Vitrectomy with internal limiting membrane (ILM) peeling versus vitrectomy with no peeling for idiopathic full-thickness macular hole (FTMH) (Review)

Spiteri Cornish K, Lois N, Scott N, Burr J, Cook J, Boachie C, Tadayoni R, la Cour M, Christensen U, Kwok A

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[Intervention Review]

Vitrectomy with internal limiting membrane (ILM) peeling versus vitrectomy with no peeling for idiopathic full-thickness macular hole (FTMH)

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ABSTRACT

Background

Several observational studies have suggested the potential benefit of internal limiting membrane (ILM) peeling to treat idiopathic full-thickness macular hole (FTMH). However, no strong evidence is available on the potential benefit(s) of this surgical manoeuvre and uncertainty remains among vitreoretinal surgeons about the indication for peeling the ILM, whether to use it in all cases or in long-standing and/or larger holes.

Objectives

To determine whether ILM peeling improves anatomical and functional outcomes of macular hole surgery compared with the no-peeling technique and to investigate the impact of different parameters such as presenting vision, stage/size of the hole and duration of symptoms in the success of the surgery.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) which contains the Cochrane Eyes and Vision Group Trials Register (*The Cochrane Library* 2013, Issue 2), 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 (LILACS) (January 1982 to February 2013), the *meta*Register of Controlled Trials (*m*RCT) (www.controlled-trials.com), ClinicalTrials.gov (www.clinicaltrials.gov) and the WHO International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/search/en). We searched the reference lists of included studies for any additional studies not identified by the electronic searches. We did not use any date or language restrictions in the electronic searches for trials. We last searched the electronic databases on 28 February 2013.

We searched reference lists of the studies included in the review for information about other studies on ILM peeling in macular hole surgery. We searched Proceedings for the following conferences up to February 2013: American Academy of Ophthalmology (AAO), Annual Meeting of the American Society of Retina Specialists (ASRS), Annual Meeting of the Retina Society, Congress of the Asia-Pacific Academy of Ophthalmology (APAO), European Association for Vision and Eye Research (EVER) Annual Congress, European Vitreoretinal Society (EVRS) Annual Meeting, Association for Research in Vision and Ophthalmology (ARVO) Meeting, International Vitreoretinal Meeting, and World Ophthalmology Congress.

Selection criteria

Only randomised controlled trials (RCTs) comparing ILM peeling with the no-peeling counterpart were included.

Data collection and analysis

Two review authors (KSC and NL) independently assessed the titles and abstracts of all RCTs identified by electronic and manual searches.

We obtained Individual patient data (IPD) from three of the four identified eligible trials. The fourth identified RCT had only been published in abstract form and no IPD were available; we included data from this published abstract for one outcome (macular hole closure).

The primary outcome was distance visual acuity at six months. Secondary outcomes included distance and near visual acuity at three and 12 months postoperatively, near visual acuity at six months postoperatively, primary (after a single surgery) and final (following more than one surgery) macular hole closure, need for additional surgical interventions, vision-related quality of life and intraoperative and postoperative complications.

We performed meta-analysis using standard techniques (the Mantel-Haenszel odds ratio (OR) for binary outcomes, mean difference (MD) for continuous outcomes) using a fixed-effect model. For two outcomes we also used the IPD to perform adjusted analyses using regression methods.

Main results

We identified and included four RCTs; these were conducted in Denmark, France, Hong Kong and the United Kingdom/Republic of Ireland and randomised 47, 80, 49 and 141 participants respectively.

There was no evidence of a difference in the primary outcome (distance visual acuity at six months), nor in distance visual acuity at 12 months between randomised groups. However, there was evidence of improved best corrected distance visual acuity in the ILM peeling group at three months (WMD -0.09, 95% CI -0.17 to -0.02). We found no evidence for a difference in near vision between groups at any of the time points investigated.

Overall, more participants in the ILM peeling group than in the no-peeling group had primary macular hole closure (OR 9.27, 95% CI 4.98 to 17.24); this held true when results were stratified by the stage of the macular hole. There was also evidence that those in the ILM peeling group were more likely to have final macular hole closure (OR 3.99, 95% CI 1.63 to 9.75). Fewer participants required further surgery in the ILM peeling group than in the no-peeling group (OR 0.11, 95% CI: 0.05 to 0.23).

Rates of intraoperative and postoperative complications were similar in both groups.

Based on the results of one study, there was no evidence that total VFQ-25 or EQ-5D scores differed between the groups at six months. Based on this same study, ILM peeling is highly likely to be cost-effective.

Authors' conclusions

Although we found no evidence of a benefit of ILM peeling in terms of the primary outcome (visual acuity at six months), ILM peeling appears to be superior to its no-peeling counterpart as it offers more favourable cost effectiveness by increasing the likelihood of primary anatomical closure and subsequently decreasing the likelihood of further surgery, with no differences in unwanted side-effects compared with no peeling.

PLAIN LANGUAGE SUMMARY

Vitrectomy with internal limiting membrane (ILM) peeling versus vitrectomy with no peeling for idiopathic full-thickness macular hole (FTMH)

A full-thickness macular hole (FTMH) affects the centre of the macula, the area responsible for detailed vision and reading. It is believed to occur because of changes in the jelly that fills the inside of the eye, the vitreous. The vitreous is stuck to the macula but, at some point in life, it may detach from around the macula but remain attached to its centre. With the daily eye movements, the vitreous pulls where it remains attached (at the centre of the macula) and if pulling is strong enough it may break the macula causing a macular hole. To date, the treatment for macular hole has involved the removal of the vitreous by doing surgery ('vitrectomy'). However, not all holes were closed with this surgery and new techniques were investigated. Among these is the 'peeling' (removal) of the internal limiting membrane (ILM) of the retina.

The purpose of this review was to find out whether peeling the ILM around the macular hole could achieve better results after surgery than leaving it in place.

This review found four studies in which people who had undergone macular hole surgery with no ILM peeling were compared with those in whom the ILM was removed during the first surgery they had received. As well as reviewing published data from these four studies, we undertook an 'individual patient data (IPD) meta-analysis'. To undertake IPD meta-analysis one needs to collect all the raw data for each participant included in each of these RCTs before and after surgery and then combine all data together and analyse them. We were able to obtain data for each individual participant included in three of these four studies, which we then analysed and present in this review.

Our results showed that at six and 12 months after the initial surgery to treat the macular hole the vision was no different between participants that received ILM peel and those who did not. At three months, however, the vision was better in those participants that received ILM peeling. More macular holes were closed and less re-operations had to be performed in participants who received ILM peeling with no differences in the number of complications between patients receiving ILM peeling or no peeling in the first surgery. There were no differences in the way participants perceived the benefits of the surgery. ILM peeling was found to be highly likely cost-effective, i.e. the cost of the treatment was justifiable by the benefits obtained from it.

We conclude that ILM peeling compared with no peeling increases the chance for a macular hole to close with a single surgery and reduces the chances of people requiring additional surgery without unwanted side effects; as ILM peeling is very likely cost-effective, it may be considered the best available option for people with idiopathic FTMH.

BACKGROUND

Description of the condition

An idiopathic full-thickness macular hole (FTMH) is a defect affecting the area of maximal vision of the retina, the fovea. When left untreated, FTMH leads to severe visual impairment with over a third of patients experiencing deterioration in vision to levels of 20/200 or worse (Allen 1998; Freeman 1997). FTMHs are common, with an estimated incidence of 7.8 persons per 100,000 population per year (McCannel 2009). Gass and colleagues described four stages (1 to 4) of FTMH (Gass 1988; Johnson 1988); randomised controlled clinical trials (RCTs) showed that macular hole surgery is effective for stages 2, 3 and 4 (Ezra 2004; Freeman 1997; Kim 1996).

Description of the intervention

Kelly 1991 published the first results of vitrectomy for macular hole in 1991. Many pre-, intra- and postoperative factors seem to influence anatomical and functional success rates following macular hole surgery (Lim 2000; Smiddy 2001). One of these is the manoeuvre of peeling the internal limiting membrane (ILM) at the time of the surgery (Brooks 2000; Gass 2003). Peeling the ILM of the retina was introduced in macular hole surgery in an attempt to improve anatomical and functional outcomes of the procedure (Eckardt 1997). Several observational studies suggested a benefit of peeling the ILM (revised by Abdelkader 2008). Recent data from RCTs have provided a stronger evidence base for the role of ILM peeling in macular hole surgery.

How the intervention might work

It has been hypothesised that the ILM may act as a scaffold, facilitating the proliferation of a variety of cells, including myofi-

broblasts, fibrocytes, retinal pigment epithelium (RPE) cells and fibrous astrocytes, which may generate tangential traction around the fovea, contributing to macular hole formation and its enlargement (Kwok 2001; Li 2002; Sach 2000). The rationale for ILM peeling is therefore to relieve tractional forces occurring around the fovea and to ensure that any epiretinal tissue that could cause foveal traction, including epiretinal membranes (ERMs), is removed (Cheng 2002; Yooh 1996).

Why it is important to do this review

Although pars plana vitrectomy is accepted as the mainstay treatment for FTMHs, the additional use of ILM peeling remains a matter of debate. Some surgeons reserve this manoeuvre to treat large holes, while others use it routinely in all cases. Evidence is required to ascertain the benefits and potential detrimental effects of ILM peeling (Haritoglou 2001; Terasaki 2001; Uemura 2003), and to determine which patients may benefit the most from this surgical manoeuvre.

OBJECTIVES

To determine whether ILM peeling improves anatomical and functional outcomes of macular hole surgery compared with no peeling, and to investigate the impact of different parameters such as presenting vision, stage/size of the hole and duration of symptoms in the success of the surgery.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) were included in this review.

Types of participants

People with idiopathic FTMH at stages 2, 3 and 4; we made no restrictions by age, gender or ethnicity. We excluded patients with macular hole secondary to trauma, high myopia (defined as $\geq$ 6 dioptres), lamellar macular hole and macular pseudohole, or any co-morbid eye and/or systemic disease affecting visual function.

Types of interventions

Macular hole surgery with ILM peeling was compared with macular hole surgery without ILM peeling.

Types of outcome measures

Primary outcomes

1. Distance visual acuity at six months postoperatively. The review includes details of charts (Early Treatment Diabetic Retinopathy Study (ETDRS), Snellen) which were used to record visual acuity and at what distance this was done (e.g. four-metre or two-metre ETDRS charts). For the purpose of statistical analysis, visual acuity values were converted into logMAR (logarithm of the Minimum Angle of Resolution) values using standardised conversion charts.

Secondary outcomes

1. Distance and near visual acuity at three and 12 months postoperatively and also near visual acuity at six months following surgery.
2. Primary macular hole closure, defined as complete apposition of the margins of the hole, following a single surgery.
3. Final macular hole closure, defined as complete apposition of the margins of the hole, following more than one surgery.
4. Need for additional surgical interventions.
5. Patient-reported outcomes: Scores of EQ-5D and VFQ-25 at six months.
6. Adverse outcomes*:* intraoperative and postoperative complications.
7. Cost effectiveness of the intervention.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) 2013, Issue 1, part of *The Cochrane Library*. www.thecochranelibrary.com (accessed 28 February 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 (LILACS) (January 1982 to February 2013), the *meta*Register of Controlled Trials (*m*RCT) (www.controlled-trials.com), ClinicalTrials.gov (www.clinicaltrials.gov) and the WHO International Clinical Trials Registry Platform (ICTRP) (

www.who.int/ictrp/search/en). We did not use any date or language restrictions in the electronic searches for trials. We last searched the electronic databases on 28 February 2013.
See: Appendices for details of search strategies for CENTRAL (Appendix 1), MEDLINE (Appendix 2), EMBASE (Appendix 3), LILACS (Appendix 4), *m*RCT (Appendix 5), ClinicalTrials.gov (Appendix 6) and the ICTRP (Appendix 7).

Searching other resources

We searched reference lists of the studies included in the review for information about other studies on ILM peeling in macular hole surgery. We contacted principal investigators of identified trials for details, when required. We searched Proceedings for the following conferences up to February 2013: American Academy of Ophthalmology (AAO), Annual Meeting of the American Society of Retina Specialists (ASRS), Annual Meeting of the Retina Society, Congress of the Asia-Pacific Academy of Ophthalmology (APAO), European Association for Vision and Eye Research (EVER) Annual Congress, European Vitreoretinal Society (EVRS) Annual Meeting, International Vitreoretinal Meeting, Association for Research in Vision and Ophthalmology (ARVO) Meeting and World Ophthalmology Congress.

Data collection and analysis

Selection of studies

Two review authors (KSC and NL) independently assessed the titles and abstracts of all RCTs identified by electronic and manual searches. Reports were labelled as A (definitely include), B (unsure) or C (definitely exclude). Studies labelled as 'C' were excluded from the review. We assessed full-text articles of abstracts labelled as 'B: unsure' according to the inclusion criteria for this review. We assessed studies labelled as 'A: definitely include' for methodological quality. We resolved differences between the two authors assessing the inclusion/exclusion of studies for this review by discussion and when needed by having a third review author as arbitrator.

Data extraction and management

We acquired individual patient data (IPD) for three of the four identified eligible trials. The authors of this review include the principal investigators of the three recently published RCTs comparing ILM peeling with no ILM peeling in macular hole surgery (Christensen 2009; Kwok 2005; Lois 2011). We obtained anonymised data for every participant in these three trials, and merged them into a specifically constructed master database for statistical analysis. The fourth identified RCT has so far only been published in abstract form (Tadayoni 2009), and no IPD were available at the time this review and IPD meta-analysis were undertaken. Data from this published abstract were included for one outcome only (macular hole closure).
We extracted the following data from each trial: demographics, duration of the macular hole, stage (based on Gass 1988 classification (Johnson 1988)) and size of the hole, lens status (phakic, pseudophakic, aphakic), baseline distance and near visual acuity (LogMAR), surgical details (including combined phacoemulsification and intraocular lens implantation; primary capsulotomy; ILM peeling; ERM peeling; type of dye used; type of gas used), days of posturing face-down postoperatively, postoperative hole status (open with or without subretinal fluid around it and closed) after a single (primary anatomical closure) or further surgery (final anatomical closure), postoperative distance and near visual acuity at three, six and 12 months (LogMAR), intraoperative or postoperative complications, number and type of additional surgical interventions and patient-reported outcomes and cost effectiveness of the procedures.

Assessment of risk of bias in included studies

Three authors (KSC, NL and NS) 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 Interventions* (Higgins 2011a). Vitrectomy with and without ILM peeling was compared for the primary and secondary outcomes stated above. The risk of bias was reported as 'low risk', 'high risk' or 'unclear'. Studies were evaluated on the basis of the following criteria:

1. Sequence generation: Studies were assessed looking at whether sufficient detail was given on the method used to generate the allocation sequence to allow an assessment of whether comparable groups were created.
2. Allocation concealment: Studies were assessed for the method used to conceal the allocation sequence.
3. Blinding: Blinding (masking) of participants (performance bias) and outcome assessors (detection bias), including whether the intended masking was achieved and effective.
4. Attrition bias: Information about incomplete outcome data was recorded. The numbers in each intervention group and reasons for any exclusions were noted, as rates of follow-up, reasons for losses to follow-up and analysis by the intention-to-treat (ITT) principle. We considered a trial to have been analysed by ITT if it included all participants randomised, including those for whom no outcome measurements were made and those who received only part or none of the intended treatment. The potential impact of attrition bias was evaluated based on whether ITT principles had been followed and whether information on the number of participants and reasons for losses to follow-up were given.
5. Reporting bias: For the meta-analysis, we obtained all

individual patient data for each study. Hence, data for all available outcomes were reported and the risk of selective reporting (i.e. omission, selective choice of data, selective reporting of analyses using the same data, selective reporting of subsets of data or selective under-reporting of data) was assessed as being low.

Measures of treatment effect

Dichotomous data: We used the Mantel-Haenszel odds ratio.
Continuous data: We used the inverse variance mean difference.
Time-to-event data: no meta-analyses were planned.

Unit of analysis issues

A small number of participants in two of the included studies had both eyes randomised separately and were therefore included twice, which leads to concerns over non-independence of eyes. In order to ensure only person-randomised data were included, for studies where eyes rather than participants were the unit of randomisation, the IPD were used to ensure that only the first randomised eye was included in the analyses. For one outcome where IPD were not available for one study, eye-randomised data from the published study were included in a sensitivity analysis, but not in the main analyses.

Dealing with missing data

Rates of missing outcome data were very low and only one included study had any missing data. We assumed that the data could be considered missing at random and conducted a complete-case analysis as the primary analysis.

Assessment of heterogeneity

We evaluated heterogeneity by looking at the overlap in confidence intervals of the forest plot and the I^2 statistic, which is used to assess the proportion of total variability explained by heterogeneity between studies (Higgins 2003). No formal cut points for heterogeneity were used, but if we observed high levels of heterogeneity, we investigated the reasons for this and if necessary did not present quantitative meta-analyses.

Assessment of reporting biases

We assessed sequence generation, allocation concealment, masking of participants and outcome assessors, incomplete outcome data, selective outcome reporting and other potential sources of bias as discussed above. To avoid reporting bias we maximised our search strategy to include research that had been published in any language as well as unpublished research. We also documented masking methods, sequence generation, allocation concealment techniques and any incomplete data.

Data synthesis

We undertook data analysis according to the guidelines set out in Chapter 9 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b).
Where individual patient data (IPD) were available, we recoded each dataset using a standard coding sheet. We then analysed each study separately and derived appropriate summary data for inclusion in each meta-analysis.
As the number of available studies for each analysis was low, we used the fixed-effect model as the primary approach to meta-analysis. For dichotomous outcomes we used the Mantel-Haenszel method to combine odds ratios, and for continuous outcomes we used the inverse-variance approach to combine differences in group means.
For two outcomes we also conducted a secondary adjusted analysis using the IPD. We merged the available IPD datasets and used regression analyses (linear regression for continuous outcomes, and logistic regression for dichotomous outcomes) to estimate the effect of ILM peeling after adjusting for the study, the size of the macular hole and its duration in months.

Subgroup analysis and investigation of heterogeneity

We undertook subgroup analyses based on stage of macular hole for selected outcomes, i.e. primary and final macular hole closure, additional surgery, visual acuity for distance and near at six months.

Sensitivity analysis

We performed sensitivity analyses to assess the impact of including outcomes where only eye-randomised instead of person-randomised data were available. We also conducted a sensitivity analysis including studies that had collected visual acuity data at last follow-up, rather than at a specified time point. An additional sensitivity analysis investigated the impact on the results of using random-effects rather than fixed-effect analyses, but this did not change the interpretation of the review.

RESULTS

Description of studies

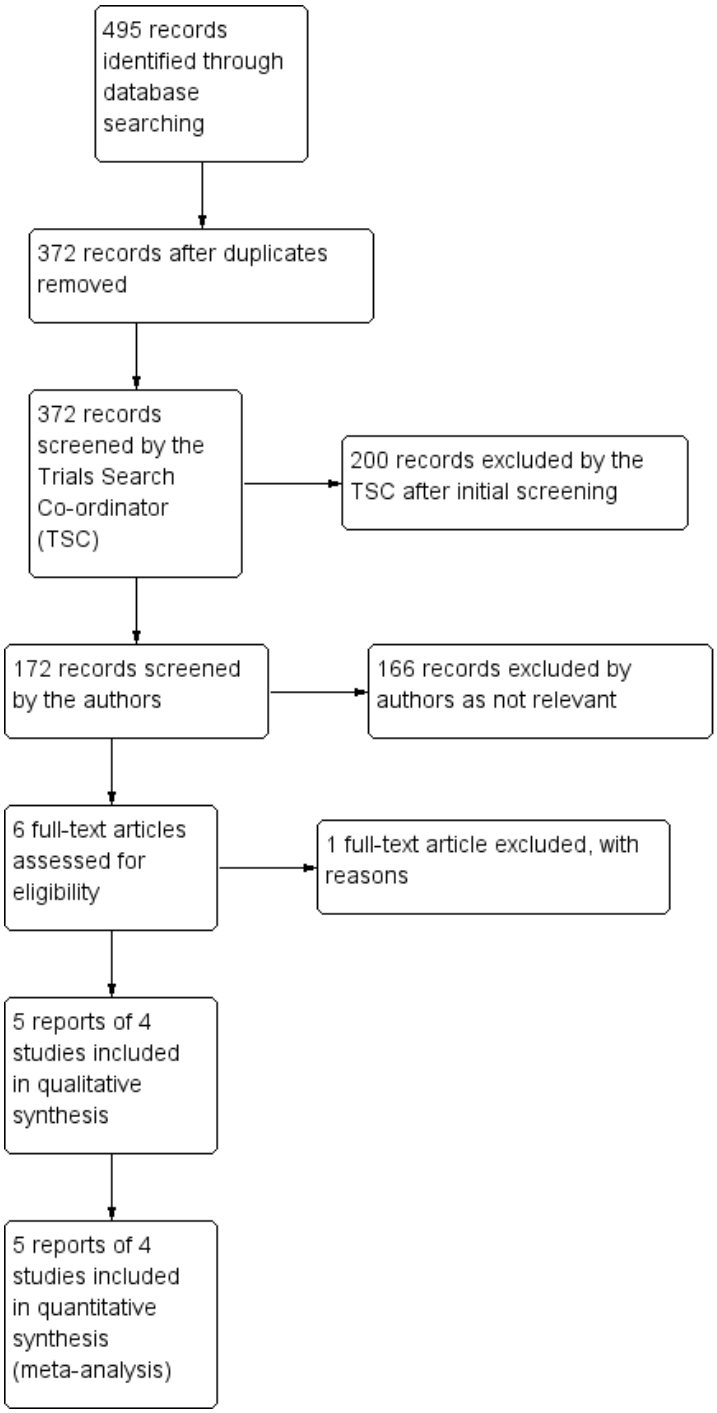
See Characteristics of included studies.

Results of the search

The electronic searches yielded a total of 372 references (Figure 1). The Trials Search Co-ordinator scanned the search results, removed duplicates and removed 200 references which were not relevant to the scope of the review. We screened the remaining 172

reports to identify potentially relevant studies. Only randomised controlled trials (RCTs) comparing ILM peeling with ILM no peeling were included in the meta-analysis. We excluded case reports, case series, case-control studies and quasi-RCTs. We further excluded 166 records after reading the abstract and obtained full-text copies of six records for further investigation. We excluded one study (Terasaki 2001) and included five reports of four studies in the review (Christensen 2009; Kwok 2005; Lois 2011; Tadayoni 2009). Individual patient data (IPD) were available for three of these four RCTs (Christensen 2009; Kwok 2005; Lois 2011) and an IPD meta-analysis was undertaken. Data from the fourth RCT were only available from a published abstract.

Figure 1. Results from searching for studies for inclusion in the review.



Included studies

Lois 2011 compared the clinical efficacy and cost effectiveness of vitrectomy with trypan blue (TB)-assisted internal limiting membrane (ILM) peeling versus surgery without ILM peeling in participants with stage 2 or 3 idiopathic full-thickness macular holes (FTMHs). One hundred and forty-one patients were randomised in this trial. Both participants and the optometrists who checked visual function were masked to treatment allocation. The vitreoretinal surgeons evaluating the state of the macular hole pre- and post-surgery were unmasked to the treatment received. The investigators measuring/analysing the size of the macular hole were masked to treatment allocation. The primary outcome was the mean difference between treatment groups in distance visual acuity (logMAR) at six months. Two-metre ETDRS visual acuity charts were used to evaluate distance visual acuity (VA). Secondary outcomes included distance VA at three months; near VA at three and six months (measured with Bailey-Lovie visual acuity charts); contrast sensitivity (measured with Pelli-Robson charts) and reading speed (using the MNRead charts) at six months; anatomical closure of the macular hole at one, three and six months; patient-reported outcomes; cost effectiveness; and adverse events. The macular hole was considered to be closed when it was no longer visible clinically (open holes with or without subretinal fluid were considered to be open). Hole closure could be confirmed by any diagnostic imaging modality, at the discretion of the investigators and as per routine clinical practice at each participating centre.

Kwok 2005 compared the efficacy of vitrectomy with indocyanine green (ICG)-assisted ILM peeling versus surgery without ILM peeling in 49 participants with stage 2, 3 or 4 idiopathic FTMH. Optometrists assessing best corrected visual acuity (BCVA) were masked to the treatment allocation. The primary outcomes were anatomical closure of the macular hole and lines of visual acuity improvement in the two groups. Visual acuity was measured with Snellen visual acuity charts. The hole was considered to be closed if there was no subretinal fluid postoperatively (both flat/closed and flat/open holes were considered closed holes). Secondary outcomes included the proportion of cases with 2 or more lines of visual improvement and the final postoperative logMAR BCVA.

As the review specified that people, not eyes, were treated as the unit of randomisation, individual patient data (IPD) were used to ensure that each participant was included only once in each analysis. Two participants had both eyes randomised. Only the results for the first randomised eye were included in our analyses. No IPD were available for one outcome (postoperative complications) for this study, but as data were reported in the study publication (including some individuals twice), we conducted a sensitivity analysis including and excluding these data.

Distance visual acuity data were only available at final follow-up; this varied from six to 23 months (median 11 months). Data from this study were excluded from the main visual acuity analyses, but we conducted two sensitivity analyses treating the data as if it had been collected at six and at 12 months.

Christensen 2009 compared the efficacy of vitrectomy with ICG-assisted ILM peeling versus surgery without ILM peeling in 47 participants with stage 2 or 3 idiopathic FTMH. An interim analysis revealed that stage 3 macular holes had a significantly increased risk of failure if the ILM was not peeled, so randomisation was changed thereafter to ICG-assisted ILM peeling versus no peeling for participants with stage 2 holes, and ICG-assisted ILM peeling versus TB-assisted ILM peeling for stage 3 holes. For the purpose of our IPD meta-analysis, only those cases randomised to peeling or no peeling were considered for the analysis (stage 2 and 3 holes prior to the interim analysis, and stage 2 holes recruited after the interim analysis). Investigators and participants were masked to intervention, and only the surgeons were aware of the surgical method used. The primary outcome measure was closure of the macular hole at three and 12 months. Macular hole closure was defined as complete apposition of the macular hole margins on optical coherence tomography (OCT). Secondary outcome measures were BCVA at 12 months after anatomical successful surgery, measured with 4-metre ETDRS visual acuity charts; visual field defects at 12 months; retinal pigment epitheliopathy; optic nerve fibre layer dehiscence; and adverse events.

After May 2006 stage 3 eyes were randomised between different types of dye, whereas other eyes continued to be randomised as before. We therefore used the IPD to exclude any participants not randomised between ILM peeling and no peeling. Three participants had both eyes randomised, but we used the IPD to include only the first randomised eye.

Tadayoni 2009 compared the efficacy of vitrectomy with TB-assisted ILM peeling versus surgery without ILM peeling in 80 patients with idiopathic macular holes larger than 400 μm. The epiretinal membrane, where present, was removed in all cases. No detail of sequence generation, allocation concealment or masking was given in the published abstract.

Only data from published sources were available for this study. We were only able to include it in the meta-analyses for one outcome (primary macular hole closure), and for subgroup analysis the data had to be assigned to the 'stage not known' subgroup. Distance visual acuity data at three months were reported only as change from baseline and therefore could not be included in the meta-analyses.

Excluded studies

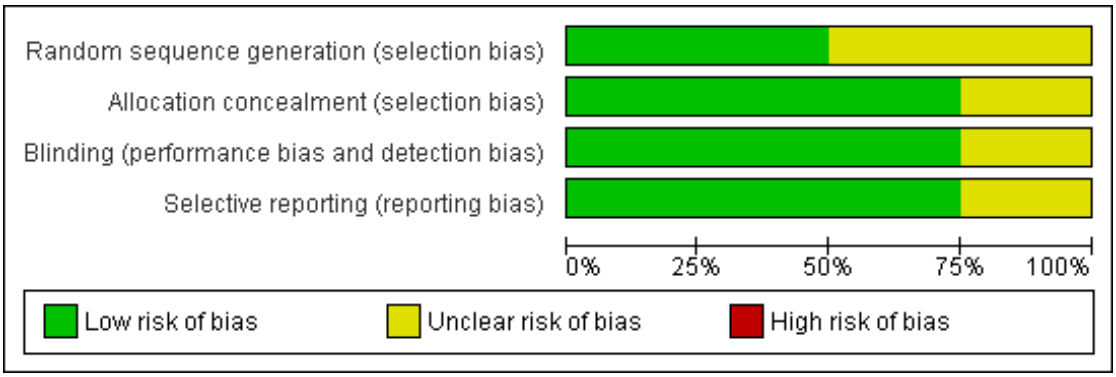
Of the 172 titles assessed, we excluded 167 papers that were not relevant to the scope of the review. We excluded nine retrospective

studies comparing ILM peeling with no peeling after reading the abstract (Al-Abdulla 2004; Ben Simon 2004; Brooks 2000; Kwok 2003; Margherio 2000; Nakamura 2009; Smiddy 2001; Tadayoni 2006; Tognetto 2006), and one quasi-randomised RCT (Terasaki 2001) after reading the full-text paper. This left four papers and one abstract covering four RCTs comparing ILM peeling with no ILM peeling which we include in this meta-analysis.

Risk of bias in included studies

See Figure 2.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Allocation

See the Characteristics of included studies.

Selection bias was assessed as being at low risk in two of the studies. In Lois 2011, all participants were randomised 1:1 into (1) vitrectomy alone without ILM peeling, or (2) vitrectomy with trypan blue (TB)-assisted ILM peeling. This was done using a central randomisation service (fully automated telephone randomisation) in the Centre for Healthcare Randomised Trials (CHaRT), Health Services Research Unit at the University of Aberdeen. A minimisation algorithm was used, considering trial centre, distance visual acuity in the study and fellow eye, duration of the macular hole, lens status, and stage of the hole.

The optometrist evaluating the patient called the telephone service line at the HSRU and was given a four-digit treatment code for each participant, which was then recorded in the case-report form (CRF). The treatment allocation was by minimisation (described above), determined by the algorithm. A list of four-digit treatment codes containing the corresponding treatments, peeling and no peeling, was produced by the programming team using random permuted blocks of size 2 and 4. This list was provided to all participating vitreoretinal surgeons, who would check at the time of the surgery which treatment to perform, based on the four-digit code written in the participant's CRF.

In Christensen 2009, generation of the random allocation sequence was performed based on a list of random numbers in blocks of four, with eyes stratified according to the stage of the macular hole. Generation of the allocation list was performed by an independent person in the department, and the list was kept in a locker at the operating room. Final assignment to intervention was performed on the day of surgery by the assisting operating nurse as consecutive patients on the allocation list. The day of operation was decided by an independent visitation office to avoid allocation bias.

In Kwok 2005, selection bias was assessed as unclear. Participants were randomised 1:1 to receive (1) vitrectomy alone without ILM peeling, or (2) vitrectomy with ICG-assisted ILM peeling. Just before surgery, the nurse would draw an envelope assigning the participant to one of the two groups.

No details of allocation concealment were available in Tadayoni 2009.

Blinding

Performance and detection bias were assessed as being at low risk in three studies. There were no details of blinding in the published abstract for Tadayoni 2009.

In Lois 2011, optometrists undertaking measures of visual function, which included the primary and secondary outcomes of the study, were masked to treatment allocation, as were the patients receiving the treatment. Vitreoretinal surgeons, evaluating the stage of the hole preoperatively and postoperatively (open/closed), were not masked to treatment allocation. The size of the hole, used for our IPD meta-analysis, which was used to help grading of the macular hole (as well as the presence/absence of posterior vitreous detachment, determined preoperatively but confirmed intraoperatively) was also undertaken in a masked fashion. All holes were measured and classified by an observer masked to the treatment received.

In Christensen 2009, investigators and participants were masked to the treatment received.

In Kwok 2005, optometrists obtaining measures of visual acuity were masked to the treatment received. The size of the hole, used for our IPD meta-analysis, which was used to help grading of the macular hole (as well as the presence/absence of posterior vitreous detachment), was also undertaken in a masked fashion. All holes were measured and classified by an observer masked to the treatment received. The vitreoretinal surgeon (Dr Kwok), evaluating the stage of the hole preoperatively and postoperatively (open/closed) was not masked to treatment allocation.

Incomplete outcome data

We contacted all authors of the included studies to ensure that data were appropriately collected for each individual in each study before we undertook IPD analysis. We used data from all four RCTs for the meta-analysis, although one RCT (Tadayoni 2009) was excluded from IPD analysis as IPD were not available and the RCT had been published only as an abstract.

Selective reporting

We assembled raw data from three of the four included RCTs to minimise the risk of reporting bias. We therefore assessed the risk of reporting bias as being low for these three studies. Selective reporting may have occurred in the fourth RCT (Tadayoni 2009), because of the inherent space limitations related to the publication in abstract form.

Other potential sources of bias

No other potential sources of bias were identified.

Effects of interventions

Primary outcome and secondary visual function outcomes

We conducted separate meta-analyses for distance (and near) visual acuity at three, six (primary outcome) and 12 months after the procedure. No analysis incorporated more than two studies and there were no eligible studies examining near visual acuity at 12 months.

There was no evidence of a difference in distance visual acuity at six months (primary outcome) between randomised groups (mean difference (MD) -0.04, 95% confidence interval (CI) -0.12 to 0.03; Analysis 1.1; Figure 3); nor were differences evident when data were stratified by the stage of the hole (Analysis 2.1). Similarly, there was no evidence of a difference in distance visual acuity at 12 months, although vision at 12 months was only reported in one trial (MD -0.09, 95% CI -0.19 to 0.01; Analysis 1.9). However, there was evidence of improved distance visual acuity (expressed in logMAR units) in the ILM peeling groups at three months (MD -0.09, 95% CI -0.17 to -0.02; Analysis 1.2; Figure 4).

Figure 3. Forest plot of comparison: 1 ILM peeling versus no peeling, outcome: 1.1 Distance visual acuity at 6 months (logMAR).

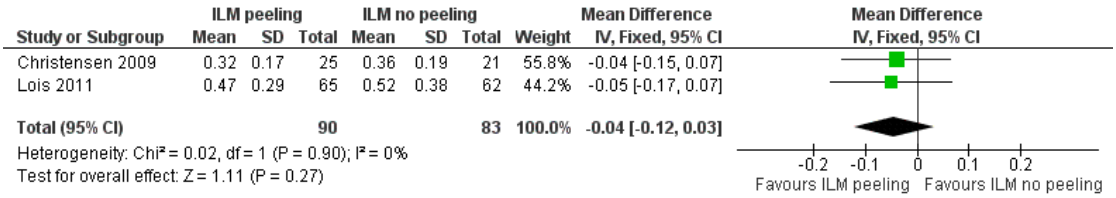
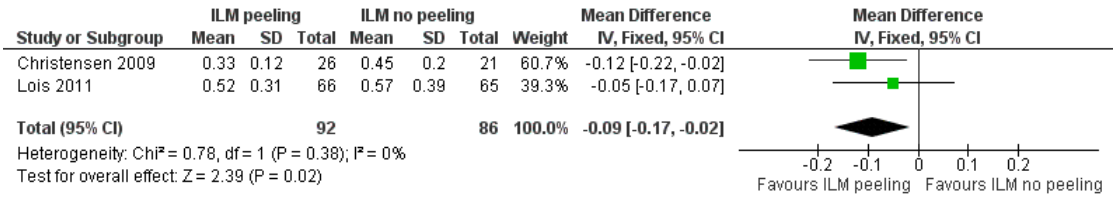


Figure 4. Forest plot of comparison: 1 ILM peeling versus no peeling, outcome: 1.2 Distance visual acuity at 3 months (logMAR).

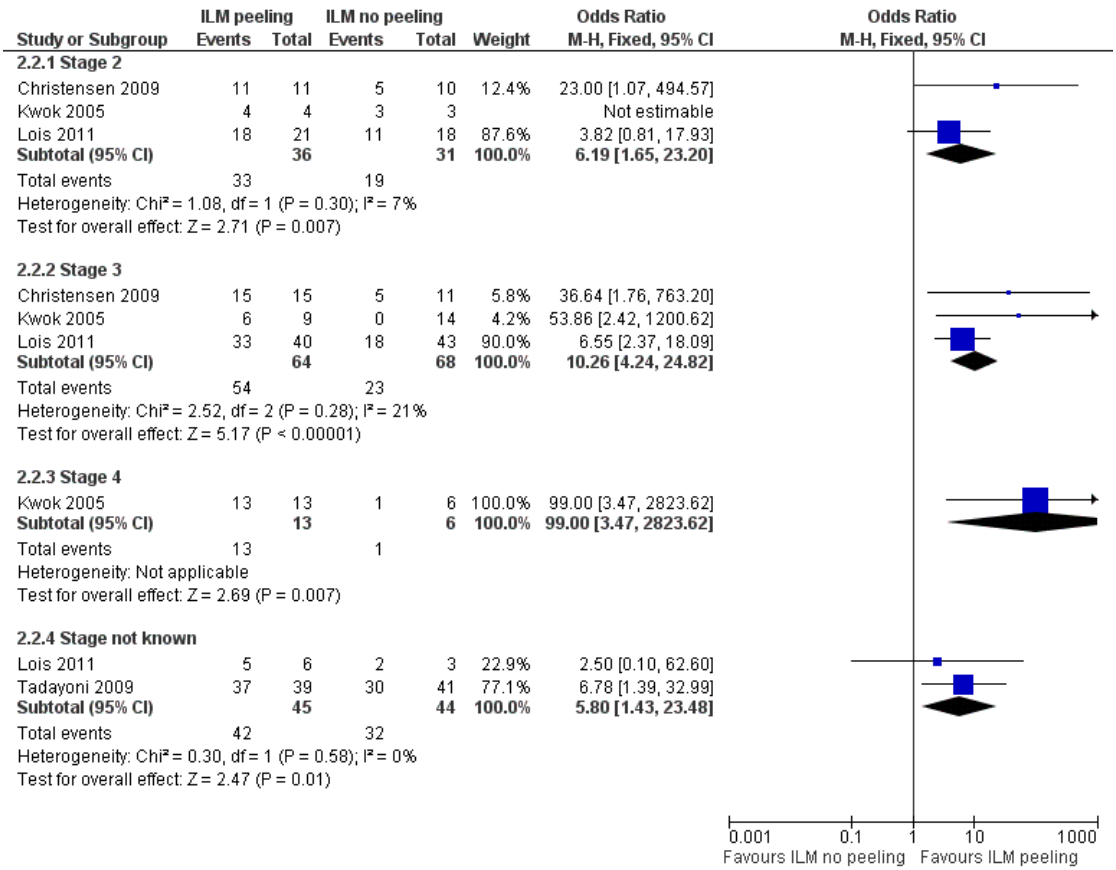


There was no evidence of a difference between the ILM peeling and no-peeling groups on near vision at any of the time points investigated. Near vision was, however, only reported in one trial (Lois 2011).

Other secondary outcomes

Overall, more participants in the ILM peeling groups than in the no-peeling groups had primary macular hole closure (142/158 versus 75/149; odds ratio (OR) 9.27, 95% CI 4.98 to 17.24; Analysis 1.3) and there were similar findings when results were stratified by the stage of the macular hole (Analysis 2.2). Progressively higher odds of macular hole closure were observed for the ILM peeling groups at each of stages 2, 3 and 4 (Figure 5).

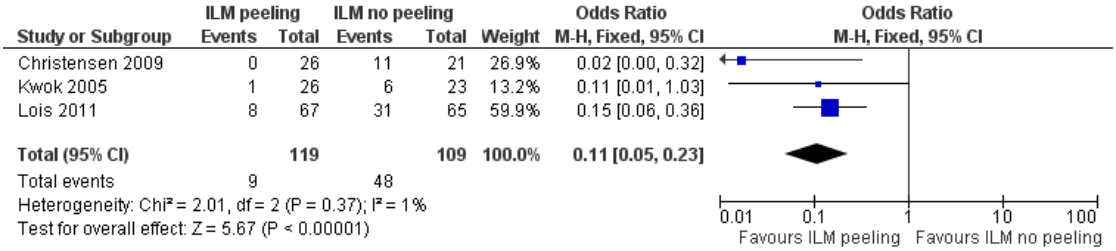
Figure 5. Forest plot of comparison of primary macular hole closure between ILM peeling versus no peeling (Subgroup Analysis by Macular Hole Stage)



There was also evidence that those in the ILM peeling groups were more likely to have final macular hole closure (110/117 versus 86/107; OR 3.99, 95% CI 1.63 to 9.75; Analysis 1.4). As the rates of hole closure were high in both groups, when the results were stratified by stage of the hole the estimates of the treatment effect of peeling could be determined less precisely, but for stages 3 and 4 there was again evidence of higher closure rates in the ILM peeling groups (Analysis 2.3).

Fewer participants required further surgery in the ILM peeling groups than in the no-peeling groups (9/119 versus 48/109; OR 0.11, 95% CI: 0.05 to 0.23; Analysis 1.5; Figure 6). The benefit of ILM peeling for reducing the need for additional surgeries was still observed for participants with stages 2 and 3 when the results were stratified by stage of the hole (Analysis 2.4).

Figure 6. Forest plot of comparison: 1 ILM peeling versus no peeling, outcome: 1.8 Additional surgery.



Rates of intraoperative and postoperative complications were similar in each group (Analysis 1.6; Analysis 1.7).

Based on the results of one study (Lois 2011), there was no evidence that total VFQ-25 or EQ-5D scores differed between randomised groups at six months.

Based on the results of one study (Lois 2011), it is highly likely that ILM peeling is cost-effective compared with no ILM peeling (see Discussion below).

Sensitivity analyses

We conducted three sensitivity analyses. Adding the published data for Kwok 2005 (where some participants had been included twice) to the meta-analysis of postoperative complications made no major change to the findings (Analysis 1.10). Similarly, when visual acuity data at last follow-up for this study were included as being assessed at six and at 12 months, again there was no change in interpretation (Analysis 1.8, Analysis 1.9).

We also conducted adjusted analyses using regression for the pooled IPD dataset. This enabled adjustment for the duration and size of the macular hole and also for the study itself. The three studies for which we had IPD were included (Christensen 2009; Kwok 2005; Lois 2011). 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 (Adj OR: 14.3, 95% CI 6.33 to 29.4).

We conducted a second adjusted analysis for distance visual acuity at six months (Analysis 1.1). Two studies (Christensen 2009; Lois 2011) were included. As with the unadjusted analysis, there was no evidence of a difference between the groups (Adj MD: -0.04, 95% CI: -0.13 to 0.05).

DISCUSSION

Summary of main results

Current evidence from randomised controlled trials

Four well-designed randomised controlled trials (RCTs) comparing macular hole surgery with or without internal limiting membrane (ILM) peeling for the treatment of idiopathic full-thickness macular hole (FTMH) were included in this review. Individual patient data (IPD) meta-analysis was carried out with data from three of the four trials; the methodology used in these RCTs and their clinical features have been summarised in the 'Characteristics of included studies' table.

No difference in the primary outcome of the studies, namely distance visual acuity at six months, was found between peeling and no-peeling groups. Similarly, near visual acuity at six months and distance and near visual acuity at 12 months did not differ between the two groups. Evidence of a difference in distance visual acuity favouring ILM peeling, however, was observed at three months, with higher levels of vision achieved after ILM peeling (P = 0.02). These findings may be explained by the fact that, following routine clinical practice and due to ethical considerations, if the macular hole had not closed after the initial surgery, which occurred more frequently in the no-peeling participants, they would have been allowed to receive further surgery, including ILM peeling which was in fact the most common type of re-operation performed. Thus, by six and 12 months the majority of people in the no-peeling arm would have received ILM peeling.

There was evidence of a benefit of ILM peeling in achieving higher rates of primary and final macular hole closure (P < 0.001 and P = 0.02 respectively). The benefit of ILM peeling in the primary closure of the macular hole was still observed when holes where stratified by stages, with higher rates of closure at each of stages 2, 3 and 4 (P = 0.02 for Stage 2 holes; P < 0.001 for stage 3 holes; P = 0.02 for stage 4 holes respectively). Although differences in final macular hole closure favouring ILM peeling were still present for macular holes at stages 3 and 4 (P = 0.04 for each), these were no longer detected for macular holes at stage 2 (P = 0.43). Furthermore, a statistically significantly higher rate of additional surgery was required in participants in whom the ILM was not peeled (P < 0.001). As for final macular hole closure, the beneficial effect of ILM peeling reducing the need for further surgery was still observed for macular holes at stages 2 and 3 in the subgroup analysis by stage of the hole. There was no evidence of a difference

in rates of intraoperative (P = 0.12) and postoperative (P = 0.82) complications between the two groups. Quality of life, measured using the EQ-5D questionnaire, and visual related quality of life, measured using the VFQ-25 questionnaire, at six months (only in Lois 2011) were no different between groups (P = 0.97). Cost effectiveness of the treatment was evaluated only in one study (Lois 2011) which found ILM peeling to be probably cost-effective, with more than a 90% probability of ILM peeling being cost-effective at a willingness-to-pay threshold of GBP 20,000 per QALY. The beneficial effect of ILM peeling, in terms of higher anatomical success rates with fewer re-operations required and the probable cost effectiveness of this treatment without any apparent detrimental effect on visual acuity or patient-reported outcomes, would support ILM peeling as the preferred treatment strategy on current evidence for patients with idiopathic FTMH stages 2, 3 and 4.

Most patients enrolled in the RCTs identified had cataract surgery prior to or at the time of macular hole surgery. Thus, data does not allow drawing conclusions about rates of cataract development following one or other procedure (ILM peeling and no peeling). The study can neither comment on the benefit or potential side effects of combining phacoemulsification and intraocular lens implantation with the vitrectomy procedure to treat the macular hole when comparing it with undertaking the macular hole surgery first and the cataract surgery at a later date or vice-versa, as patients were not randomised to one or the other in the trials included.

Overall completeness and applicability of evidence

Participants included in the above-mentioned RCTs (Christensen 2009; Kwok 2005; Lois 2011; Tadayoni 2009) should be representative of the majority of patients encountered in clinical practice. However, it should be noted that patients with long-standing macular holes were only included in one of the three RCTs for which data were pulled on IPD meta-analysis (Kwok 2005); those with macular holes for more than 12 months (Christensen 2009) and more than 18 months (Lois 2011) were excluded. In two of the three RCTs (Christensen 2009; Lois 2011) for which data were available for the IPD meta-analysis, phacoemulsification was undertaken prior to or at the time of the macular hole surgery; in the other (Kwok 2005) cataract surgery may or may not have been conducted during the study period. Thus, the results presented in Kwok 2005 may not be reproduced in populations in which the majority of patients do not have their cataracts removed prior to or at the time of their macular hole surgery.

Quality of the evidence

All four RCTs present strong evidence on the benefits of ILM peeling in macular hole surgery. However one of the included RCTs (Tadayoni 2009) has been published only in abstract form and individual patient data were not yet available for inclusion in the IPD meta-analysis. Masking to treatment allocation, randomisation and masking of participants and outcome assessors were reported in two of the studies (Christensen 2009; Lois 2011) and are assessed as being at low risk of bias, but are unclear in the published abstract (Tadayoni 2009). In Kwok 2005, masking to treatment allocation and randomisation were assessed as being unclear, while masking of personnel was assessed as being at low risk of bias.

Agreements and disagreements with other studies or reviews

Peeling of the ILM was introduced in macular hole surgery in an attempt to improve functional and anatomical outcomes of the procedure. Following its introduction, many case series and prospective and retrospective studies suggested higher rates of closure of macular holes with ILM peeling. Large studies (with 50 or more participants) have been summarised in Table 1. Primary macular hole closure was statistically significantly higher following ILM peeling in several studies (Al-Abdulla 2004; Ben Simon 2004; Brooks 2000; Tadayoni 2006; Tognetto 2006). Statistically significant results, however, were not found in other studies (Kwok 2003; Margherio 2000; Nakamura 2009; Smiddy 2001). With the exception of two studies (Ben Simon 2004; Brooks 2000), there was no statistically significant difference in visual acuity between peeling and no-peeling groups; this agreed with the results of a quasi-randomised clinical trial (Terasaki 2001) which included 48 patients (49 eyes) and aimed to evaluate macular function by using focal macular electroretinogram.

There were limitations, however, to the interpretation of previously published findings. Most studies were retrospective with unmasked treatment allocation and consequent risk of bias; non-standardised visual acuity (Al-Abdulla 2004; Brooks 2000); non-uniform ILM peeling (Smiddy 2001); variable use of intraoperative adjuvants (Al-Abdulla 2004; Kwok 2003; Tognetto 2006); included macular hole of different standing and different posturing regimes and postoperative tamponades (Al-Abdulla 2004; Kwok 2003; Tognetto 2006); had variable follow-up (Al-Abdulla 2004; Kwok 2003; Tognetto 2006); and a small number of participants (Ben Simon 2004; Kwok 2003; Nakamura 2009).

It remained unclear which patients could benefit from ILM peeling, whether it was required only in holes of longer standing and/or larger FTMH, or whether it should be undertaken in all holes regardless of these characteristics. Preliminary data had indicated that ILM peeling may not be needed in FTMH of less than 400 microns in size (Tadayoni 2006).

Furthermore, there were concerns about potential deleterious side effects of ILM peeling. Terasaki 2001 reported a statistically significant difference in the amplitude gain of the b-wave of the focal macular electroretinogram (FMERG) when comparing participants with FTMH who had undergone surgery without ILM

peeling with those that had macular holes repaired with ILM removal. They found that the percentage increase in the amplitude of the b-wave six months postoperatively was significantly greater in the ILM-on group compared with the ILM-off group. Small, mostly asymptomatic paracentral scotomas had also been reported following ILM peeling (Haritoglou 2001).

There was therefore a need for more robust evidence to evaluate the extra surgical step of ILM peeling (Benson 2001). Evidence from RCTs currently supports the performance of ILM peeling to treat FTMH at all stages and standing.

RCT data on visual function, including distance vision from our IPD meta-analysis and on near vision, contrast sensitivity, reading speed and patient-reported outcomes from Lois 2011, fail to show any clinically relevant deleterious effect of ILM peeling. Further research in the form of functional-anatomical studies using microperimetry and spectral domain optical coherence tomography and fundus autofluorescence imaging, and the impact of any possible findings on the perceived visual gain experienced by people undergoing macular hole surgery, would provide more insight into the potential benefits and/or deleterious effects of ILM peeling. Although it must be acknowledged that ILM peeling could have an effect on retinal function, our meta-analysis has confirmed that it does not seem to affect the overall visual acuity or quality of life of people undergoing this procedure. Furthermore, our review provides evidence that ILM peeling is not associated with increased rates of intraoperative or postoperative complications when compared to vitrectomy without peel.

We found strong evidence that ILM peeling is associated with higher rates of macular hole closure postoperatively. This agrees with findings from other studies (Al-Abdulla 2004; Ben Simon 2004; Brooks 2000; Tadayoni 2006; Tognetto 2006). A previous meta-analysis of 1654 eyes from published reports also showed significantly higher anatomical success rates with ILM peeling in macular hole surgery (Mester 2000). This meta-analysis had various limitations, most notably the lack of RCTs available at the time it was undertaken. Unlike some studies (Al-Abdulla 2004; Margherio 2000; Tognetto 2006) and the Mester 2000 meta-analysis, we saw no evidence of higher long-term postoperative visual acuity with ILM peeling. However, as stated above, due to ethical considerations and following standard clinical practice, many patients in the no-peeling arms of the included RCTs received ILM peeling if the macular hole had not initially closed by the time the functional outcomes had been measured. This reduced the chance of detecting differences between groups, even where they originally existed. Our current results also confirm previous evidence that ILM peeling is not associated with a higher risk of adverse outcomes.

AUTHORS' CONCLUSIONS

Implications for practice

There is evidence from this meta-analysis and IPD meta-analysis to support ILM peeling in the treatment of idiopathic FTMH; the data supports ILM peeling at each of stages 2, 3 and 4. Compared with the no-peeling technique, ILM peeling achieves higher anatomical success with a reduced need for additional surgical interventions. The lack of deleterious effects, supported by a lack of significant difference in postoperative visual acuity, patient-reported outcomes, or adverse outcomes between ILM peeling and ILM no-peeling techniques and the probable cost effectiveness of the former compared with the latter, further support ILM peeling as the current treatment of choice for people with idiopathic FTMH.

Implications for research

Our review highlights the lack of evidence to support one particular dye or gas over another, and neither provides insight on whether or not face-down posturing (and for how long) should be recommended in the treatment of FTMH. Other than distance and near visual acuity, contrast sensitivity and reading speed, there is no other evidence on the possible effects of ILM peeling on macular function. The efficacy and cost-effectiveness of undertaking combined phacoemulsification and intraocular lens implantation at the time of the macular hole surgery when compared with performing the cataract surgery before or after the macular hole repair have not been addressed in previous studies. Further research into these areas would be beneficial.

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imaging: Ayyakkawnu Manivannan. Data Monitoring Committee: Prof Gordon Murray (Chair), Mr Bill Aylward and Mr Tom Williamson.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Christensen 2009

Methods	RCT
Participants	Patients with idiopathic FTMH stages 2 - 3 according to Gass classification, with < 12 months duration, visual acuity of > 34 ETDRS letters, and intraocular pressure of < 23 mmHg.
Interventions	Vitrectomy alone (with no touch of the retinal surface), including detachment and removal of the posterior hyaloid, or vitrectomy, including detachment and removal of the posterior hyaloid + ICG-assisted ILM peeling and gas tamponade with 10 - 15% C3F8 and face-down posturing for at least 10 hours per day for five days
Outcomes	Primary outcome: closure of the macular hole (complete apposition of the macular hole margins on OCT) at 3 and 12 months after surgery Secondary outcomes: BCVA (distance) 12 months after successful surgery; visual field defects at 12 months following surgery, retinal pigment epitheliopathy, optic nerve fibre layer, dehiscence, intraoperative and postoperative complications
Notes	All phakic patients underwent cataract extraction prior to entering the trial

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Generation of the random allocation sequence was performed based on a list of random numbers in blocks of four, with eyes stratified according to macular hole size in stage 2 and 3. The two highest numbers allocated patients to vitrectomy alone and lowest numbers allocated patients to ICG-assisted ILM peeling.
Allocation concealment (selection bias)	Low risk	Generation of the allocation list was performed by an independent person in the department, and the list was kept in a locker at the operating room. Final assignment to intervention was performed on the day of the surgery by the assisting operating nurse as consecutive participants on the allocation list. The day of the surgery was decided by an independent visitation office.
Blinding (performance bias and detection bias) All outcomes	Low risk	All participants and assessors were masked to intervention.
Selective reporting (reporting bias)	Low risk	Data from all participants randomised (with the exception of one person lost to follow-up due to disseminated cancer) appear to be presented.

Kwok 2005

Methods	RCT
Participants	Patients with idiopathic FTMH stages 2 - 4 according to Gass classification
Interventions	Vitrectomy alone (with no touch of the retinal surface), including detachment and removal of the posterior hyaloid, or vitrectomy, including detachment and removal of the posterior hyaloid, + ICG-assisted ILM peeling and gas tamponade with 12% C3F8 and face-down posturing for two weeks postoperatively
Outcomes	Primary outcome: anatomical closure of the macular hole and lines of distance visual acuity improvement Secondary outcomes: Proportion of cases with 2 or more lines of distance visual acuity improvement and final postoperative BCVA
Notes	Cataract extraction was not routinely performed prior to or at the time of the macular hole surgery and could be undertaken during the follow-up period. Phacoemulsification and intraocular lens implantation was performed in 28 (54.9%) eyes. There was no significant difference in the proportion of eyes that underwent combined surgery between the two groups (Chi^2 test, P = 0.20). 12/26 and 16/25 in the ILM peeling and no-peeling groups had combined vitrectomy and cataract surgery

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details of the method of random sequence generation used were given in the published study.
Allocation concealment (selection bias)	Low risk	Sealed opaque envelopes were used.
Blinding (performance bias and detection bias) All outcomes	Low risk	All participants and assessors were masked to intervention.
Selective reporting (reporting bias)	Low risk	Data from all participants randomised appear to have been presented

Lois 2011

Methods	RCT
Participants	Patients with idiopathic FTMH stages 2 - 3 according to Gass classification, with < 18 months duration, visual acuity of < 69 ETDRS letters in the study eye.
Interventions	Vitrectomy alone (with no touch of the retinal surface), including detachment and removal of the posterior hyaloid, or vitrectomy, including detachment and removal of the posterior hyaloid, + trypan blue (0.15%)-assisted ILM peeling and gas tamponade with 12% C3F8 and face-down posturing for 5 - 7 days

Outcomes	Primary outcome: Mean difference between treatment groups in the ETDRS distance visual acuity score at six months Secondary outcomes: ETDRS distance visual acuity at three months, near visual acuity at three and six months, contrast sensitivity at six months, reading speed in the study eye and with both eyes opened at six months, anatomical closure of the macular hole at one, three and six months, adverse events, patient-reported outcomes and cost effectiveness of the surgery
Notes	All phakic patients underwent phacoemulsification and intraocular lens implantation at the time of the vitrectomy in both peeling and no-peeling groups Due to ethical considerations and following standard clinical practice, participants in whom the macular hole was not closed with the primary (initial) surgery could received further surgery, including ILM peeling in participants in the no-peeling group

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation was undertaken using the existing central randomisation service (fully automated telephone randomisation) in the Centre for Healthcare Randomised Trials (CHaRT), Health Services Research Unit at the University of Aberdeen. A four-digit code was obtained in this manner. A list of codes was then generated with the corresponding procedure (ILM peeling/no ILM peeling). A minimisation algorithm (according to Taves, with P = 0.999) was used that allocated treatment by minimising imbalance in trial centre, distance visual acuity in study and fellow eye (20/40 - 20/160; 20/200 - 20/500, < 20/500), stage of the macular hole (2 or 3), duration of symptoms (≤ 1 year and > 1 year), and lens status (phakic, pseudophakic and aphakic)
Allocation concealment (selection bias)	Low risk	A list with codes and the corresponding procedure (ILM peeling/no ILM peeling) was kept by the vitreoretinal surgeon and was not accessible to participants, optometrists or investigators obtaining measures of the macular hole. Similarly, the Case Report Form containing details of the surgery was not filed with the participant's notes but was kept locked by the vitreoretinal surgeon (another copy was sent to the trial's office)
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants, optometrists obtaining visual function outcomes, and investigators measuring the size of the macular hole were masked to the treatment allocation. Vitreoretinal surgeons performing the surgery and confirming eligibility of participants prior to and at the time of the surgery (presence of an attached posterior vitreous, by definition of stages 2 and 3 idiopathic FTMH) were not masked to the allocated treatment.

Lois 2011 (*Continued*)

Selective reporting (reporting bias)	Low risk	Analysis followed intention-to-treat. CONSORT diagram available.

Tadayoni 2009

Methods	RCT
Participants	Patients with idiopathic FTMH > 400 microns.
Interventions	Vitrectomy alone (peeling of any epiretinal membrane was allowed), including detachment and removal of the posterior hyaloid, or vitrectomy, including detachment and removal of the posterior hyaloid, + trypan blue-assisted ILM peeling and gas tamponade with 17% C2F6 and face-down posturing (duration of posturing unreported)
Outcomes	Primary outcome: anatomical closure of the macular hole at three months following surgery Secondary outcomes: ETDRS distance visual acuity, progression of cataract and complications
Notes	Cataract extraction was not routinely performed prior to or at the time of the macular hole surgery. Epiretinal membrane, where present, was removed in all cases. Trial details only available in abstract form.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details of randomisation available in the published abstract.
Allocation concealment (selection bias)	Unclear risk	No details of allocation concealment available in the published abstract.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No details available on the published abstract.
Selective reporting (reporting bias)	Unclear risk	No detailed information available on the published abstract.

BCVA: best corrected visual acuity
ETDRS: Early Treatment Diabetic Retinopathy Study
FTMH: full-thickness macular hole
ICG: indocyanine green
ILM: internal limiting membrane
RCT: randomised controlled trial

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Terasaki 2001	This study is quasi-randomised because day of week was used as method of randomisation

DATA AND ANALYSES

Comparison 1. ILM peeling versus no peeling

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Distance visual acuity at 6 months (logMAR)	2	173	Mean Difference (IV, Fixed, 95% CI)	-0.04 [-0.12, 0.03]
2 Distance visual acuity at 3 months (logMAR)	2	178	Mean Difference (IV, Fixed, 95% CI)	-0.09 [-0.17, -0.02]
3 Primary macular hole closure	4	307	Odds Ratio (M-H, Fixed, 95% CI)	9.27 [4.98, 17.24]
4 Final macular hole closure	3	224	Odds Ratio (M-H, Fixed, 95% CI)	3.99 [1.63, 9.75]
5 Additional surgery	3	228	Odds Ratio (M-H, Fixed, 95% CI)	0.11 [0.05, 0.23]
6 Intraoperative complications	3	228	Odds Ratio (M-H, Fixed, 95% CI)	0.94 [0.47, 1.87]
7 Postoperative complications	2	173	Odds Ratio (M-H, Fixed, 95% CI)	0.83 [0.45, 1.52]
8 Sensitivity analysis: distance visual acuity at 6 months (including Kwok 2005)	3	222	Mean Difference (IV, Fixed, 95% CI)	-0.06 [-0.14, 0.01]
9 Sensitivity analysis: distance visual acuity at 12 months (including Kwok 2005)	2	96	Mean Difference (IV, Fixed, 95% CI)	-0.09 [-0.19, 0.01]
10 Sensitivity analysis: postoperative complications (including eye-randomised studies)	3	222	Odds Ratio (M-H, Fixed, 95% CI)	0.98 [0.56, 1.74]

Comparison 2. ILM peeling versus no peeling (Subgroup Analysis)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Distance visual acuity at 6 months (logMAR)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 Stage 2	2	59	Mean Difference (IV, Fixed, 95% CI)	0.07 [-0.02, 0.16]
1.2 Stage 3	2	106	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.20, 0.01]
1.3 Stage not known	1	8	Mean Difference (IV, Fixed, 95% CI)	0.02 [-0.21, 0.25]
2 Primary macular hole closure	4		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Stage 2	3	67	Odds Ratio (M-H, Fixed, 95% CI)	6.19 [1.65, 23.20]
2.2 Stage 3	3	132	Odds Ratio (M-H, Fixed, 95% CI)	10.26 [4.24, 24.82]
2.3 Stage 4	1	19	Odds Ratio (M-H, Fixed, 95% CI)	99.0 [3.47, 2823.62]
2.4 Stage not known	2	89	Odds Ratio (M-H, Fixed, 95% CI)	5.80 [1.43, 23.48]
3 Final macular hole closure	3		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Stage 2	3	67	Odds Ratio (M-H, Fixed, 95% CI)	3.69 [0.14, 96.22]
3.2 Stage 3	3	130	Odds Ratio (M-H, Fixed, 95% CI)	2.99 [1.03, 8.71]
3.3 Stage 4	1	19	Odds Ratio (M-H, Fixed, 95% CI)	27.0 [1.11, 654.40]
3.4 Stage not known	1	8	Odds Ratio (M-H, Fixed, 95% CI)	0.43 [0.01, 14.08]

4 Additional surgery	3		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Stage 2	3	67	Odds Ratio (M-H, Fixed, 95% CI)	0.26 [0.07, 0.97]
4.2 Stage 3	3	137	Odds Ratio (M-H, Fixed, 95% CI)	0.11 [0.04, 0.28]
4.3 Stage 4	1	19	Odds Ratio (M-H, Fixed, 95% CI)	0.07 [0.00, 1.67]
4.4 Stage not known	1	9	Odds Ratio (M-H, Fixed, 95% CI)	0.13 [0.00, 4.32]

Analysis 1.1. Comparison 1 ILM peeling versus no peeling, Outcome 1 Distance visual acuity at 6 months (logMAR).

Review: Vitrectomy with internal limiting membrane (ILM) peeling versus vitrectomy with no peeling for idiopathic full-thickness macular hole (FTMH)

Comparison: 1 ILM peeling versus no peeling

Outcome: 1 Distance visual acuity at 6 months (logMAR)

Study or subgroup	ILM peeling N	Mean(SD)	ILM no peeling N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Christensen 2009	25	0.32 (0.17)	21	0.36 (0.19)		55.8 %	-0.04 [-0.15, 0.07]
Lois 2011	65	0.47 (0.29)	62	0.52 (0.38)		44.2 %	-0.05 [-0.17, 0.07]
Total (95% CI)	**90**		**83**			**100.0 %**	**-0.04 [-0.12, 0.03]**

Heterogeneity: Chi^2 = 0.02, df = 1 (P = 0.90); I^2 =0.0%

Test for overall effect: Z = 1.11 (P = 0.27)

Test for subgroup differences: Not applicable

Analysis 1.2. Comparison 1 ILM peeling versus no peeling, Outcome 2 Distance visual acuity at 3 months (logMAR).

Review: Vitrectomy with internal limiting membrane (ILM) peeling versus vitrectomy with no peeling for idiopathic full-thickness macular hole (FTMH)

Comparison: 1 ILM peeling versus no peeling

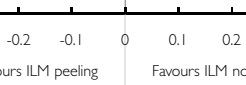
Outcome: 2 Distance visual acuity at 3 months (logMAR)

Study or subgroup	ILM peeling N	Mean(SD)	ILM no peeling N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Christensen 2009	26	0.33 (0.12)	21	0.45 (0.2)		60.7 %	-0.12 [-0.22, -0.02]
Lois 2011	66	0.52 (0.31)	65	0.57 (0.39)		39.3 %	-0.05 [-0.17, 0.07]
Total (95% CI)	**92**		**86**			**100.0 %**	**-0.09 [-0.17, -0.02]**

Heterogeneity: $Chi^2 = 0.78$, df = 1 (P = 0.38); $I^2 = 0.0\%$

Test for overall effect: Z = 2.39 (P = 0.017)

Test for subgroup differences: Not applicable



Analysis 1.3. Comparison 1 ILM peeling versus no peeling, Outcome 3 Primary macular hole closure.

Review: Vitrectomy with internal limiting membrane (ILM) peeling versus vitrectomy with no peeling for idiopathic full-thickness macular hole (FTMH)

Comparison: 1 ILM peeling versus no peeling

Outcome: 3 Primary macular hole closure

Study or subgroup	ILM peeling n/N	ILM no peeling n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Christensen 2009	26/26	10/21		2.9 %	58.05 [3.13, 1076.53]
Kwok 2005	23/26	4/23		6.6 %	36.42 [7.24, 183.20]
Lois 2011	56/67	31/64		70.3 %	5.42 [2.41, 12.20]
Tadayoni 2009	37/39	30/41		20.2 %	6.78 [1.39, 32.99]
Total (95% CI)	**158**	**149**		**100.0 %**	**9.27 [4.98, 17.24]**
Total events: 142 (ILM peeling), 75 (ILM no peeling)					
Heterogeneity: Chi^2 = 6.10, df = 3 (P = 0.11); I^2 =51%					
Test for overall effect: Z = 7.03 (P < 0.00001)					
Test for subgroup differences: Not applicable					

Analysis 1.4. Comparison 1 ILM peeling versus no peeling, Outcome 4 Final macular hole closure.

Review: Vitrectomy with internal limiting membrane (ILM) peeling versus vitrectomy with no peeling for idiopathic full-thickness macular hole (FTMH)

Comparison: 1 ILM peeling versus no peeling

Outcome: 4 Final macular hole closure

Study or subgroup	ILM peeling n/N	ILM no peeling n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Christensen 2009	26/26	20/21		8.1 %	3.88 [0.15, 100.23]
Kwok 2005	23/26	10/23		23.8 %	9.97 [2.32, 42.85]
Lois 2011	61/65	56/63		68.1 %	1.91 [0.53, 6.86]
Total (95% CI)	**117**	**107**		**100.0 %**	**3.99 [1.63, 9.75]**

Total events: 110 (ILM peeling), 86 (ILM no peeling)
Heterogeneity: Chi^2 = 2.79, df = 2 (P = 0.25); I^2 =28%
Test for overall effect: Z = 3.03 (P = 0.0025)
Test for subgroup differences: Not applicable

Analysis 1.5. Comparison 1 ILM peeling versus no peeling, Outcome 5 Additional surgery.

Review: Vitrectomy with internal limiting membrane (ILM) peeling versus vitrectomy with no peeling for idiopathic full-thickness macular hole (FTMH)

Comparison: 1 ILM peeling versus no peeling

Outcome: 5 Additional surgery

Study or subgroup	ILM peeling n/N	ILM no peeling n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Christensen 2009	0/26	11/21		26.9 %	0.02 [0.00, 0.32]
Kwok 2005	1/26	6/23		13.2 %	0.11 [0.01, 1.03]
Lois 2011	8/67	31/65		59.9 %	0.15 [0.06, 0.36]
Total (95% CI)	**119**	**109**		**100.0 %**	**0.11 [0.05, 0.23]**

Total events: 9 (ILM peeling), 48 (ILM no peeling)
Heterogeneity: Chi^2 = 2.01, df = 2 (P = 0.37); I^2 =1%
Test for overall effect: Z = 5.67 (P < 0.00001)
Test for subgroup differences: Not applicable

Analysis 1.6. Comparison 1 ILM peeling versus no peeling, Outcome 6 Intraoperative complications.

Review: Vitrectomy with internal limiting membrane (ILM) peeling versus vitrectomy with no peeling for idiopathic full-thickness macular hole (FTMH)

Comparison: 1 ILM peeling versus no peeling

Outcome: 6 Intraoperative complications

Study or subgroup	ILM peeling n/N	ILM no peeling n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
Christensen 2009	2/26	2/21		0.79 [0.10, 6.15]
Kwok 2005	0/26	0/23		0.0 [0.0, 0.0]
Lois 2011	21/67	21/65		0.96 [0.46, 1.99]
Total (95% CI)	**119**	**109**		**0.94 [0.47, 1.87]**

Total events: 23 (ILM peeling), 23 (ILM no peeling)

Heterogeneity: $Chi^2 = 0.03$, df = 1 (P = 0.86); $I^2 = 0.0\%$

Test for overall effect: Z = 0.19 (P = 0.85)

Test for subgroup differences: Not applicable

Analysis 1.7. Comparison 1 ILM peeling versus no peeling, Outcome 7 Postoperative complications.

Review: Vitrectomy with internal limiting membrane (ILM) peeling versus vitrectomy with no peeling for idiopathic full-thickness macular hole (FTMH)

Comparison: 1 ILM peeling versus no peeling

Outcome: 7 Postoperative complications

Study or subgroup	ILM peeling n/N	ILM no peeling n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Christensen 2009	13/26	8/21		19.4 %	1.63 [0.50, 5.23]
Lois 2011	21/64	27/62		80.6 %	0.63 [0.31, 1.31]
Total (95% CI)	**90**	**83**		**100.0 %**	**0.83 [0.45, 1.52]**

Total events: 34 (ILM peeling), 35 (ILM no peeling)

Heterogeneity: Chi^2 = 1.81, df = 1 (P = 0.18); I^2 =45%

Test for overall effect: Z = 0.62 (P = 0.54)

Test for subgroup differences: Not applicable

Analysis 1.8. Comparison 1 ILM peeling versus no peeling, Outcome 8 Sensitivity analysis: distance visual acuity at 6 months (including Kwok 2005).

Review: Vitrectomy with internal limiting membrane (ILM) peeling versus vitrectomy with no peeling for idiopathic full-thickness macular hole (FTMH)

Comparison: 1 ILM peeling versus no peeling

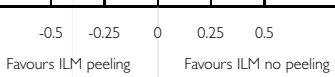
Outcome: 8 Sensitivity analysis: distance visual acuity at 6 months (including Kwok 2005)

Study or subgroup	ILM peeling N	Mean(SD)	ILM no peeling N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Christensen 2009	25	0.32 (0.17)	21	0.36 (0.19)		48.3 %	-0.04 [-0.15, 0.07]
Kwok 2005	26	0.56 (0.33)	23	0.75 (0.38)		13.3 %	-0.19 [-0.39, 0.01]
Lois 2011	65	0.47 (0.29)	62	0.52 (0.38)		38.4 %	-0.05 [-0.17, 0.07]
Total (95% CI)	**116**		**106**			**100.0 %**	**-0.06 [-0.14, 0.01]**

Heterogeneity: Chi^2 = 1.77, df = 2 (P = 0.41); I^2 =0.0%

Test for overall effect: Z = 1.71 (P = 0.087)

Test for subgroup differences: Not applicable



Analysis 1.9. Comparison 1 ILM peeling versus no peeling, Outcome 9 Sensitivity analysis: distance visual acuity at 12 months (including Kwok 2005).

Review: Vitrectomy with internal limiting membrane (ILM) peeling versus vitrectomy with no peeling for idiopathic full-thickness macular hole (FTMH)

Comparison: 1 ILM peeling versus no peeling

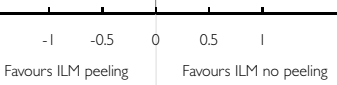
Outcome: 9 Sensitivity analysis: distance visual acuity at 12 months (including Kwok 2005)

Study or subgroup	ILM peeling N	Mean(SD)	ILM no peeling N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Christensen 2009	26	0.26 (0.14)	21	0.32 (0.24)		75.0 %	-0.06 [-0.18, 0.06]
Kwok 2005	26	0.56 (0.33)	23	0.75 (0.38)		25.0 %	-0.19 [-0.39, 0.01]
Total (95% CI)	**52**		**44**			**100.0 %**	**-0.09 [-0.19, 0.01]**

Heterogeneity: Chi^2 = 1.21, df = 1 (P = 0.27); I^2 =17%

Test for overall effect: Z = 1.81 (P = 0.071)

Test for subgroup differences: Not applicable



Analysis 1.10. Comparison 1 ILM peeling versus no peeling, Outcome 10 Sensitivity analysis: postoperative complications (including eye-randomised studies).

Review: Vitrectomy with internal limiting membrane (ILM) peeling versus vitrectomy with no peeling for idiopathic full-thickness macular hole (FTMH)

Comparison: 1 ILM peeling versus no peeling

Outcome: 10 Sensitivity analysis: postoperative complications (including eye-randomised studies)

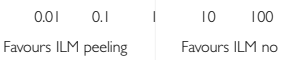
Study or subgroup	ILM peeling n/N	ILM no peeling n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Christensen 2009	13/26	8/21		18.7 %	1.63 [0.50, 5.23]
Kwok 2005	5/26	1/23		3.6 %	5.24 [0.56, 48.65]
Lois 2011	21/64	27/62		77.7 %	0.63 [0.31, 1.31]
Total (95% CI)	**116**	**106**		**100.0 %**	**0.98 [0.56, 1.74]**

Total events: 39 (ILM peeling), 36 (ILM no peeling)

Heterogeneity: $Chi^2 = 4.30$, df = 2 (P = 0.12); $I^2 = 53\%$

Test for overall effect: Z = 0.05 (P = 0.96)

Test for subgroup differences: Not applicable

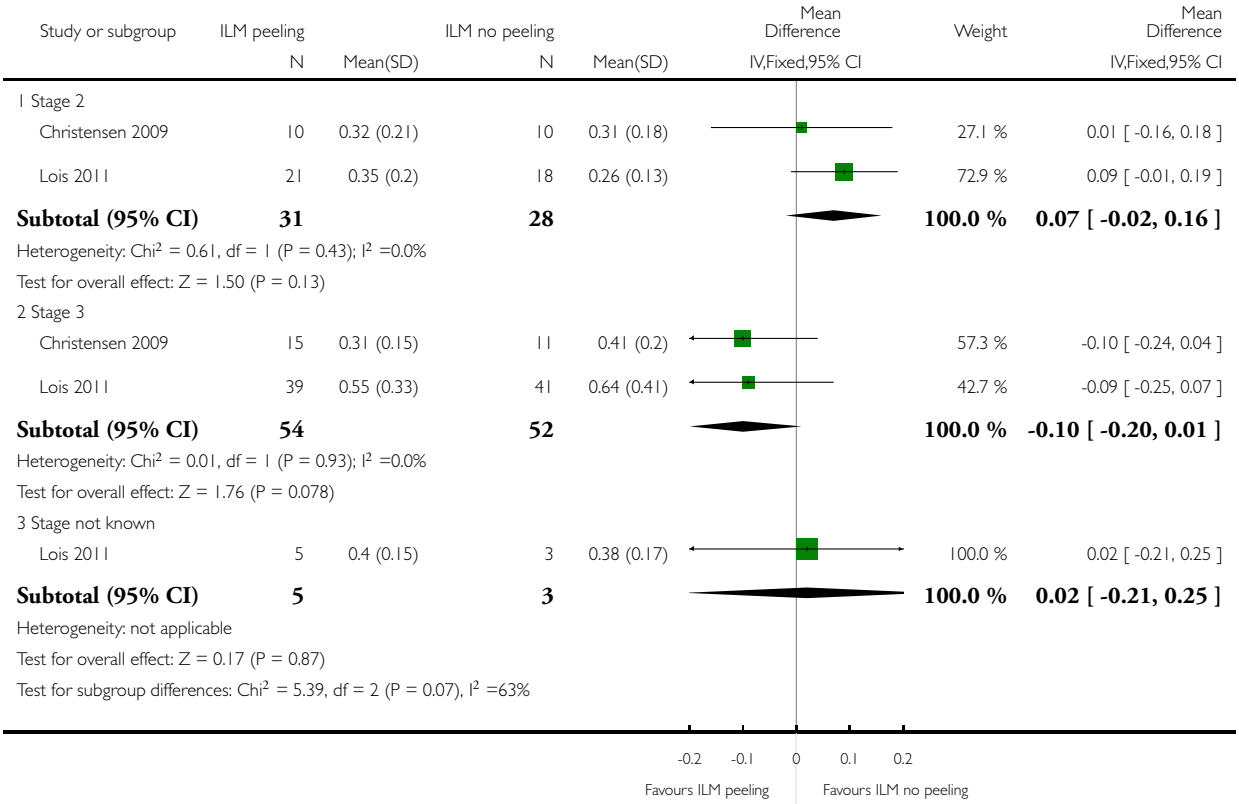


Analysis 2.1. Comparison 2 ILM peeling versus no peeling (Subgroup Analysis), Outcome 1 Distance visual acuity at 6 months (logMAR).

Review: Vitrectomy with internal limiting membrane (ILM) peeling versus vitrectomy with no peeling for idiopathic full-thickness macular hole (FTMH)

Comparison: 2 ILM peeling versus no peeling (Subgroup Analysis)

Outcome: 1 Distance visual acuity at 6 months (logMAR)

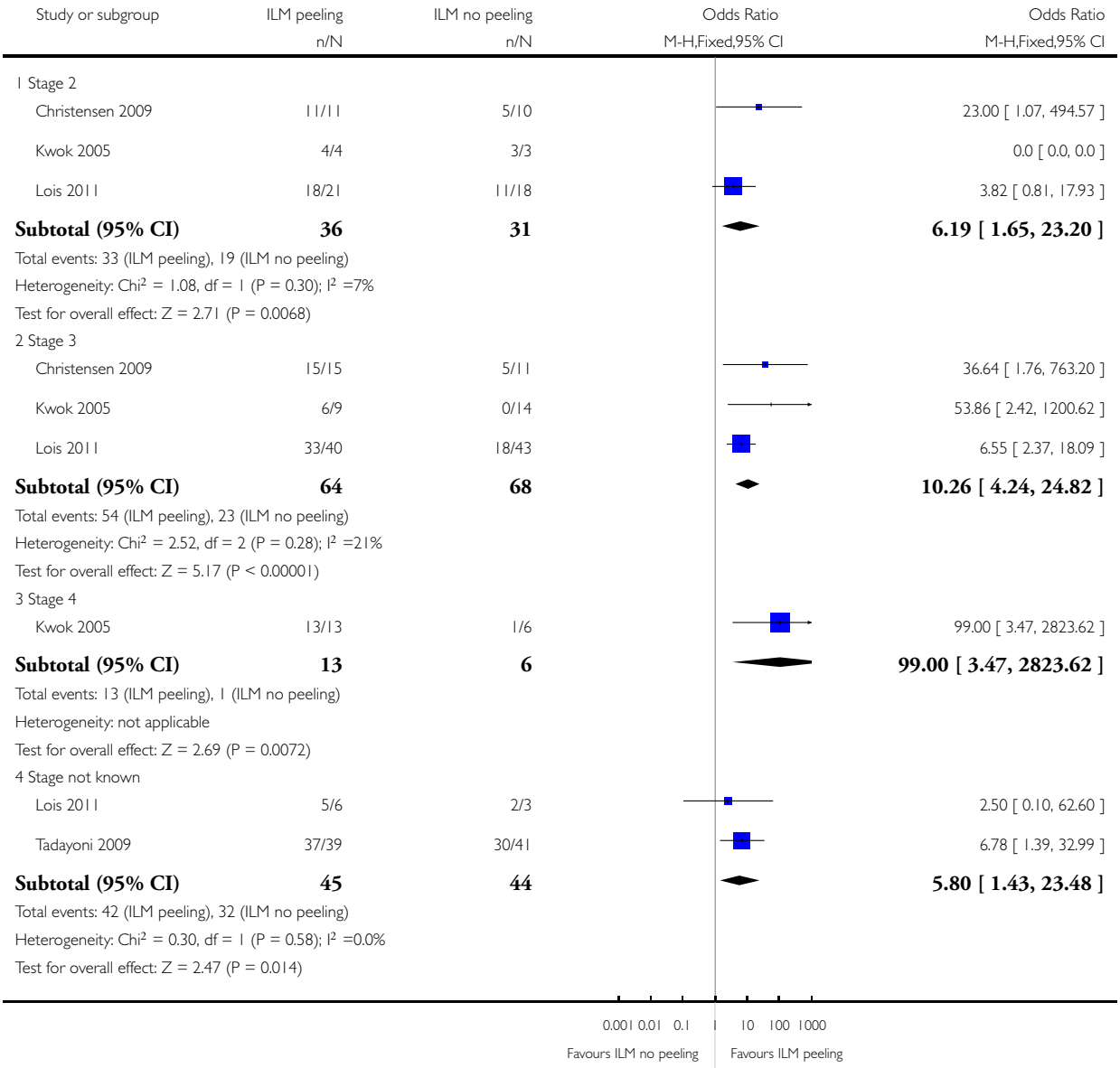


Analysis 2.2. Comparison 2 ILM peeling versus no peeling (Subgroup Analysis), Outcome 2 Primary macular hole closure.

Review: Vitrectomy with internal limiting membrane (ILM) peeling versus vitrectomy with no peeling for idiopathic full-thickness macular hole (FTMH)

Comparison: 2 ILM peeling versus no peeling (Subgroup Analysis)

Outcome: 2 Primary macular hole closure

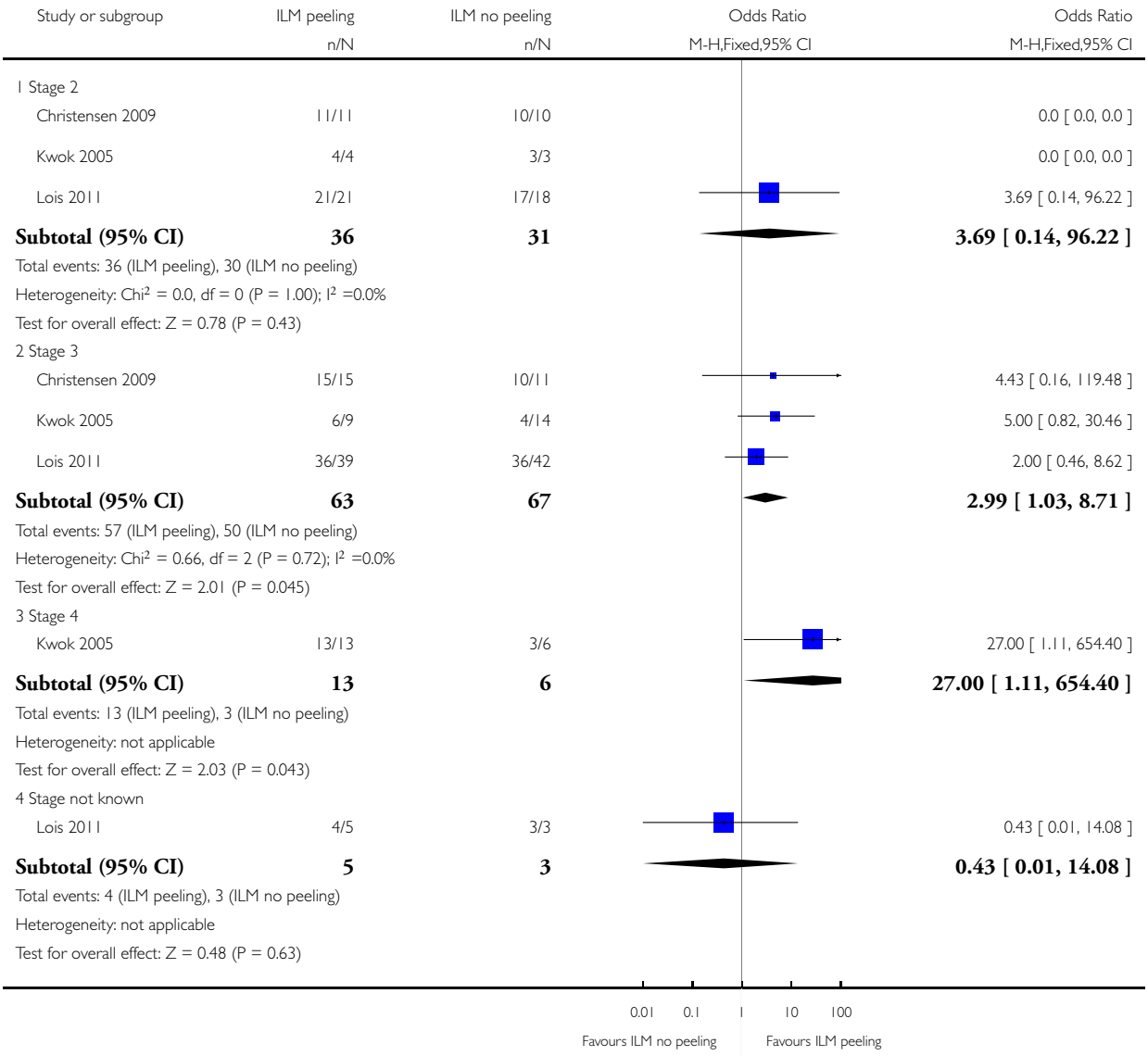


Analysis 2.3. Comparison 2 ILM peeling versus no peeling (Subgroup Analysis), Outcome 3 Final macular hole closure.

Review: Vitrectomy with internal limiting membrane (ILM) peeling versus vitrectomy with no peeling for idiopathic full-thickness macular hole (FTMH)

Comparison: 2 ILM peeling versus no peeling (Subgroup Analysis)

Outcome: 3 Final macular hole closure

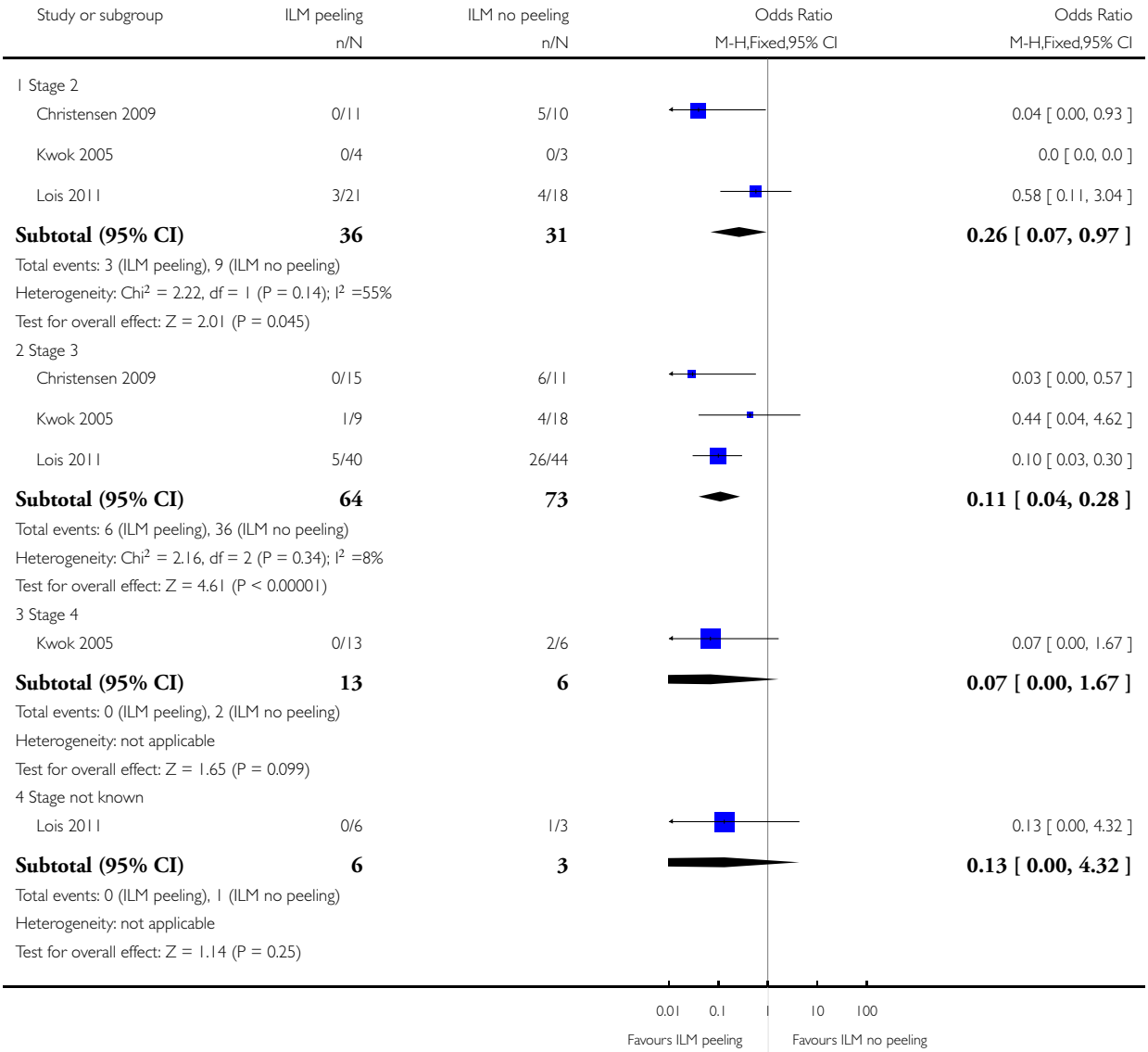


Analysis 2.4. Comparison 2 ILM peeling versus no peeling (Subgroup Analysis), Outcome 4 Additional surgery.

Review: Vitrectomy with internal limiting membrane (ILM) peeling versus vitrectomy with no peeling for idiopathic full-thickness macular hole (FTMH)

Comparison: 2 ILM peeling versus no peeling (Subgroup Analysis)

Outcome: 4 Additional surgery



ADDITIONAL TABLES

Table 1. Studies (non-randomised controlled trials, n > 50) comparing ILM peeling with no ILM peeling for full-thickness macular hole

Paper	Group Allocation (Number of Patients)	Mean VA pre-op (Snellen or logMAR)	Mean VA post-op	Primary Hole Closure, n (%)	Final Hole Closure (> 1 surgery)	Re-opening, n (%)	ERM peeled, n (%)	Complications, n (%)	ILM peeling versus ILM no peeling
Nakamura 2009	Group I No ILM peeling (21)	0.82		75 (!00)	N/A	0 (0)	N/A	N/A	Visual acuity difference was not significant between the three groups at 1, 2 and 3 years.
	Group II ILM peeling without ICG (38)	0.82 0.81	0.33 0.28	21 (100) 38 (100)					
	Group III ILM peeling with ICG (16)		0.41	16 (100)					
Brooks 2000	Group I No ILM peeling (44)	20/100						Retinal tears 44 (18)	Visual acuity better in ILM peeling group (P < 0.00001)
	Group II ILM peeling (116)	20/80 20/250	20/60 20/40	27 (61) 116 (100)	N/A* 116 (100)	11 (25) 0 (0)	0 (0) 100 (55)**	RD 44 (4.5) PVR 5 (2.2)	Lower reopening rate with ILM peeling (P < 0.00001)
	Group III ILM peeling (65)		20/70	63 (97)	64 (98)	0 (0)			Higher primary hole closure rates with ILM peeling (P < 0.00001)

Table 1. Studies (non-randomised controlled trials, n > 50) comparing ILM peeling with no ILM peeling for full-thickness macular hole (*Continued*)

Al-Abdulla 2004	Group I No peeling (116) Group II ERM peeling (27) Group III ERM + ILM peeling (56) Group IV ILM peeling (29)	20/100 - 1 20/125 - 2 20/125 - 2 20/125 - 1	20/50 + 1 20/63 + 1 20/63 20/63	92 (79.3) 23 (85.1) 52 (92.9) 29 (100)	99 (85.3) 25 (92.6) 54 (96.4) 29 (100)	5 (4.3) 1 (3.7) N/A 0 (0)	0 (0) 27 (100) 56 (100) 0 (0)	N/Aϕ N/A N/A N/A	ILM peeling has higher primary macular hole closure than ERM peeling or no peeling (P = 0.01) No statistically significant difference in final VA.
Tognetto 2006	Group I ILM peeling (1100) Group II No peeling (527)	47.7% >1.0 24.8% 0.7 - 1.0 27.5% 0.0 - 0.7 44.9% > 1.0 27.4% 0.7 - 1.0 27.7% 0.0 - 0.7	N/A N/A	N/A N/A	1035 (94.1) 469 (89)	N/A N/A	N/A N/A	12 (2.3) 32 (2.9)	Significantly higher rate of hole closure in ILM peeling group (P < 0.001) Holes of less than 6 month duration had higher chance of successful closure (3.12 times, P < 0.001) No statistically significant difference in final VA.
Ben Simon 2004	Group I ILM peeling (16)	0.78	0.47	13 (81.0)	15 (94.0)	2 (12.5)		Total 9 (11.3)	Anatomic closure of macular

Table 1. Studies (non-randomised controlled trials, n > 50) comparing ILM peeling with no ILM peeling for full-thickness macular hole (*Continued*)

	Group II No peeling (32)	0.97	0.69	16 (50.0)	28 (87.5)	12 (37.5)	N/A 0 (0)		hole higher in ILM peeling group (P = 0.036) Difference in final VA higher in ILM peel group (P = 0.017).
Smiddy 2001	Group I Complete ILM peeling (44)	27 (68) ≥ 20/50	33 (83) > 2 lines[¥]	N/A	40 (90.9)	N/A	N/A	Total 62 (32)	No statistically significant difference in anatomic success (P = 0.08). Final VA was better in participants with more complete ILM peeling (P = 0.045).
	Group II Partial ILM peeling (83)	49 (66) ≥ 20/50	51 (69) > 2 lines[¥]	N/A	74 (89.2)	N/A	N/A		
	Group III Dissection but no ILM peeling (66)	31 (45) ≥ 20/50	47 (72) > 2 lines[¥]	N/A	65 (98.5)	N/A	N/A		
Kwok 2003	Group I ILM peeling (18)	1.00	0.64	16 (88.9)	N/A	N/A	N/A	1 (5.6)	Primary closure and final visual acuity were better in the ILM peeling group, but not statistically significant (P = 0.038 and 0.036 respectively)
	Group II No peeling (22)	0.98	0.85	13 (59.1)	N/A	N/A	N/A	0 (0)	

Table 1. Studies (non-randomised controlled trials, n > 50) comparing ILM peeling with no ILM peeling for full-thickness macular hole (*Continued*)

Tadayoni 2006	Group I ILM peeling (N/A)	N/A	N/A	N/A (100)	N/A	N/A	N/A	N/A	Primary closure was higher with ILM peeling (P = 0.009), in small holes (< 400 μm)
	Group II No peeling (N/A)	N/A	N/A	N/A (83.3)	N/A	N/A	N/A	N/A	
Terisaki 2001	Group I ILM peeling (30)	0.91	0.31	N/A	N/A	N/A	N/A	N/A	The removal of the ILM had no adverse effect on visual acuity.
	Group II ILM no peeling (19)	0.77	0.27	N/A	N/A	N/A	N/A	N/A	
Margherio 2000	Group I ILM peeling (59)	20/125	20/56	N/A	51 (86.4)	N/A	N/A	17 (28.8)	Anatomic success or visual improvement were not significantly different in the two groups (P = 0.39 and P = 0.07 respectively)
	Group II No peeling (48)	20/125	20/43	N/A	44 (91.7)	N/A	N/A	14 (29.2)	

ICG: indocyanine green
ILM: internal limiting membrane
VA: visual acuity

APPENDICES

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor Retinal Perforations
#2 macula* near/3 hole*
#3 (#1 OR #2)
#4 MeSH descriptor Vitrectomy
#5 vitrectom*
#6 PPV
#7 (#4 OR #5 OR #6)
#8 MeSH descriptor Epiretinal Membrane
#9 internal near/2 limit* near/2 membrane*
#10 ILM
#11 peel*
#12 (#8 OR #9 OR #10 OR #11)
#13 (#3 AND #7 AND #12)

Appendix 2. MEDLINE (OvidSP) search strategy

1. randomized controlled trial.pt.
2. (randomized or randomised).ab,ti.
3. placebo.ab,ti.
4. dt.fs.
5. randomly.ab,ti.
6. trial.ab,ti.
7. groups.ab,ti.
8. or/1-7
9. exp animals/
10. exp humans/
11. 9 not (9 and 10)
12. 8 not 11
13. exp retinal perforations/
14. (macula$ adj3 hole$).tw.
15. or/13-14
16. exp vitrectomy/
17. vitrectom$.tw.
18. PPV.tw.
19. or/16-18
20. Epiretinal Membrane/
21. (internal adj2 limit$ adj2 membrane$).tw.
22. ILM.tw.
23. peel$.tw.
24. or/20-23
25. 15 and 19 and 24
26. 12 and 25

The search filter for trials at the beginning of the MEDLINE strategy is from the published paper by Glanville et al (Glanville 2006).

Appendix 3. EMBASE (OvidSP) search strategy

1. exp randomized controlled trial/
2. exp randomization/
3. exp double blind procedure/
4. exp single blind procedure/
5. random$.tw.
6. or/1-5
7. (animal or animal experiment).sh.
8. human.sh.
9. 7 and 8
10. 7 not 9
11. 6 not 10
12. exp clinical trial/
13. (clin$ adj3 trial$).tw.
14. ((singl$ or doubl$ or trebl$ or tripl$) adj3 (blind$ or mask$)).tw.
15. exp placebo/
16. placebo$.tw.
17. random$.tw.
18. exp experimental design/
19. exp crossover procedure/
20. exp control group/
21. exp latin square design/
22. or/12-21
23. 22 not 10
24. 23 not 11
25. exp comparative study/
26. exp evaluation/
27. exp prospective study/
28. (control$ or prospectiv$ or volunteer$).tw.
29. or/25-28
30. 29 not 10
31. 30 not (11 or 23)
32. 11 or 24 or 31
33. retina tear/
34. (macula$ adj3 hole$).tw.
35. or/33-34
36. exp vitrectomy/
37. vitrectom$.tw.
38. PPV.tw.
39. or/36-38
40. Epiretinal Membrane/
41. (internal adj2 limit$ adj2 membrane$).tw.
42. ILM.tw.
43. peel$.tw.
44. or/40-43
45. 35 and 39 and 44
46. 32 and 45

Appendix 4. LILACS search strategy

macula$ and vitrectom$ or PPV and ILM or peel$

Appendix 5. *meta*Register of Controlled Trials search strategy

macula hole AND vitrectomy

Appendix 6. ClinicalTrials.gov search strategy

macula hole AND vitrectomy AND peel

Appendix 7. ICTRP search strategy

Vitrectomy AND Macular Hole

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Designing the review: KSC, NL, JB

Co-ordinating the review: KSC, NL

Data collection for the review: KSC, NL, NS

Designing search strategies: KSC, NL

Undertaking searches: KSC, NL

Screening search results: KSC, NL

Organising retrieval of papers: KSC, NL

Screening retrieved papers against inclusion criteria: KSC, NL

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Obtaining and screening data on unpublished studies: KSC, NL

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Providing a clinical perspective: KSC, NL, RT, MLC, UC, AK

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INDEX TERMS

Medical Subject Headings (MeSH)

Membranes [surgery]; Randomized Controlled Trials as Topic; Retina [surgery]; Retinal Perforations [*surgery]; Treatment Outcome; Visual Acuity; Vitrectomy [*methods]

MeSH check words

Humans