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


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

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To determine whether ILM peeling improves anatomical and functional outcomes of macular hole surgery when 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.
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 described four stages (1 to 4) of FTMH (Gass 1988; Johnson 1988); randomised controlled clinical trials showed that macular hole surgery is effective for stages 2, 3 and 4 (Ezra 2004; Freeman 1997; Kim 1996).

Description of the intervention
Kelly et al published the first results of vitrectomy for macular hole in 1991 (Kelly 1991). Many pre-, intra- and postoperative factors seem to influence anatomic 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 (Abdelkader 2008). Recent data from randomised controlled trials (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 myofibroblasts, 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; Such 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 (ERM), is removed (Cheng 2002; Yoooh 1996).

Why it is important to do this review
Although pars plana vitrectomy is accepted as the mainstay of treatment for FTMHs, the additional use of ILM peeling remains a matter of debate. Some surgeons reserve this manoeuvre to treat large holes, others use it routinely in all cases. Evidence is required to ascertain the benefits and potential detrimental effects of ILM peeling (Terasaki 2001) 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 when 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
We will consider randomised controlled trials (RCTs) for inclusion in this review.

Types of participants
We will include participants who have an idiopathic FTMH. There will be no restrictions with regards to age, gender or ethnicity. We will exclude patients with macular hole secondary to trauma, high myopia (defined as ≥ 6 dioptres), patients with lamellar macular hole and macular pseudohole, and any co-morbid eye and/or systemic disease affecting visual function.

Types of interventions
Macular hole surgery with ILM peeling will be compared with macular hole surgery without ILM peeling.

Types of outcome measures

Primary outcomes
1. Distance visual acuity at six months postoperatively. The review will include details of charts (ETDRS (Early Treatment Diabetic Retinopathy Study), Snellen) which were used to record visual acuity and at what distance it was done (such as four metre or two metre ETDRS charts). For the purpose of statistical analysis, we will convert visual acuity 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. 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. Cost-effectiveness: we will tabulate data on the cost-effectiveness of macular hole surgery using ILM peeling compared with the no peeling counterpart if reported in the included studies.
6. Visual-related quality of life: we will tabulate data on visual-related quality of life if reported in the included studies.
7. Adverse outcomes: we will classify the main adverse outcomes of ILM peeling into two categories: intraoperative and postoperative.

Search methods for identification of studies

Electronic searches

We will search the Cochrane Central Register of Controlled Trials (CENTRAL) (which contains the Cochrane Eyes and Vision Group Trials Register) (The Cochrane Library), MEDLINE, EMBASE, LILACS (Latin American and Caribbean Literature on Health Sciences) and the metaRegister of Controlled Trials (mRCT) (www.controlled-trials.com) and ClinicalTrials.gov (www.clinicaltrial.gov). There will be no language or date restrictions in the electronic search for trials.

See: Appendices for details of search strategies for CENTRAL (Appendix 1), MEDLINE (Appendix 2), EMBASE (Appendix 3), LILACS (Appendix 4), mRCT (Appendix 5) and ClinicalTrials.gov (Appendix 6).

Searching other resources

We will search the reference lists of the studies included in the review for information about other studies on ILM peeling in macular hole surgery. We will contact the primary investigators of identified trials for details of any additional trials. Proceedings for these conferences will be searched: 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, and World Ophthalmology Congress.

Data collection and analysis

Selection of studies

Two review authors (KSC and NL) will independently assess the titles and abstracts of all RCTs identified by electronic and manual searches. We will label each report A (definitely include), B (unsure) or C (definitely exclude). We will exclude studies labelled ‘definitely exclude’ from the review. We will assess full-text articles of abstracts labelled as ‘unsure’ according to the inclusion criteria for this review. We will contact authors of studies labelled ‘unsure’ for further clarification. We will assess studies labelled as ‘definitely include’ for methodological quality. Any differences between the two authors (KSC and NL) assessing the inclusion/exclusion of studies in this review will be resolved by discussion and if needed by having a third review author as an arbitrator.

Data extraction and management

We will seek individual patient data from all identified eligible trials. The proposed authorship includes representatives of known RCTs in this area - four recently published RCTs comparing ILM peeling with no ILM peeling in macular hole surgery (Christensen 2009; Kwok 2005; Lois 2008; Lois 2011; Tadayoni 2009). We will invite principal investigators of each RCT identified to collaborate on this review. They will be supplied with an electronic data extraction sheet and asked to supply pertinent anonymised data for every patient in the trial. We will merge all data into a specifically constructed master database for statistical analysis. From each trial, we will extract the following data: demographics, duration of the macular hole, stage (based on Gass classification (Gass 1988; Johnson 1988)) and size of the hole, lens status (phakic, pseudophakic, aphakic), baseline distance visual acuity (LogMAR), surgical details (including combined phacoemulsification and intraocular lens implantation, primary capsulotomy, ILM peeling, ERM peeling, type of gas used, type of dye used), days of posturing face-down postoperatively, postoperative hole status (open with subretinal fluid around it, open with no subretinal fluid around it, closed) after a single surgery, postoperative distance and near visual acuity at three, six and 12 months (LogMAR), intraoperative or postoperative complications and number of additional surgical interventions and type.

Assessment of risk of bias in included studies

Three authors (KSC, NL and NS) will independently assess 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). We will compare vitrectomy with and without ILM peeling with regards to the primary and secondary outcomes stated above. We will report risk of bias as ‘low risk’,...
'high risk' or 'unclear'. We will evaluate the studies for the following criteria.

1. Sequence generation: we will report the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether comparable groups have been created. If there is insufficient information about the sequence generation process to permit judgement, we will consider it as 'unclear' and contact the primary investigators for clarification.

2. Allocation concealment: we will describe the method used to conceal the allocation sequence.

3. Blinding: we will note blinding (masking) of participants (performance bias) and outcome assessors (detection bias), including whether the intended masking was achieved and effective.

4. Attrition bias: we will report incomplete outcome data. We will note the numbers in each intervention group and reasons for any exclusions. We will examine rates of follow up, reasons for lost to follow up and analysis by the intention-to-treat (ITT) principle. We will consider a trial to have been analysed by ITT if it analysed all participants that were randomised, including those who received only part or none of the intended treatment.

5. Reporting bias: we will assess the potential impact of selective outcome reporting.

If any of the above domains is graded as 'unclear', we will contact the investigators of the published eligible RCTs in order to obtain additional information. In the event of failure to communicate with the study investigators or failure to respond within a reasonable time period, we will assess the methodological quality of that trial based on the available information. We will resolve any disagreements on the above assessments between the authors through discussion until a consensus is reached.

**Measures of treatment effect**

Dichotomous data: we will summarise as risk ratios or odds ratios, and will include:

- number of eyes (and odds of) achieving 3 line ETDRS (or corresponding logMAR) visual acuity improvement in both groups (ILM peel versus non-ILM peel);
- number of eyes (and odds of) achieving 0.3 logMAR or better vision (6/12 or better on Snellen chart) in both groups (ILM peel versus non-ILM peel);
- odds of having successful hole closure with one procedure (open versus closed FTMH in ILM peel group versus control);
- relative risk of developing complications from ILM peel (adverse outcomes); and
- relative risk of needing more than one surgical procedure for macular hole closure.

Continuous data: we will summarise as a mean difference, and will include:

- difference in mean visual acuity between ILM peel group and non-ILM peel group; and
- difference in mean quality of life between ILM peel group and control group.

We will calculate standardised mean difference when outcomes are measured on different scales.

**Time-to-event data:** no meta-analyses are planned.

**Unit of analysis issues**

We will review studies where eyes rather than participants are the unit of randomisation in detail, such that only the eye that was randomised for the study will be included in the analysis. This will reduce the risk of sequence generation bias and ensure data with appropriate randomisation to be analysed.

**Dealing with missing data**

We will conduct a complete case analysis as the primary analysis.

We will contact primary investigators for missing data.

**Assessment of heterogeneity**

We will test for heterogeneity by looking at the overlap in confidence intervals of the forest plot, and using the Q test and the I² statistic. We will use the I² statistic to assess the proportion of total variability explained by heterogeneity between studies.

**Assessment of reporting biases**

We will assess sequence generation, allocation concealment, masking of participants and outcome assessors, incomplete outcome data, selective outcome reporting and other potential sources of bias as above. We will overcome reporting bias by maximising our search strategy to include research that has been published in different languages as well as unpublished research. If appropriate, we will investigate publication bias by looking at a funnel plot of the data. We will document masking methods, sequence generation, allocation concealment techniques and any incomplete data. Where any information is unclear, we will contact the primary investigators for clarification.

**Data synthesis**

We will perform data analysis according to the guidelines set out in Chapter 9 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b).

The primary meta-analysis will be a random-effects model.

We plan a two-stage approach, where outcomes are analysed in their original trial following which the individual trial results are combined in a meta-analysis to give an overall measure of effect. Where individual patient data (IPD) are received, we will analyze each study separately and extract appropriate data for inclusion
in standard meta-analyses. If IPD are received for all studies, we will consider a more sophisticated analysis approach including adjustment for relevant patient characteristics. We will use Stata software or SPSS if an IPD analysis is undertaken. If it proves impossible to perform a formal meta-analysis we will undertake a narrative review of the available evidence.

Subgroup analysis and investigation of heterogeneity

We will undertake subgroup analyses based on:

- baseline distance vision;
- stage of the macular hole (stage 2, 3 or 4, Gass Classification (Gass 1988));
- size of the macular hole (classified as continuous data in micrometres); and
- duration of the hole (defined as more than or less than one year).

Sensitivity analysis

We will examine the impact of excluding studies with lower risk of bias, unpublished data and industry-funded data in sensitivity analyses.

ACKNOWLEDGEMENTS

We would like to thank the Cochrane Eyes and Vision Group (CEVG) for their assistance in preparing this protocol. We thank James Bainbridge and Catey Bunce for their comments on this protocol.

REFERENCES

Additional references

Abdelkader 2008

Allen 1998

Brooks 2000

Cheng 2002

Christensen 2009

Eckardt 1997

Ezra 2004

Freeman 1997

Gass 1988

Gass 2003

Glanville 2006

Higgins 2011a
Higgins 2011b

Johnson 1988

Kelly 1991

Kim 1996

Kwok 2001

Kwok 2005

Li 2002

Lim 2000

Lois 2008

Lois 2011

McCannel 2009

Sach 2000

Smiddy 2001

Tadayoni 2009

Terasaki 2001

Yoooh 1996

* Indicates the major publication for the study

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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 (OVID) 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/
15. or/13-14
16. exp vitrectomy/
17. vitrectom$.tw.
18. PPV.tw.
19. or/16-18
20. Epiretinal Membrane/
22. ILM.tw.
23. peel$.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 (OVID) search strategy

1. exp randomized controlled trial/
2. exp randomization/
3. exp double blind procedure/
4. exp single blind procedure/
5. random$.tw.
6. or/1-5
7. (animal or animal experiment).sh.
8. human.sh.
9. 7 and 8
10. 7 not 9
11. 6 not 10
12. exp clinical trial/
14. ((singl$ 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. metaRegister of Controlled Trials search strategy
macula hole AND vitrectomy

Appendix 6. ClinicalTrials.gov search strategy
macula hole AND vitrectomy AND peel

HISTORY
Protocol first published: Issue 9, 2011

CONTRIBUTIONS OF AUTHORS
Conceiving the review: NL, JB
Designing the review: KSC, NL, JB
Co-ordinating the review: KSC, NL
Data collection for the review
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
Appraising quality of papers: KSC, NL
Extracting data from papers: KSC, NL
Writing to authors of papers for additional information: KSC, NL
Providing additional data about papers: KSC, NL
Obtaining and screening data on unpublished studies: KSC, NL
Data management for the review
Entering data into RevMan: KSC, NL
Analysis of data: NS, JC, CB
Interpretation of data
Providing a methodological perspective: KSC, NL, NS, JB, JC
Providing a clinical perspective: KSC, NL, RT, MLC, UC, AK
Providing a policy perspective: NL, JB, JC
Providing a consumer perspective: NL, RT, MLC, UC, AK
Writing the review: KSC, NL
Draft the final review: KSC, NL, NS
Providing general advice on the review: KSC, NL, NC, JB, JC, CB, RT, MLC, UC, AK
Securing funding for the review: KSC, NL

**DECLARATIONS OF INTEREST**
None declared. No conflict of interest or financial interest.

**SOURCES OF SUPPORT**

**Internal sources**
- NHS Grampian Endowment Fund, UK.
  Application has been made to NHS Grampian Endowment Fund

**External sources**
- No sources of support supplied