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Early vitrectomy for exogenous endophthalmitis following surgery (Review)

Muqit MMK, Mehat M, Bunce C, Bainbridge JW

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[Intervention Review]

Early vitrectomy for exogenous endophthalmitis following surgery

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ABSTRACT

Background

Endophthalmitis is a sight-threatening emergency that requires prompt diagnosis and treatment. The condition is characterised by purulent inflammation of the intraocular fluids caused by an infective agent. In exogenous endophthalmitis, the infective agent is foreign and typically introduced into the eye through intraocular surgery or open globe trauma.

Objectives

To assess the potential role of combined pars plana vitrectomy and intravitreal antibiotics in the acute management of exogenous endophthalmitis, versus the standard of care, defined as vitreous tap and intravitreal antibiotics.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL; which contains the Cochrane Eyes and Vision Trials Register; 2022, Issue 5); Ovid MEDLINE; Ovid Embase; the International Standard Randomised Controlled Trial Number registry; ClinicalTrials.gov, and the World Health Organization International Clinical Trials Registry Platform. There were no restrictions to language or year of publication. The date of the search was 5 May 2022.

Selection criteria

We included randomised controlled trials (RCTs) that compared pars plana vitrectomy and intravitreal injection of antibiotics versus intravitreal injection of antibiotics alone, for the immediate management of exogenous endophthalmitis.

Data collection and analysis

We used standard methods expected by Cochrane. Two review authors independently screened search results and extracted data. We considered the following outcomes: visual acuity improvement and change in visual acuity at three and six months; additional surgical procedures, including vitrectomy and cataract surgery, at any time during follow-up; quality of life and adverse effects. We assessed the certainty of the evidence using the GRADE approach.

Main results

We identified a single RCT that met our inclusion criteria. The included RCT enrolled a total of 420 participants with clinical evidence of endophthalmitis, within six weeks of cataract surgery or secondary intraocular lens implantation. Participants were randomly assigned according to a 2 x 2 factorial design to either treatment with vitrectomy (VIT) or vitreous tap biopsy (TAP) and to treatment with or without systemic antibiotics. Twenty-four participants did not have a final follow-up: 12 died, five withdrew consent to be followed up, and seven were not willing to return for the visit.

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The study did not report visual acuity according to the review's predefined outcomes. At three months, 41% of all participants achieved 20/40 or better visual acuity and 69% had 20/100 or better acuity. The study authors reported that there was no statistically significant difference in visual acuity between treatment groups (very low-certainty evidence). There was low-certainty evidence of a similar requirement for additional surgical procedures (risk ratio RR 0.90, 95% confidence interval 0.66 to 1.21). Adverse effects included: VIT group: dislocated intraocular lens (n = 2), macular infarction (n = 1). TAP group: expulsive haemorrhage (n = 1). Quality of life and mean change in visual acuity were not reported.

Authors' conclusions

We identified a single RCT (published 27 years ago) for the role of early vitrectomy in exogenous endophthalmitis, which suggests that there may be no difference between groups (VIT vs TAP) for visual acuity at three or nine months' follow-up.

We are of the opinion that there is a clear need for more randomised studies comparing the role of primary vitrectomy in exogenous endophthalmitis. Moreover, since the original RCT study, there have been incremental changes in the surgical techniques with which vitrectomy is performed. Such advances are likely to influence the outcome of early vitrectomy in exogenous endophthalmitis.

PLAIN LANGUAGE SUMMARY

Is the outcome of severe postoperative eye infection improved by early surgery to remove the vitreous gel?

What is exogenous endophthalmitis?
The eye is a relatively self-contained organ that is lined by light-sensitive cells that make up the retina. The retina lines the back of the eyeball and the centre is filled with a clear gel, known as the vitreous. Like all organs, the eye can become infected. Infection inside the eye (endophthalmitis) is rare but sight-threatening. Exogenous endophthalmitis is defined as an infection which enters the eye from the surrounding environment, usually following routine surgery such as cataract surgery, or due to an open wound following trauma. Prompt management is required in order to protect sight.

How is exogenous endophthalmitis treated?
Although endophthalmitis is rare, the consequence following an infection maybe be profound. Prompt and appropriate treatment is critical. Currently, the majority of endophthalmitis infections have a diagnostic biopsy of the vitreous gel and are then treated with antibiotics. The biopsy involves a ‘tap’ in which a small sample of the vitreous gel is removed, in order to identify the type of infection. People will then have antibiotics injected into the fluid inside the eyeball to treat the infection. If this does not work, an eye operation is sometimes required later on, where the infected jelly inside the eyeball is removed (known as a “vitrectomy” operation). Vitrectomy involves surgical removal of the vitreous gel from inside the eye. In individuals with endophthalmitis, vitrectomy may aid in removing the infection, help the eye recover more quickly and potentially limit the damage caused by the infection. However, the impact of vitrectomy on the management of endophthalmitis remains unclear.

What did we want to find out?
The aim of this Cochrane Review was to assess the role of vitrectomy in the treatment of endophthalmitis.

What did we do?
We conducted a systematic review of studies of people with endophthalmitis who had undergone vitrectomy for the treatment of endophthalmitis following surgery or an eye injury.

What did we find?
We identified one randomised control trial (RCT) that studied vitrectomy compared to antibiotic eye injections in endophthalmitis after cataract surgery. The single RCT suggested that vitrectomy had no advantage over standard treatment of intravitreal antibiotics alone.

What are the limitations of the evidence?
The results of our review were based on a single RCT, which was conducted over 27 years ago. Since this time there have been several surgical advances that may potentially alter the outcome of people undergoing vitrectomy.

How up to date is this evidence?
We searched for studies up to 5 May 2022.

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SUMMARY OF FINDINGS

Summary of findings 1. Vitrectomy compared with vitreous tap biopsy and antibiotic injection for endophthalmitis following intraocular surgery

Vitrectomy compared with vitreous tap biopsy and antibiotic injection for endophthalmitis following intraocular surgery

Patient or population: people with endophthalmitis following intraocular surgery

Setting: hospital

Intervention: vitrectomy

Comparison: vitreous tap biopsy and antibiotic injection

Outcomes	Anticipated absolute effects		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with vitreous tap biopsy	Risk with vitrectomy				
Proportion of people with a visual acuity improvement of 10 letters or more Follow-up: 3 months.	At 3 months, 41% of all participants achieved 20/40 or better visual acuity and 69% had 20/100 or better acuity. There was no statistically significant difference in visual acuity between treatment groups.			420 (1 RCT)	VERY LOW[a]	At final follow-up (9 to 12 months), 53% of participants achieved visual acuity of 20/40 or better, 74% achieved 20/100 or better, and 15% had an acuity worse than 5/200. At the final follow-up visit, 5% of participants had no light-perception vision.
Mean change in best-corrected visual acuity Follow-up: 6 months.	Not reported					
Additional surgical procedure, including vitrectomy and cataract surgery. Follow-up: 6 months.	300 per 1000	270 per 1000 (198 to 363)	RR 0.90 (0.66 to 1.21)	420 (1 RCT)	LOW[b]	-
Quality of life. Follow-up: 6 months. Measured using validated questionnaire.	Not reported					

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Any adverse effects	VIT group: dislocated intraocular lens (N = 2), macular infarction (N = 1). TAP group: expulsive haemorrhage (N = 1)	420 (1 RCT)	VERY LOW[c]	-

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention group (and its 95% CI).

CI: confidence interval; RR: risk ratio; TAP: vitreous biopsy; VIT: immediate pars plana vitrectomy

GRADE working group grades of evidence

High-certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate-certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low-certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low-certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded one level for risk of bias as the study was at risk of selection and performance bias; downgraded one level for imprecision as it is likely the optimal information size is not met; and one level for indirectness as available data on visual acuity only indirectly provides information on the prespecified outcome.
[b]Downgraded one level for risk of bias as the study was at risk of selection and performance bias; downgraded one level for imprecision as CI ranges from 0.66 to 1.21.
c Downgraded one level for risk of bias as the study was at risk of selection and performance bias; downgraded two levels for imprecision as very few events.

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BACKGROUND

Description of the condition

Endophthalmitis is a sight-threatening emergency that requires prompt diagnosis and treatment (Kresloff 1998). The condition is characterised by purulent (containing pus) inflammation of the intraocular fluids, caused by an infective agent. Endophthalmitis is broadly categorised into exogenous or endogenous forms. In the exogenous form of endophthalmitis, the infective agent is typically introduced into the eye through open globe trauma or intraocular surgeries, such as intravitreal injections, cataract, glaucoma, vitrectomy, or corneal surgery (Callegan 2007). The incidence of exogenous endophthalmitis is variable and depends on the surgical intervention by which the infection is introduced into the eye. The incidence of endophthalmitis following intravitreal injection ranges from 0.033% to 0.082% (Clarke 2018). The postcataract surgery endophthalmitis rate is between 0.06% and 0.2% (Du 2014). The endophthalmitis incidence following pars plana vitrectomy (operations that remove the eye's internal jelly) is between 0.02 to 13% (Scott 2011). Although the frequency of endophthalmitis is relatively low, the volume of intraocular surgeries performed is expected to increase in response to the ageing global population.

Description of the intervention

Pars plana vitrectomy (PPV) is an established surgical technique for the removal of the vitreous cavity contents. PPV surgery has changed significantly with recent advances in small gauge surgical instrumentation, wide-field viewing systems, and the availability of silicone oil for long-term retinal tamponade (the silicone oil prevents the flow of fluid through the retinal break; de Oliveira 2016). There are recognised risks of PPV surgery that include infection, bleeding, loss of vision, eye pressure changes, macular oedema, cataract, retinal detachment, and suprachoroidal haemorrhage (Stein 2009). PPV is most commonly performed under local anaesthesia, with or without sedation; some people may require general anaesthesia.

How the intervention might work

The current standard of care for suspected exogenous endophthalmitis is an urgent vitreous tap (biopsy), with an injection of intravitreal antibiotics at the time of clinical presentation. The response to treatment is then usually reassessed. Only in those people who experience continued clinical deterioration is a surgical intervention in the form of PPV performed. PPV has the advantage of clearing the visual axis and promoting healing by removing the infected vitreous, which contains bacteria, bacterial endotoxins, immune cells, inflammatory cytokines, and other toxic mediators, which may incite retinal tissue damage (Forster 1980; Kuhn 2005). Failure to promptly remove these harmful factors will result in continued exposure of the retina to toxins and pro-inflammatory products, even after the eye is sterilised by antibiotics (Astley 2016).

Why it is important to do this review

The early diagnosis and treatment of endophthalmitis is crucial in preventing irreversible eye damage and preserving visual function (Maguire 2008). Prompt delivery of intravitreal injection and sampling is well established as the standard of care for exogenous endophthalmitis (Kresloff 1998). However, the role of early PPV and intravitreal injection of antibiotics, defined as within one week of presentation, is less clearly understood, particularly in the context of non-cataract surgery-related endophthalmitis (Relhan 2018). A systematic review may help to ascertain whether early PPV intervention in exogenous endophthalmitis is beneficial, compared to the current standard of care.

OBJECTIVES

To assess the potential role of combined pars plana vitrectomy and intravitreal antibiotics in the acute management of exogenous endophthalmitis, versus the standard of care, defined as vitreous tap and intravitreal antibiotics.

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 trials in which participants were defined as people who developed endophthalmitis within six weeks of any intraocular surgery or intervention and had a best-corrected visual acuity of worse than 30 letters, measured with an Early Treatment Diabetic Retinopathy Study (ETDRS) chart, at a starting distance of four metres. The types of surgery included; cataract surgery, glaucoma surgery, intravitreal injections, vitrectomy surgery or corneal surgery. We excluded participants with a diagnosis of endogenous endophthalmitis.

Types of interventions

- Early intervention group. Early pars plana vitrectomy (PPV) surgery and intravitreal antibiotic, with a second intravitreal antibiotic dose within 48 hours for eyes that were non-responsive to the initial PPV and intravitreal antibiotic dose.
- Comparator group. A second intravitreal antibiotic, 48 hours later, for eyes that were non-responsive to the first intravitreal antibiotic dose. The response to treatment was assessed on day five, and in non-responsive eyes, further management was actioned according to the hospital standard of care protocols, which included a third intravitreal antibiotic dose.

Types of outcome measures

Primary outcomes

We defined the primary outcome as the proportion of people at three months postintervention that had an improvement of 10 letters or more on a standard ETDRS chart, at a distance of four metres.

Secondary outcomes

We defined secondary outcomes as follows.

- The proportion of people that had a visual acuity improvement of 10 letters or more from intervention to six months postrandomisation, measured with an ETDRS chart, at a starting distance of four metres.
- The proportion of people that required an additional surgical procedure, including vitrectomy and cataract surgery, between randomisation and six months postrandomisation.

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- Mean change in best-corrected visual acuity (BCVA), between randomisation and three months postrandomisation, measured with an ETDRS chart, at a starting distance of four metres.
- Mean change in BCVA, between randomisation and six months postrandomisation, measured with an ETDRS chart, at a starting distance of four metres.
- Quality of life: mean quality of life scores at six months postrandomisation, measured using a validated questionnaire.
- Adverse effects: any adverse effects identified during the follow-up period of the study, including: retinal detachment, hypotony, intraocular haemorrhage and glaucoma.

Search methods for identification of studies

Electronic searches

We searched the following databases for randomised controlled trials and controlled clinical trials. There were no restrictions to language or year of publication. The date of the search was 5 May 2022.

- Cochrane Central Register of Controlled Trials (CENTRAL; 2022, Issue 5; which contains the Cochrane Eyes and Vision Trials Register) in the Cochrane Library (searched 5 May 2022) (Appendix 1).
- MEDLINE Ovid (1946 to 5 May 2022) (Appendix 2).
- Embase Ovid (1980 to 5 May 2022) (Appendix 3).
- International Standard Randomised Controlled Trial Number registry (www.isrctn.com/editAdvancedSearch; searched 5 May 2022) (Appendix 4).
- US National Institutes of Health Ongoing Trials Register - ClinicalTrials.gov (www.clinicaltrials.gov; searched 5 May 2022) (Appendix 5).
- World Health Organization International Clinical Trials Registry Platform (www.who.int/ictrp; searched 5 May 2022) (Appendix 6).

Searching other resources

The lead author scanned the reference lists of the studies included in the review for information about further trials.

Data collection and analysis

Selection of studies

We (MM and MMKM) included randomised controlled trials that compared PPV with intravitreal injection of antibiotics, versus intravitreal injection of antibiotics alone, for the immediate management of exogenous endophthalmitis. The two review authors independently carried out the study selection from the results of the searches (title and abstracts) to identify relevant studies. We divided studies into 'definitely include', 'definitely exclude', and 'possibly include' categories, and resolved disagreements by discussion or consultation (or both) with the third review author. In general, we did not document in the review all the citations considered not relevant, other than to note the number of these in the flow chart. We obtained full-text copies of all relevant trials, and made a final judgement regarding the inclusion or exclusion of studies in the 'possibly include' category after obtaining these. Two review authors independently reviewed all the full-text reports and resolved disagreements by discussion or consultation (or both) with a third review author. The review authors were not masked to study authors, institutions and journals.

For the eligible studies identified from trials registers, we undertook the following.

- If the study had a completion date of more than two years ago, we looked for publications of this trial, and contacted the investigators if necessary to obtain published or unpublished data from the trial. If eligible, we included the study in the review, regardless of whether we could identify a publication.
- If the study had a completion date within the past two years, or in the future, we documented the study in the ongoing studies section.

Data extraction and management

Two review authors (MM and MMKM) independently extracted data, using web-based online review management software (Covidence). We ensured that the trial participants met our inclusion criteria for participants as described above. We imported all data directly into Review Manager 5 (Review Manager 2020), and one author checked the accuracy of the imported data.

We extracted the following study characteristics from each of the included studies.

1. Methods: method of allocation, masking (participant, provider, outcome), exclusions after randomisation, losses to follow-up, and compliance.
2. Participants: number randomised, age, sex, main inclusion and exclusion criteria.
3. Interventions: treatment, comparison intervention (control).
4. Outcomes: relevant outcomes for which data were collected in the trial and length of follow-up.
5. Notes: additional details relevant to that particular trial (e.g. funding sources).

See Appendix 7.

Assessment of risk of bias in included studies

Two review authors (MM and MMKM) independently assessed the risk of bias for each included study, using Cochrane's risk of bias tool (Higgins 2017).

We resolved disagreements by discussion.

We considered and reported on the following parameters of bias.

1. 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 and enroling participants, and to participants?
2. Performance bias — masking of participants and researchers — were the recipients of care unaware of their assigned intervention? Were the persons providing care unaware of the assigned intervention?
3. Detection bias — masking outcome assessors — were persons evaluating outcomes unaware of the assigned intervention?
4. 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 postrandomisation exclusions?

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5. Selective outcome reporting bias — is there any evidence that the outcomes that were measured were not reported?

We classified each domain as low risk of bias, high risk of bias or unclear (lack of information or uncertainty of potential for bias).

Measures of treatment effect

We planned to calculate the risk ratio for the following dichotomous outcomes.

- Proportion of people with a visual acuity improvement of 10 letters or more, measured with an ETDRS chart, at a starting distance of four metres, from randomisation to three months postrandomisation.
- Proportion of people with a visual acuity improvement of 10 letters or more, measured with an ETDRS chart, at a starting distance of four metres, from randomisation to six months postrandomisation.

We planned to compute odds ratios for the following outcomes (because these are rare, less than 10%).

- Proportion of people suffering harm during follow-up.
- Proportion of people requiring additional surgical procedures during follow-up.

We planned to calculate the mean difference for the following continuous outcomes.

- Mean change in best-corrected visual acuity, between randomisation and three months postrandomisation, measured with an ETDRS chart, at a starting distance of four metres.
- Mean change in best-corrected visual acuity, between randomisation and six months postrandomisation, measured with an ETDRS chart, at a starting distance of four metres.
- Mean quality of life score at six months postrandomisation measuring using a validated questionnaire.

Unit of analysis issues

Typically, exogenous endophthalmitis is unilateral, so the unit of analysis issue does not arise. In the study included in this review, one eye per person was enrolled in the study and therefore no unit of analysis issues applied.

Cluster-randomised trials and cross-over studies are not relevant here as the treatment is applied to individuals and is a one-off treatment. In future updates of this review, if there are studies with multiple treatment arms, the most appropriate intervention group will be selected, or combined, as needed.

Dealing with missing data

We reported the degree of missing data and checked to see the reasons provided by the authors. We looked to see if these were similar between treatment arms.

Assessment of heterogeneity

Given that only a single study met the inclusion criteria of the review, we did not assess heterogeneity.

Assessment of reporting biases

Given that we only included one trial and did not undertake a meta-analysis, there was no need to construct funnel plots or consider tests for asymmetry to assess publication bias.

Data synthesis

Given that only a single study met the inclusion criteria of the review, a data synthesis was not required or performed.

Subgroup analysis and investigation of heterogeneity

We did not plan or perform any subgroup analyses.

Sensitivity analysis

We did not perform a sensitivity analysis as we only identified a single study that met the inclusion criteria.

Summary of findings and assessment of the certainty of the evidence

We prepared a summary of findings table presenting relative and absolute risks (see Summary of findings 1). Two authors (MM and MKKM) independently graded the overall certainty of the evidence for each outcome using the GRADE classification GRADEpro GDT.

We planned to include these outcomes in the table.

- Proportion of people with a visual acuity improvement of 10 letters or more at three months follow-up
- Mean change in best-corrected visual acuity at six months follow-up
- Proportion of people requiring additional surgical procedures, including vitrectomy and cataract surgery, at any time during follow-up
- Mean quality of life scores at six months follow-up
- Proportion of people suffering adverse effects at any time during follow-up

RESULTS

Description of studies

Results of the search

Searches run on 5 May 2022 yielded a total of 1496 records (Figure 1). After 329 duplicates were removed, the Cochrane Information Specialist (CIS) screened the remaining 1167 records and removed 1119 references that were not relevant to the scope of the review. We screened the remaining 48 references and assessed them against the inclusion criteria. We excluded 47 references and obtained the full-text report of one study, which we included in the review (EVS Group 1995).

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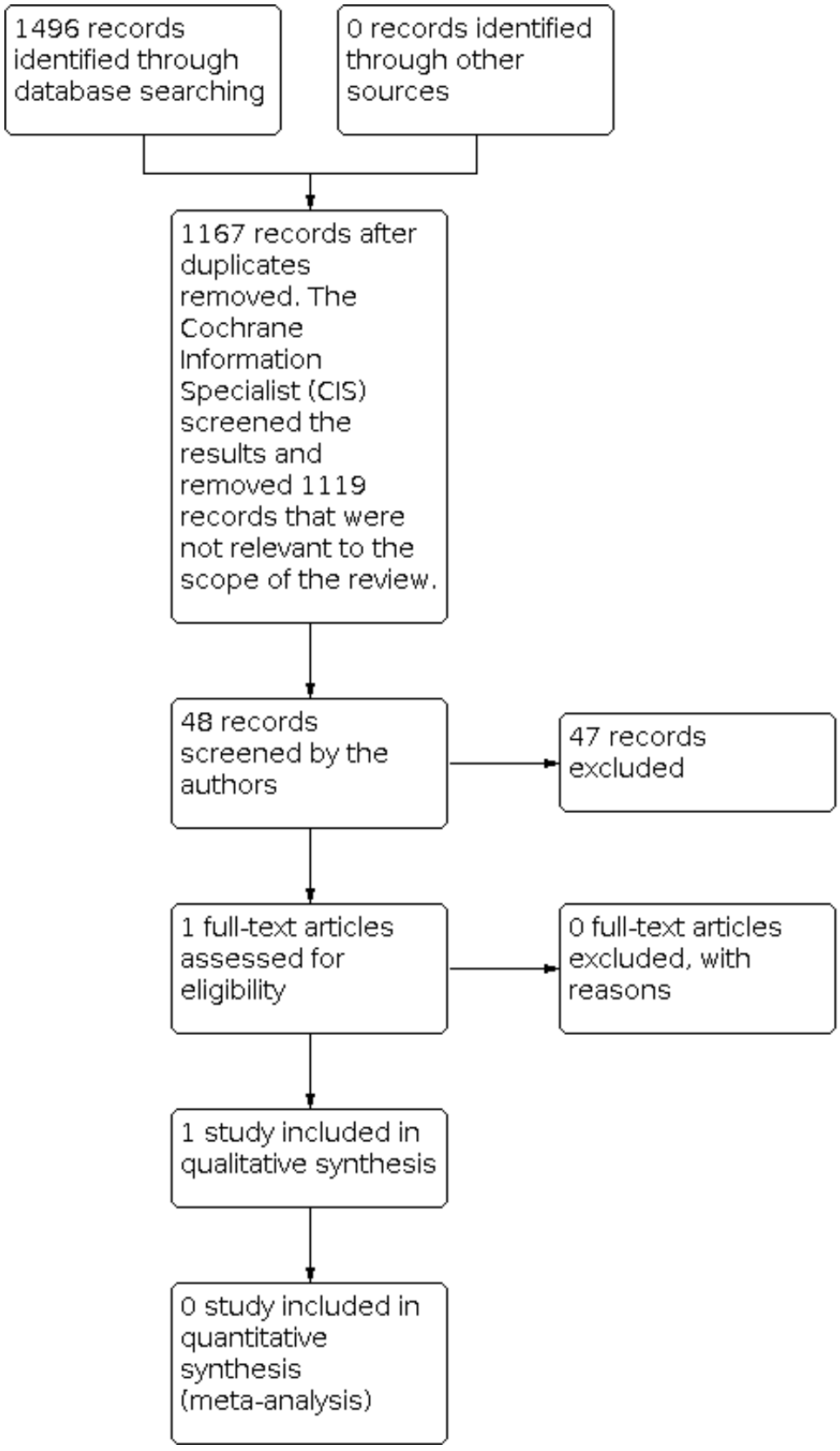
Figure 1. PRISMA study flow diagram



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Included studies

We included one RCT study (EVS Group 1995) that met our inclusion criteria. The endophthalmitis vitrectomy study (EVS Group 1995) was a multicentre RCT that recruited a total of 420 participants with clinical evidence of endophthalmitis, within six weeks of cataract surgery or secondary intraocular lens implantation. Participants were randomly assigned according to a 2 x 2 factorial design to either treatment with vitrectomy (VIT) or vitreous tap biopsy (TAP) and to treatment with or without systemic antibiotics. All participants received treatment within six hours of initial assessment and randomisation. From this study, we extracted primary and secondary outcome measures as specified in our protocol (Muqit 2020).

Excluded studies

We did not exclude any studies on full-text review.

Risk of bias in included studies

We assessed the risk of bias for EVS Group 1995 using the Cochrane risk of bias assessment tool. This considers sequence generation, allocation concealment, masking of physicians and participants, incomplete outcome data, selective outcome reporting and other potential threats to validity. 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

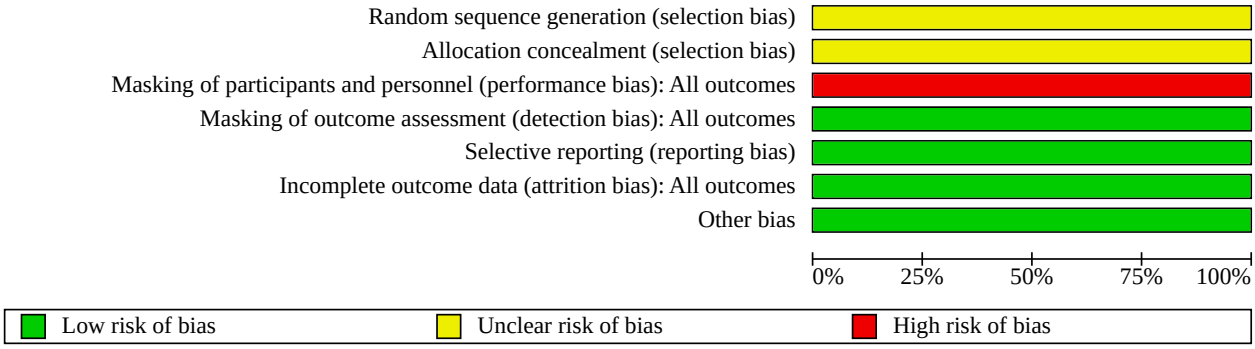

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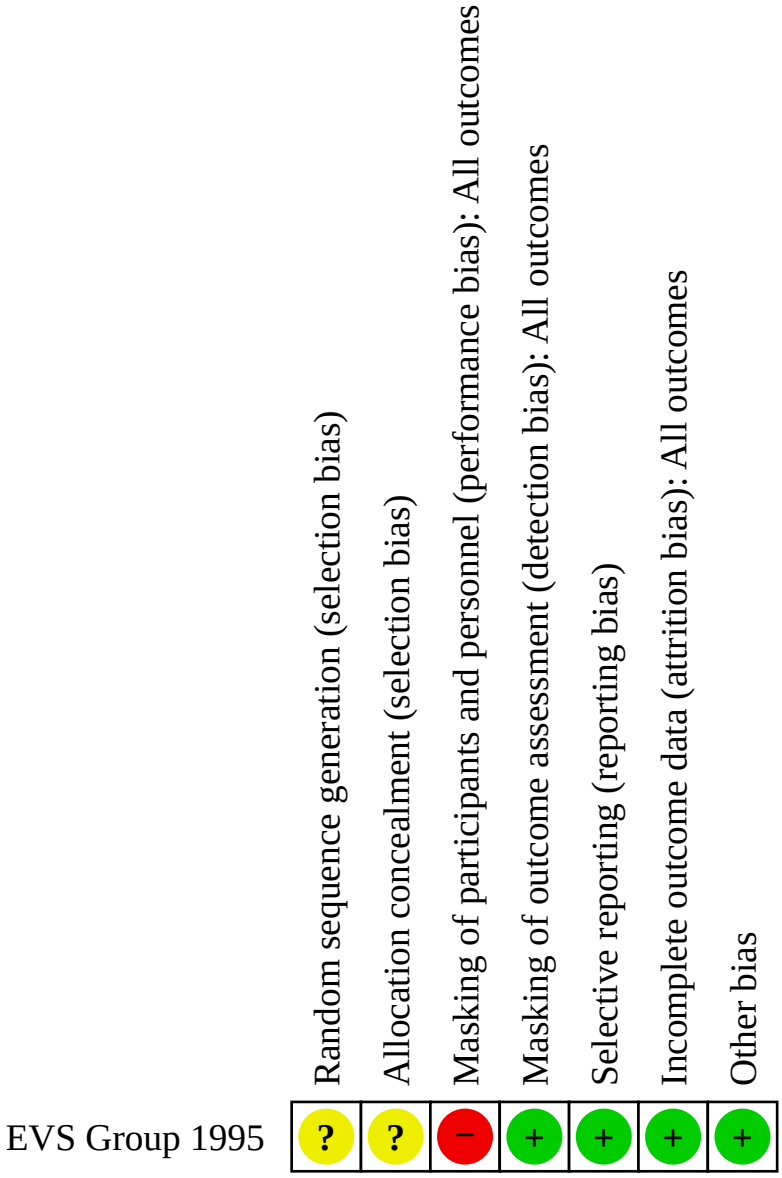
Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for the included study



Allocation

Following an initial assessment for trial eligibility, participants were immediately randomly assigned according to a 2 x 2 factorial design to one of four treatment groups: initial VIT with intravenous (IV) antibiotics, initial VIT without IV antibiotics, initial TAP with IV antibiotics or initial TAP without IV antibiotics. The method of randomisation was not reported, nor were details of allocation concealment of the intervention detailed. Therefore, we assessed the study to have an unclear risk of bias for these domains.

Blinding

The primary endpoints for the study were visual acuity and media clarity. Best-corrected visual acuity was measured using ETDRS visual acuity charts by certified technicians who were masked to treatment assignment. Grading of media opacity was also performed using masked observers at the EVS Photographic Reading Centre. We considered the trial to have a low risk of bias for outcome assessment (detection bias), but a high risk of bias for masking of participants and personnel (performance bias) because it was not possible to mask the surgical intervention.

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Incomplete outcome data

Of the 420 participants recruited, 396 (94%) completed the final follow-up. Twenty-four participants did not have a final follow-up: 12 died, five withdrew consent to be followed up, and seven were not willing to return for the visit. These participants were distributed equally across all treatment groups. Of the 396 participants with final visit data, two were missing visual acuity data and four were missing clinical assessment of media clarity. Subsequently, visual acuity and media clarity were reported in 394 and 392 participants, respectively. Three participants who were recruited into the trial were noted to have had exclusionary criteria. These were considered in the analysis based on the principle of 'intention-to-treat', so we considered the trial to have a low risk of attrition bias.

Selective reporting

There is no evidence to suggest that the study was subject to reporting bias. The outcome measures listed in the methods were detailed in the results of the study, so we judged the trial to have a low risk of reporting bias.

Other potential sources of bias

The trial was not noted to be subject to any other sources of bias, so we recorded a low risk of bias for this domain.

Effects of interventions

See: **Summary of findings 1** Vitrectomy compared with vitreous tap biopsy and antibiotic injection for endophthalmitis following intraocular surgery

In view of the single study inclusion, a meta-analysis was not possible. Therefore, we have presented the results in a descriptive format.

Primary outcome

Proportion with visual acuity improvement of 10 letters at three months

The primary outcome for the single study included in this review was visual acuity and media clarity at follow-up visits in months three and nine. An additional assessment at month 12 was included only for those participants who underwent an additional procedure, based on the results of the month-nine visit. Best-corrected visual acuity was measured following refraction using ETDRS visual acuity charts. Three thresholds of visual outcome were predefined as: 20/40 or better, 20/100 or better and 5/200 or better.

The primary outcome for this review was the proportion of people with visual acuity improvement of 10 letters or more on an ETDRS chart at three months after randomisation. Visual acuity at three months was measured in the EVS Group 1995 study. At three months, 41% of all participants achieved 20/40 or better visual acuity and 69% had 20/100 or better acuity. The authors conducted a statistical analysis of visual acuity across all treatment arms, based on Cox regression analysis that compared VIT with TAP and IV (intravenous antibiotics) with NOIV (no intravenous antibiotics), which found no evidence of a difference in visual acuity outcome at three months.

Secondary outcomes

Proportion with visual acuity improvement of 10 letters at six months

The secondary outcome for this review was the proportion of people with a visual acuity improvement of 10 letters or more from randomisation to six months following the randomised intervention.

At 9 to 12 months in the EVS Group 1995 study, 53% of participants achieved visual acuity of 20/40 or better, 74% achieved 20/100 or better, and 15% had an acuity worse than 5/200. At the final follow-up visit, 5% of participants had no light-perception vision.

Proportion requiring an additional surgical procedure, including vitrectomy and cataract surgery at six months

The EVS Group 1995 study reported follow-up surgery, defined as procedures performed more than 60 hours from the initial study intervention (such as vitreous opacities, macular pucker or opacified posterior capsule). At the final follow-up visit, 59 of 218 participants in the VIT group and 61 of 202 participants in the TAP group had undergone follow-up surgery. The specific procedures performed were not reported.

Adverse effects

Immediate adverse events relating to the initial procedure included dislocation of intraocular lens (n = 2) in the VIT group and an expulsive haemorrhage (n = 1) in the TAP group. One participant also developed macular infarct in the VIT group with IV antibiotics. Renal complications were defined by an increase in serum creatine level. Five per cent of participants had an increase in serum creatine levels of 26 µmol/L or greater (≥ 0.3 mg/dL) and less than 1% demonstrated an increase of 53 µmol/L or greater (≥ 0.6 mg/dL). No statistical difference in the rise of serum creatine levels was noted between the IV and NOIV groups.

Outcomes not reported

- Mean change in best-corrected visual acuity (BCVA) at three and six months
- Quality of life

DISCUSSION

Summary of main results

We identified a single RCT study that met our inclusion criteria (EVS Group 1995). The included study was a multicentre RCT that enrolled a total of 420 participants who presented with clinical evidence of endophthalmitis within six weeks of cataract surgery or secondary intraocular lens implantation. The study randomly assigned participants according to a 2 x 2 factorial design to treatment with vitrectomy (VIT) or intravitreal biopsy (TAP) and to treatment with or without systemic antibiotics. All participants received treatment within six hours of initial assessment and randomisation. In the VIT group, an undiluted vitreous specimen was obtained with the cutter placed into the mid-vitreous and 0.2 to 0.5 mL of vitreous gel excised and aspirated into a syringe using manual aspiration and a high cut-rate. In the TAP group, a standard vitreous specimen was collected by either a trans-pars plana vitreous needle aspiration or using a vitreous cutter through a single port. A vitreous sample of 0.1 to 0.3 mL was collected. The

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infusion was only turned on once the sample had been collected. In the absence of a posterior vitreous separation, no attempt was made to induce a posterior vitreous detachment and only a core vitrectomy was performed, with the aim of removing at least 50% of the vitreous gel. Results from the EVS Group 1995 study provided very low-certainty evidence of no difference in final visual acuity or media clarity The EVS trial was well-designed and undertaken as a multicentre RCT. In the absence of other RCTs investigating the role of early VIT, it provides the only available data to support the role of early VIT in people with endophthalmitis who present with light perception or worse vision.

Overall completeness and applicability of evidence

The published literature on the role of PPV for the management of exogenous endophthalmitis is largely composed of retrospective studies or case series. Only one RCT was identified in this review, which provides limited evidence for the role of PPV in participants who presented with a visual acuity of light perception, resulting in a three-fold increase in the frequency of achieving 20/40 or better visual acuity (33% vs 11%). However, this study did not address the role of a second intravitreal antibiotic dose at 48 hours after the initial intervention in those participants who demonstrated an inadequate clinical response to either primary PPV or intravitreal antibiotic.

The conclusions of this review are limited as they are drawn from a single RCT with a relatively homogenous participant population. The participants recruited in the EVS Group 1995 study were all from North America. How applicable this evidence is to other regions of the world where the microbiological spectrum of the infections can differ is unknown. The EMS working group 2021 has recently published a study protocol aiming to answer this question.

Since the original publication of this single RCT investigating the role of early vitrectomy in exogenous endophthalmitis, there have been innumerable advances in ophthalmic surgical techniques, including those for PPV. These changes include; small gauge surgical instrumentation, improved wide-field viewing systems, and the availability of silicone oil for long-term retinal tamponade (de Oliveira 2016). These technological advances are likely to have a positive effect on surgical outcomes, including long-term vision and potential adverse effects.

The EVS Group 1995 also conducted a subgroup analysis of the data to determine if a particular study intervention was superior to another for any subset of participants. The study reported that participants with light perception vision at presentation who underwent VIT compared to those who underwent TAP had a three times greater chance of achieving 20/40 final visual acuity (33% vs 11%), almost double the chance of achieving 20/100 final visual acuity (56% vs 30%), and less than half the risk of severe visual acuity loss of less than 5/200 (20% vs 47%). Based on this evidence, the American Academy of Ophthalmology has recommended the role of pars plana vitrectomy and intravitreal antibiotics in their preferred practice pattern (AAO 2021).

Quality of the evidence

The single RCT study that we included for our analysis appeared to be well-designed, multicentred, and adequately powered for some outcomes. However, not all aspects of the study were well reported, and the study was not masked. The method by which participants were randomised was not clearly specified in the publication. Despite this, the overall study design of the Forster 1995 study was good. The study did not address all of our prespecified outcomes; in particular, we downgraded the visual acuity outcome for indirectness. There were few adverse events, and we downgraded the certainty of the evidence on adverse events to very low certainty due to sparse data.

Potential biases in the review process

We are unaware of any potential bias in the review process, but there were limited data available.

Agreements and disagreements with other studies or reviews

Currently, the EVS Group 1995 study provides the only robust evidence for the role of early vitrectomy in exogenous endophthalmitis following surgery. Given that this is the only RCT on this subject, it cannot be directly compared with other studies. However, the results of the EVS Group 1995 do complement the results from other published retrospective and case series studies, which support the role of early vitrectomy in the management of endophthalmitis (Kuhn 2005; Tan 2008).

AUTHORS' CONCLUSIONS

Implications for practice

The single published RCT for the role of early vitrectomy in exogenous endophthalmitis suggests that there may be no difference between groups for visual acuity at three or nine months' follow-up.

Implications for research

This review highlights the need for further RCTs to investigate the role of early vitrectomy in exogenous endophthalmitis, with a particular emphasis on the role of administering a second intravitreal antibiotic injection delivered within 48 hours for eyes that are non-responsive to the first intravitreal antibiotic dose.

ACKNOWLEDGEMENTS

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Gianni Virgili and Jennifer Evans, Co-ordinating Editors for CEV, signed the review off for publication.

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REFERENCES

References to studies included in this review

EVS Group 1995 *{published data only}*10.1001/archopht.1995.01100120009001

* EVS Group. Results of the Endophthalmitis Vitrectomy Study. A randomized trial of immediate vitrectomy and of intravenous antibiotics for the treatment of postoperative bacterial endophthalmitis. Endophthalmitis Vitrectomy Study Group. *Archives of Ophthalmology* 1995;**113**:1479-96.

Additional references

AAO 2021

American Academy of Ophthalmology. Cataract in the Adult Eye Preferred Practice Pattern; 2021. www.aao.org/preferred-practice-pattern/cataract-in-adult-eye-ppp-2021-in-press .

Astley 2016

Astley RA, Coburn PS, Parkunan SM, Callegan MC. Modeling intraocular bacterial infections. *Progress in Retinal and Eye Research* 2016;**54**:30-48.

Callegan 2007

Callegan MC, Gilmore MS, Gregory M, Ramadan RT, Wiskur BJ, Moyer AL, et al. Bacterial endophthalmitis: therapeutic challenges and host-pathogen interactions. *Progress in Retinal and Eye Research* 2007;**26**(2):189-203.

Clarke 2018

Clarke B, Williamson TH, Gini G, Gupta B. Management of bacterial postoperative endophthalmitis and the role of vitrectomy. *Surveys in Ophthalmology* 2018;**63**(5):677-93.

Covidence [Computer program]

Veritas Health Innovation Covidence. Version accessed 5 May 2022. Melbourne, Australia: Veritas Health Innovation. Available at covidence.org.

de Oliveira 2016

de Oliveira PR, Berger AR, Chow DR. Vitreoretinal instruments: vitrectomy cutters, endoillumination and wide-angle viewing systems. *International Journal of Retina and Vitreous* 2016;**2**(28):1-15.

Du 2014

Du DT, Wagoner A, Barone SB, Zinderman CE, Kelman JA, MaCurdy TE, et al. Incidence of endophthalmitis after corneal transplant or cataract surgery in a medicare population. *Ophthalmology* 2014;**121**(1):290-8.

EMS working group 2021

Das T, Dave VP, Dogra A, Joseph J, Sharma S, EMS working group. Endophthalmitis management study. Report #1. Protocol. *Indian Journal of Ophthalmology* 2021;**69**(7):1936-41.

Forster 1980

Forster RK, Abbott RL, Gelender H. Management of infectious endophthalmitis. *Ophthalmology* 1980;**87**(4):313-9.

Forster 1995

Forster RK. The endophthalmitis vitrectomy study. *Archives of Ophthalmology* 1995;**113**(12):1555-7.

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 [Computer program]

McMaster University (developed by Evidence Prime) GRADEpro GDT. Version accessed 4 November 2021. Hamilton (ON): McMaster University (developed by Evidence Prime). Available at gradepro.org.

Higgins 2017

Higgins JP, Altman DG, Sterne JA, editor(s). Chapter 8: Assessing risk of bias in included studies. In: Higgins JP, 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.

Kresloff 1998

Kresloff MS, Castellarin AA, Zarbin MA. Endophthalmitis. *Survery of Ophthalmology* 1998;**43**(3):193-224.

Kuhn 2005

Kuhn F, Gini G. Ten years after... are findings of the Endophthalmitis Vitrectomy Study still relevant today? *Graefe's Archive for Clinical and Experimental Ophthalmology* 2005;**243**(12):1197–9.

Maguire 2008

Maguire JI. Postoperative endophthalmitis: optimal management and the role and timing of vitrectomy surgery. *Eye* 2008;**22**(10):1290-300.

Relhan 2018

Relhan N, Forster RK, Flynn HW Jr. Endophthalmitis: then and now. *American Journal of Ophthalmology* 2018;**187**:xx-vii. [DOI: 10.1016/j.ajo.2017.11.021]

Review Manager 2020 [Computer program]

The Cochrane Collaboration Review Manager 5 (RevMan). Version 5.4. Copenhagen: The Cochrane Collaboration, 2020.

Scott 2011

Scott IU, Flynn HW Jr, Acar N, Dev S, Shaikh S, Mittra RA, et al. Incidence of endophthalmitis after 20-gauge vs 23-gauge vs 25-gauge pars plana vitrectomy. *Graefes Archive Clinical and Experimental Ophthalmology* 2011;**249**(3):377-80.

Stein 2009

Stein JD, Zacks DN, Grossman D, Grabe H, Johnson MW, Sloan FA. Adverse events after pars plana vitrectomy among medicare beneficiaries. *Archives of Ophthalmology* 2009;**127**(12):1656-63.

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Tan 2008

Tan CS, Wong HK, Yang FP, Lee JJ. Outcome of 23-gauge sutureless transconjunctival vitrectomy for endophthalmitis. *Eye* 2008;**22**(1):150-1.

References to other published versions of this review

Muqit 2020

Muqit MM, Mehat M, Bunce C, Bainbridge JW. Early vitrectomy for exogenous endophthalmitis following surgery. *Cochrane Database of Systematic Reviews* 2020, Issue 10. Art. No: CD013760. [DOI: 10.1002/14651858.CD013760]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

EVS Group 1995

Study characteristics	
Methods	Investigator-initiated, multicentre, randomised clinical trial.
Participants	**Country:** USA **Total number of participants:** 420 **Number (%) of men and women:** men = 179 (42.6%) **Average age and age range:** 74.8 (24 to 95) years **Inclusion criteria:** clinical signs and symptoms of bacterial endophthalmitis within 6 weeks of cataract surgery or secondary intraocular lens implantation. **Exclusion criteria**: pre-existing eye disease limiting visual acuity to 20/100 or worse before the development of cataract, prior intraocular surgery other than cataract or intraocular lens surgery, prior penetrating ocular trauma, previous injection of intravitreal antibiotics, prior pars plana VIT, retinal detachment or choroidal detachment that was moderately high, probable intolerance to any study drugs (with the exception of penicillin allergy, in which case alternatives to ß-lactam drugs were used), strong suspicion of fungal endophthalmitis, age younger than 18 years, unsuitability for surgery, or likelihood that the patient would not return for follow-up visits.
Interventions	**Intervention:** VIT (N = 118) **Comparator:** TAP (N = 202) Random assignment according to a 2 x 2 factorial design to intravitreal antibiotics (amikacin) treatment with VIT or TAP and to treatment with or without systemic antibiotics (ceftazidime and amikacin).
Outcomes	**Primary outcome** was defined as visual acuity assessed by an Early Treatment Diabetic Retinopathy Study acuity chart and media clarity assessed both clinically and photographically at 9 months postintervention.
Notes	**Date conducted:** February 1990 to January 1994 **Sources of funding:** not reported **Declaration of interest:** not reported **Included in trials registry:** ClinicalTrials.gov Identifier: NCT00000130

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Details regarding method of randomisation were not specified in the methodology.

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EVS Group 1995 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Details regarding method of randomisation were not specified in the methodology.
Masking of participants and personnel (performance bias) All outcomes	High risk	Given the nature of the intervention, i.e. surgery, it was not possible to mask participants.
Masking of outcome assessment (detection bias) All outcomes	Low risk	Reading centre and technicians undertaking visual acuity measurements were masked.
Selective reporting (reporting bias)	Low risk	No evidence of reporting bias noted in the study.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing or incomplete data were considered in the analysis based on the principle of 'intention to treat'.
Other bias	Low risk	No other bias was identified.

VIT: pars plana vitrectomy; TAP: vitreous tap or biopsy

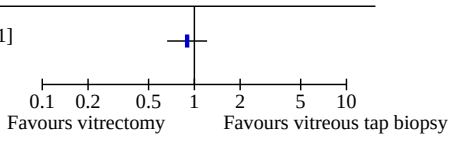
DATA AND ANALYSES

Comparison 1. Vitrectomy compared with vitreous tap biopsy and injection

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Additional surgical procedure	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1: Vitrectomy compared with vitreous tap biopsy and injection, Outcome 1: Additional surgical procedure

Study or Subgroup	Vitrectomy Events	Vitrectomy Total	Vitreous tap biopsy Events	Vitreous tap biopsy Total	Risk Ratio M-H, Fixed, 95% CI
EVS Group 1995 (1)	59	218	61	202	0.90 [0.66 , 1.21]



Footnotes
(1) Follow-up: 9 months

APPENDICES

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor: [Vitrectomy]
#2 PPV*

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#3 vitrectomy
#4 #1 or #2 or #3
#5 MeSH descriptor: [Endophthalmitis]
#6 endophthalmitis
#7 ophthalmia
#8 #5 or #6 or #7
#9 #4 and #8

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. vitrectomy/
14. PPV$.tw.
15. vitrectom$.tw.
16. or/13-15
17. exp endophthalmitis/
18. endophthalmitis.tw.
19. ophthalmia.tw.
20. or/17-19
21. 16 and 20
22. 12 and 21

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/

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27. exp prospective study/
28. (control$ or prospectiv$ or volunteer$).tw.
29. or/25-28
30. 29 not 10
31. 30 not (11 or 23)
32. 11 or 24 or 31
33. vitrectomy/
34. PPV$.tw.
35. vitrectom$.tw.
36. or/33-35
37. exp endophthalmitis/
38. endophthalmitis.tw.
39. ophthalmia.tw.
40. or/37-39
41. 36 and 40
42. 32 and 41

Appendix 4. ISRCTN search strategy

(vitrectomy OR PPV) AND (endophthalmitis)

Appendix 5. ClinicalTrials.gov search strategy

(vitrectomy OR PPV) AND (endophthalmitis)

Appendix 6. WHO ICTRP search strategy

vitrectomy AND endophthalmitis OR vitrectomy AND PPV

Appendix 7. Data on study characteristics

Mandatory items	Details	Optional items
Methods		
Study design	· **Parallel group RCT** i.e. people randomised to treatment · **Within-person RCT** i.e. eyes randomised to treatment · **Cluster-RCT** i.e. communities randomised to treatment · **Cross-over RCT** · Other, specify	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**, specify how eye selected · **Two eyes included in study, both eyes received same treatment**, briefly specify how analysed (best/worst/average/both and adjusted for within person correlation/both and not adjusted for within person correlation) and specify if mixture one eye and two eyes	

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(Continued)

	· **Two eyes included in study, eyes received different treatments,** specify if correct pair-matched analysis done	
Participants		
Country		Setting Ethnic group Equivalence of baseline characteristics (Y/N)
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, please indicate.	
Number (%) of men and women		
Average age and age range		
Inclusion criteria		
Exclusion criteria		
Interventions		
Intervention (N =) Comparator (N =) **See MECIR 66**	· Number of people randomised to this group · Drug (or intervention) name · Dose · Frequency · Route of administration	
Outcomes		
Primary and secondary outcomes as defined in study reports **See MECIR R67**	List outcomes Adverse events reported (Y/N) Length of follow-up and intervals at which outcomes assessed	Planned and 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 **See MECIR 69**		
Declaration of interest **See MECIR 70**		

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(Continued)

Included in trials registry	Y/N; include registration number if available

HISTORY

Protocol first published: Issue 10, 2020

CONTRIBUTIONS OF AUTHORS

- Conceiving the review: MMKM
- Designing the review: MMKM, MM, CB, JWB
- Co-ordinating the review: MMKM, CB
- Data collection for the review
  - Designing search strategies: Cochrane Eyes and Vision
  - Undertaking searches: Cochrane Eyes and Vision
  - Screening search results: MMKM, MM
  - Organising retrieval of papers: MMKM, MM
  - Screening retrieved papers against inclusion criteria: MMKM, MM
  - Appraising quality of papers: MMKM, MM
  - Extracting data from papers: MMKM, MM
- Data management for the review
  - Entering data into RevMan: MMKM, MM
- Analysis of data: MMKM, MM, CB
- Interpretation of data
  - Providing a methodological perspective: MMKM, MM, CB
  - Providing a clinical perspective: MMKM, MM, JWB
  - Providing a policy perspective: MMKM, MM, CB, JWB
  - Providing a consumer perspective: MMKM, MM, JWB
- Writing the review: MMKM, MM
- Providing general advice on the review: JWB, CB

DECLARATIONS OF INTEREST

MMKM is a Consultant on a Scientific Advisory Board for Pixium Vision and joint-principal investigator for an NIHR-funded feasibility study investigating early vitrectomy in endophthalmitis. These are unpaid roles.
MM: no conflicts of interest to declare.
CB is a co-applicant on a study investigating early vitrectomy in endophthalmitis.
JWB has received payment for consultancy work from MeiraGTx Ltd and Novartis. Neither company has a direct interest in the subject of this review. He is also a joint-principal investigator for an NIHR-funded feasibility study investigating early vitrectomy in endophthalmitis; this is an unpaid role.

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Internal sources

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  The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS or the Department of Health.
- Public Health Agency, UK, UK

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- Queen's University Belfast, UK

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We only identified one study and the study enrolled one eye per person. For that reason, the following methods were planned but not used in the review.

- **Unit of analysis:** in the event that there were any studies that included two eyes, we planned to report this and assess whether both eyes received the same treatment or different, and to ensure that our analysis accounted for this.
- **Assessment of heterogeneity:** We planned to examine evidence of heterogeneity by reviewing the study characteristics and examining the forest plots. We also planned to assess the inconsistency of effect estimates across studies using the I^2 statistic and the Chi^2 test for heterogeneity. If the I^2 statistic was greater than 50%, we would have considered this to be substantial heterogeneity. We also planned to consider the magnitude and direction of effects in addition to I^2.
- **Data synthesis:** In our protocol, we planned the following data synthesis approach."If the I^2 is greater than 50%, and if there is significant clinical heterogeneity, we will not conduct a meta-analysis. Instead, we will present a tabulated or narrative summary, or both. If the I^2 is less than 50%, and there is no clinical heterogeneity, we will combine the effect estimates in a meta-analysis, using a random-effects model (provided we have three or more trials). We will use a fixed-effect model if there is no statistical or clinical heterogeneity, and if the number of trials is fewer than three. This is to avoid reporting less robust effect estimates that may result from random-effects models in situations with very few trials. If I^2 is greater than 50%, but effect estimates are in the same direction, we may meta-analyse, but will stress the need for caution."
- **Sensitivity analysis:** Our plans were to "perform sensitivity analyses to examine the impact of excluding studies at high risk of bias in any domain. We will examine whether the summary effect estimate is influenced by any assumptions that have been made during the review."

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