figure 2. Forest plot of comparison of distance visual acuity (VA) at 6 months between internal limiting membrane (ILM) peel and no peel groups. CI = confidence interval; SD = standard deviation; IV = independent variables.

Because the number of available studies for each analysis was low, fixed-effect models were used as the primary approach to meta-analysis. For dichotomous outcomes, the Mantel−Haenszel method was used to combine odds ratios (ORs). For continuous outcomes, the inverse-variance approach was used to combine differences in group means.

A small number of participants in 2 of the included studies had both eyes randomized separately and were therefore included twice, which leads to concerns about nonindependence of eyes. To ensure that only patient-randomized data were included, for studies in which eyes rather than participants were the unit of randomization, the IPD were used to ensure that only the first randomized eye was included in the analyses. For 1 outcome where IPD were not available for 1 study, eye-randomized data from the published study were included in a sensitivity analysis, but not in the main analyses. We also used sensitivity analyses to explore including a study where follow-up for VA had not been made at fixed time points.

For 2 outcomes, a secondary adjusted analysis also was conducted using the IPD. The available IPD datasets were merged together, and regression analyses (linear regression for continuous outcomes, logistic regression for dichotomous outcomes) were used to estimate the effect of ILM peeling after adjusting for the study, the stage of the macular hole, and its duration (in months).

Results

Search Results

The search strategy resulted in 172 titles and abstracts (Fig 1). Four RCTs were identified[16–20]; IPD were received from 3 RCTs.[16–18] One RCT had been published only in an abstract form (ARVO Meeting Abstracts 2009;50:5206), and no IPD were available at the time this systematic review and IPD meta-analysis were undertaken. Data from this published abstract could be used for 1 outcome (macular hole closure). The number of patients (eyes) included in the IPD meta-analysis were 71 in the peel group and 67 in the no-peel group from Lois et al,[18] 39 in the peel group and 41 in the no-peel group from Tadayoni et al (ARVO Meeting Abstracts 2009;50:5206), 26 in the peel group and 23 in the no-peel group from Kwok et al,[16] and 26 in the peel group and 21 in the no-peel group from Christensen et al.[17] In all included RCTs, octafluoropropane was used as postoperative tamponade with the exception of that by Tadayoni et al (ARVO Meeting Abstracts 2009;50:5206), in which hexafluoroethane was used. The recommended duration of posturing was 5 days,[17] 5 to 7 days,[18] and 14 days.[16]

Risk of Bias

Two studies were considered to be at low risk of selection bias,[17,18] which was unclear in the other 2 RCTs (ARVO Meeting Abstracts 2009;50:5206).[16] Performance, detection, and attrition bias were assessed as low risk in 3 studies[16–18] and unclear in 1 study (ARVO Meeting Abstracts 2009;50:5206). The IPD were collected to minimize the risk of reporting bias. Raw data from 3 of the possible 4 RCTs were collected, but possible selective reporting may have occurred in the fourth RCT (ARVO Meeting Abstracts 2009;50:5206) because of the inherent space limitations related to publication in an abstract form. No other potential sources of bias were identified in any of the 4 RCTs.

Primary and Secondary Outcomes

No evidence of a difference in distance VA at 6 months (primary outcome) was observed between randomized groups (mean difference, −0.04; 95% confidence interval [CI], −0.12 to 0.03; $P = 0.27$) (Fig 2). Likewise, there was no evidence of a difference in distance VA at 12 months or in near VA at 3 months (mean difference, −0.01; 95% CI, −0.13 to 0.11) and 6 months (mean difference, 0.01; 95% CI, −0.10 to 0.12). However, there was evidence of improved distance VA after ILM peeling at 3 months (mean difference, −0.09; 95% CI, −0.17 to 0.02; $P = 0.02$) (Fig 3).

There was evidence of a higher primary (OR, 9.27; 95% CI, 4.98−17.24; $P < 0.00001$) (Fig 4) and final (OR, 3.99; 95% CI, 1.63−9.75; $P = 0.02$) (Fig 5) macular hole closure rate in the ILM peel group. Differences in primary macular hole closure favoring ILM peeling were observed for all stages of macular hole (2, 3, and 4). Fewer participants in the ILM peel group

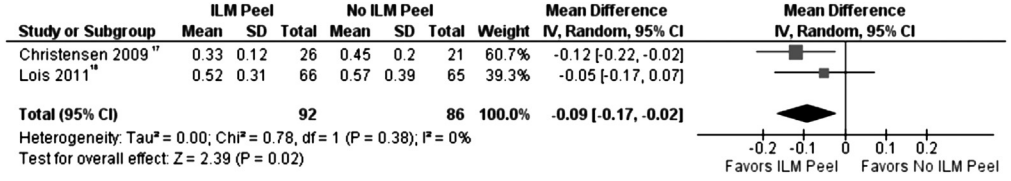

Figure 3. Forest plot of comparison of distance visual acuity at 3 months between internal limiting membrane (ILM) peel and no peel groups. CI = confidence interval; SD = standard deviation.

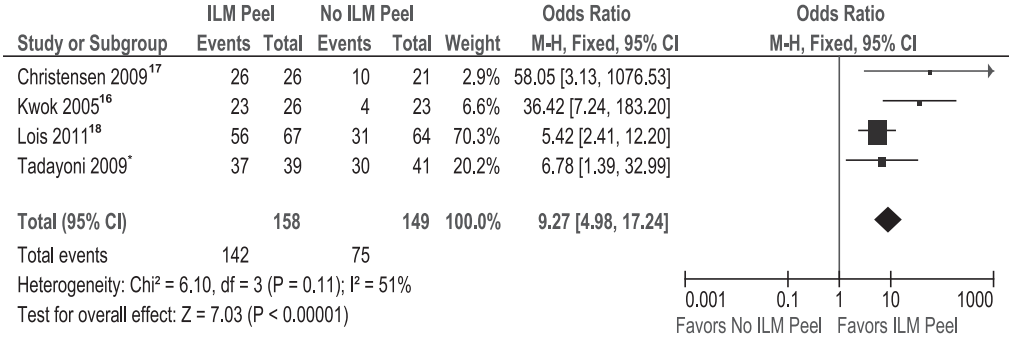

Figure 4. Forest plot of comparison of primary macular hole (M-H) closure rates between internal limiting membrane (ILM) peel and no peel groups. *Association for Research in Vision and Ophthalmology (ARVO) Meeting Abstracts 2009;50:5206. CI = confidence interval.

required additional surgery (OR, 0.11; 95% CI, 0.05−0.23; $P < 0.00001$) (Fig 6); differences favoring ILM peeling were observed for holes at stage 2 and 3. There was no evidence of a difference in rates of intraoperative (OR, 0.94; 95% CI, 0.47−1.87; $P = 0.85$) or postoperative (OR, 0.83; 95% CI, 0.45−1.52; $P = 0.54$) complications between groups. Likewise, no evidence of a difference in composite scores of VFQ-25 (mean difference, −0.10; 95% CI, −4.65 to 4.45) or EQ-5D scores (mean difference, −0.02; 95% CI, −0.09 to 0.05) at 6 months was found, although only 1 RCT contributed to this analysis.[19] On the basis of the results of 1 RCT,[19] it is highly likely that ILM peeling is cost-effective compared with no ILM peeling.

Subgroup Analyses

Differences favoring ILM peeling were observed for stage 2 and 3 macular holes in terms of primary macular hole closure (OR, 6.19; 95% CI, 1.65−23.20) and final macular hole closure (OR, 3.69; 95% CI, 0.14−96.22) with less need for additional surgery (OR, 0.26; 95% CI, 0.07−0.97).

Sensitivity Analyses

For the study by Kwok et al,[16] data on postoperative complications were available only from the study publication (where some patients had been included twice). When this study was added to the meta-analysis of postoperative complications, there was no major change in interpretation. The study by Kwok et al also was excluded from the main VA analyses because each participant was reviewed once, but not a fixed time point. When VA data for this study were included in the meta-analysis as being assessed at 6 months and 12 months, again there was no change in interpretation.

Adjusted analyses using regression also were conducted for the pooled IPD dataset. This enabled adjustment for the duration and stage of the macular hole and for the study itself. The 3 studies for which IPD were received[16−18] were included. For primary macular hole closure, the adjusted results were consistent with the unadjusted results, suggesting a higher rate of hole closure in the ILM peeling groups (adjusted OR, 14.3; 95% CI, 6.33−29.4).

A second adjusted analysis was conducted for distance VA at 6 months. Two studies[17,18] were included. As for the unadjusted analyses, there was no evidence of a difference between the groups (adjusted mean difference, −0.04; 95% CI, −0.13 to 0.05).

Discussion

This was a successful IPD collaboration that enabled the inclusion of results from 3 of the 4 identified randomized trials. This allowed more precise results than for a single study alone, and we have increased the generalizability of the results by including a range of international studies. We also were able to use the IPD to adjust our results for important covariates. We hope to update the review with results from the fourth trial once these data have been published.

Four RCTs[16−18] comparing macular hole surgery with or without ILM peeling for the treatment of idiopathic FTMH were included in this study. No evidence of a difference in

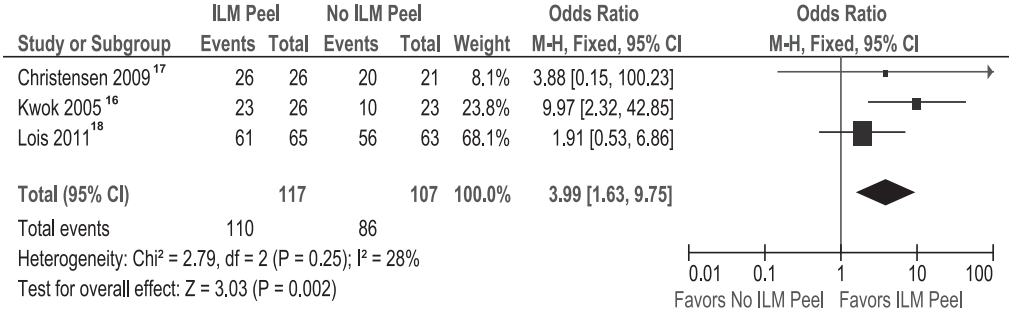

Figure 5. Forest plot of comparison of final macular hole (M-H) closure rates between internal limiting membrane (ILM) peel and no peel groups. CI = confidence interval.

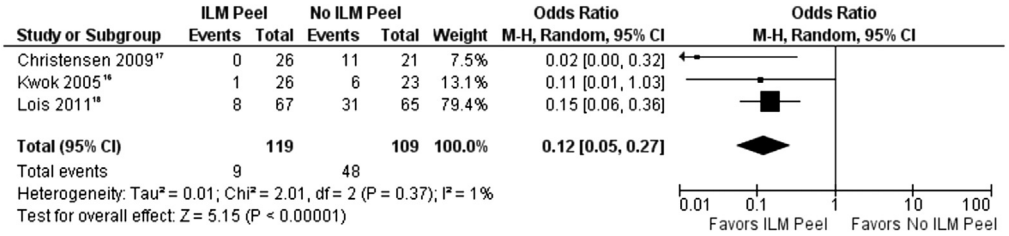

Figure 6. Forest plot of comparison of need for additional surgery between internal limiting membrane (ILM) peel and no peel groups. CI = confidence interval; M-H = macular hole.

distance vision or PROs at 6 months was detected between patients undergoing ILM peeling and no ILM peeling. However, there was evidence favoring ILM peeling with regard to distance vision at 3 months, primary and final macular hole closure, and requirement of additional surgery with no increase in intraoperative or postoperative complications. Furthermore, ILM peeling was found to be highly likely cost-effective, suggesting that this therapeutic approach may be the most advisable for the treatment of patients with idiopathic FTMH.

Visual acuity findings (no evidence of a difference in distance vision at 6 months between groups but superiority of ILM peeling compared with the no-peeling counterpart in distance vision at 3 months) are likely explained by the fact that because of ethical considerations and following standard clinical practice, patients were allowed to receive further surgery, including ILM peeling, if the macular hole had not closed after the initial (primary) surgery, which occurred more frequently in the no ILM peeling arm. Thus, by 6 and 12 months the majority of patients in the no ILM peeling arm had undergone ILM peeling, and it is likely that for this reason the differences observed in VA at 3 months were no longer present at later data points.

The lack of VA differences at 6 months between the peel and no-peel groups also was accompanied by a lack of differences in PROs, assessed by the scores obtained from the EQ-5D and VFQ-25 questionnaires. The EQ-5D and VFQ-25 scores were available in one of the RCTs included,[18] where these questionnaires were obtained at baseline and at 6 months postoperatively. Similarly to VA results, it is likely that the lack of differences in PROs between groups could be explained by the fact that by 6 months most patients in the no-peel group would have received ILM peeling and may have scored similarly to those in the peel arm. It is possible that differences in PROs may have been observed if EQ-5D and VFQ-25 tests had been done at 3 months, when differences in VA were present between groups. Despite the higher number of surgeries required in patients receiving no peel surgery, PROs were not different at 6 months between groups, suggesting that it is the final result (improved vision and quality of life) rather than what happens on the way to achieving it (e.g., surgery, hospital visits) that seems to be influencing patients most.

Evidence was found in this study in favor of ILM peeling with regard to the requirement of additional surgeries, which were more frequently performed in eyes in which the ILM was not peeled, with no increased risk of intraoperative or postoperative complications. Additional surgery was found to be the main driver of the increased costs of macular hole surgery with no ILM peeling when compared with the ILM peeling counterpart in one of the included RCTs.[20]

In a retrospective case series, Tadayoni et al[21] found high macular hole closure rates in small holes (≤400 μm), even when the ILM was not peeled. The study included 33 macular holes ≤400 μm and had a retrospective design, and peeling of epiretinal tissues was undertaken in some cases. The effect of other variables that may influence rates of macular hole closure, such as duration of the macular hole, was not taken into account in the evaluation of the results. A recently published RCT of 69 patients (divided into 2 groups of 34 and 35) that included evaluating the effect of posturing in macular hole surgery found high closure rates after surgery in small macular holes (≤400 μm) without ILM peeling.[22] Other studies have looked at macular hole size (or stage) as a prognostic factor.[23,24] Ullrich et al[23] showed a negative correlation between macular hole base diameter and postoperative visual function in a case series of 94 patients. It was also noted that the rate of primary macular hole closure was higher in smaller holes, a finding confirmed in a case series of 40 patients.[24] Although smaller holes (≤400 μm) appear to close more successfully than larger holes (>400 μm), the evidence presented disclosed higher rates of primary and final macular hole closure after macular hole surgery with ILM peeling, even for small macular holes (stage 2 holes, ≤400 μm). The advantage of ILM peeling also was observed with regard to fewer additional surgeries required even for small macular holes of ≤400 μm in size.

Patients included in the 4 RCTs in the current study[17,18] should be representative of the majority of patients encountered in clinical practice. However, patients with macular holes of long duration (≥18 months) and patients with stage 4 holes were included in only 1[16] of the 3 RCTs for which data were pulled on IPD meta-analysis. Kwok et al[16] showed a higher closure rate among holes with duration of less than 12 months, but it was consistently higher when the ILM was peeled, irrespective of the duration of symptoms.

Some concerns have been raised about potential deleterious side effects of ILM peeling. The ILM is the basal lamina of Müller cells, and it is known to have essential functions during development (summarized by Abdelkader

and Lois[6]). Müller cells provide architectural support to the retina, stretching nearly fully across its thickness. Among other functions, Müller cells provide nutrients and remove waste products to and from neural cells, respectively, and protect them from exposure to high levels of neurotoxic neurotransmitters (e.g., glutamate) and electrolytes (e.g., potassium). Müller cells also are thought to synthesize retinoic acid from retinol.[25,26]

Terasaki et al[10] studied the electrophysiologic changes occurring after ILM peeling in eyes with FTMH.[10] These authors found a delay in the implicit time and a reduction in the amplitude of the focal electroretinogram (ERG) b-wave soon after ILM peeling. Although the former recovered 6 months after surgery, the latter improved throughout the follow-up but remained lower than that measured in patients in whom the ILM had not been removed.[10] This suggests incomplete recovery of Müller cells in eyes in which the ILM was peeled, although it remains unclear whether a full recovery could have been achieved with longer follow-up. Furthermore, the clinical impact of this abnormality remains to be elucidated. The occurrence of dissociated optic nerve fiber layer, first described by Tadayoni et al[27] after epiretinal membrane peeling but subsequently described also after ILM peeling,[28] has been reported. Despite the anatomic change observed in dissociated optic nerve fiber layer (arcuate striae running along the optic nerve fiber layer bundle, seen on optical coherence tomography as focal dehiscences in the nerve fiber layer), no functional consequences have been attributed to this finding in terms of VA, macular sensitivity, or microperimetry.[28] Small, mostly asymptomatic paracentral scotomas also have been reported after ILM peeling.[9] Paracentral absolute and relative microscotomas associated with reduced retinal sensitivity were detected after ILM peeling in 8 of 16 eyes with large macular holes (>400 μm) in a retrospective nonrandomized comparative study using microperimetry.[29] The clinical implications of these functional results remain to be elucidated. The lack of differences observed in the near VA, reading speed, contrast sensitivity, and PROs (EQ-5D and VFQ-25 scores) between the ILM peel and no-ILM peel groups in one of the multicenter RCTs included in this IPD meta-analysis suggests that these functional abnormalities observed after ILM peeling may not be of clinical relevance to patients.[18] Further investigations on the effect of ILM peeling (when compared with the no peeling counterpart) on macular function using multifocal ERG, pattern ERG, microperimetry, or other functional tests would be helpful in addressing further the safety of ILM peeling.

In conclusion, although no differences in distance VA were observed long-term between patients with FTMH in whom the ILM was peeled when compared with those in whom the ILM was left in situ, ILM peeling achieved higher anatomic success with a reduced need for additional surgical interventions. The lack of evidence for differences in post-operative VA, vision-related quality of life, or adverse outcomes between ILM peeling and non-ILM peeling and the cost-effectiveness of the former compared with the latter further support the use of ILM peeling to treat patients with idiopathic stage 2−4 FTMHs.

References

1. Lim SL, Dunbar MT. Update on current surgical management of idiopathic macular holes. Clin Eye Vis Care 2000;12:51–60.
2. Smiddy WE, Feuer W, Cordahi G. Internal limiting membrane peeling in macular hole surgery. Ophthalmology 2001;108:1471–6.
3. Brooks HL Jr. Macular hole surgery with and without internal limiting membrane peeling. Ophthalmology 2000;107:1939–48.
4. Gass CA, Haritoglou C, Schaumberger M, Kampik A. Functional outcome of macular hole surgery with and without indocyanine green-assisted peeling of the internal limiting membrane. Graefes Arch Clin Exp Ophthalmol 2003;241:716–20.
5. Eckardt C, Eckardt U, Groos S, et al. Removal of the internal limiting membrane in macular holes. Clinical and morphological findings [in German]. Ophthalmologe 1997;94:545–51.
6. Abdelkader E, Lois N. Internal limiting membrane peeling in vitreo-retinal surgery. Surv Ophthalmol 2008;53:368–96.
7. Cheng L, Azen SP, El-Bradey MH, et al; Vitrectomy for Macular Hole Study Group. Effects of preoperative and postoperative epiretinal membranes on macular hole closure and visual restoration. Ophthalmology 2002;109:1514–20.
8. Yooh HS, Brooks HL Jr, Capone A Jr, et al. Ultrastructural features of tissue removed during idiopathic macular hole surgery. Am J Ophthalmol 1996;122:67–75.
9. Haritoglou C, Gass CA, Schaumberger M, et al. Macular changes after peeling of the internal limiting membrane in macular hole surgery. Am J Ophthalmol 2001;132:363–8.
10. Terasaki H, Miyake Y, Nomura R, et al. Focal macular ERGs in eyes after removal of macular ILM during macular hole surgery. Invest Ophthalmol Vis Sci 2001;42:229–34.
11. Uemura A, Kanda S, Sakamoto Y, Kita H. Visual field defects after uneventful vitrectomy for epiretinal membrane with indocyanine green-assisted internal limiting membrane peeling. Am J Ophthalmol 2003;136:252–7.
12. Spiteri Cornish K, Lois N, Scott N, et al. Vitrectomy with internal limiting membrane (ILM) peeling versus vitrectomy with no peeling for idiopathic full-thickness macular hole (FTMH). Cochrane Database Syst Rev 2013;6:CD009306.
13. Higgins JP, Altman DG, eds, Cochrane Statistical Methods Group, Cochrane Bias Methods Group. Assessing risk of bias in included studies. In: Higgins JP, Green S, eds. Cochrane Handbook for Systematic Reviews of Interventions. version 5.0.2. Hoboken, NJ: Wiley; 2008:187−241.
14. Gass JD. Idiopathic senile macular hole: its early stages and pathogenesis. 1988. Retina 2003;23(Suppl):629–39.
15. Johnson RN, Gass JD. Idiopathic macular holes. Observations, stages of formation, and implications for surgical intervention. Ophthalmology 1988;95:917–24.
16. Kwok AK, Lai TY, Wong VW. Idiopathic macular hole surgery in Chinese patients: a randomised study to compare indocyanine green-assisted internal limiting membrane peeling with no internal limiting membrane peeling. Hong Kong Med J 2005;11:259–66.
17. Christensen UC, Kroyer K, Sander B, et al. Value of internal limiting membrane peeling in surgery for idiopathic macular

hole stage 2 and 3: a randomised clinical trial. Br J Ophthalmol 2009;93:1005–15.
18. Lois N, Burr J, Norrie J, et al; Full-thickness Macular Hole and Internal Limiting Membrane Peeling Study (FILMS) Group. Internal limiting membrane peeling versus no peeling for idiopathic full-thickness macular hole: a pragmatic randomized controlled trial. Invest Ophthalmol Vis Sci 2011;52:1586–92.
19. Lois N, Burr J, Norrie J, et al; Full-thickness macular hole and Internal Limiting Membrane peeling Study (FILMS) Group. Clinical and cost-effectiveness of internal limiting membrane peeling for patients with idiopathic full thickness macular hole. Protocol for a randomised controlled trial: FILMS (Full-thickness Macular Hole and Internal Limiting Membrane Peeling Study). Trials [serial online] 2008;9:61. Available at: http://www.trialsjournal.com/content/9/1/61. Accessed September 17, 2013.
20. Ternent L, Vale L, Boachie C, et al; Full-Thickness Macular Hole and Internal Limiting Membrane Peeling Study (FILMS) Group. Cost-effectiveness of internal limiting membrane peeling versus no peeling for patients with an idiopathic full-thickness macular hole: results from a randomised controlled trial. Br J Ophthalmol 2012;96:438–43.
21. Tadayoni R, Gaudric A, Haouchine B, Massin P. Relationship between macular hole size and the potential benefit of internal limiting membrane peeling. Br J Ophthalmol 2006;90:1239–41.
22. Tadayoni R, Vicaut E, Devin F, et al. A randomized controlled trial of alleviated positioning after small macular hole surgery. Ophthalmology 2011;118:150–5.
23. Ullrich S, Haritoglou C, Gass C, et al. Macular hole size as a prognostic factor in macular hole surgery. Br J Ophthalmol 2002;86:390–3.
24. Ip MS, Baker BJ, Duker JS, et al. Anatomical outcomes of surgery for idiopathic macular hole as determined by optical coherence tomography. Arch Ophthalmol 2002;120:29–35.
25. Turner DL, Cepko CL. A common progenitor for neurons and glia persists in rat retina late in development. Nature 1987;328:131–6.
26. Reichenbach A, Robinson SR. The involvement of Müller cells in the outer retina. In: Djamgoz MB, Archer SN, Vallerga S, eds. Neurobiology and Clinical Aspects of the Outer Retina. London: Chapman & Hall; 1995:395–416.
27. Tadayoni R, Paques M, Massin P, et al. Dissociated optic nerve fiber layer appearance of the fundus after idiopathic epiretinal membrane removal. Ophthalmology 2001;108:2279–83.
28. Ito Y, Terasaki H, Takahashi A, et al. Dissociated optic nerve fiber layer appearance after internal limiting membrane peeling for idiopathic macular holes. Ophthalmology 2005;112:1415–20.
29. Tadayoni R, Svorenova I, Erginay A, et al. Decreased retinal sensitivity after internal limiting membrane peeling for macular hole surgery. Br J Ophthalmol 2012;96:1513–6.

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