Cochrane Library

Cochrane Database of Systematic Reviews

Surgery for idiopathic epiretinal membrane (Protocol)

Yusuf A, Bizrah M, Bunce C, Bainbridge JW

Yusuf A, Bizrah M, Bunce C, Bainbridge JW.
Surgery for idiopathic epiretinal membrane.
Cochrane Database of Systematic Reviews 2019, Issue 4. Art. No.: CD013297.
DOI: 10.1002/14651858.CD013297.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Protocol]

Surgery for idiopathic epiretinal membrane

Ammar Yusuf[1], Mukhtar Bizrah[1], Catey Bunce[2], James W Bainbridge[1]

[1]UCL Institute of Ophthalmology, London, UK. [2]School of Population Health & Environmental Sciences, Faculty of Life Sciences & Medicine, King's College London, London, UK

Contact address: James W Bainbridge, UCL Institute of Ophthalmology, 11-43 Bath Street, London, EC1V 9EL, UK. j.bainbridge@ucl.ac.uk.

Editorial group: Cochrane Eyes and Vision Group.
Publication status and date: New, published in Issue 4, 2019.

Citation: Yusuf A, Bizrah M, Bunce C, Bainbridge JW. Surgery for idiopathic epiretinal membrane. *Cochrane Database of Systematic Reviews* 2019, Issue 4. Art. No.: CD013297. DOI: 10.1002/14651858.CD013297.

ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To determine the effects of surgery compared to no intervention for epiretinal membrane.

BACKGROUND

Epiretinal membrane (ERM) is a sheet of fibrocellular tissue that develops on the inner surface of the retina. The condition affects 7% of people overall and approximately 20% of people older than 75 years (Folk 2016). Its prevalence varies according to ethnic origin (Aung 2013). Our aim is to determine the value of surgical intervention for ERM by identifying evidence of its outcomes compared to the natural history of the condition.

Description of the condition

Epiretinal membrane can develop as a consequence of pre-existing ocular conditions (including trauma, retinal detachment, inflammation and retinal vascular disease) or therapeutic intervention (including laser or cryo-retinopexy and surgery). Idiopathic, or primary, ERM occurs in the absence of any identified pre-existing condition but may develop as a consequence of anomalous age-related separation of the aging vitreous from the retina (Bu 2014). Epiretinal membranes are comprised of a variety of cell types (including glia, hyalocytes, macrophages, fibroblasts and myofibroblasts) and extracellular matrix containing collagenous fibrils. Gradually progressive contraction of the membrane causes thickening and distortion of retinal architecture, with consequent impairment of sight (McDonald 2006), though the relationship between structure and function is not consistent. The severity of the condition and its impact on vision range from mild and asymptomatic to progressively disabling impairment of visual acuity, binocular fusion and stereopsis (Smiddy 1989).

Description of the intervention

The intervention is removal of the ERM by peeling it surgically from the inner retinal surface, having gained safe access to the retina by pars plana vitrectomy (Kwok 2005). This can result in improvement of visual acuity (Dawson 2014).
Several modifications have been developed to improve the outcomes of surgery. To minimise recurrent ERM owing to proliferation of residual cellular elements not apparent during surgery, the inner limiting membrane (ILM) of the retina may also be removed from the inner retinal surface. To facilitate the complete and safe removal of ERM and ILM, vital dyes may be used in-

traoperatively to enhance their visibility to the operating surgeon. To protect against harm from intraocular inflammation following surgery, various anti-inflammatory medications may be administered perioperatively (Donati 1998).

Surgical intervention involving vitrectomy predictably promotes the development of cataract, and presents a risk of lasting harm to sight owing to other adverse events including retinal detachment, intraocular infection, intraocular haemorrhage, macular oedema and secondary glaucoma. The indication for surgical intervention is conventionally considered to be disabling impairment of sight, though this is poorly defined.

How the intervention might work

Surgical removal of ERM may improve the outcomes by relieving the abnormal tractional forces that distort retinal architecture, and consequently promoting healthy vision.

The potential benefit of the intervention is improved quality of life by improving and/or protecting high-quality eyesight (Ghazi-Nouri 2006).

Why it is important to do this review

High-quality evidence is critical to determine whether surgery for ERM improves the outcomes (Grewing 1996). Our aim is to determine the value of surgical intervention for ERM by comparing its outcomes with the natural history of the condition.

We do not propose to investigate the value of modifications to the surgical technique. The value of these technical modifications is secondary to the value of the surgical intervention itself.

OBJECTIVES

To determine the effects of surgery compared to no intervention for epiretinal membrane.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials (RCTs) in this review.

Types of participants

We will include individuals identified as having idiopathic epiretinal membrane (ERM).

Types of interventions

Intervention: surgical intervention (vitrectomy plus ERM peel).

Comparator: no intervention or sham intervention.

Types of outcome measures

Primary outcomes

- Mean change in best corrected visual acuity in the study eye between baseline (before randomisation), six months, and 12 months later, as measured by a logMAR chart at a starting distance of 4 m.

Secondary outcomes

- Proportion of people with a gain of 0.3 logMAR of uncorrected visual acuity in the study eye, as measured by a logMAR chart at a starting distance of 4 m, at six months and 12 months after randomisation.
- Proportion of people with a loss of 0.3 logMAR of uncorrected visual acuity in the study eye, as measured by a logMAR chart at a starting distance of 4 m, at six months and 12 months after randomisation.
- Mean quality-of-life score at six months and 12 months following surgery, measured using a validated questionnaire.
- Any harm identified during follow-up.

Search methods for identification of studies

Electronic searches

The Cochrane Eyes and Vision Information Specialist will search the following electronic databases. There will be no restrictions on language or year of publication.

- Cochrane Central Register of Controlled Trials (CENTRAL) (which contains the Cochrane Eyes and Vision Trials Register) in the Cochrane Library (latest issue) (Appendix 1).
- MEDLINE Ovid (1946 to present) (Appendix 2).
- Embase Ovid (1980 to present) (Appendix 3).
- ISRCTN registry (www.isrctn.com/editAdvancedSearch) (Appendix 4).
- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov) (Appendix 5).

- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp) (Appendix 6).

Searching other resources

We will use the Science Citation Index to find studies that have cited the individual trials. We will contact relevant pharmaceutical companies for any clinical trials information that has not been released for publication. We will not handsearch conference proceedings or journals specifically for the review.

Data collection and analysis

Selection of studies

Two review authors will independently carry out the study selection from the results of searches (titles and abstracts) to identify relevant studies. We will divide studies into 'definitely include', 'definitely exclude', and 'possibly include' categories, and disagreements will be resolved by discussion or consultation (or both) with a third review author. In general, all citations considered irrelevant at this stage will not be documented in the review, other than to note the number of these in a flow chart.

We will obtain full-text copies of potentially relevant trials. We will make a final judgement regarding the inclusion or exclusion of studies in the 'possibly include' category after obtaining the full-text of each of these articles. Where necessary, we will obtain translations of abstracts and full-text articles into English before making a final decision. We will take care to identify multiple reports of the same study.

Review authors will not be masked with respect to study authors, institution or journal, and we will correspond with study authors to clarify study eligibility, as appropriate.

Data extraction and management

See Appendix 7.

Two review authors will extract data independently using an online form developed by Cochrane Eyes and Vision (Covidence). We will resolve discrepancies by discussion. We will contact trial investigators for missing data. All data will be imported directly into Review Manager 5 (Review Manager 2014) and the accuracy of the data import will be checked by one author.

Assessment of risk of bias in included studies

Two review authors will independently assess the risk of bias in the included studies using Cochrane's 'Risk of bias' tool, as described in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2017).

We will grade each domain as low risk of bias, high risk of bias, or unclear (lack of information or uncertainty of potential for bias). We will contact trial investigators for clarification of parameters graded as 'unclear'.

We will resolve disagreements by discussion.

We will specifically consider and report on the following sources of bias.

- Selection bias (random sequence generation, allocation concealment): was the sequence of allocation generated using a random procedure and was the allocation concealed to people recruiting/enrolling participants and to participants?
- Performance bias (masking of participants and researchers): were the recipients of care unaware of their assigned intervention? Were persons providing care unaware of the assigned intervention?
- Detection bias (masking of outcome assessors): were persons evaluating outcomes unaware of the assigned intervention?
- Attrition bias: were the rates of follow-up and compliance similar in the groups? Was the analysis by intention-to-treat and were there any post-randomisation exclusions?
- Selective outcome reporting bias: is there any evidence that the outcomes that were measured were not reported?

Measures of treatment effect

We will calculate the mean difference for the following continuous outcomes.

- Mean change in best corrected visual acuity between baseline (before surgery) and 12 months later, as measured by a logMAR chart.
- Mean quality-of-life score at 12 months following surgery, measured using a validated questionnaire.

Where possible, we will check for the skewness of continuous data (Altman 1996).

We will calculate the risk ratio for the following dichotomous outcomes.

- Proportion of people with a gain of 0.3 logMAR lines of uncorrected visual acuity, as measured by a logMAR chart at six months and 12 months after randomisation.
- Proportion of people with a loss of 0.3 logMAR lines of uncorrected visual acuity, as measured by a logMAR chart at six months and 12 months after randomisation.

We will compute odds ratios for adverse events, as these are relatively good approximations when risks are rare (less than 10%). However, if the included studies reported a variety of adverse events and only one trial reported each type, we will simply collate this information.

Unit of analysis issues

We do not anticipate any unit of analysis issues with respect to eyes, because ERM is usually uniocular or affects eyes asymmetrically

and therefore people will be randomised to treatment and one eye per person treated and reported.

Dealing with missing data

If possible, we will conduct an intention-to-treat (ITT) analysis. We will use imputed data if computed by the trial investigators using an appropriate method, but will not impute missing data ourselves.
If ITT data are not available, we will do an available case analysis. This assumes that data are missing completely at random. We will assess whether this assumption is reasonable by collecting data from each included trial on the number of participants excluded or lost to follow-up, and reasons for loss to follow-up by treatment group, if reported.

Assessment of heterogeneity

We will examine the overall characteristics of the studies, in particular the type of participants and types of interventions, to assess the extent to which the studies are similar enough to make pooling of study results sensible.
We will look at the forest plots of study results to see how consistent the results of the studies are, considering in particular the size and direction of effects.
We will calculate the I^2, which is the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance) (Higgins 2002). We will consider I^2 values over 50% to indicate substantial inconsistency, but will also consider the Chi^2 P value. As this may have low power when the number of studies are few, we will consider a P value of less than 0.1 to indicate statistical significance of the Chi^2 test.

Assessment of reporting biases

We will use the applicable domain of the 'Risk of bias' tool (i.e. risk of selective outcome reporting bias) to look for selective or incomplete reporting.

Data synthesis

We will pool data using a random-effects model in Review Manager 5.3 (Review Manager 2014). If there are fewer than three trials in a comparison we will use a fixed-effect model.
If there is inconsistency between individual study results such that a pooled result may not be a good summary of the individual trial results - for example, the effects are in different directions or the I^2 value is above 50% and P value less than 0.1 - we will not pool the data but will describe the pattern of the individual study results.
If there is statistical heterogeneity but all the effect estimates are in the same direction, such that a pooled estimate would seem to provide a good summary of the individual trial results, we may pool the data.

Subgroup analysis and investigation of heterogeneity

We do not intend to perform subgroup analyses.

Sensitivity analysis

We do not intend to perform sensitivity analyses.

Summary of findings

We will prepare a 'Summary of findings' table presenting relative and absolute risks. Two review authors will independently grade the overall quality of the evidence for each outcome, using the GRADE classification (GRADEpro GDT 2015).

ACKNOWLEDGEMENTS

Cochrane Eyes and Vision (CEV) will create and execute the electronic search strategies. We thank David Steel and Jennifer Evans for their comments, and Anupa Shah for her assistance throughout the review process.

REFERENCES

Additional references

Altman 1996
Altman DG, Bland JM. Detecting skewness from summary information. *BMJ* 1996;**313**(7066):1200.

Aung 2013
Aung KZ, Makeyeva G, Adams MK, Chong EW, Busija L, Giles GG, et al. The prevalence and risk factors of epiretinal membranes: the Melbourne Collaborative Cohort Study. *Retina* 2013;**33**(5):1026–34.

Bu 2014
Bu SC, Kuijer R, Li XR, Hooymans JM, Los LI. Idiopathic epiretinal membrane. *Retina* 2014;**34**(12):2317–35.

Covidence [Computer program]
Veritas Health Innovation. Covidence. Melbourne, Australia: Veritas Health Innovation, accessed prior to 13 February 2019.

Dawson 2014
Dawson SR, Shunmugam M, Williamson TH. Visual acuity outcomes following surgery for idiopathic epiretinal

membrane: an analysis of data from 2001 to 2011. *Eye* 2014;**28**(2):219–24.

Donati 1998
Donati G, Kapetanios AD, Pournaras CJ. Complications of surgery for epiretinal membranes. *Graefe's Archive for Clinical and Experimental Ophthalmology* 1998;**236**(10): 739–46.

Folk 2016
Folk JC, Adelman RA, Flaxel CJ, Hyman L, Pulido JS, Olsen TW. Idiopathic epiretinal membrane and vitreomacular traction preferred practice pattern (®) guidelines. *Ophthalmology* 2016;**123**(1):P152–81.

Ghazi-Nouri 2006
Ghazi-Nouri SM, Tranos PG, Rubin GS, Adams ZC, Charteris DG. Visual function and quality of life following vitrectomy and epiretinal membrane peel surgery. *British Journal of Ophthalmology* 2006;**90**(5):559–62.

Glanville 2006
Glanville JM, Lefebvre C, Miles JN, Camosso-Stefinovic J. How to identify randomized controlled trials in MEDLINE: ten years on. *Journal of the Medical Library Association* 2006; **94**(2):130–6.

GRADEpro GDT 2015 [Computer program]
accessed prior to 13 February 2019. GRADEpro GDT. Version McMaster University (developed by Evidence Prime). Hamilton (ON): accessed prior to 13 February 2019, 2015.

Grewing 1996
Grewing R, Mester U. Results of surgery for epiretinal membranes and their recurrences. *British Journal of Ophthalmology* 1996;**80**(4):323–6.

Higgins 2002
Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Statistics in Medicine* 2002;**21**(11):1539–58.

Higgins 2017
Higgins JPT, Altman DG, Sterne JAC, editor(s). Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Churchill R, Chandler J, Cumpston MS, editor (s), Cochrane Handbook for Systematic Reviews of Interventions version 5.2.0 (updated June 2017), Cochrane, 2017. Available from www.training.cochrane.org/handbook.

Kwok 2005
Kwok AKh, Lai TY, Yuen KS. Epiretinal membrane surgery with or without internal limiting membrane peeling. *Clinical and Experimental Ophthalmology* 2005;**33**(4): 379–85.

McDonald 2006
McDonald HR, Johnson RN, Ai E, Jumper JM, AD Fu. *Macular Epiretinal Membranes*. Missouri: Elsevier Inc, 2006.

Review Manager 2014 [Computer program]
Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager 5 (RevMan 5). Version 5.3. Copenhagen: Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Smiddy 1989
Smiddy WE, Maguire AM, Green WR, Michels RG, de la Cruz Z, Enger C, et al. Idiopathic epiretinal membranes. Ultrastructural characteristics and clinicopathologic correlation. *Ophthalmology* 1989;**96**(6):811–20.

* *Indicates the major publication for the study*

APPENDICES

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor: [Epiretinal Membrane] this term only
#2 epiretinal near/2 membrane*
#3 ERM
#4 membrane* near/2 (epimacular or premacular or preretinal)
#5 cellophane near/2 (maculopath* or retinopath*)
#6 premacular fibrosis
#7 macular pucker*
#8 (retina* or retinopath*) near/2 wrinkl*
#9 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8
#10 MeSH descriptor: [Vitrectomy] explode all trees
#11 vitrectom*
#12 PPV
#13 (ILM or membrane) near/2 peel*

#14 foveal near/2 spar*
#15 #10 or #11 or #12 or #13 or #14
#16 #9 and #15

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. Epiretinal Membrane/
14. (epiretinal adj2 membrane$).tw.
15. ERM.tw.
16. (membrane$ adj2 (epimacular or premacular or preretinal)).tw.
17. (cellophane adj2 (maculopath$ or retinopath$)).tw.
18. premacular fibrosis.tw.
19. macular pucker$.tw.
20. ((retina$ or retinopath$) adj2 wrinkl$).tw.
21. or/13-20
22. exp vitrectomy/
23. vitrectom$.tw.
24. PPV.tw.
25. ((ILM or membrane) adj2 peel$).tw.
26. (foveal adj2 spar$).tw.
27. or/22-26
28. 21 and 27
29. 12 and 28

The search filter for trials at the beginning of the MEDLINE strategy is from the published paper by 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$.tw.
6. or/1-5
7. (animal or animal experiment).sh.
8. human.sh.
9. 7 and 8
10. 7 not 9
11. 6 not 10
12. exp clinical trial/
13. (clin$ 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$).tw.
29. or/25-28
30. 29 not 10
31. 30 not (11 or 23)
32. 11 or 24 or 31
33. epiretinal membrane/
34. (epiretinal adj2 membrane$).tw.
35. ERM.tw.
36. (membrane$ adj2 (epimacular or premacular or preretinal)).tw.
37. (cellophane adj2 (maculopath$ or retinopath$)).tw.
38. premacular fibrosis.tw.
39. macular pucker$.tw.
40. ((retina$ or retinopath$) adj2 wrinkl$).tw.
41. or/33-40
42. exp vitrectomy/
43. vitrectom$.tw.
44. PPV.tw.
45. ((ILM or membrane) adj2 peel$).tw.
46. (foveal adj2 spar$).tw.
47. or/42-46
48. 41 and 47
49. 32 and 48

Appendix 4. ISRCTN search strategy

epiretinal membrane OR epimacular membrane OR premacular membrane OR preretinal membrane) AND vitrectomy

Appendix 5. ClinicalTrials.gov search strategy

(epiretinal membrane OR epimacular membrane OR premacular membrane OR preretinal membrane OR macular pucker) AND vitrectomy

Appendix 6. WHO ICTRP search strategy

epiretinal membrane AND vitrectomy OR epimacular membrane AND vitrectomy OR premacular membrane AND vitrectomy OR preretinal membrane AND vitrectomy OR macular pucker AND vitrectomy

Appendix 7. Data on study characteristics

Mandatory items		**Optional items**
Methods		
Study design	· **Parallel group RCT**	Exclusions after randomisation Losses to follow up Number randomised/analysed How were missing data handled? *e.g., available case analysis, imputation methods* Reported power calculation (Y/N*), if yes, sample size and power* Unusual study design/issues
Eyes *or* Unit of randomisation/ unit of analysis	· **One eye included in study** - Epiretinal membrane (ERM) is usually uniocular or affects eyes asymmetrically. Paired (where one eye is treated with one intervention and the fellow eye receives the comparator) and cluster (where both eyes of a participant receive the same intervention) will not be included	
Participants	We will include individuals identified as having idiopathic EPR	
Country	*This information should be collected for total study population recruited into the study. If these data are only reported for the people who were followed up only, please indicate.*	Setting Ethnic group Equivalence of baseline characteristics (Y/
Total number of participants		
Number (%) of men and women		
Average age and age range		
Inclusion criteria		
Exclusion criteria		
Interventions		
Intervention (n=) Comparator (n=) ***See MECIR 65 and 70***	· Number of people randomised to this group · Drug (or intervention) name · Dose · Frequency · Route of administration	
Outcomes		

(*Continued*)

Primary and secondary outcomes *as defined in study reports* ***See MECIR R70***	List outcomes Adverse events reported (Y/N) Length of follow up and intervals at which outcomes assessed	Planned/actual length of follow up
Notes		
Date conducted	Specify dates of recruitment of participants mm/yr to mm/yr	Full study name: *(if applicable)* Reported subgroup analyses (Y/N) Were trial investigators contacted?
Sources of funding		
Declaration of interest ***See MECIR 69***		

CONTRIBUTIONS OF AUTHORS

JB, AY and MB developed the protocol. CB reviewed the protocol and the statistical section.

DECLARATIONS OF INTEREST

AY: no known conflicts of interest to declare.

MB: no known conflicts of interest to declare.

CB: no known conflicts of interest to declare.

JB: no known conflicts of interest to declare.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- National Institute for Health Research, UK.
- Richard Wormald, Co-ordinating Editor for the Cochrane Eyes and Vision Group (CEVG) acknowledges financial support for his CEVG research sessions from the Department of Health through the award made by the NIHR to Moorfields Eye Hospital NHS Foundation Trust and UCL Institute of Ophthalmology for a Specialist Biomedical Research Centre for Ophthalmology.
- This protocol was supported by the NIHR, via Cochrane Infrastructure funding to the CEV UK editorial base.

The views expressed in this publication are those of the authors and not necessarily those of the NIHR, NHS, or the Department of Health.