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[Intervention Review]

Surgery for idiopathic epiretinal membrane

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ABSTRACT

Background

Epiretinal membrane is an abnormal sheet of avascular fibrocellular tissue that develops on the inner surface of the retina. Epiretinal membrane can cause impairment of sight as a consequence of progressive distortion of retinal architecture.

Objectives

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

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE Ovid, Embase Ovid, ISRCTN registry, US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov, and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP). There were no restrictions to language or year of publication. The databases were last searched on 20 May 2020.

Selection criteria

We included randomised controlled trials (RCTs) assessing surgical removal of idiopathic epiretinal membrane compared to placebo, no treatment or sham treatment. Paired or within-person studies were included, as well as those where both eyes of a single participant were treated.

Data collection and analysis

We used standard methods expected by Cochrane, and assessed certainty using the GRADE system. We considered the following five outcome measures: mean change in best corrected visual acuity (BCVA) in the study eye between baseline (before randomisation), 6 months and 12 months later; proportion of people with a gain of 0.3 logMAR or more of visual acuity in the study eye as measured by a logMAR chart at a starting distance of 4 m at 6 months and 12 months after randomisation; proportion of people with a loss of 0.3 logMAR or more of visual acuity in the study eye as measured by a logMAR chart at a starting distance of 4 m at 6 months and 12 months after randomisation; mean quality of life score at 6 months and 12 months following surgery, measured using a validated questionnaire; and any harm identified during follow-up.

Main results

We included one study in the review. This was a RCT including 53 eyes of 53 participants with mild symptomatic epiretinal membrane and BCVA of 65 or more Early Treatment Diabetic Retinopathy Study (ETDRS) letters. Participants were randomly allocated to immediate surgery or to watchful waiting with deferred surgery if indicated by evidence of disease progression. The study was limited by imprecision owing to the small number of participants and was at some risk of bias owing to inconsistencies in the time points for outcome assessment and in the management of lens opacity.

At 12 months, the visual acuity in the immediate surgery group was higher by a mean of 2.1 (95% confidence interval (CI) -2.0 to 6.2 ETDRS letters; 53 participants; low-certainty evidence) than the watchful waiting/deferred surgery group.

The evidence of the effect of immediate surgery on gains of 0.3 logMAR or more of visual acuity is very uncertain (risk ratio (RR) 0.55, 95% CI 0.06 to 4.93; 53 participants; very low-certainty evidence).

At 12 months, no participant in either group sustained a loss of 0.3 logMAR or more of visual acuity (53 participants; low-certainty evidence).

The included study did not measure quality of life.

At 12 months, no serious adverse event was identified in any participant. One participant developed chronic minimal cystoid macular oedema following immediate surgery (53 participants; low-certainty evidence).

Authors' conclusions

We found no RCT that directly investigated the effect of surgery compared to no intervention. For severe disabling epiretinal membrane, the lack of a RCT comparing surgery to no intervention may reflect evidence from non-randomised studies in favour of surgery; a RCT may be considered unnecessary and ethically unacceptable because a superior effect of surgery is widely accepted. For mild symptomatic epiretinal membrane, however, the value of surgery is uncertain. Low-certainty evidence from this review suggests that watchful waiting or deferred surgery may offer outcomes as favourable as immediate surgery. However, this finding needs to be confirmed in further RCTs with appropriate statistical power, masking of treatment allocation, consistent management of cataract, and measurement of outcomes including patient-reported quality of life over a more extended time frame.

PLAIN LANGUAGE SUMMARY

What are the benefits and risks of surgery for epiretinal membrane (a disease of the eye)?

Why is this question important?
An epiretinal membrane is an abnormal layer of tissue that develops at the back of the eye. It affects around one in five people aged 75 years and older. In most people, the development of an epiretinal membrane is linked to the normal ageing processes in the eye and is described as 'idiopathic'. In other instances, epiretinal membrane is caused by a pre-existing condition affecting the retina, such as inflammation or poor circluation. Epiretinal membrane can also develop after eye surgery.

Epiretinal membrane typically forms over the part of the eye responsible for seeing fine detail (the macula). In some people, this does not affect vision. In others, it causes distorted or blurred vision, which can affect people's quality of life. For example, an epiretinal membrane may impair people's ability to read or drive.

If an epiretinal membrane affects vision, it is commonly removed by surgery. A local anaesthetic (medication) is used to numb the eye area. As with any procedure, this surgery carries risks of harm from side effects. These include potential problems such as cataract, detached retina, infection and bleeding in the eye.

To understand when the benefits of surgery outweigh its risks, we reviewed the research evidence.

How did we identify and evaluate the evidence?
First, we searched the medical literature for studies:

- in which epiretinal membrane was not caused by a pre-existing condition or surgery;

- that compared the effects of surgery against no surgery or a placebo (sham) procedure; and

- where people were randomly assigned to one of two groups: a group that underwent surgery for epiretinal membrane, and a group that did not have surgery for epiretinal membrane.

We then summarised the evidence and rated our confidence in it, based on factors such as study methods and size.

What did we find?
We found only one study that met our criteria. This study took place in Denmark and included 53 people who had epiretinal membranes causing mild impairment of sight. Participants were randomly assigned to one of two groups. Those in one group had immediate surgery. Those in the other group were watched closely and in the event of any deterioration in their condition were invited to have surgery. People in both groups were followed up for one year.

The study results suggest that immediate surgery for epiretinal membrane causing mild impairment of sight:

- may not benefit vision 12 months after surgery; and

- may not lead to serious unwanted effects. One person treated with immediate surgery experienced an unwanted effect that was not considered serious. This was the development of an eye condition caused by fluid building up at the back of the eye.

The study did not investigate the impact of surgery on participants' quality of life.

How confident are we in the evidence?
We are not confident in the evidence, because:

- it is based on one small study; and

- some of the methods used by the researchers who conducted it may have introduced errors in its results.

What does this mean?
For epiretinal membrane causing severe disabling impairment of sight, we found no carefully-controlled study that measured the effect of surgery. For severe epiretinal membrane, surgery is widely considered to improve the outcome and is routine practice. A carefully controlled trial comparing surgery to no treatment is considered unecessary and ethically inappropriate.

For epiretinal membrane causing mild impairment of sight, however, the effect of surgery is uncertain. There is some evidence that the outcome of watchful waiting may be as good as the effect of immediate surgery. However, the evidence is not strong enough to draw firm conclusions. Further studies that use robust methods and measure outcomes including quality of life in the longer term would help to determine effect of surgery with more confidence.

How up-to-date is this review?
The evidence in this Cochrane Review is current to May 2020.

SUMMARY OF FINDINGS

Summary of findings 1. Surgery compared with no surgery for epiretinal membrane

Surgery compared with no surgery for epiretinal membrane

Patient or population: people with epiretinal membrane

Settings: eye hospital

Intervention: surgery

Comparison: no surgery (watchful waiting/deferred surgery)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Watchful waiting/deferred surgery	Surgery (immediate surgery)				
Mean change in VA assessed with: ETDRS letters read at 4 m (more letters read = better vision) Scale from: -50 to 50 follow-up: 12 months	VA improved by 3.1 ETDRS letters in the control group (95% CI 0.3 to 5.8 letters)	The mean change in VA was 2.1 ETDRS letters better in the immediate surgery group (2 letters worse to 6.2 letters better) compared with the no surgery group (watchful waiting/deferred surgery)		53 (1 RCT)	⊕⊕⊖⊖ **low** [a]	-
Proportion of eyes with gain in VA by 0.3 logMAR or greater assessed with: ETDRS letters at 4 m follow-up: 12 months	90 per 1,000	50 per 1,000 (5 to 444)	RR 0.55 (0.06 to 4.93)	53 (1 RCT)	⊕⊖⊖⊖ **very low** [b]	-
Proportion of eyes with loss in VA by 0.3 logMAR or greater assessed with: ETDRS letters at 4 m follow-up: 12 months	No participant in either group sustained a loss of 0.3 logMAR or greater VA at 12 months.				⊕⊕⊖⊖ **low** [c]	-
Quality of life	This outcome was not measured.				NA	-
Adverse effects	The authors reported no serious adverse effect in any participant. One participant developed chronic minimal cystoid macular oedema.				⊕⊕⊖⊖ **low** [3]	-

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **ETDRS:** Early Treatment of Diabetic Retinopathy Study; **RR:** risk ratio; **VA:** visual acuity; **NA:** not applicable.

GRADE Working Group grades of evidence
High-certainty: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate-certainty: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low-certainty: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low-certainty: We are very uncertain about the estimate.

[a]Downgraded one level for risk of bias (because the time points for outcome assessment and the management of lens opacity were inconsistent between the treatment groups) and one level for imprecision (95% confidence intervals include 0, no effect).
[b]Downgraded one level for risk of bias (because the time points for outcome assessment and the management of lens opacity were inconsistent between the treatment groups) and two levels for imprecision (very wide confidence intervals include 1, no effect).
[c]Downgraded one level for risk of bias (because the time points for outcome assessment and the management of lens opacity were inconsistent between the treatment groups) and one level for imprecision (the study was underpowered to consider rare outcomes).

BACKGROUND

Description of the condition

Epiretinal membrane is an abnormal sheet of avascular fibrocellular tissue that develops on the inner surface of the retina. Epiretinal membrane affects 7% of people overall and is increasingly common with age, affecting approximately 20% of people older than 75 years (Aung 2013; Folk 2016). 'Idiopathic' epiretinal membrane occurs in the absence of any identified pre-existing condition, possibly as a consequence of anomalous separation of the ageing vitreous from the retina (Bu 2014). Secondary epiretinal membrane results from pre-existing ocular conditions including inflammation, retinal vascular disease, retinal tear and trauma. Epiretinal membranes are comprised histologically of several cell types (including glia, hyalocytes, macrophages, fibroblasts and myofibroblasts) and extracellular matrix components including collagen.

Epiretinal membrane can cause impairment of sight as a consequence of progressive contraction that causes thickening and distortion of the underlying neurosensory retina (McDonald 2006). Idiopathic epiretinal membrane can be stable or progressive. The severity of the condition and its impact on vision range from mild and asymptomatic to progressively severe, causing disabling impairment of visual acuity, binocular fusion and stereopsis (McDonald 2006; Smiddy 1989), and adversely affecting quality of life. Mild epiretinal membrane can resolve spontaneously in a small minority (3% per year) (Byon 2015).

Description of the intervention

Conventional intervention involves surgical removal of the epiretinal membrane from the surface of the inner retina (Kwok 2005). The aim is to improve the outcome for vision by protecting against harm from progressive disease and by promoting restoration of normal retinal anatomy.

To improve the outcomes of surgery, several modifications of the surgical technique have been developed. To minimise recurrence of epiretinal membrane owing to proliferation of residual cellular elements not evident during surgery, the inner limiting membrane of the retina may also be removed from its surface. To facilitate the complete and safe removal of epiretinal membrane and inner limiting membrane, vital dyes may be used intraoperatively to enhance their visibility to the operating surgeon. Adjunctive anti-inflammatory medications may be administered perioperatively to protect against harm from intraocular inflammation following surgery (Donati 1998).

How the intervention might work

Surgical removal of epiretinal membrane is believed to improve the outcome by relieving the abnormal tractional forces that distort retinal architecture, and consequently promoting normal vision. The potential benefit of the intervention is improved quality of life by improving eyesight or protecting high-quality eyesight (Ghazi-Nouri 2006).

Why it is important to do this review

Vitrectomy surgery for epiretinal membrane is performed with the aim of improving the outcome for vision, but also presents a risk of harm from adverse effects. Vitrectomy surgery predictably promotes the development of cataract and presents a risk of lasting harm to sight from other adverse effects including retinal detachment, intraocular infection, intraocular haemorrhage, macular oedema and secondary glaucoma (Dawson 2014). For severe epiretinal membrane that is causing progressive or disabling impairment of sight, or both, the balance of benefits and risks is conventionally considered to favour surgical intervention. This consensus is based on evidence from uncontrolled case series in which surgery is followed by improved visual function that would not be expected from the natural history (Dawson 2014; Grewing 1996). For mild asymptomatic epiretinal membrane with good visual acuity, in contrast, the balance of risks is considered to favour conservative (non-surgical) management because progressive impairment of vision develops in only a minority of eyes (10% to 21% in four years) (Byon 2015; Luu 2019). For mild but symptomatic epiretinal membrane, however, the balance of benefits versus risks is unclear and the indications for surgical intervention are undefined. Although the scope to improve visual acuity in mild epiretinal membraneis relatively limited owing to a ceiling effect, surgery may offer benefit by protecting against harm from disease progression (Dawson 2014). The aim of this review is to evaluate the high-level evidence for the effect of surgery for epiretinal membrane on the outcome for vision.

OBJECTIVES

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

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) in this review.

Types of participants

We included individuals identified as having idiopathic epiretinal membrane.

Types of interventions

Intervention: surgical intervention (vitrectomy plus epiretinal membrane peel). Comparator: no intervention or sham intervention. Our aim was to determine the value of surgical intervention for epiretinal membrane by comparing its outcomes with the natural history of the condition. We did not investigate any additional effect of modifications to the surgical technique, which are secondary to the effect of the surgical intervention itself.

Types of outcome measures

Primary outcomes

- Mean change in best corrected visual acuity (BCVA) in the study eye between baseline (before randomisation), 6 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 or more of uncorrected visual acuity in the study eye, as measured by a

logMAR chart at a starting distance of 4 m, at 6 months and 12 months after randomisation.

- Proportion of people with a loss of 0.3 logMAR or more of uncorrected visual acuity in the study eye, as measured by a logMAR chart at a starting distance of 4 m, at 6 months and 12 months after randomisation.
- Mean quality of life score at 6 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 searched the following electronic databases. There were no restrictions to language or year of publication. The date of the search was 20 May 2020.

- Cochrane Central Register of Controlled Trials (CENTRAL; 2020, Issue 5) (which contains the Cochrane Eyes and Vision Trials Register) in the Cochrane Library (searched 20 May 2020) (Appendix 1).
- MEDLINE Ovid (1946 to 20 May 2020) (Appendix 2).
- Embase Ovid (1980 to 20 May 2020) (Appendix 3).
- ISRCTN registry (www.isrctn.com/editAdvancedSearch; searched 20 May 2020) (Appendix 4).
- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov; searched 20 May 2020) (Appendix 5).
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp; searched 20 May 2020) (Appendix 6).

Searching other resources

We used the Science Citation Index to find studies that have cited the individual trials. We planned to contact relevant pharmaceutical companies for information regarding any clinical trial not released for publication. We elected not to handsearch conference proceedings or journals specifically for the review.

Data collection and analysis

Selection of studies

Two review authors independently identified relevant studies from the results of searches (titles and abstracts). We divided studies into ‘definitely include’, ‘definitely exclude’, and ‘possibly include’ categories. We resolved any disagreements through discussion or in consultation with a third review author. In general, we did not document citations considered irrelevant to the review at this stage, other than to note the number of these in a flow chart.

We obtained full-text copies of potentially relevant trials. We made 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 planned to obtain translations of abstracts and full-text articles into English before making a final decision. We identified and excluded duplicate reports of the same study.

Review authors were unmasked with respect to study authors, institution or journal, and could correspond with study authors to clarify study eligibility, as appropriate.

Data extraction and management

See Appendix 7.

Two review authors independently extracted data from the included study using an online review management software (Covidence). We resolved discrepancies through discussion. We contacted trial investigators for missing data. We imported data directly into Review Manager 5 (RevMan 5) (Review Manager 2020), and one review author checked the accuracy of the data import.

Assessment of risk of bias in included studies

Two review authors independently assessed the risk of bias in the included studies using Cochrane's 'Risk of bias' (RoB 1) tool, as described in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2017).

We graded each domain as low risk of bias, high risk of bias, or unclear (lack of information or uncertainty of potential for bias). We contacted trial investigators where appropriate for clarification of parameters graded as 'unclear'. We resolved disagreements through discussion.

We specifically considered and reported 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 or 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 (ITT) 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 planned to calculated the mean difference for the following continuous outcomes.

- Mean change in BCVA 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 intended to check for the skewness of continuous data (Altman 1996).

Where relevant, we calculated the risk ratio for the following dichotomous outcomes.

- Proportion of people with a gain of 0.3 logMAR or more of uncorrected visual acuity, as measured by a logMAR chart at 6 months and 12 months after randomisation.
- Proportion of people with a loss of 0.3 logMAR or more of uncorrected visual acuity, as measured by a logMAR chart at 6 months and 12 months after randomisation.

We planned to 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 planned simply to collate this information.

Unit of analysis issues

We did not anticipate any unit of analysis issues with respect to eyes, because epiretinal membrane is usually uniocular or affects eyes asymmetrically and therefore people would be randomised to treatment and one eye per person treated and reported.

Dealing with missing data

We planned to conduct an intention-to-treat (ITT) analysis. We would use imputed data if computed by the trial investigators using an appropriate method, but would not impute missing data ourselves.

Where ITT data were not available, we planned an available case analysis. This assumes that data are missing completely at random. We planned to 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 planned to 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 planned to 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 planned to 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 planned to consider I^2 values over 50% to indicate substantial inconsistency, but would also consider the Chi^2 P value. As this may have low power when the number of studies are few, we considered a P value of less than 0.1 to indicate statistical significance of the Chi^2 test.

Assessment of reporting biases

We used 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 planned to pool data using a random-effects model in Review Manager 5 (RevMan 5) (Review Manager 2020). If there were fewer than three trials in a comparison, we planned to use a fixed-effect model. In the event of 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 would not pool the data but describe the pattern of the individual study results. In the event of 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 would consider pooling the data.

Subgroup analysis and investigation of heterogeneity

We did not intend to perform subgroup analyses.

Sensitivity analysis

We did not intend to perform sensitivity analyses.

Summary of findings and assessment of the certainty of the evidence

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

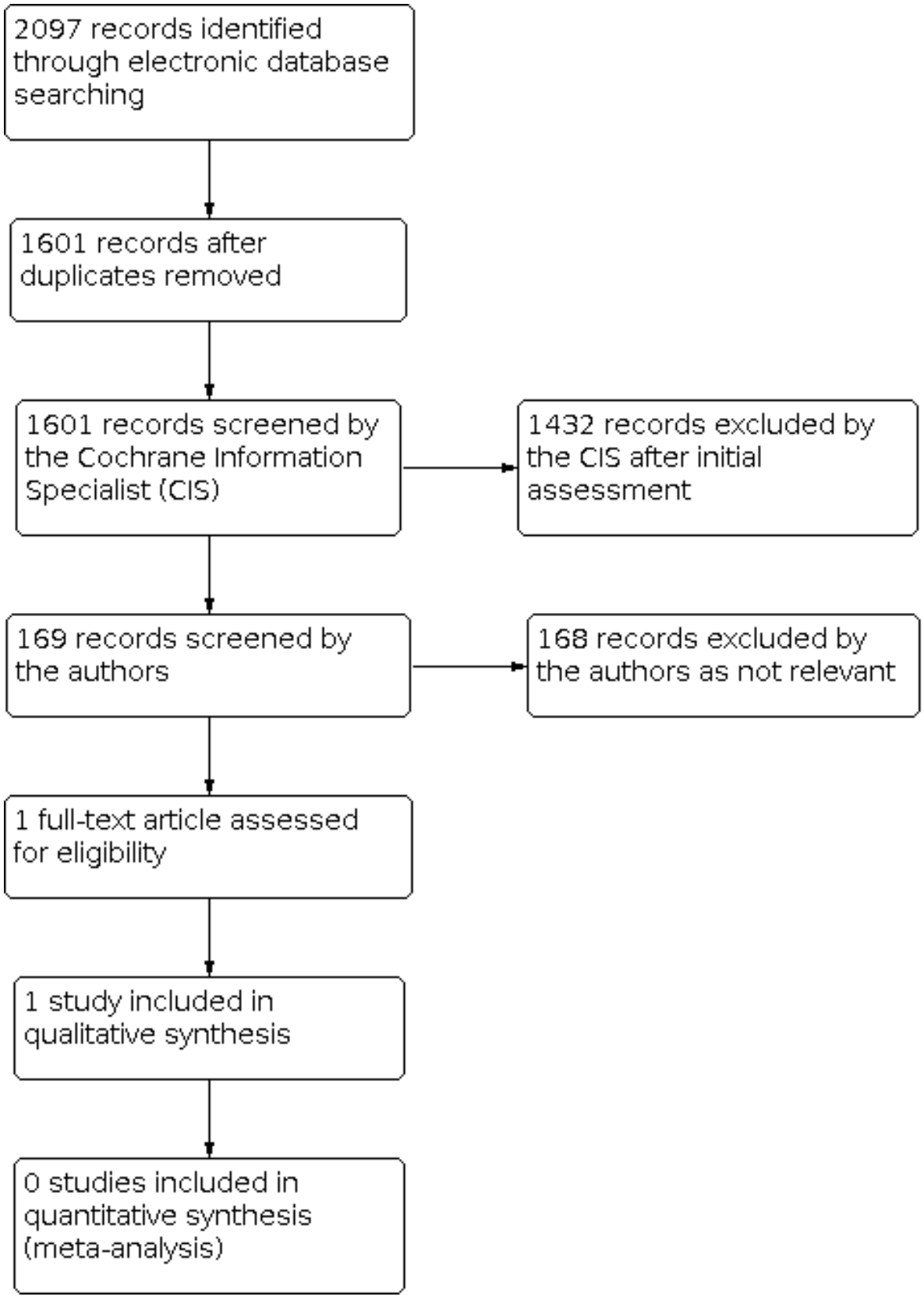
RESULTS

Description of studies

Results of the search

The electronic searches identified 2097 references (Figure 1). After 496 duplicates were removed, the Cochrane Information Specialist (CIS) screened the remaining 1601 records and removed 1432 references that were not relevant to the scope of the review. We screened the remaining 169 references and obtained one full-text report for further assessment. This study was judged to meet the inclusion criteria (Kofod 2016).

Figure 1. Study flow diagram.



Included studies

A single study met the inclusion criteria (Kofod 2016). This was a RCT including 53 eyes of 53 participants with mild symptomatic epiretinal membrane and BCVA of 65 or more Early Treatment Diabetic Retinopathy Study (ETDRS) letters. Participants were randomly allocated to immediate surgery (20 eyes) or to watchful waiting with deferred surgery if indicated by evidence of disease progression during the subsequent 12 months (33 eyes). The primary outcome of the study was mean BCVA after 12 months. Secondary outcome measures included the number of participants having deferred surgery within 12 months for progressive impairment of sight.

In planning the trial, the authors of this study anticipated that half the participants in the watchful waiting/deferred surgery arm would have surgery for progressive ERM, and therefore randomised participants 1:2 to immediate surgery or to watchful waiting/deferred surgery. The publication describes a power calculation indicating that 60 participants would be needed to detect a 5 ETDRS letter change with a 95% CI (Kofod 2016). An interim analysis after inclusion of 36 people, however, showed that fewer participants than anticipated had surgery for progressive ERM. For this reason, randomisation was changed from 1:2 to 1:1 and recruitment was closed once 20 participants had been randomised to immediate surgery. The authors calculated that, assuming surgery could improve the visual acuity outcome by 15 ETDRS letters with a standard deviation of 8 ETDRS letters, a difference in effect size of 7.5 ETDRS letters could be detected with a statistical power of 0.8 (Bainbridge 2020 [pers comm]).

Excluded studies

No study was excluded.

Risk of bias in included studies

We evaluated the risk of bias in the one included study in the review (Kofod 2016). See Figure 2 and Figure 3.

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

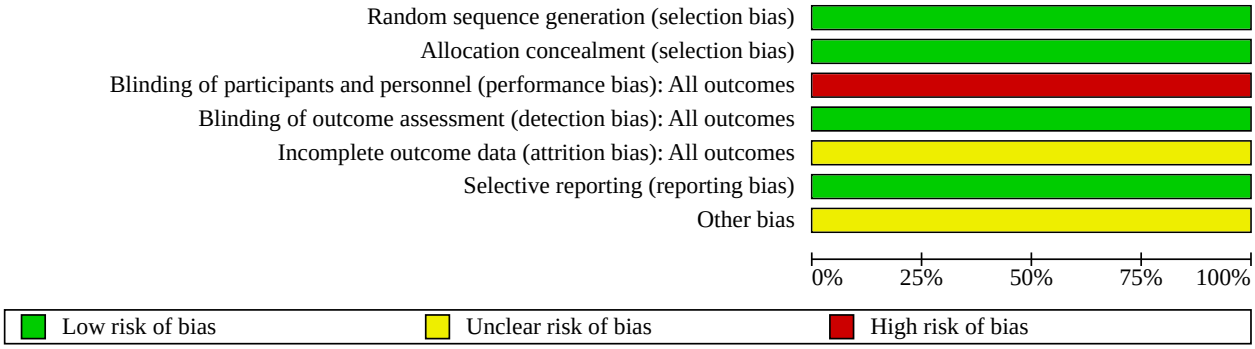
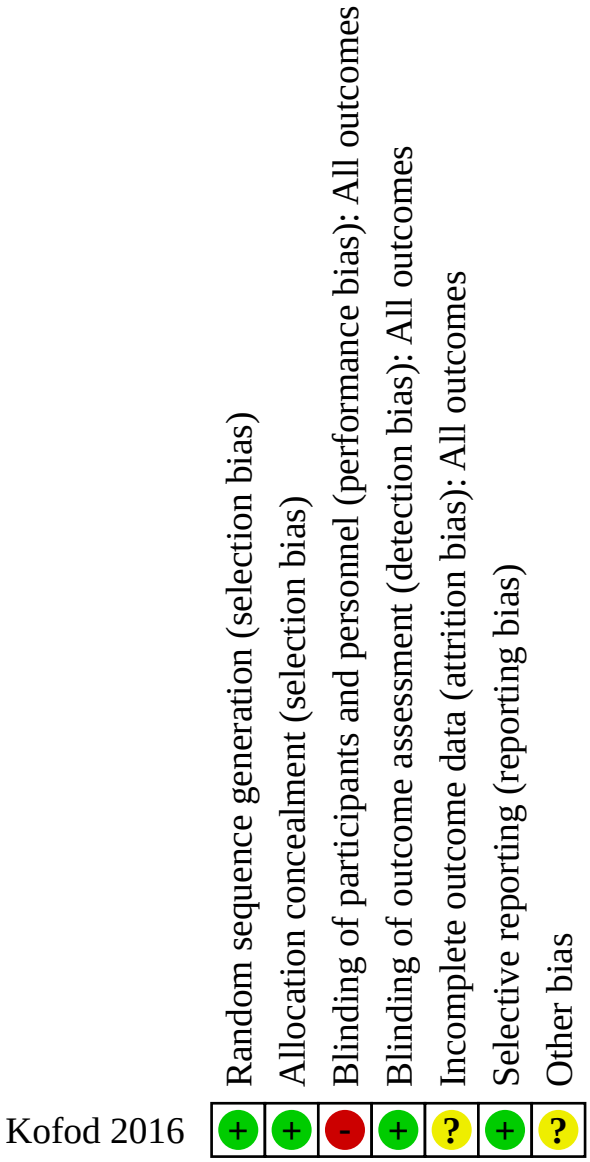


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Randomisation was generated in Microsoft Excel by a masked assistant and appears to present low risk of bias. Allocation concealment was not described, but we identified no source of selection bias.

Blinding

The participants, operating surgeons, clinical team and study authors all appeared to be unmasked to treatment allocation. A technician masked to treatment allocation evaluated the primary outcome. The subjective nature of visual acuity assessment by unmasked participants may have allowed for performance bias.

Incomplete outcome data

There was a low risk of attrition bias. One participant withdrew prior to randomisation. The final (12 month) outcome was not available for two participants. In these instances, data from the penultimate (9 month) assessment were carried forward for the analysis.

Selective reporting

No risk of reporting bias was identified. There was no evidence that any measured outcome was not reported.

Other potential sources of bias

There was some risk of systematic bias owing to inconsistent timing of primary outcome assessment in the watchful waiting/deferred surgery group (Bainbridge 2020 [pers comm]). For all participants, the baseline visual acuity was measured at recruitment. For those participants allocated to immediate surgery and those who had no surgery, the outcome was measured 12 months after recruitment. For those participants who had surgery after a period of watchful waiting, however, the outcome was measured 12 months after surgery, which itself was performed after a variable period according to disease progression.

For eyes that were phakic at recruitment, the potentially confounding effect of vitrectomy-induced cataract on visual outcome was addressed in the trial design by cataract surgery prior to vitrectomy surgery for epiretinal membrane. However, since only those who had surgery for epiretinal membrane also had surgery for cataract, a potential source of bias persists.

Effects of interventions

See: **Summary of findings 1** Surgery compared with no surgery for epiretinal membrane

Primary outcome

The primary outcome for this review was the mean change in logMAR visual acuity from baseline to 6 months and 12 months. The visual acuity at 6 months was measured but not reported for the individual treatment groups. The mean gain in best corrected logMAR visual acuity 12 months after immediate surgery was 5.2 ETDRS letters (standard error of the mean (SEM) 1.3, 95% CI 2.7 to 7.8), and after watchful waiting/deferred surgery was 3.1 ETDRS letters (SEM 1.4, 95% CI 0.3 to 5.8) (P = 0.30) (see Summary of findings 1). The visual acuity in the immediate surgery group was higher by a mean of 2.1 ETDRS letters (95% CI -2.0 to 6.2) than the no surgery (watchful waiting/deferred surgery) group. Since the data were not available to us, we were not able to determine the skewness of continuous data (Altman 1996).

The primary outcome for the study included in this review was the logMAR visual acuity at 12 months after recruitment (or after surgery if deferred). The median visual acuity at 12 months after immediate surgery was 85 ETDRS letters (interquartile range (IQR) 25% 79.5 to 86.0), and after watchful waiting/deferred surgery was 83.0 ETDRS letters (IQR 74.75 to 87.0) (P = 0.65 Mann-Whitney Rank sum) (Bainbridge 2020 [pers comm]).

Secondary outcomes

The proportion of eyes with a gain of 0.3 logMAR or more of visual acuity at 12 months after immediate surgery was 5% (1 of 20 eyes), and after watchful waiting/deferred surgery was 9% (3 of 33 eyes) (Bainbridge 2020 [pers comm]). No participant in either group sustained a loss of 0.3 logMAR or more of visual acuity at 12 months.

Quality of life was not reported.

The authors reported no serious adverse effect in any participant. One participant developed chronic minimal cystoid macular oedema that was unresponsive to anti-inflammatory eye drops. Harm from progressive epiretinal membrane was managed in the study design by deferred surgery and was not treated as an adverse event.

An additional secondary outcome of the trial was the number of participants in the watchful waiting/deferred surgery group having deferred surgery within 12 months for progressive impairment of sight. In this group, 24% (8 participants) experienced progressive epiretinal membrane to a severity that met the criteria for deferred surgery. In longer term informal follow-up outside the formal trial, the authors reported that the majority (> 50%) of participants who had originally been allocated to watchful waiting/deferred surgery had surgery for epiretinal membrane within three years of recruitment.

DISCUSSION

Summary of main results

We identified 1601 reports of studies and judged one of these to meet the inclusion criteria (Kofod 2016). The included study was a RCT that included participants with mild symptomatic epiretinal membrane and best corrected visual acuity (BCVA) of 65 ETDRS letters or more. The trial compared the effect of immediate surgery with the outcome of watchful waiting with deferred surgery for progressive epiretinal membrane. The quality of the evidence is weak owing to the imprecision of a small number of participants (1 study; 53 participants), and the risk of bias. The effect of immediate surgery was a mean benefit to visual acuity by 2.1 ETDRS letters (95% CI -2.0 to 6.2; P = 0.30). The study found no evidence of benefit of immediate surgery for mild symptomatic epiretinal membrane compared to the outcome of watchful waiting with deferred surgery for progressive epiretinal membrane. The study was not designed to determine whether watchful waiting/deferred surgery was non-inferior.

Watchful waiting involves a long-term commitment to repeated assessments. The majority of participants in this study had surgery within three years.

Overall completeness and applicability of evidence

We found no RCT that directly addressed the effect of surgery compared to no surgery, and none that included eyes with severe epiretinal membrane. The one study we included investigated the impact of surgery for mild symptomatic epiretinal membrane on visual acuity after 12 months. We identified no RCT that included assessment of quality of life.

Quality of the evidence

The one study included for analysis was a RCT with some risk of bias. There was some risk of bias owing to inconsistent timing of primary outcome assessment in the treatment groups, and some risk of bias from attrition. Since cataract surgery was performed only in those participants who had surgery for epiretinal membrane, this may have introduced some bias in favour of surgical intervention. There was some risk of performance bias as the participants were unmasked to treatment allocation. Since only one study was included, inconsistency and publication bias cannot be assessed. The quality of the evidence provides low certainty of the effect estimate, limited by the imprecision of a small number of participants (1 study; 53 participants) and the risks of bias.

Potential biases in the review process

We are aware of no potential bias in the review process. We excluded studies lacking randomisation to non-surgical management and believe that identification of relevant RCTs was complete.

Agreements and disagreements with other studies or reviews

For epiretinal membrane that is relatively severe and causing progressive or disabling impairment of sight, or both, the balance of benefits and risks is conventionally considered to favour surgical intervention. Some evidence of the benefit of surgery for relatively severe epiretinal membrane is provided by uncontrolled case-series that show improved visual function that would not normally be expected from the natural history (Dawson 2014; Grewing 1996). In contrast, for asymptomatic epiretinal membrane with good visual acuity at presentation, progressive impairment of vision is evident in only a minority (up to 10% to 21%) of eyes over two years (Byon 2015; Luu 2019), and the balance of risks is considered to justify conservative (non-surgical) management. For mild symptomatic epiretinal membrane, however, the balance of benefits versus risks is unclear and the indications for surgical intervention are undefined. Although the scope to improve visual function in mild epiretinal membrane is relatively limited owing to the ceiling effect, early surgical intervention offers the potential for benefit by protecting against harm from progressive disease (Dawson 2014; Kauffmann 2015).

AUTHORS' CONCLUSIONS

Implications for practice

For severe disabling epiretinal membrane, the lack of a RCT comparing surgery to no intervention may reflect evidence from non-randomised studies in favour of surgery, which is accepted standard practice.

For mild symptomatic epiretinal membrane, however, the effect of surgery is uncertain. The single study included in the review compared the outcome of immediate surgery to watchful waiting with deferred surgery if indicated by evidence of disease progression. The study found no evidence that immediate surgery for mild symptomatic epiretinal membrane improves the outcome by 7.5 letters at 12 months compared to watchful waiting/deferred surgery. The findings provide some evidence that watchful waiting/deferred surgery may offer outcomes as good as immediate surgery, but do not provide conclusive evidence of non-inferiority. The findings provide low-certainty evidence of the effect, being limited by imprecision owing to the small number of participants (1 study; 53 participants) and the risks of bias.

Implications for research

For severe disabling epiretinal membrane, a RCT may be considered unnecessary and ethically unacceptable because a superior effect of surgery is widely accepted.

For mild symptomatic epiretinal membrane, high quality evidence to guide optimal management of is limited. The effect of surgery might be measured with more confidence by further RCTs with appropriate statistical power, masking of treatment allocation, consistent management of cataract, and measurement of patient-reported outcomes including quality of life. Since the rate of epiretinal progression can be low, measurement of outcomes over a more extended time period would be informative.

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CHARACTERISTICS OF STUDIES

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

Kofod 2016

Study characteristics	
Methods	Study design: parallel group randomised trial
Participants	Country: Denmark Total number of participants: 53 Number (%) of men and women: 43% men; 57% women Average age and age range: Data not provided Inclusion criteria: Residency in Denmark; symptoms of visual loss and metamorphopsia with binocular complaints explained by ocular coherence tomography (OCT); ERM in one eye with duration of symptoms shorter than 24 months; best corrected visual acuity at presentation ≥ 65 Early Treatment Diabetic Retinopathy Study (ETDRS) letters measured at 4 m. Exclusion criteria: participants were excluded if the surgeon and the patient deemed that surgery was necessary or if the patients were unwilling to undergo surgery. Other exclusion criteria were other significant retinal conditions such as age-related maculopathy worse than hard drusen, any diabetic retinopathy or prior intraocular surgery apart from cataract surgery.
Interventions	Intervention (n = 20) Comparator (n = 33)
Outcomes	The main outcome of interest in the review was a secondary end point in this study. The primary outcome for this study was the logMAR visual acuity at 12 months after recruitment (or after surgery if deferred). Adverse events reported: Y Length of follow-up and intervals at which outcomes were assessed: follow-up was for 12 months after recruitment (or after surgery if deferred). Participants randomised to the intervention of immediate surgery were examined at 1, 3, 6, 9 and 12 months after the surgery. Participants randomised to watchful waiting were examined at 3, 6, 9 and 12 months after inclusion.
Notes	Date conducted: 2008-2011 Sources of funding: the Synoptik Foundation; the Danish Agency for Science, Technology and Innovation: FSS09-065546; the Bagenkop Nielsen Eye Foundation. Declaration of interest: none declared Trial registration ID: NCT00902629

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Kofod 2016 *(Continued)*

Random sequence generation (selection bias)	Low risk	Randomisation was generated by a masked assistant in Microsoft Excel and appears to present low risk of bias.
Allocation concealment (selection bias)	Low risk	Allocation concealment was not described, but we identified no source of selection bias.
Blinding of participants and personnel (performance bias) All outcomes	High risk	The participants, operating surgeons, clinical team and study authors all appeared unmasked to treatment allocation. The subjective nature of visual acuity assessment by unmasked participants may have allowed for performance bias.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The primary outcome was evaluated by a technician masked to treatment allocation.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	There was a low risk of attrition bias. One participant withdrew prior to randomisation. The final (12 month) outcome was not available for 2 participants; in these instances, data from the penultimate (9 month) assessment were carried forward for the analysis.
Selective reporting (reporting bias)	Low risk	No risk of reporting bias was identified. There was no evidence that any measured outcome was not reported.
Other bias	Unclear risk	There was some risk of systematic bias owing to inconsistent timing of primary outcome assessment in the watchful waiting/deferred surgery group (personal communication). For all participants, the baseline visual acuity was measured at recruitment. For those participants allocated to immediate surgery and those who had no surgery, the outcome was measured 12 months after recruitment. For those participants who had surgery after a period of watchful waiting, however, the outcome was measured 12 months after surgery, which was performed after a variable period according to disease progression. For eyes that were phakic at recruitment, the potentially confounding influence of vitrectomy-induced cataract on visual outcome was addressed in the trial design by cataract surgery prior to vitrectomy surgery for epiretinal membrane. Since only those who had surgery for epiretinal membrane also had surgery for cataract, however, this nonetheless presents a potential source of bias.

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
Eyes *or* Unit of randomisation/ unit of analysis	· **One eye included in study** - Epiretinal membrane 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.	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

(Continued)

Participants	We will include individuals identified as having idiopathic epiretinal membrane.	
Country		Setting
Total number of participants	*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.*	Ethnic group
Number (%) of men and women		Equivalence of baseline characteristics (Y/N)
Average age and age range		
Inclusion criteria		
Exclusion criteria		
Interventions		
Intervention (n=)	· Number of people randomised to this group	
Comparator (n=)	· Drug (or intervention) name	
	· Dose	
	· Frequency	
	· Route of administration	
Outcomes		
Primary and secondary outcomes *as defined in study reports*	List outcomes	Planned/actual length of follow-up
	Adverse events reported (Y/N)	
	Length of follow-up and intervals at which outcomes assessed	
Notes		
Date conducted	Specify dates of recruitment of participants mm/yr to mm/yr	Full study name: *(if applicable)*
Sources of funding		Reported subgroup analyses (Y/N)
Declaration of interest		Were trial investigators contacted?

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Review first published: Issue 3, 2021

CONTRIBUTIONS OF AUTHORS

JB, AY and MB developed the protocol. JB and AY performed the review. JB, AY and CB wrote the review manuscript.

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AY: no conflicts of interest to declare.

MB: no conflicts of interest to declare.
CB: no conflicts of interest to declare.
JB: no conflicts of interest to declare.

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