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Ocriplasmin for symptomatic vitreomacular adhesion (Review)

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[Intervention Review]

Ocriplasmin for symptomatic vitreomacular adhesion

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ABSTRACT

Background

Symptomatic vitreomacular adhesion (sVMA) is a recognised cause of visual loss and by tradition has been managed by pars plana vitrectomy (PPV). A less invasive alternative to surgery in some people is enzymatic vitreolysis, using an intravitreal injection of ocriplasmin.

Objectives

To assess the efficacy and safety of ocriplasmin compared to no treatment, sham or placebo for the treatment of sVMA.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (which contains the Cochrane Eyes and Vision Trials Register) (2017, Issue 1), MEDLINE Ovid (1946 to 24 February 2017), Embase Ovid (1947 to 24 February 2017), PubMed (1946 to 24 February 2017), the ISRCTN registry (www.isrctn.com/editAdvancedSearch); searched 24 February 2017, ClinicalTrials.gov (www.clinicaltrials.gov); searched 24 February 2017 and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictcp/search/en); searched 24 February 2017. We did not use any date or language restrictions in the electronic searches for trials.

Selection criteria

We included randomised controlled trials (RCTs) of people with sVMA. The intervention was intravitreal ocriplasmin 125 µg injection, and this was compared to placebo or sham injection (control). Placebo was defined as a single intravitreal injection of 0.10 mL placebo with identical drug vehicle diluted with saline. A sham injection was defined as the syringe hub or blunt needle touching the conjunctiva to simulate an injection.

Data collection and analysis

Two authors independently selected relevant trials, assessed methodological quality and extracted data. We graded the certainty of the evidence using the GRADE approach.

Main results

This review included four RCTs conducted in Europe and the USA with a total of 932 eyes of 932 participants. Participants were 18 to 97 years of age, with evidence of focal vitreomacular adhesion (VMA) on optical coherence tomography (OCT) imaging, with a best corrected visual acuity (BCVA) of 20/25 or worse in the study eye and 20/400 or better in the fellow eye. The interventions compared were intravitreal ocriplasmin versus sham (two RCTs) or placebo (two RCTs) injection. Both sham and placebo injection were classified as the control group. The main outcome measures were assessed at 28 days and six months. Overall, we judged the studies to have a low or unclear risk of bias. All four RCTs were sponsored by the manufacturers of ocriplasmin.

Compared with control, ocriplasmin treatment was more likely to result in VMA release within 28 days (risk ratio (RR) 3.46, 95% confidence interval (CI) 2.00 to 6.00; 859 eyes, 4 RCTs, high-certainty evidence). Approximately 97/1000 eyes will have VMA release within 28 days

without treatment. An additional 237 eyes will have VMA release within 28 days for every 1000 eyes treated with ocriplasmin (95% CI 96 more to 482 more).

Treatment with ocriplasmin was also more likely to result in macular hole closure (RR 2.87, 95% CI 1.50 to 5.51; 229 eyes, 3 RCTs, high-certainty evidence). Approximately 123/1000 eyes with macular holes will have closure with no treatment. An additional 231 eyes will have macular hole closure for every 1000 eyes treated with ocriplasmin (95% CI 62 more to 556 more).

Eyes receiving ocriplasmin were also more likely to have complete posterior vitreous detachment (PVD) within 28 days (RR 2.94, 95% CI 1.39 to 6.24; 689 eyes, 3 RCTs, high-certainty evidence). Approximately 40/1000 eyes will have complete PVD within 28 days without treatment. An additional 78 eyes will have complete PVD within 28 days for every 1000 eyes treated with ocriplasmin (95% CI 16 more to 210 more).

Eyes receiving ocriplasmin were more likely to achieve 3-line or greater improvement in BCVA at six months (RR 1.95, 95% CI 1.07 to 3.53; 674 eyes, 3 RCTs, moderate-certainty evidence). Approximately 61/1000 eyes will have a 3-line or greater improvement in BCVA at six months without treatment. An additional 58 eyes will have 3-line or greater improvement in BCVA at six months for every 1000 eyes treated with ocriplasmin (95% CI 9 more to 154 more).

Receiving ocriplasmin also reduced the requirement for vitrectomy at six months (RR 0.67, 95% CI 0.50 to 0.91; 689 eyes, 3 RCTs, moderate-certainty evidence). Approximately 265/1000 eyes will require vitrectomy at six months without treatment and 87 fewer eyes will require vitrectomy for every 1000 eyes treated with ocriplasmin (95% CI 24 fewer to 132 fewer).

Treatment with ocriplasmin resulted in a greater improvement in validated Visual Function Questionnaire form score at six months (mean improvement difference 2.7 points, 95% CI 0.8 to 4.6; 652 eyes, 2 RCTs, moderate-certainty evidence).

Eyes receiving ocriplasmin were more likely to have an adverse event (RR 1.22, 95% CI 1.09 to 1.37, 909 eyes, 4 RCTs, moderate-certainty evidence). Approximately 571/1000 eyes will have an adverse event with sham or placebo injection and 106 more eyes will have an adverse event for every 1000 eyes treated with ocriplasmin (95% CI 52 more to 212 more).

Authors' conclusions

Evidence from a limited number of RCTs suggests that ocriplasmin is useful in the treatment of sVMA. However, up to 20% of eyes treated with ocriplasmin will still require additional treatment with PPV within six months. There were more ocular adverse events in eyes treated with ocriplasmin than control (sham or placebo injection) treatment. Many of these adverse events, particularly vitreous floaters and photopsia, are known to be associated with posterior vitreous detachment. At present however, there is minimal published long-term safety data on eyes treated with ocriplasmin. Further large RCTs comparing ocriplasmin with other management options for sVMA would be beneficial.

PLAIN LANGUAGE SUMMARY

Ocriplasmin for symptomatic vitreomacular adhesion

What is the aim of this review?

The aim of this Cochrane Review was to find out how well ocriplasmin works in the treatment of symptomatic vitreomacular adhesion (sVMA). Cochrane Review authors collected and analysed all relevant studies to answer this question and found four studies.

Key messages

People with sVMA treated with ocriplasmin have an increased chance of release of sVMA and improved vision compared with people who are not treated with ocriplasmin (high-certainty evidence). They are also probably less likely to require surgery, but one in five people with sVMA treated with ocriplasmin will probably still require surgery at a later date to treat sVMA (moderate-certainty evidence).

What was studied in the review?

With age, the gel-like substance (vitreous) that fills the eye begins to pull away from the back of the eye (retina). Sometimes the vitreous remains attached to the retina and causes damage to the retina as it pulls away, leading to visual loss. This is known as symptomatic vitreomacular adhesion or sVMA. sVMA includes two related conditions, vitreomacular traction and macular hole.

The standard treatment for sVMA is surgery. Ocriplasmin is an alternative, less invasive, treatment. This is an enzyme that can be injected directly into the eye to release the vitreous from the retina.

What are the main results of the review?

Cochrane Review authors found four studies that compared ocriplasmin with control (sham or placebo treatment) for the treatment of sVMA. All four studies were sponsored by the manufacturers of ocriplasmin.

The review showed that:

- ocriplasmin increases the chance of sVMA resolution compared with no treatment (high-certainty evidence);

- people with sVMA treated with ocriplasmin have improved vision compared with people who are not treated with ocriplasmin (high-certainty evidence);
- treatment with ocriplasmin probably reduces the requirement for surgery, but approximately one in five people treated with ocriplasmin may require further surgery at a later date (moderate-certainty evidence);
- there were more ocular adverse events in eyes treated with ocriplasmin than control (sham or placebo injection) treatment.

How up-to-date is this review?

Cochrane Review authors searched for studies that had been published up to 24 February 2017.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Ocriplasmin injection compared with control for symptomatic vitreomacular adhesion

Ocriplasmin injection compared with control for symptomatic vitreomacular adhesion

Patient or population: people with symptomatic vitreomacular adhesion

Settings: eye hospital

Intervention: ocriplasmin injection

Comparison: sham or placebo injection

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of eyes (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Sham or placebo injection	Ocriplasmin injection				
Complete release of vitreous adhesion Follow-up: 28 days	97 per 1000	334 per 1000 (193 to 579)	RR 3.46 (2.00 to 6.00)	859 (4 studies)	⊕⊕⊕⊕ High	-
Closure of macular hole Follow-up: 28 days to 24 months	123 per 1000	354 per 1000 (185 to 679)	RR 2.87 (1.50 to 5.51)	229 (3 studies)	⊕⊕⊕⊕ High	-
Complete posterior vitreous detachment Follow-up: 28 days	40 per 1000	118 per 1000 (56 to 250)	RR 2.94 (1.39 to 6.24)	689 (3 studies)	⊕⊕⊕⊕ High	-
3-line or greater improvement in best-corrected visual acuity Follow-up: 6 months	61 per 1000	119 per 1000 (70 to 215)	RR 1.95 (1.07 to 3.53)	674 (3 studies)	⊕⊕⊕⊙ Moderate^a	-
Requirement for vitrectomy Follow-up: 6 months	265 per 1000	178 per 1000 (133 to 241)	RR 0.67 (0.50 to 0.91)	689 (3 studies)	⊕⊕⊕⊙ Moderate^a	-
Mean change in validated visual function questionnaire score from baseline	Mean change in NEI-VFQ score was 0.7	NEI-VFQ score was 2.7 higher (0.8 higher to 4.6 higher)	-	652 (2 studies)	⊕⊕⊕⊙ Moderate^a	-

Score ranges from 0 to 100, higher scores are better visual function						
Follow-up: 6 months						
Any ocular adverse event	571 per 1000	697 per 1000	RR 1.22	909	⊕⊕⊕⊖	-
Follow-up: 6 months		(623 to 783)	(1.09 to 1.37)	(4 studies)	Moderate^a	

*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; **NEI-VFQ:** National Eye Institute Visual Function Questionnaire; **RCT:** randomised controlled trial; **RR:** risk ratio.

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.

^aDowngraded one level for imprecision (-1).

BACKGROUND

Description of the condition

In healthy eyes, the posterior vitreous face lies in contact with the internal limiting membrane (ILM) of the retina with various points of stronger adhesion such as the macula, vasculature and optic disc. Over time, the structure of the vitreous liquefies in a process known as synchysis, with reduction in the adhesive forces between vitreous and ILM. This often results in the vitreous gel detaching from all parts of the retina, except at the vitreous base anteriorly, in a normal process known as posterior vitreous detachment (PVD) (Foos 1982). The process usually starts with focal detachment in the perifovea of the superior quadrant and then extends slowly for years until eventually resulting in a complete PVD with release of vitreopapillary adhesion (Ito 2003; Johnson 2010; Uchino 2001). However, in certain cases, incomplete PVD may occur, leaving the vitreous in contact with the macula or optic disc, or both.

Although, anatomically, vitreomacular adhesion (VMA) may refer to a normal asymptomatic state, clinically, the term is used when VMA occurs in the context of an incomplete PVD. There is a spectrum of VMA associated with incomplete PVD, which ranges from asymptomatic, non-tractional VMA to extensive distortion of the retinal structure due to vitreomacular traction (VMT) which may result in loss of visual function. These distinctions tend to be based on optical coherence tomography (OCT), sometimes in reference to defined photographic standards (Simpson 2012). However, it is important to note that the OCT changes, which may include retinal thickening and intraretinal oedema, do not always correlate with visual function and symptoms.

Symptomatic vitreomacular adhesion (svMA) is defined as visual loss secondary to foveal damage caused by abnormal VMT. svMA includes isolated VMT, impending macular hole (MH) and MH with persisting vitreous attachment (Jackson 2013a). Impending MH is often grouped with VMT. Epiretinal membrane (ERM) often coexists with svMA. It is possible that VMA influences the clinical course of, or may be associated with, other diseases such as diabetic macular oedema, retinal vein occlusion or neovascular age-related macular degeneration, although the data are sometimes conflicting (Jackson 2013a; Jackson 2013b; Nomura 2014; Simpson 2012; Terao 2014; Waldstein 2014; Yoon 2014). Whilst there may be an association between svMA and these other diseases, it is not certain that this is causal (Simpson 2012). Consequently, it is difficult to define the prevalence of svMA. One study reported that VMA may occur in isolation or in association with other eye disease in approximately 1.5% of the population (Jackson 2013a). However, the majority of these cases occurred alongside ERM, and thus the VMA may not be responsible for visual loss. Excluding cases associated with ERM reduced the prevalence to 0.35% in the same population-based study; however, this figure also included cases with other diseases, such as wet age-related macular degeneration and diabetic macular oedema (Jackson 2013a). If only cases of isolated VMA/VMT with or without MH were considered, then the prevalence of svMA was 171.5 per 100,000 population (Jackson 2013a).

The natural history of svMA varies. svMA may spontaneously resolve, with detachment of the posterior vitreous face from the ILM (Steel 2013). One study of 53 eyes showed a complete PVD occurred in 11% of eyes over 60 months' follow-up (Hikichi 1995). Weinard and colleagues reported that approximately 10% of cases

of VMT syndrome resolve spontaneously (Weinard 2009). Other studies have found spontaneous resolution in 17% to 35% of cases with VMT (Almeida 2015; Theodossiadis 2014; Zhang 2015). Eyes with VMT and isolated inner retinal distortion, as well as those receiving vitreous injections, have an increased likelihood of VMT release (Almeida 2015). Poor prognostic indicators for spontaneous release include the presence of ERM and large horizontal adhesion diameter (Haller 2015; Jackson 2016; Theodossiadis 2014; Zhang 2015). It has been shown that many, if not most, MHs result from persistent VMT which either fully detaches from the retina causing an MH, or remains attached at the edge of the hole (Chauhan 2000; Gass 1988; Gaudric 1999; La Cour 2002; Tanner 2001).

Description of the intervention

Treatment strategies for VMA vary depending on disease severity. Asymptomatic VMT can be observed, since separation of the posterior vitreous face may occur spontaneously and without sequelae. However, a longer duration of VMT may lead to loss of vision and possibly lower efficacy of any subsequent intervention, and therefore treatment is often considered if symptoms are significant or visual acuity is reduced (Hikichi 1995; Melberg 1995; Sonmez 2008). If VMT progresses to MH then intervention is usually advised, and an evolving VMT/impending MH may likewise necessitate intervention.

If intervention is considered for svMA, various strategies may be considered. Traditionally, pars plana vitrectomy (PPV) is the standard approach for VMT or MH (Steel 2013). Small uncontrolled studies reported that an intravitreal gas bubble can pneumatically release VMT, without the need for PPV, with success rates varying from 71% to 95% (Chan 1995; Mori 2007; Rodrigues 2013).

Pharmacological vitreolysis has been investigated as an alternative treatment for VMT, and for MH with persisting VMA (Benz 2010; De Smet 2009; Stalmans 2010; Stalmans 2012). Autologous plasmin, an enzyme that breaks down the laminin and fibronectin bonds maintaining vitreous adhesion, has been used perioperatively to induce a PVD during vitrectomy (Margherio 1998; Sakuma 2006; Williams 2001). However, autologous plasmin is not suited to the treatment of VMT due to its autolytic instability (Gandorfer 2008). Based on autologous plasmin, a recombinant DNA molecule, initially referred to as microplasmin, and more recently ocriplasmin (Jetrea; ThromboGenics, Leuven, Belgium), was developed to provide the same catalytic properties but with greater stability.

Ocriplasmin is administered as a single intravitreal injection of 125 µg in 0.1 mL. It has marketing authorisation for the treatment of VMT, including when associated with MH of diameter of 400 µm or less (SmPC 2013). In the UK, the National Institute for Health and Care Excellence (NICE) supports the use of ocriplasmin for adults with VMT causing severe sight problems or a macula hole up to 400 µm, in the absence of ERM (NICE 2013).

How the intervention might work

Ocriplasmin is a proteolytic enzyme which targets laminin and fibronectin, both of which are important structural components of the interface between the vitreous and the retina. It is a truncated form of the human serine protease plasmin which functions in a two-stage mechanism; liquefaction of the vitreous and vitreoretinal separation (Kupfermann 2012).

Why it is important to do this review

Ocriplasmin has marketing authorisation in Europe and the USA and is the only licensed, non-surgical treatment for sVMA. MH is the second most common indication for PPV, and both MH and VMT can cause substantial visual problems (Jackson 2013c). This review is important as it assessed the efficacy and safety of ocriplasmin treatment.

OBJECTIVES

To assess the efficacy and safety of ocriplasmin compared to no treatment, sham or placebo for the treatment of sVMA.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) only.

Types of participants

We included participants with a diagnosis of sVMA, including VMT and MH of 400 µm or less with persisting VMA. There were no restrictions with regards to gender, age or ethnicity.

Types of interventions

We included any RCT in which intravitreal ocriplasmin was compared to no treatment, sham injection or placebo.

Types of outcome measures

Primary outcomes

- Proportion of eyes with complete release of vitreous adhesion as determined by analysis of OCT images captured 28 days after ocriplasmin, sham or placebo treatment.

Secondary outcomes

- Proportion of eyes with closure of MH as determined by analysis of OCT images captured 28 days after ocriplasmin, sham or placebo treatment.
- Proportion of eyes with complete PVD as measured by clinical examination or B-scan ultrasonography 28 days after ocriplasmin, sham or placebo treatment.
- Proportion of eyes with 3-line or greater improvement in best corrected visual acuity (BCVA) from baseline, measured using Early Treatment Diabetic Retinopathy Study (ETDRS) at 4 m or Snellen chart, at six months after ocriplasmin, sham or placebo treatment.
- Proportion of eyes requiring PPV within six months of ocriplasmin, sham or placebo treatment (as recommended by the investigator if the underlying condition deteriorated, BCVA worsened by more than 2 lines on ETDRS or Snellen chart, or if the underlying condition had not improved within 28 days after treatment).
- Mean change in validated Visual Function Questionnaire (VFQ) score from baseline, measured at six months after ocriplasmin, sham or placebo treatment.

Safety outcomes

- Description of ocular adverse events and serious adverse events, and any non-ocular serious adverse events attributed to ocriplasmin or no treatment/sham/placebo.

Search methods for identification of studies

Electronic searches

The Cochrane Eyes and Vision Information Specialist conducted systematic searches in the following databases for randomised controlled trial and controlled clinical trials. There were no language or publication year restrictions. The date of the search was 24 February 2017.

- Cochrane Central Register of Controlled Trials (CENTRAL; 2017, Issue 1) (which contains the Cochrane Eyes and Vision Trials Register) in the Cochrane Library (searched 24 February 2017) (Appendix 1);
- MEDLINE Ovid (1946 to 24 February 2017) (Appendix 2);
- Embase Ovid (1980 to 24 February 2017) (Appendix 3);
- PubMed (1946 to 24 February 2017) (Appendix 4);
- ISRCTN registry (www.isrctn.com/editAdvancedSearch; searched 24 February 2017) (Appendix 5);
- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov; searched 24 February 2017) (Appendix 6);
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictip; searched 24 February 2017) (Appendix 7).

Searching other resources

We searched the reference lists of included studies for other possible studies. We did not search proceedings from conferences specifically, because such RCTs presented at these meetings were searched by Cochrane Eyes and Vision and included in CENTRAL.

Data collection and analysis

Selection of studies

Three authors (JN, VK and TJ) independently assessed the results identified by the searches and classified each record as either possibly relevant or definitely not relevant. We then obtained full-text copies of all possibly relevant records, and three authors (JN, VK and TJ) classified them as definitely include, unsure or definitely exclude based on the criteria for inclusion. In the event of any difficulty in classification due to lack of clarity or data, we contacted study investigators for further information. All contacted authors responded to our requests. We resolved discrepancies by consensus following discussion between authors (JN, VK and TJ) and documented this in the review. All excluded records were documented.

Data extraction and management

Two authors (JN and VK) independently extracted trial data for the primary and secondary outcomes onto paper data extraction forms developed by Cochrane Eyes and Vision. Subsequently, data were transcribed into Review Manager 5 (RevMan 2014) by one author (JN) and verified by a second author (VK). Any discrepancies were resolved by consensus between authors (JN, VK and TJ) and documented in the review.

We collected the following information on study characteristics (see [Appendix 8](#)):

- study design: parallel group RCT/within-person RCT/one or both eyes reported;
- participants: country, total number of participants, age, sex, inclusion and exclusion criteria;
- intervention and comparator details: including number of people (eyes) randomised to each group;
- primary and secondary outcomes as measured and reported in the trials, adverse events;
- length of follow-up;
- date study conducted;
- funding and conflicts of interest.

We extracted the following data from each included study for intervention and comparator groups separately:

- number of events and number of participants for outcome data collected for dichotomous variables (release of vitreous adhesion at 28 days, closure of MH at 28 days and complete PVD at 28 days);
- mean, standard deviation and number of participants for outcome data measured for continuous variables (change in BCVA at six months and change in validated VFQ at six months). To compare visual acuity across studies, the mean BCVA was converted to logarithm of the minimum angle of resolution units (logMAR). Counting fingers vision was assigned a logMAR acuity of 1.6, hand movements 1.9, light perception 2.2 and no light perception 2.5 ([Westheimer 1979](#)). The default VFQ assessed was the National Eye Institute Visual Functioning Questionnaire - 25 (NEI-VFQ25).

We collected evidence of harm from RCTs only.

Assessment of risk of bias in included studies

Two authors (JN and VK) independently assessed the included trials for bias using the methods and grades described in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011a](#)). We assessed the following: methods of sequence generation used for randomisation; allocation concealment; masking (blinding) of outcome assessors; masking of participants and personnel; incomplete outcome data; selective outcome reporting; other bias. We considered the use, or not, of independent masked OCT image analysis assessors in the assessment of bias. We then classified each item as 'low,' 'high' or 'unclear' risk of bias.

Measures of treatment effect

We presented dichotomous data as risk ratios (RR) with 95% confidence intervals (CI);

- Primary outcome:
 - * resolution of VMA.
- Secondary outcomes:
 - * closure of MH;
 - * complete PVD;
 - * proportion of eyes with 3-line or greater gain in BCVA;
 - * requirement for PPV.

We presented continuous data as mean differences with 95% CIs:

- change in validated VFQ measure.

Unit of analysis issues

Trials randomised one or both eyes to the intervention or comparator. If people were randomly allocated to treatment but only one eye per person was included in the trial then there was no unit of analysis issue. In these cases, we documented how the eye was selected and if this was done before randomisation. If people were randomly allocated to treatment but both eyes were included and reported, we planned to analyse as 'clustered data,' that is, adjust for within-person correlation. If the study was a within-person study, that is, one eye was randomly allocated to intervention and the other eye received the comparator, then we planned to analyse as paired data. We planned to contact the trial investigators for further information to do this if necessary.

Dealing with missing data

In the event of missing trial outcome data, we contacted the authors of the trial to understand why the data were missing. If no response was received within four weeks, we used the information provided in the published articles. Missing data were handled in accordance with the guidelines given in Chapter 16 of the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011b](#)). We planned to perform sensitivity analyses on the impact of missing data and comment on the findings in the discussion of the review.

Assessment of heterogeneity

We assessed heterogeneity and inconsistency among trials statistically using an I^2 value ($> 50\%$) to assess if variability in effect was due to sampling error. We also planned to assess diversity among studies by reviewing participant characteristics and trial methodology.

Assessment of reporting biases

We assessed selective outcome reporting by comparing intended outcomes in published protocols, published methods papers and clinical trial registries to reported outcomes in the results sections of trial reports. If there were 10 or more eligible RCTs, we planned to use a funnel plot to assess for study-reporting bias.

Data synthesis

If there were three or fewer eligible RCTs then we planned to use a fixed-effect model for the meta-analyses. If there were more than three included trials, we planned to use a random-effects model instead. If we had evidence of high heterogeneity (e.g. $I^2 > 50\%$), it would not be sensible to pool the data from different trials; in which case, we planned to do a narrative summary of the results.

Subgroup analysis and investigation of heterogeneity

If trials demonstrated clinical heterogeneity and sufficient data were available, including age (< 65 years, 65 years and over), presence of ERM, size of adhesion (less than 1500 μm , 1500 μm or greater) and sVMA subtype (isolated VMT, and MH with persisting vitreous attachment), we planned to perform subgroup analyses for the primary outcome.

Sensitivity analysis

We planned to conduct one sensitivity analysis, excluding studies that were at high risk of bias in one or more domains.

'Summary of findings' table

We prepared a 'Summary of findings' table for the following outcomes:

- resolution of VMA at 28 days;
- complete PVD at 28 days;
- closure of MH at 28 days;
- proportion gaining 3-line or greater improvement in BCVA at six months;
- requirement of PPV at six months;
- change in validated VFQ measure at six months;
- adverse and serious adverse events.

Two authors (JN and VK) independently graded the overall certainty of the evidence for each outcome using the GRADE Working Group classification ([GRADEpro 2014](#)).

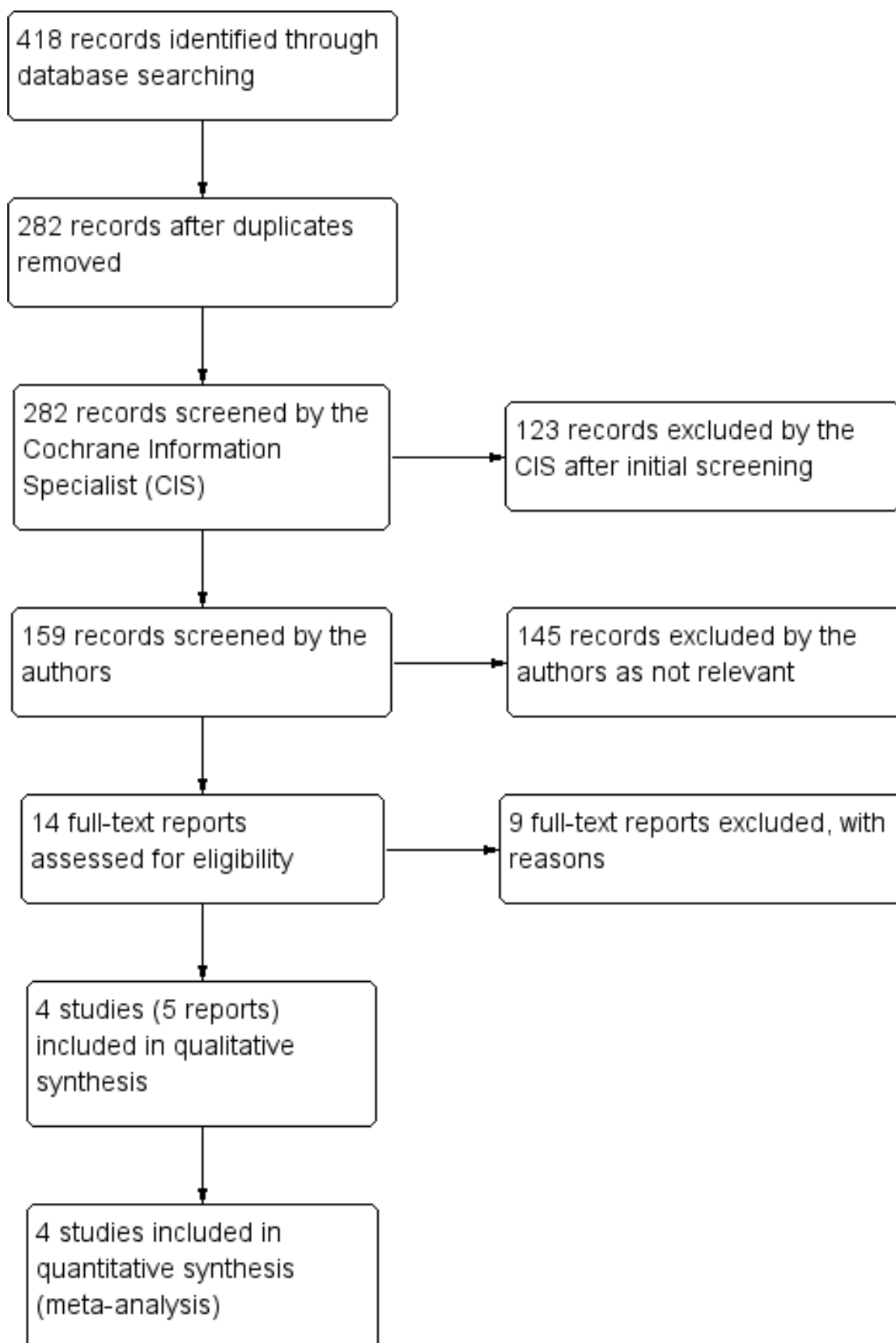
RESULTS

Description of studies

Results of the search

The electronic searches yielded 418 records ([Figure 1](#)). The Cochrane Information Specialist scanned the search results, removed 136 duplicates and then removed 123 references which were irrelevant to the scope of the review. We screened the remaining 159 reports and obtained 14 full-text reports for further assessment. We included five reports of four RCTs, three reports ([Haller 2015](#); [Stalmans 2012](#); [Varma 2015](#)) analysed separate outcomes from the same two RCTs ([TG-MV-006 2012](#); [TG-MV-007 2012](#)). We excluded nine reports of nine studies (see [Characteristics of excluded studies](#) for details). We did not identify any ongoing studies from our searches of clinical trials registries.

Figure 1. Study flow diagram.



Included studies

The following is a summary of the characteristics of the four RCTs that met the review inclusion criteria (MIVI-IIT 2010; OASIS 2016; TG-MV-006 2012; TG-MV-007 2012). All data were initially obtained from published literature, then verified for discrepancies using the clinical trials registries described in the [Methods](#) section. See the [Characteristics of included studies](#) table for further information.

Types of participants

The four RCTs included enrolled 932 participants (932 eyes). All participants received individually randomised, parallel group treatment to a single eye. The age range of all included participants was 18 to 97 years. All included participants had evidence of focal VMA on OCT, BCVA of 20/25 or worse in the study eye and 20/400 or better in the fellow eye (ETDRS acuity chart). Exclusion criteria were: active proliferative diabetic retinopathy, high myopia (axial length greater than 26 mm or more than -8 dioptres), previous vitrectomy or uncontrolled glaucoma, previous intravitreal injections within the past three months in the study eye, intraocular surgery or laser photocoagulation within the past three months in the study eye or rhegmatogenous retinal detachment in either eye. Additional exclusion criteria in TG-MV-007 2012 were: neovascular age-related macular degeneration, retinal vascular occlusion, aphakia, MH greater than 400 µm in diameter, vitreous opacification or lenticular or zonular instability. In OASIS 2016, eyes with an ERM were also excluded from enrolment.

Types of interventions

MIVI-IIT 2010 compared a single injection of ocriplasmin 75 µg, ocriplasmin 125 µg or ocriplasmin 175 µg with sham injection (conjunctiva touched with a blunt needle to simulate an injection) to establish the optimal dose. A fourth cohort of participants underwent an initial injection of ocriplasmin 125 µg, but also a

repeat injection at four and eight weeks if VMA was still present on OCT. Therefore, only data from participants receiving ocriplasmin 125 µg in this study were extracted and pooled for analysis. TG-MV-006 2012 and TG-MV-007 2012 both compared a single injection of ocriplasmin 125 µg with placebo injection (of the same vehicle used in the ocriplasmin injection). OASIS 2016 compared a single injection of ocriplasmin 125 µg with sham injection (syringe hub pressed into conjunctiva to simulate an injection).

Types of outcome measures

All four studies reported data for some of our primary and secondary outcome measures. No trial reported data for every outcome measure. Two trial reports (OASIS 2016; Varma 2015) provided data on participant-reported outcome measures using the NEI-VFQ25.

Data synthesis, subgroup and sensitivity analyses

As the search identified four trials, we used a random-effects model (see [Data synthesis](#)). As there was no evidence of significant heterogeneity for the primary outcomes ($I^2 < 50\%$), we pooled data and performed no subgroup analyses of the primary outcome. Since no studies had a high risk of bias in any domain, we did not conduct a sensitivity analysis.

Excluded studies

We excluded nine articles after reviewing full-text copies (Benz 2010; De Smet 2009; Dugel 2015; Elbendary 2011; Lanzetta 2014a; Lanzetta 2014b; Lescrauwaet 2016; Jackson 2017; Novack 2015). See [Characteristics of excluded studies](#) table for details.

Risk of bias in included studies

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.

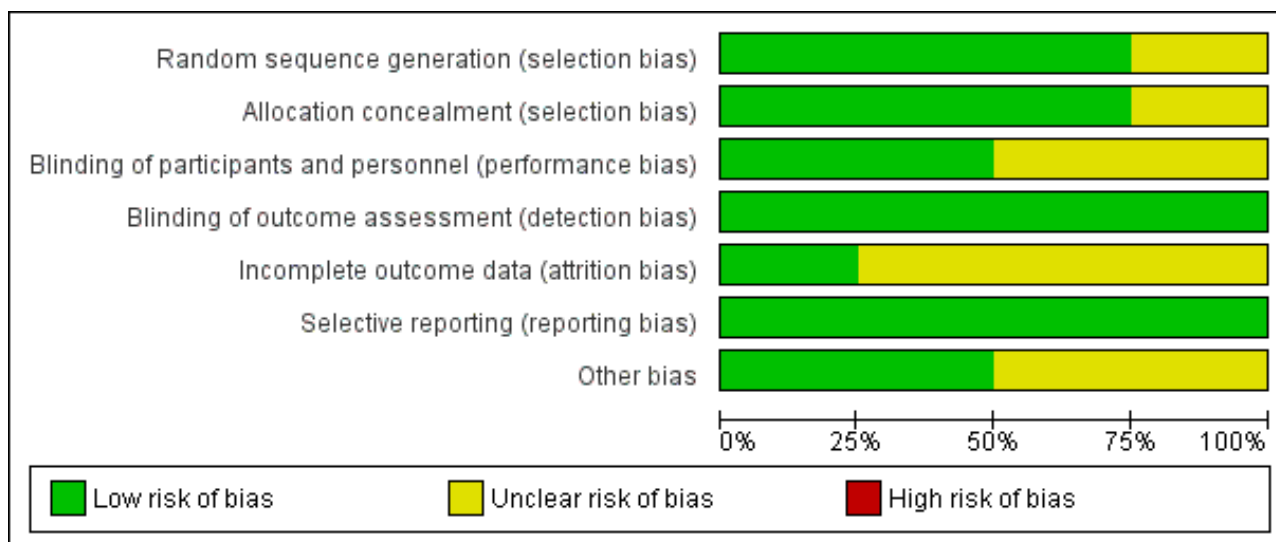


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
MIVI-IIT 2010	?	?	?	+	+	+	+
OASIS 2016	+	+	?	+	?	+	+
TG-MV-006 2012	+	+	+	+	?	+	?
TG-MV-007 2012	+	+	+	+	?	+	?

Allocation

MIVI-IIT 2010 did not describe the method of sequence generation, and provided insufficient information to also assess allocation concealment (Stalmans 2010). TG-MV-006 2012 and TG-MV-007 2012 clearly described randomisation and allocation concealment, which as a centralised telephone-based system with blocks of treatment assigned to sites (Haller 2015; Stalmans 2012; Varma 2015). OASIS 2016 clearly described the method of randomisation, which used a centralised interactive voice response system.

Blinding

Two trials adequately masked participants and investigators (TG-MV-006 2012; TG-MV-007 2012). However, two trials did not mask investigators to sham injections (MIVI-IIT 2010; OASIS 2016), which

may have induced a different sensation to a true injection. The risk of performance bias was graded as unclear for both studies.

Incomplete outcome data

We graded risk of bias as low in one study (MIVI-IIT 2010), and unclear in the other three studies (OASIS 2016; TG-MV-006 2012; TG-MV-007 2012). Unclear risk was due to losses to follow-up not being reported and being unequal in different study groups. In addition, OASIS 2016 randomised 200 participants, but 50 participants were later found to be incorrectly enrolled by the central reading centre for a variety of reasons including MH greater than 400 µm, presence of ERM or no VMA at baseline. A subgroup analysis of this smaller cohort of participants, who met the inclusion and exclusion criteria, was performed, but only on outcome data for VMA release.

One trial reported a dilution error, which resulted in an extra participant treated in the ocriplasmin 125 µg cohort and one less participant in the ocriplasmin 175 µg cohort (MIVI-IIT 2010).

Selective reporting

All studies reported on all prespecified primary and secondary outcomes (MIVI-IIT 2010; OASIS 2016; TG-MV-006 2012; TG-MV-007 2012).

Other potential sources of bias

Two studies reported a baseline imbalance between study groups as pseudophakia was more common in the ocriplasmin group than in the placebo group and there were more women in the ocriplasmin group than in the placebo group (TG-MV-006 2012; TG-MV-007 2012). Therefore, this was at unclear risk of bias.

Effects of interventions

See: [Summary of findings for the main comparison Ocriplasmin injection compared with control for symptomatic vitreomacular adhesion](#)

See [Summary of findings for the main comparison](#).

1. Proportion of eyes with complete release of vitreous adhesion

All four RCTs provided data for proportion of eyes with complete release of vitreous adhesion as determined by analysis of OCT images captured 28 days after ocriplasmin, sham or placebo treatment (MIVI-IIT 2010; OASIS 2016; TG-MV-006 2012; TG-MV-007 2012). After excluding participants with protocol violations from OASIS 2016, analysis of the pooled data showed higher complete release of vitreous adhesion in the ocriplasmin group compared with control (placebo or sham) treatment (RR 3.46, 95% CI 2.00 to 6.00; 859 eyes; 4 studies; high-certainty evidence; [Analysis 1.1](#)). A total of 97/1000 eyes had VMA release within 28 days without treatment. An additional 237 eyes had VMA release within 28 days for every 1000 eyes treated with ocriplasmin (95% CI 96 more to 482 more).

2. Proportion of eyes with closure of macular hole

Three studies provided data for proportion of eyes with closure of MH as determined by analysis of OCT images captured 28 days after ocriplasmin, sham or placebo treatment (OASIS 2016; TG-MV-006 2012; TG-MV-007 2012); data from MIVI-IIT 2010 could not be included in this analysis as the original paper did not provide a breakdown of the ocriplasmin doses used to treat MH. OASIS 2016 measured MH closure at three months and the closure rate remained the same to the end of the study at 24 months. After excluding 14 participants incorrectly enrolled in OASIS 2016 due to MH being greater than 400 µm, analysis of the pooled data showed higher closure of MH in the ocriplasmin group compared with control (placebo or sham) treatment (RR 2.87, 95% CI 1.50 to 5.51; 229 eyes; 3 studies; high-certainty evidence; [Analysis 1.2](#)). A total of 123/1000 eyes with MHs had closure with no treatment. An additional 231 eyes had MH closure for every 1000 eyes treated with ocriplasmin (95% CI 62 more to 556 more).

3. Proportion of eyes with complete posterior vitreous detachment

Three studies provided data for proportion of eyes with complete PVD as measured by clinical examination or B-scan ultrasonography 28 days after ocriplasmin, sham or placebo treatment (MIVI-IIT 2010; TG-MV-006 2012; TG-MV-007 2012). Analysis revealed a higher incidence of complete PVD at 28 days in eyes treated with ocriplasmin compared with control (placebo or sham) treatment (RR 2.94, 95% CI 1.39 to 6.24; 689 eyes; 3 studies; high-certainty evidence; [Analysis 1.3](#)). A total of 40/1000 eyes had complete PVD within 28 days without treatment. An additional 78 eyes had complete PVD within 28 days for every 1000 eyes treated with ocriplasmin (95% CI 16 more to 210 more).

4. Proportion of eyes with 3-line or greater improvement in best corrected visual acuity

Three studies provided data for proportion of eyes with 3-line or greater improvement in BCVA measured using the ETDRS scale, at six months after ocriplasmin, sham or placebo treatment (MIVI-IIT 2010; TG-MV-006 2012; TG-MV-007 2012). Due to separate outcomes reported for eyes with and without full-thickness MH, and large numbers of participants not meeting eligibility criteria, data were not included from OASIS 2016. Eyes that had undergone PPV in MIVI-IIT 2010 during this six-month period were also excluded. Analysis of the pooled data revealed that eyes treated with ocriplasmin without PPV were more likely to achieve 3-line or greater improvement in BCVA than control (sham or placebo) eyes (RR 1.95, 95% CI 1.07 to 3.53; 674 eyes; 3 studies; moderate-certainty evidence; [Analysis 1.4](#)). A total of 61/1000 eyes had 3-line or greater improvement in BCVA at six months without treatment. An additional 58 eyes had 3-line or greater improvement in BCVA at six months for every 1000 eyes treated with ocriplasmin (95% CI 9 more to 154 more).

5. Proportion of eyes requiring vitrectomy within six months of ocriplasmin, sham or placebo treatment

Three studies provided data for proportion of eyes requiring vitrectomy (MIVI-IIT 2010; TG-MV-006 2012; TG-MV-007 2012). All three RCTs defined the requirement for vitrectomy as "recommended by the investigator if the underlying condition deteriorated, BCVA worsened by more than two lines on ETDRS or Snellen chart, or if the underlying condition had not improved within 28 days after treatment." Due to separate outcomes reported for eyes with and without full-thickness MH, and large numbers of participants not meeting eligibility criteria, data were not included from OASIS 2016. Analysis revealed a lower requirement for vitrectomy in eyes treated with ocriplasmin compared with control (placebo or sham) treatment (RR 0.67, 95% CI 0.50 to 0.91; 689 eyes; 3 studies; moderate-certainty evidence; [Analysis 1.5](#)). A total of 265/1000 eyes required vitrectomy at six months without treatment and 87 fewer eyes required vitrectomy for every 1000 eyes treated with ocriplasmin (95% CI 24 fewer to 132 fewer).

6. Mean change in validated Visual Function Questionnaire score from baseline measured at six months after ocriplasmin, sham or placebo treatment

One trial reported data for mean change in validated VFQ score from baseline (Varma 2015), which analysed pooled participant-reported visual function outcomes for TG-MV-006 2012 and TG-MV-007 2012. In all eyes across both studies, mean increases in

the composite NEI-VFQ25 score at six months from baseline were greater in eyes treated with ocriplasmin (464 eyes) than placebo (188 eyes) (mean change: 3.4 with ocriplasmin versus 0.7 with placebo; $P = 0.005$). We calculated the mean difference as 2.7 (95% CI 0.8 to 4.6). Visual function data was also reported in [OASIS 2016](#), but this was not reported for the subgroup who met the inclusion and exclusion criteria following central reading centre analysis.

7. Adverse effects

Due to inconsistencies between the studies and differences in control groups (placebo injection versus sham injection), we did not perform a pooled analysis of adverse events. Instead, a descriptive account of the types of ocular adverse event is provided below, based on data from three studies ([OASIS 2016](#); [TG-MV-006 2012](#); [TG-MV-007 2012](#)). Although a large number of participants were incorrectly enrolled in [OASIS 2016](#), safety data are presented for all participants who underwent intervention with ocriplasmin or control treatment.

7.1. Any ocular adverse events

These were defined as any ocular adverse event that did not meet the criteria for a serious ocular adverse event (see '7.2. Any serious ocular adverse events'). All four RCTs provided data for any ocular adverse event ([MIVI-IIT 2010](#); [OASIS 2016](#); [TG-MV-006 2012](#); [TG-MV-007 2012](#)). Analysis revealed more ocular adverse events in eyes treated with ocriplasmin compared with placebo or sham-treated eyes (RR 1.22, 95% CI 1.09 to 1.37; 909 eyes; 4 studies; moderate-certainty evidence; [Analysis 1.6](#)).

A breakdown of the most frequently reported ocular adverse events is listed in the table below (n = number of eyes affected, **not** total number of events). The first five ocular adverse events were participant-reported. The most commonly reported ocular adverse events following ocriplasmin treatment were vitreous floaters (affecting 133/611 eyes or 21.8%), photopsia (affecting 98/611 eyes or 16.0%) and injection-related eye pain (affecting 83/611 eyes or 13.6%). The incidence of vitreous floaters, photopsia, injection-related eye pain, blurred vision and visual impairment was significantly greater in eyes treated with ocriplasmin than those treated with sham or placebo injection.

Study	MIVI-IIT 2010		TG-MV-006 2012		TG-MV-007 2012		OASIS 2016	
	Ocriplas- min (n = 25)	Control (n = 12)	Ocriplas- min (n = 220)	Control (n = 106)	Ocriplas- min (n = 245)	Control (n = 81)	Ocriplas- min (n = 146)	Control (n = 74)
Any ocular adverse event	21	9	159	62	159	38	106	47
Vitreous floaters ^a	-	-	42	9	36	5	55	6
Photopsia ^a	-	-	36	4	19	1	43	5
Injection-related eye pain ^a	-	-	33	6	30	5	20	6
Blurred vision ^a	-	-	24	4	16	2	27	4
Visual impairment ^a	-	-	21	3	4	0	21	4
Conjunctival haemorrhage	8	3	34	14	34	10	14	1
Increased intraocular pressure ^a	-	-	9	10	9	0	10	10
Retinal tear ^a	-	-	5	2	1	3	2	5
Cataract ^a	-	-	14	12	12	5	19	10
Anterior chamber cells ^b	1	0	-	-	-	-	-	-
Iridocyclitis ^b	1	0	-	-	-	-	-	-
Vitritis ^b	3	0	-	-	-	-	-	-

^aOcular adverse events not reported in MIVI-IIT.

^bOcular adverse events not reported in [OASIS 2016](#), [TG-MV-006 2012](#), or [TG-MV-007 2012](#).

Note: the control group in [MIVI-IIT 2010](#) and [OASIS 2016](#) was sham injection. The control group in [TG-MV-007 2012](#) and [TG-MV-006 2012](#) was placebo injection.

7.2. Any serious ocular adverse events

Two studies defined serious ocular adverse event as: an event resulting in persistent or clinically significant disability, incapacity or both; an event requiring inpatient hospitalisation or prolongation of an existing hospital stay; or an event that was considered to be medically important ([TG-MV-006 2012](#); [TG-MV-007 2012](#)). One study did not provide a definition of a serious ocular adverse event ([OASIS 2016](#)). [MIVI-IIT 2010](#) reported no instances of serious ocular adverse events.

A breakdown of the most frequently reported serious ocular adverse events is listed in the table below (n = number of eyes affected, **not** total number of events). The total incidence of serious ocular adverse events was 66/611 (10.8%) in eyes treated with ocriplasmin compared with 35/261 (13.4%) treated with sham or placebo injection. Most frequently reported was an increased or new macular hole, which occurred in 47/611 (7.7%) of eyes treated with ocriplasmin compared with 26/261 (9.9%) of eyes treated with sham or placebo injection. None of the included studies reported any cases of endophthalmitis.

Study	MIVI-IIT 2010		TG-MV-006 2012		TG-MV-007 2012		OASIS 2016	
	Ocriplas- min (n = 25)	Control (n = 12)	Ocriplas- min (n = 220)	Control (n = 106)	Ocriplas- min (n = 245)	Control (n = 81)	Ocriplas- min (n = 146)	Control (n = 74)
Any serious ocular adverse event	0	0	21	11	15	9	30	15
Macular hole (increased or new)	-	-	15	11	9	5	23	10
Retinal detachment	-	-	2	2	0	1	1	1
Reduced visual acuity	-	-	1	0	2	1	18	18
Endophthalmitis	0	0	0	0	0	0	0	0

Note: the control group in [MIVI-IIT 2010](#) and [OASIS 2016](#) was sham injection. The control group in [TG-MV-007 2012](#) and [TG-MV-006 2012](#) was placebo injection.

DISCUSSION

Summary of main results

We identified four RCTs, with 932 eyes, comparing ocriplasmin with control (placebo or sham injection) treatment. On full-text analysis, we excluded 50 participants due to breaches of our inclusion criteria, and 23 participants because they received a different dose of ocriplasmin, giving 859 eyes for outcome analysis. The studies were conducted in Europe and the USA. We found that treatment with ocriplasmin increased the likelihood of complete release of vitreous traction compared to control (sham or placebo injection) treatment. Ocriplasmin was also associated with a 3-line or greater improvement in BCVA and improvement in participant-reported visual function.

There were however, more ocular adverse events in eyes treated with ocriplasmin than control (placebo or sham injection) treatment. Many of these adverse events, particularly vitreous floaters and photopsia, are known to be associated with posterior vitreous detachment. Of the serious ocular adverse events, increased or new macular hole was the most frequently reported. Given the high incidence in all eyes regardless of treatment, this most likely represents the natural history of VMT in a significant proportion of patients.

Overall completeness and applicability of evidence

Three of the included studies were large and contributed the majority of included participants (834) for our analysis ([OASIS 2016](#); [TG-MV-006 2012](#); [TG-MV-007 2012](#)). The other study, designed to determine the appropriate dose, contributed a relatively small number (25) of participants ([MIVI-IIT 2010](#)). The control groups in the trials also varied, with participants in [TG-MV-006 2012](#) and [TG-MV-007 2012](#) receiving a placebo injection, and participants in [MIVI-IIT 2010](#) and [OASIS 2016](#) receiving a sham injection. Due to the mechanical nature of the primary outcome, the variation in control group intervention could impact on the validity of the results, particularly adverse events. All four trials reported the same primary outcome and follow-up periods were identical. One trial reported additional secondary outcome data at 24-months ([OASIS 2016](#)).

It is important to note that [OASIS 2016](#) initially randomised and treated 220 participants, but subsequent central reading centre analysis revealed 50 participants were ineligible due to lack of sVMA, presence of ERM or presence of MH greater than 400 µm. To comply with the inclusion and exclusion criteria of this review, we used only data from this smaller, central reading centre verified cohort of participants. Despite this attrition bias, sufficient pooled data were available, hence the impact of this bias was deemed small.

Quality of the evidence

Generally, we graded the risk of bias as low. However, two studies reported cases that did not complete the study on the ClinicalTrials.gov database (see [Characteristics of included studies](#) table) but the publications did not describe these losses to follow-up ([TG-MV-006 2012](#); [TG-MV-007 2012](#)). The authors confirmed

using the last-observation-carried-forward (LOCF) method for their missing outcome data, assuming the outcome was unlikely to change after discontinuation of treatment and likely to improve spontaneously over time. As these losses to follow-up were not described in the original papers, we judged the risk of bias for incomplete outcome data as unclear.

Potential biases in the review process

We followed a standard Cochrane protocol ([Neffendorf 2015](#)), to minimise potential methodological biases in the review process.

Agreements and disagreements with other studies or reviews

In the UK, NICE recommends the use of ocriplasmin for adults with VMT causing severe sight problems or a MH up to 400 µm, in the absence of ERM. Our findings support this.

Subsequent publications and postmarket surveillance studies have addressed the safety of ocriplasmin. One large postmarket surveillance study found lower rates of adverse events than were reported in the registration studies, but noted that under-reporting is common in post-market surveillance studies ([Hahn 2015](#)). Members of the British and Eire Association of VitreoRetinal Surgeons (BEAVRS) have reported their experience with ocriplasmin in comparison to the MIVI-TRUST trial data ([Haynes 2017](#)). They found a lower rate of MH closure and increased incidence of adverse events with ocriplasmin compared to the registration studies, but there is an uncertain risk of reporting bias.

Our review found a higher rate of vitreous floaters and photopsia with ocriplasmin, but no increased risk of loss in visual acuity and retinal detachment. There have been reports of acute reduction in visual acuity, electroretinography changes, dyschromatopsia, phacodonesis and OCT ellipsoid zone alteration, but the majority have been transient ([Khan 2016](#); [Neffendorf 2016](#)).

Various studies and reviews have suggested certain subgroups of sVMA participants may be more likely to respond successfully to ocriplasmin treatment based on baseline characteristics such as adhesion diameter, lack of coexisting ERM, and the angle between the posterior vitreous cortex and the ILM ([Haller 2015](#); [Jackson 2016](#); [Paul 2017](#)). However, such analyses are exploratory, and without confirmatory prospective RCTs they are beyond the scope of this review.

There are different approaches to potentially manage sVMA including PPV, intravitreal gas injection, ocriplasmin and observation. Further research, ideally in a head-to-head trial, would be beneficial.

AUTHORS' CONCLUSIONS

Implications for practice

We found evidence to support the use of ocriplasmin for the treatment of symptomatic vitreomacular adhesion (sVMA), although the number of studies was low. There are reported concerns about the safety of ocriplasmin treatment and there is debate within the vitreoretinal community regarding the advantages and disadvantages of ocriplasmin.

Implications for research

Further large randomised controlled trials would augment our current understanding of the safety and efficacy of ocriplasmin. Ideally these would compare ocriplasmin with other commonly used management options, in particular observation or pars plana vitrectomy. Randomised controlled trials recruiting participants with baseline characteristics thought to improve the efficacy of ocriplasmin are warranted.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

MIVI-IIT 2010

Methods	<p>Study design: RCT, single treated eye.</p> <p>Number randomised: 60 total; 48 microplasmin; 12 sham injection.</p> <p>Exclusions after randomisation: none.</p> <p>Number analysed: at 28 days and 6 months; 60 total; 48 microplasmin; 12 sham injection.</p> <p>Unit of analysis: eyes.</p> <p>Losses to follow-up: 0 participants total.</p> <p>How was missing data handled? no missing data.</p> <p>Power calculation: not documented.</p>
Participants	<p>Country: Belgium.</p> <p>Mean age: 70.0 years overall; 69.9 years for ocriplasmin group; 70.0 years for sham injection group.</p> <p>Gender: 33/60 (55%) women, 27/60 (45%) men total; 27/48 (56%) women, 21/48 (44%) men in microplasmin group; 6/12 (50%) women, 6/12 (50%) men in sham injection group.</p> <p>Inclusion criteria: aged > 18 years; partial PVD on ultrasound examination; OCT evidence of at least a partial attachment in the foveal area, resulting in a macular thickness of ≥ 250 μm; BCVA $\leq 20/40$ in study eye; BCVA $\geq 20/400$ in fellow eye.</p> <p>Exclusion criteria: active PDR; high myopia (axial length > 26 mm); previous vitrectomy or uncontrolled glaucoma; previous intravitreal injections in the past 3 months in study eye; intraocular surgery or laser photocoagulation in the past 3 months in study eye; rhegmatogenous retinal detachment in either eye.</p> <p>Equivalence of baseline characteristics: no; more participants in microplasmin group had tractional diabetic macular oedema compared with sham injection group.</p>
Interventions	<p>Intervention 1: single intravitreal injection microplasmin 125 μg.</p>

MIVI-IIT 2010 (Continued)

Intervention 2: single intravitreal injection microplasmin 75 µg.

Intervention 3: single intravitreal injection microplasmin 175 µg.

Intervention 4: intravitreal injection of microplasmin 125 µg at baseline, followed by a further microplasmin 125 µg intravitreal injection at 28 days if VMA was still present, followed by a further microplasmin 125 µg intravitreal injection at 56 days after baseline if VMA was still present.

Comparator: sham injection (conjunctiva touched with a blunt needle by a non-masked investigator and no injection given).

Length of follow-up: planned 180 days, actual 180 days.

As the recommended dose of ocriplasmin is 125 µg, and this is the subject of this review, only data from the first and fourth intervention arms were analysed.

Outcomes	<p>Primary outcome, as defined in study reports: "the primary outcome of this study was total PVD induction at Day 14, as assessed by a central reading centre."</p> <p>Secondary outcomes, as defined in study reports: total PVD at other time points assessed by the central reading centre and investigators; resolution of index condition (VMA or MH); resolution of VMA; progression of PVD; need for vitrectomy; resolution of macular oedema; change in BCVA; BCVA 5-, 10- and 15-letter improvement.</p> <p>Adverse events reported: yes.</p> <p>Intervals at which outcomes assessed: 3, 7, 14, 28, 90 and 180 days.</p>	
Notes	<p>Funding sources: study sponsored by ThromboGenics NV.</p> <p>Study period: 2 years; 2007-2009.</p> <p>Reported subgroup analyses: yes.</p> <p>Full results of study were presented at EURetina 2009, Nice, France.</p> <p>NCT00435539.</p>	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	<p>Method of sequence generation for the MIVI-IIT RCT not described.</p> <p>Quote: "Four cohorts of 15 patients were randomised as 4:1 to treatment or sham injection, resulting in 12 patients receiving microplasmin and 3 patients receiving the sham injection in each cohort." p. 1123.</p>
Allocation concealment (selection bias)	Unclear risk	<p>Insufficient information documented to assess allocation concealment.</p> <p>Quote: "Four cohorts of 15 patients were randomised as 4:1 to treatment or sham injection, resulting in 12 patients receiving microplasmin and 3 patients receiving the sham injection in each cohort." p. 1123.</p>
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	<p>Sham injection was performed, rather than actual placebo injection.</p> <p>Quote: "In the patients receiving a sham injection, microplasmin was prepared in the same manner, but instead of an intraocular injection, the conjunctiva was touched with a blunt needle by a nonmasked investigator and no injection was given." p. 1123.</p>

MIVI-IIT 2010 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "All patient examinations before drug allocation and in the 6-month follow-up period after the last injection were performed by masked investigators and study personnel." p. 1123. "Posterior vitreous detachment status and macular thickness were assessed by the investigator as well as by a central reading center (CRC), located in Munich, Germany." p. 1124.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No incomplete outcome data.
Selective reporting (reporting bias)	Low risk	All outcomes defined in trial registry were reported.
Other bias	Low risk	

OASIS 2016

Methods	<p>Study design: RCT, single treated eye.</p> <p>Number randomised: 220 total; 146 ocriplasmin; 74 sham.</p> <p>Exclusions after randomisation: 50 participants subsequently deemed ineligible by central reading centre.</p> <p>Number analysed: at 28 days: 168 total; 111 ocriplasmin; 59 sham.</p> <p>Unit of analysis: eyes.</p> <p>Losses to follow-up: 2 participants total; 1 ocriplasmin group (1 lost to follow-up); 1 sham group (1 lost to follow-up).</p> <p>How was missing data handled? other than VMA release at 28 days, no data published regarding cohort who met central reading centre eligibility criteria.</p> <p>Power calculation: 210 participants for at least 90% power at 2-sided alpha of 0.05 to assume a primary endpoint of 37% in ocriplasmin group and a 14% rate in placebo group.</p>
Participants	<p>Country: USA.</p> <p>Mean age: 69.1 years overall; 69.4 years for ocriplasmin group; 68.5 years for sham group.</p> <p>Gender: 147/218 (67.4%) women, 71/218 (32.6%) men total; 102/145 (70.3%) women, 43/145 (29.7%) men in ocriplasmin group; 45/73 (61.6%) women, 28/73 (38.4%) men in sham group.</p> <p>Inclusion criteria: aged > 18 years; presence of VMA; BCVA ≤ 20/32 in study eye; BCVA ≥ 20/800 in non-study eye.</p> <p>Exclusion criteria: history or current evidence of proliferative retinopathy, exudative AMD or retinal vein occlusion in the study eye; people with any vitreous haemorrhage or any other vitreous opacification which precludes either visualisation of the posterior pole by visual inspection OR adequate assessment of the macula by OCT; MH > 400 µm in diameter in the study eye; presence of epiretinal membrane; aphakia in study eye; high myopia (> -8 dioptres in study eye); history of rhegmatogenous retinal detachment in either eye; prior vitrectomy in study eye; previous participation in this trial or prior administration of ocriplasmin in study eye.</p> <p>Equivalence of baseline characteristics: yes.</p>
Interventions	<p>Intervention: single intravitreal injection of ocriplasmin 125 µg in 0.10 mL volume.</p>

Ocriplasmin for symptomatic vitreomacular adhesion (Review)

OASIS 2016 (Continued)

Comparator: sham (the same syringe hub was pressed against the conjunctiva to simulate an injection).

Length of follow-up: planned 24 months, actual 24 months. Data of central reading centre approved study participants only reported at 28 days.

Outcomes

Primary outcome, as defined in study reports: "proportion of subjects with pharmacological vitreomacular adhesion (VMA)/vitreomacular traction (VMT) resolution at day 28. Pharmacological VMA resolution without anatomical defect, based on spectral domain optical coherence tomography and determined by the masked central reading center (CRC), with post-resolution vitrectomy considered as a failure."

Secondary outcomes, as defined in study reports: "proportion of subjects with a ≥ 2 line improvement in best-corrected visual acuity (BCVA) from baseline at month 24, irrespective of vitrectomy."

Adverse events reported: yes.

Intervals at which outcomes assessed: 7 and 28 days; 3, 6, 9, 12, 15, 18, 21 and 24 months.

Notes

Funding sources: study sponsored by ThromboGenics NV.

Study period: 3 years; 2011-2014.

Reported subgroup analyses: yes.

Additional information: large proportion of participants were deemed eligible, recruited and treated by investigators. Retrospective central reading centre review found 50 participants ineligible for following reasons (MH > 400 μ m, presence of epiretinal membrane or no sVMA at baseline). Our analysis only included data reported for correctly eligible cohort of participants.

NCT01429441.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Method of random sequence generation for the MIVI-IIT RCT described Quote: "Randomization was stratified on the basis of the presence or absence of FTMH at baseline and was centralized through an interactive voice response system." p. 2233.
Allocation concealment (selection bias)	Low risk	Method of allocation concealment for MIVI-IIT RCT described. Quote: "Randomization was stratified on the basis of the presence or absence of FTMH at baseline and was centralized through an interactive voice response system." p. 2233.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Performance bias explained. Quote: "The trial was conducted in a double-masked manner. To maintain the masking of the investigator, an unmasked injecting physician was assigned to perform the injection and access the interactive voice response system to receive the assigned treatment. The unmasked personnel did not perform or participate in any other trial-related procedures or assessments." p. 2233.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Detection bias appropriately explained. Quote: "The trial was conducted in a double-masked manner. To maintain the masking of the investigator, an unmasked injecting physician was assigned to perform the injection and access the interactive voice response system to

OASIS 2016 (Continued)

receive the assigned treatment. The unmasked personnel did not perform or participate in any other trial-related procedures or assessments." p. 2233.		
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Large proportion of participants deemed eligible, recruited and treated by investigators. Retrospective central reading centre review found 50 participants ineligible for following reasons (MH > 400 µm, presence of epiretinal membrane or no SVMA). Outcome data for correct eligible cohort of participants only given for primary outcome. No secondary outcome data described.
Selective reporting (reporting bias)	Low risk	All outcomes defined in trial registry were reported.
Other bias	Low risk	No other source of bias.

TG-MV-006 2012

Methods	<p>Study design: RCT, single treated eye.</p> <p>Number randomised: 326 total; 219 ocriplasmin; 107 placebo.</p> <p>Exclusions after randomisation: 0.</p> <p>Number analysed: at 28 days: 326 total; 219 ocriplasmin; 107 placebo. At 180 days: 298 total; 200 ocriplasmin; 98 placebo.</p> <p>Unit of analysis: eyes.</p> <p>Losses to follow-up: 28 participants total; 19 ocriplasmin group (2 adverse event, 8 withdrawal by participants, 6 lost to follow-up, 3 death); 9 placebo group (2 adverse event, 4 withdrawal by participants, 3 lost to follow-up).</p> <p>How was missing data handled? missing data not reported in study publications.</p> <p>Power calculation: 320 participants for > 90% power at 2-sided alpha of 0.05 to assume a primary end-point of 27.5% in ocriplasmin group and 10.0% in placebo group.</p>
Participants	<p>Country: USA.</p> <p>Mean age: 71.4 years overall; 71.5 years for ocriplasmin group; 71.1 years for placebo group.</p> <p>Gender: 207/326 (63.5%) women, 119/326 (36.5%) men total; 148/219 (67.6%) women, 71/219 (32.4%) men in ocriplasmin group; 59/107 (55.1%) women, 52/107 (48.6%) men in placebo group.</p> <p>Inclusion criteria: aged > 18 years; focal VMA (vitreous adhesion to macula within 6-mm central retinal field surrounded by elevation of posterior vitreous cortex, as seen on OCT that in the opinion of investigator was related to decreased visual function (e.g. metamorphopsia, decreased visual acuity or other visual complaint); BCVA ≤ 20/25 in study eye; BCVA ≥ 20/800 in non-study eye.</p> <p>Exclusion criteria: any evidence of proliferative retinopathy (including PDR or other ischaemic retinopathies involving vitreoretinal vascular proliferation) or exudative AMD or retinal vein occlusion in study eye; people with any vitreous haemorrhage or any other vitreous opacification which precludes either: visualisation of posterior pole by visual inspection OR adequate assessment of macula by either OCT or fluorescein angiogram (or both) in study eye; MH > 400 µm in diameter in study eye; aphakia in study eye; high myopia (> -8 dioptres); uncontrolled glaucoma; lenticular or zonular instability; history of retinal detachment in either eye; prior vitrectomy or prior laser photocoagulation of macula; treatment with ocular surgery, intravitreal injection or retinal laser photocoagulation in the previous 3 months.</p> <p>Equivalence of baseline characteristics: no; pseudophakia more common in ocriplasmin group than in placebo group; more women in ocriplasmin group than in placebo group.</p>

TG-MV-006 2012 (Continued)

Interventions	<p>Intervention: single intravitreal injection of ocriplasmin 125 µg in 0.10 mL volume.</p> <p>Comparator: single intravitreal injection of 0.10 mL placebo with identical drug vehicle diluted with saline.</p> <p>Length of follow-up: planned 180 days, actual 180 days.</p>
Outcomes	<p>Primary outcome, as defined in study reports: "the primary end point was the proportion of subjects with nonsurgical resolution of vitreomacular adhesion at day 28 post-injection, as determined by masked OCT evaluation obtained from the central reading centre."</p> <p>Secondary outcomes, as defined in study reports: proportion of participants with total PVD at day 28, as determined by B-scan ultrasound; need for vitrectomy; closure of an MH; gain \geq 3-lines BCVA without vitrectomy; change from baseline in BCVA and VFQ-25 score at 6 months.</p> <p>Adverse events reported: yes.</p> <p>Intervals at which outcomes assessed: 7, 14, 28, 90 and 180 days.</p>
Notes	<p>Funding sources: study sponsored by ThromboGenics NV.</p> <p>Study period: 2 years; 2008-2009.</p> <p>Reported subgroup analyses: yes.</p> <p>NCT00781859.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Supplementary material: "subjects will be randomised centralized through a telephone-based Interactive Voice Response System (IVRS) to either microplasmin intravitreal injection or placebo in a 3:1 allocation ratio. Blocks of treatment will be assigned to sites in a manner expected to minimize the potential for imbalance in the desired randomization ratio." Protocol p. 17.
Allocation concealment (selection bias)	Low risk	Supplementary material: "subjects will be randomised centralized through a telephone-based Interactive Voice Response System (IVRS) to either microplasmin intravitreal injection or placebo in a 3:1 allocation ratio. Blocks of treatment will be assigned to sites in a manner expected to minimize the potential for imbalance in the desired randomization ratio." Protocol p. 17.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Patients randomly assigned to the ocriplasmin group received an intravitreal injection of ocriplasmin (125 µg in a 0.10-ml volume) drawn from a vial containing ocriplasmin into which 0.75 ml of commercial saline had been injected (1875 µg of ocriplasmin in a 0.75-ml drug vehicle). Patients randomly assigned to placebo received an intravitreal injection of 0.10 ml of the identical drug vehicle diluted with saline, the method used being the same as that used to prepare ocriplasmin." p. 608.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Trained readers at a central reading center (Duke University OCT Reading Center, Durham, NC) who were unaware of the group assignments evaluated the OCT images. All ultrasonographic studies were standardized and performed by certified technicians who underwent special training for the study. Staging of posterior vitreous detachment was based on dynamic ultrasonographic evaluation and performed by an investigator who was unaware of the group assignments." p. 608.
Incomplete outcome data (attrition bias)	Unclear risk	No description found in article, but 28 participants reported as not completing study on ClinicalTrials.gov. The corresponding author of Stalmans and col-

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TG-MV-006 2012 (Continued)

All outcomes

leagues (2012) was contacted to query this. ThromboGenics NV responded by confirming use of last observation carried forward (LOCF) approach to input missing data for visits postdiscontinuation. Their explanation was: "use of LOCF was appropriate when the outcome is not expected to change after discontinuation and is a conservative method when the outcome is expected to improve spontaneously over time. The primary endpoint, pharmacological VMA resolution in particular, is an outcome of that nature." As these losses to follow-up were not reported in original paper, risk of attrition bias was deemed unclear.

Selective reporting (reporting bias)	Low risk	All defined outcomes in methods were reported.
Other bias	Unclear risk	Baseline imbalance between study groups as pseudophakia was more common in ocriplasmin group than in placebo group and there were more women in ocriplasmin group than in placebo group.

TG-MV-007 2012

Methods

Study design: RCT, single treated eye.

Number randomised: 326 total; 245 ocriplasmin; 81 placebo.

Exclusions after randomisation: none.

Number analysed: at 28 days: 326 total; 245 ocriplasmin; 81 placebo. At 180 days: 309 total; 235 ocriplasmin; 74 placebo.

Unit of analysis: eyes.

Losses to follow-up: 17 participants total; 10 ocriplasmin group (5 withdrawal by participant, 2 lost to follow-up, 2 adverse event, 1 death); 7 placebo group (1 physician decision, 4 withdrawal by participant, 2 lost to follow-up).

How was missing data handled? missing data not reported in study publications.

Power calculation: 320 participants for > 90% power at 2-sided alpha of 0.05 to assume a primary endpoint of 27.5% in ocriplasmin group and 10.0% rate in placebo group.

Participants

Countries: Belgium, Czech Republic, Germany, Poland, Spain, UK, USA.

Mean age: 72.0 years overall; 72.6 years for ocriplasmin group; 70.2 years for placebo group.

Gender: 222/326 (68.1%) women, 104/326 (31.9%) men total; 166/245 (67.8%) women, 79/245 (32.2%) men in ocriplasmin group; 56/81 (69.1%) women, 25/81 (30.9%) men in placebo group.

Inclusion criteria: aged > 18 years; focal VMA (vitreous adhesion to macula within 6-mm central retinal field surrounded by elevation of posterior vitreous cortex, as seen on OCT that in the opinion of investigator was related to decreased visual function (e.g. metamorphopsia, decreased visual acuity or other visual complaint); BCVA ≤ 20/25 in study eye; BCVA ≥ 20/800 in non-study eye.

Exclusion criteria: any evidence of proliferative retinopathy (including PDR or other ischaemic retinopathies involving vitreoretinal vascular proliferation) or exudative AMD or retinal vein occlusion in study eye; people with any vitreous haemorrhage or any other vitreous opacification which precludes either: visualisation of posterior pole by visual inspection OR adequate assessment of macula by either OCT or fluorescein angiogram (or both) in study eye; MH > 400 µm in diameter in study eye; aphakia in study eye; high myopia (> -8 dioptres); uncontrolled glaucoma; lenticular or zonular instability; history of retinal detachment in either eye; prior vitrectomy or prior laser photocoagulation of macula; treatment with ocular surgery, intravitreal injection or retinal laser photocoagulation in the previous 3 months.

TG-MV-007 2012 (Continued)

Equivalence of baseline characteristics: no; pseudophakia more common in ocriplasmin group than in placebo group; more women in ocriplasmin group than in placebo group.

Interventions	<p>Intervention: single intravitreal injection of ocriplasmin 125 µg in 0.10 mL volume.</p> <p>Comparator: single intravitreal injection of 0.10 mL placebo with identical drug vehicle diluted with saline.</p> <p>Length of follow-up: planned 180 days, actual 180 days.</p>
Outcomes	<p>Primary outcome, as defined in study reports: "the primary end point was the proportion of subjects with nonsurgical resolution of VMA at day 28 post-injection, as determined by masked OCT evaluation obtained from the central reading centre."</p> <p>Secondary outcomes, as defined in study reports: proportion of participants with total PVD at day 28, as determined by B-scan ultrasound; need for vitrectomy; closure of an MH; gain ≥ 3-lines BCVA without vitrectomy; change from baseline in BCVA and VFQ-25 score at 6 months.</p> <p>Adverse events reported: yes.</p> <p>Intervals at which outcomes assessed: 7, 14, 28, 90 and 180 days.</p>
Notes	<p>Funding sources: study sponsored by ThromboGenics NV.</p> <p>Study period: 2 years; 2008-2010.</p> <p>Reported subgroup analyses: yes.</p> <p>NCT00798317.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Supplementary material: "subjects will be randomised centralized through a telephone-based Interactive Voice Response System (IVRS) to either microplasmin intravitreal injection or placebo in a 3:1 allocation ratio. Blocks of treatment will be assigned to sites in a manner expected to minimize the potential for imbalance in the desired randomization ratio." Protocol p. 17.
Allocation concealment (selection bias)	Low risk	Supplementary material: "subjects will be randomised centralized through a telephone-based Interactive Voice Response System (IVRS) to either microplasmin intravitreal injection or placebo in a 3:1 allocation ratio. Blocks of treatment will be assigned to sites in a manner expected to minimize the potential for imbalance in the desired randomization ratio." Protocol p. 17.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Patients randomly assigned to the ocriplasmin group received an intravitreal injection of ocriplasmin (125µg in a 0.10-ml volume) drawn from a vial containing ocriplasmin into which 0.75ml of commercial saline had been injected (1875µg of ocriplasmin in a 0.75-ml drug vehicle). Patients randomly assigned to placebo received an intravitreal injection of 0.10 ml of the identical drug vehicle diluted with saline, the method used being the same as that used to prepare ocriplasmin". p. 608.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Trained readers at a central reading center (Duke University OCT Reading Center, Durham, NC) who were unaware of the group assignments evaluated the OCT images. All ultrasonographic studies were standardized and performed by certified technicians who underwent special training for the study. Staging of posterior vitreous detachment was based on dynamic ultrasonographic evaluation and performed by an investigator who was unaware of the group assignments." p. 608.

TG-MV-007 2012 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No description found in article, but 17 participants reported as not completing study on ClinicalTrials.gov. The corresponding author of Stalmans and colleagues (2012) was contacted to query this. ThromboGenics NV responded by confirming use of last observation carried forward (LOCF) approach to input missing data for visits postdiscontinuation. Their explanation was: "use of LOCF was appropriate when the outcome is not expected to change after discontinuation and is a conservative method when the outcome is expected to improve spontaneously over time. The primary endpoint, pharmacological VMA resolution in particular, is an outcome of that nature." As these losses to follow-up were not reported in original paper, risk of attrition bias was deemed unclear.
Selective reporting (reporting bias)	Low risk	All defined outcomes in methods were reported.
Other bias	Unclear risk	Baseline imbalance between study groups as pseudophakia was more common in ocriplasmin group than in placebo group and there were more women in ocriplasmin group than in placebo group.

AMD: age-related macular degeneration; BCVA: best corrected visual acuity; FTMH: full-thickness macular hole; MH: macular hole; OCT: optical coherence tomography; PDR: proliferative diabetic retinopathy; PVD: posterior vitreous detachment; RCT: randomised controlled trial; sVMA: symptomatic vitreomacular adhesion; VFQ-25: Visual Function Questionnaire 25; VMA: vitreomacular adhesion.

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Benz 2010	Indication for ocriplasmin was not symptomatic vitreomacular adhesion. It was investigating whether 125 µg microplasmin would induce vitreous release in people scheduled for PPV.
De Smet 2009	Investigated safety and efficacy of 4 different doses of intravitreal microplasmin prior to pre-planned PPV. Subsequent PPV occurred either 1-2 hours, 24 hours or 7 days following ocriplasmin, meaning the participant population and outcome measures were not eligible for inclusion in our review.
Dugel 2015	Post hoc analysis of data from studies we already extracted data from (TG-MV-006 and TG-MV-007).
Elbendary 2011	Autologous plasmin injected into participants with diabetic macular oedema associated with vitreomacular traction.
Jackson 2017	Incorrect study design; post hoc analysis.
Lanzetta 2014a	Postmarket surveillance study, not an RCT, therefore not eligible for inclusion.
Lanzetta 2014b	Post-hoc analysis of data, not an RCT, therefore excluded.
Lescrauwaet 2016	Not an RCT.
Novack 2015	Eligible participants for this study required exudative age-related macular degeneration, which did not meet inclusion criteria for our review.

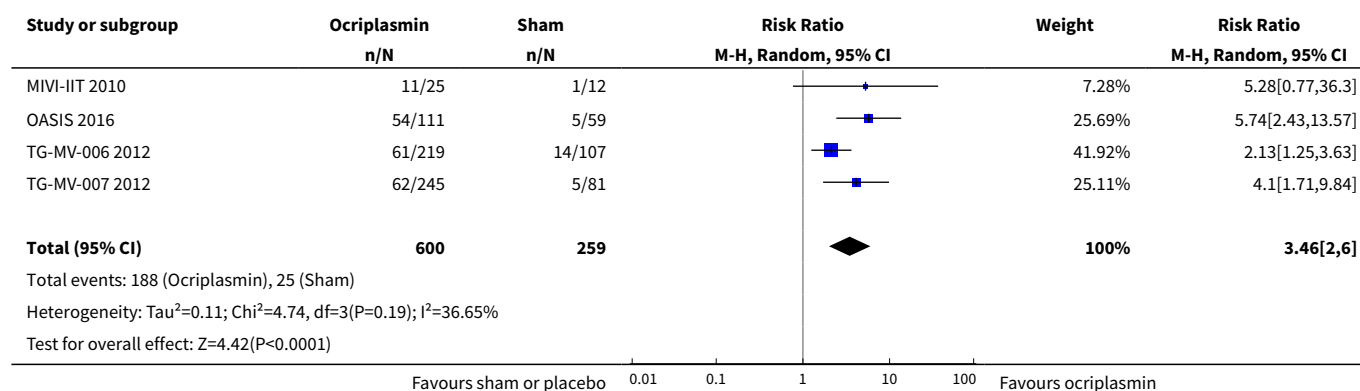
PPV: pars plana vitrectomy; RCT: randomised controlled trial.

DATA AND ANALYSES

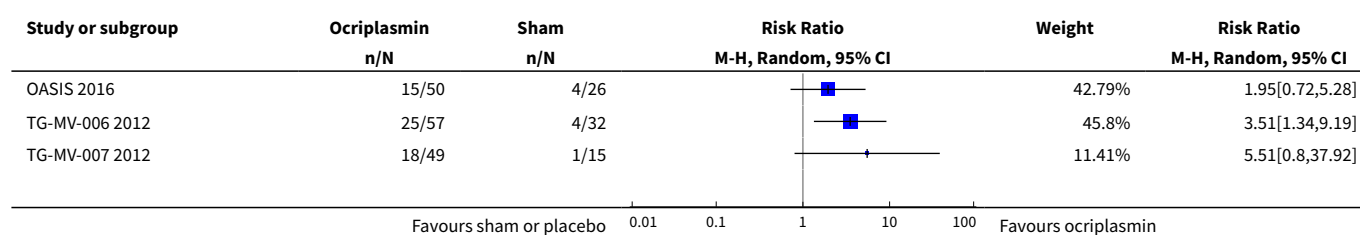
Comparison 1. Ocriplasmin versus sham injection

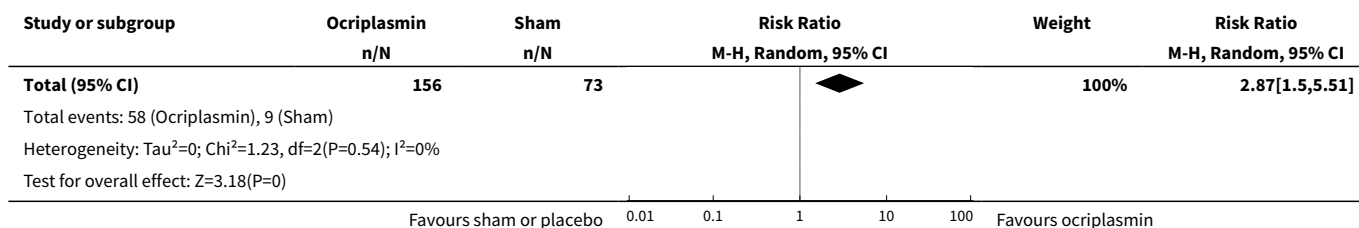
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Complete release of vitreous adhesion 28 days after treatment	4	859	Risk Ratio (M-H, Random, 95% CI)	3.46 [2.00, 6.00]
2 Closure of macular hole 28 days after treatment	3	229	Risk Ratio (M-H, Random, 95% CI)	2.87 [1.50, 5.51]
3 Complete posterior vitreous detachment 28 days after treatment	3	689	Risk Ratio (M-H, Random, 95% CI)	2.94 [1.39, 6.24]
4 > 3-line improvement in BCVA 6 months after treatment	3	674	Risk Ratio (M-H, Random, 95% CI)	1.95 [1.07, 3.53]
5 Requirement for pars plana vitrectomy at month 6	3	689	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.50, 0.91]
6 Any ocular adverse event	4	909	Risk Ratio (M-H, Random, 95% CI)	1.22 [1.09, 1.37]

Analysis 1.1. Comparison 1 Ocriplasmin versus sham injection, Outcome 1 Complete release of vitreous adhesion 28 days after treatment.

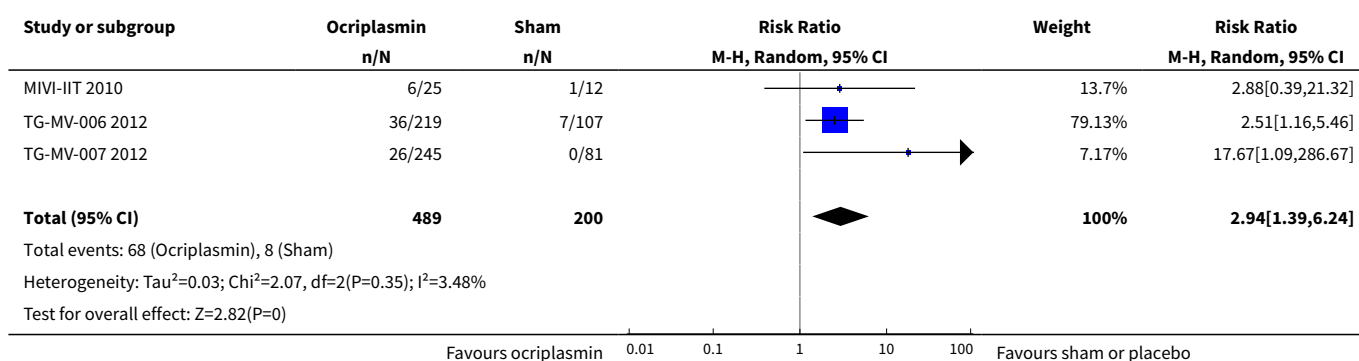


Analysis 1.2. Comparison 1 Ocriclasmin versus sham injection, Outcome 2 Closure of macular hole 28 days after treatment.

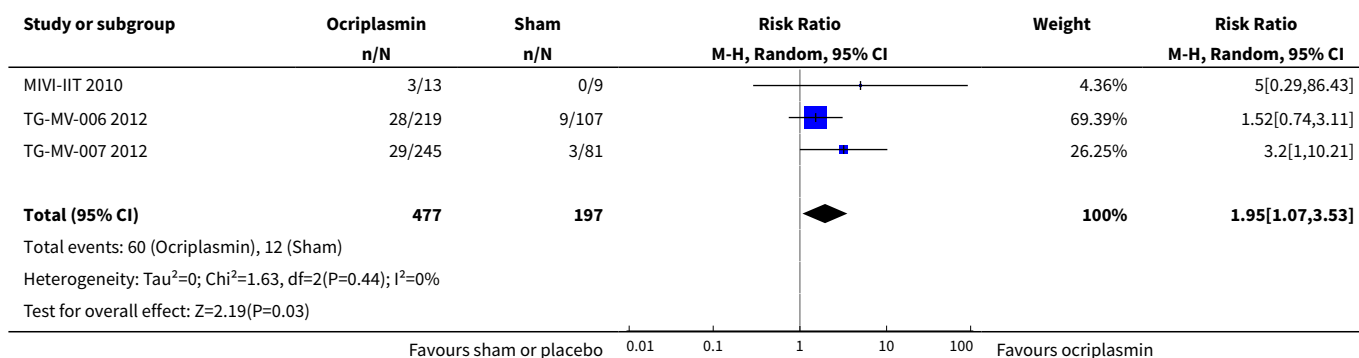




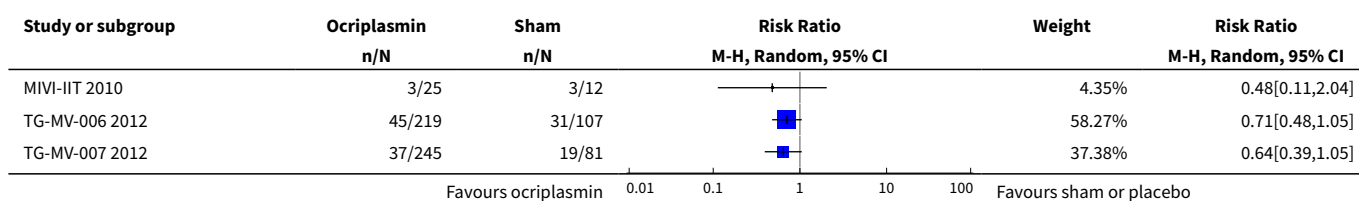
Analysis 1.3. Comparison 1 Ocriplasmin versus sham injection, Outcome 3 Complete posterior vitreous detachment 28 days after treatment.

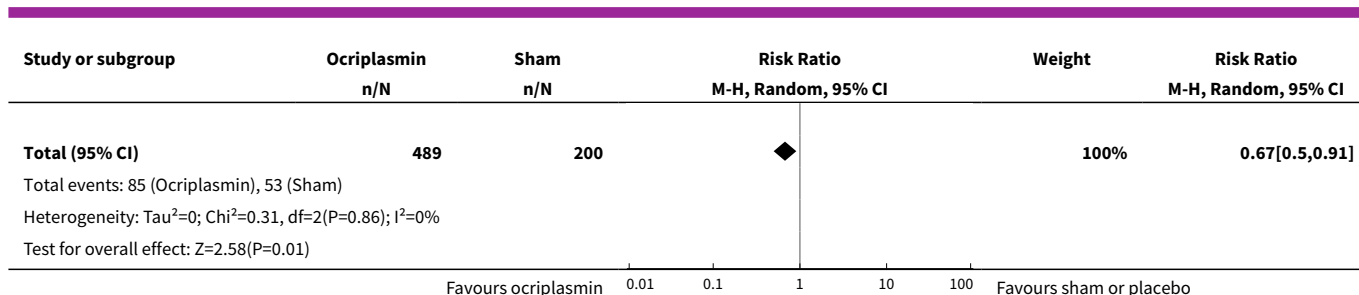


Analysis 1.4. Comparison 1 Ocriplasmin versus sham injection, Outcome 4 > 3-line improvement in BCVA 6 months after treatment.

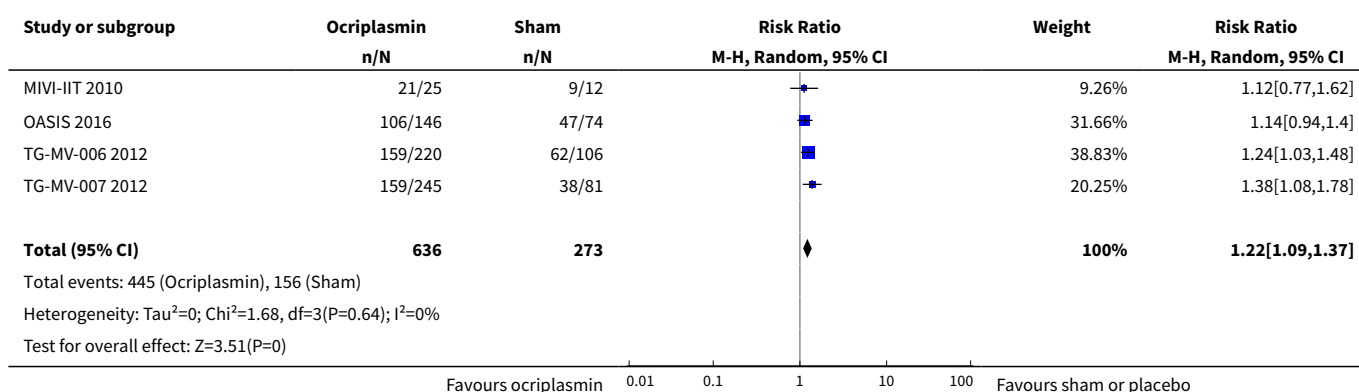


Analysis 1.5. Comparison 1 Ocriplasmin versus sham injection, Outcome 5 Requirement for pars plana vitrectomy at month 6.





Analysis 1.6. Comparison 1 Ocriplasmin versus sham injection, Outcome 6 Any ocular adverse event.



APPENDICES

Appendix 1. CENTRAL search strategy

- #1 MeSH descriptor: [Vitreous Body] this term only
- #2 MeSH descriptor: [Vitreous Detachment] this term only
- #3 MeSH descriptor: [Retinal Perforations] this term only
- #4 MeSH descriptor: [Tissue Adhesions] this term only
- #5 vitreomacular near/3 (adhesion* or traction*)
- #6 VMA* or VMT*
- #7 macula* near/2 hole*
- #8 #1 or #2 or #3 or #4 or #5 or #6 or #7
- #9 MeSH descriptor: [Fibrinolysin] this term only
- #10 MeSH descriptor: [Fibrinolytic Agents] this term only
- #11 MeSH descriptor: [Proteolysis] this term only
- #12 MeSH descriptor: [Peptide Fragments] this term only
- #13 ocriplasmin* or Jetrea* or Microplasmin*
- #14 #9 or #10 or #11 or #12 or #13
- #15 #8 and #14

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. Vitreous Body/
14. Vitreous Detachment/
15. Retinal Perforations/
16. Tissue Adhesions/
17. (vitreomacular adj3 (adhesion\$ or traction\$)).tw.
18. (VMA\$ or VMT\$).tw.
19. (macula\$ adj2 hole\$).tw.
20. or/13-19
21. Fibrinolysin/
22. Fibrinolytic Agents/
23. Proteolysis/
24. Peptide Fragments/
25. (ocriplasmin\$ or Jetrea\$ or Microplasmin\$).tw.
26. or/21-25
27. 20 and 26
28. 12 and 27

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. vitreous body detachment/
34. vitreous disease/
35. retina tear/
36. tissue adhesion/

37. (vitreomacular adj3 (adhesion\$ or traction\$)).tw.
38. (VMA\$ or VMT\$).tw.
39. (macula\$ adj2 hole\$).tw.
40. or/33-39
41. ocriplasmin/
42. fibrinolytic agent/
43. peptide fragment/
44. (ocriplasmin\$ or Jetrea\$ or Microplasmin\$).tw.
45. or/41-44
46. 40 and 45
47. 32 and 46

Appendix 4. PubMed search strategy

((vitreous body[MeSH Terms]) OR (vitreous detachment[MeSH Terms]) OR (Retinal Perforations[MeSH Terms]) OR (tissue adhesions[MeSH Terms]) OR (vitreomacular adhesion*[Text Word]) OR (vitreomacular traction*[Text Word]) OR (VMA*[Text Word] OR VMT*[Text Word]) OR (macula* AND hole*[Text Word])) AND ((fibrinolysis[MeSH Terms]) OR (fibrinolytic agents[MeSH Terms]) OR (proteolysis[MeSH Terms]) OR (peptide fragments[MeSH Terms]) OR (ocriplasmin*[Text Word] OR Jetrea*[Text Word] OR Microplasmin*[Text Word])) AND (((randomized controlled trial[Publication Type]) OR (controlled clinical trial[Publication Type]) OR (random*[Text Word] OR placebo*[Text Word] OR trial*[Text Word] OR group*[Text Word])) AND (Medline[sb]))

Appendix 5. ISRCTN search strategy

Ocriplasmin OR Jetrea OR Microplasmin

Appendix 6. ClinicalTrials.gov search strategy

(vitreomacular adhesion OR vitreomacular traction OR macular hole) AND (Ocriplasmin OR Jetrea OR Microplasmin)

Appendix 7. WHO ICTRP search strategy

vitreomacular adhesion OR vitreomacular traction OR macular hole = Intervention AND Ocriplasmin OR Jetrea OR Microplasmin = Condition

Appendix 8. Data on study characteristics

Mandatory items		Optional items
Methods		
Study design	<ul style="list-style-type: none"> Parallel group RCT <i>i.e. people randomised to treatment</i> Within-person RCT <i>i.e. eyes randomised to treatment</i> Cluster RCT <i>i.e. communities randomised to treatment</i> Cross-over RCT Other, specify 	Exclusions after randomisation Losses to follow-up Number randomised/analysed
Eyes or Unit of randomisation/unit of analysis	<ul style="list-style-type: none"> 1 eye included in study, <i>specify how eye selected</i> 2 eyes included in study, both eyes received same treatment, <i>briefly specify how analysed (best/worst/mean/both and adjusted for within-person correlation/both and not adjusted for within-person correlation) and specify if mixture 1 eye and 2 eyes</i> 2 eyes included in study, eyes received different treatments, <i>specify if correct pair-matched analysis done</i> 	How were missing data handled? <i>e.g. available case analysis, imputation methods</i> Reported power calculation (Y/N), <i>if yes, sample size and power</i> Unusual study design/issues
Participants		
Country		Setting

(Continued)

Total number of participants	<i>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.</i>	Ethnic group
Number (%) of men and women		Equivalence of baseline characteristics (Y/N)
Mean age and age range		
Inclusion criteria		
Exclusion criteria		
Interventions		
Intervention (n =)	<ul style="list-style-type: none">• Number of people randomised to this group• Drug (or intervention) name• Dose• Frequency• Route of administration	
Comparator (n =)		
See MECIR 65 and 70		
Outcomes		
Primary and secondary outcomes <i>as defined in study reports</i>	List outcomes	Planned/actual length of follow-up
	Adverse events reported (Y/N)	
	Length of follow-up and intervals at which outcomes assessed	
See MECIR R70		
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?
See MECIR 69		

MECIR: Methodological expectations for Cochrane Intervention Reviews; mm: month; n: number of participants; RCT: randomised controlled trial; yr: year.

Appendix 9. Glossary of abbreviations

BCVA: best corrected visual acuity.

BEAVRS: British and Eire vitreoretinal surgeons.

ERM: epiretinal membrane.

ETDRS: Early Treatment Diabetic Retinopathy Study.

GRADE: Grading of Recommendations, Assessment, Development and Evaluation working group.

ILM: internal limiting membrane.

logMAR: logarithm of the minimum angle of resolution.

MH: macular hole.

NEI-VFQ 25: National Eye Institute Visual Function Questionnaire - 25.

NICE: National Institute for Health and Care Excellence.

OCT: optical coherence tomography.

PVD: posterior vitreous detachment.

RCT: randomised controlled trial.

svMA: symptomatic vitreomacular adhesion.

VFQ: Visual Function Questionnaire.

VMA: vitreomacular adhesion.

VMF: vitreomacular traction.

WHO: World Health Organization.

CONTRIBUTIONS OF AUTHORS

JN: wrote the first draft of the protocol and review and reviewed the electronic search results.

VK: reviewed the electronic search results, carried out the statistical analysis and critically appraised the review.

EP: critically appraised the review.

TJ: reviewed the electronic search results, and critically appraised all drafts of the protocol and review.

DECLARATIONS OF INTEREST

JN: financial support to attend conferences (COPHy 2014 - ThromboGenics; AAO 2016, Retinal World Congress 2017 - VisionCare).

VK: financial support to attend conferences (ARVO 2017 - Bayer).

EP: no disclosures.

TJ: received an honorarium in 2016 to attend the EVER conference in Nice: ThromboGenics; advisory boards: Alcon, Bausch & Lomb, DORC; research grant support (employer): Novartis.

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Internal sources

- No sources of support supplied

External 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.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Due to the reporting of BCVA in the included studies, we changed our secondary outcome measure from "mean change in BCVA" to "proportion gaining 3-line or greater improvement in VA, measured using the ETDRS scale".

We added a secondary outcome measure, the requirement of PPV. This gives a good measure of how successful the intervention of ocriplasmin has been (i.e. conventional treatment for sVMA has been PPV, and indeed this remains the treatment modality of choice who fail ocriplasmin therapy).

We added information regarding "other bias" that could not be accurately categorised under the other categories of bias.

INDEX TERMS

Medical Subject Headings (MeSH)

*Vitreous Body; Fibrinolytic Agents [*administration & dosage] [adverse effects]; Fibrinolytic Agents [*administration & dosage] [adverse effects]; Intravitreal Injections; Peptide Fragments [*administration & dosage] [adverse effects]; Randomized Controlled Trials as Topic; Retinal Diseases [*drug therapy]; Time Factors; Tissue Adhesions [drug therapy]; Visual Acuity; Vitrectomy; Vitreous Detachment [drug therapy] [etiology]

MeSH check words

Adult; Aged; Aged, 80 and over; Humans; Middle Aged