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Anti-vascular endothelial growth factor for prevention of postoperative vitreous cavity haemorrhage after vitrectomy for proliferative diabetic retinopathy (Review)

Smith JM, Steel DHW

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[Intervention Review]

Anti-vascular endothelial growth factor for prevention of postoperative vitreous cavity haemorrhage after vitrectomy for proliferative diabetic retinopathy

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ABSTRACT

Background

Postoperative vitreous cavity haemorrhage (POVCH) is a significant complication following vitrectomy for proliferative diabetic retinopathy (PDR). It delays visual recovery and can make further treatment difficult if the view of the fundus is significantly obscured. A number of interventions to reduce the incidence of POVCH have been proposed, including the perioperative use of anti-vascular endothelial growth factor (anti-VEGF). Anti-VEGFs reduce vascular proliferation and the vascularity of neovascular tissue, which is often the source of bleeding following vitrectomy.

Objectives

This updated review aimed to summarise the effects of anti-VEGF use to reduce the occurrence of POVCH after vitrectomy surgery for PDR.

Search methods

We searched CENTRAL (which contains the Cochrane Eyes and Vision Group Trials Register) (2015, Issue 4), Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid MEDLINE Daily, Ovid OLDMEDLINE (January 1946 to May 2015), PubMed (January 1966 to May 2015), EMBASE (January 1980 to May 2015), Latin American and Caribbean Health Sciences (LILACS) (January 1982 to May 2015), the ISRCTN registry (www.isrctn.com/editAdvancedSearch), ClinicalTrials.gov (www.clinicaltrials.gov), and the the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/search/en). We did not use any date or language restrictions in the electronic searches for trials. We last searched the electronic databases on 26 May 2015.

Selection criteria

We included all randomised controlled trials (RCTs) and quasi-RCTs that looked at the use of anti-VEGFs and the incidence of POVCH in people undergoing vitrectomy for PDR.

Data collection and analysis

Both review authors independently assessed and extracted the data. We used standard methodological procedures expected by Cochrane.

The primary outcomes of the review were the incidence of early and late POVCH following perioperative anti-VEGF administration. Secondary outcomes included best-corrected visual acuity at six months following surgery, the incidence of vitreous cavity washout or revision vitrectomy at six months, adverse effects of intervention (cataract, iris rubeosis and rubeotic glaucoma, retinal detachment, increased inflammation and systemic side effects), quality of life measures performed at least six months following vitrectomy, and density of POVCH.

Main results

The current review included 12 RCTs that looked at the pre- or intraoperative use of intravitreal bevacizumab to prevent postoperative vitreous haemorrhage during pars plana vitrectomy for complications of PDR. The studies were conducted in a variety of countries (three from Iran, two from Italy, two from Egypt, and the remaining from South Korea, USA, Mexico, Pakistan, and Japan). The inclusion criteria for entry into the studies were standard complications of proliferative retinopathy: non-clearing vitreous haemorrhage, tractional retinal detachment involving the macula, or combined tractional rhegmatogenous detachment. The included studies randomised a total of 654 eyes. The average age of the participants was 54 years.

We identified methodological issues in all included studies. Risk of bias was highest for masking of participants and investigators (four studies were an 'open label' design), and a number of studies were unclear when describing randomisation methods and sequence allocation.

Participants receiving intravitreal bevacizumab in addition to pars plana vitrectomy were less likely to experience early POVCH (grade 2) compared to people undergoing pars plana vitrectomy alone (risk ratio (RR) 0.28, 95% confidence interval (CI) 0.08 to 0.96, 2 studies, 144 eyes, high-quality evidence). This corresponds to an absolute effect of 130 fewer people (95% CI 167 fewer to 7 fewer) with early POVCH per 1000 people when treated with intravitreal bevacizumab. We saw similar results for all grades of POVCH (RR 0.35, 95% CI 0.23 to 0.53, 9 studies, 512 eyes) and when excluding cases where assessment of outcome was impossible due to presence of silicone oil (RR 0.34, 95% CI 0.19 to 0.60, 6 studies, 302 eyes).

The effect of pre- or intraoperative intravitreal bevacizumab on the incidence of late postoperative haemorrhage was uncertain (RR 0.72, 95% CI 0.30 to 1.72, 3 studies, 196 eyes, low-quality evidence). The absolute effect was 55 fewer people (95% CI 138 fewer to 143 more) with late POVCH per 1000 people when treated with intravitreal bevacizumab. This outcome was rarer and was only reported in a few studies. We are currently unable to provide an estimate of the effect of intravitreal bevacizumab on postoperative visual acuity due to significant study heterogeneity.

No local or systemic complications of intravitreal bevacizumab were reported by the RCTs. The risk of postoperative retinal detachment was lower in the participants treated with pre- or intraoperative bevacizumab (RR 0.46, 95% CI 0.19 to 1.08, 7 studies, 372 participants, low-quality evidence); the absolute effect was 49 fewer people (95% CI:73 fewer to 8 more) with postoperative retinal detachment per 1000 people when treated with intravitreal bevacizumab.

Authors' conclusions

The use of pre- or intraoperative bevacizumab lowers the incidence of early POVCH. The reported complications from its use appear to be low. Futher randomised studies that look at other anti-VEGF medications are ongoing and will strengthen the current review findings, giving both surgeons and patients evidence to guide treatment choices in the management of proliferative retinopathy.

PLAIN LANGUAGE SUMMARY

Anti-VEGF for prevention of postoperative vitreous cavity haemorrhage after vitrectomy for proliferative diabetic retinopathy

Review question

Does anti-vascular endothelial growth factor (anti-VEGF) reduce the occurrence of posterior vitreous cavity haemorrhage (POVCH) after vitrectomy surgery for proliferative diabetic retinopathy?

Background

POVCH is a significant complication following vitrectomy (removal of the vitreous gel from the posterior chamber of the eye) for the treatment of proliferative retinopathy (the growth of abnormal blood vessels from the retina, a layer of tissue at the back of the eye), occurring in approximately 30% of cases. POVCH has two main forms: early, when haemorrhage (bleeding) is present in the first few postoperative days, and late, when haemorrhage occurs a number of months after surgery. The presence of POVCH delays visual recovery, can lead to elevated pressure within the eye, and can make further treatment for diabetic retinopathy difficult. Ten per cent of patients require revision surgery, which has significant implications for resources, time, and cost. The use of anti-VEGF before surgery (preoperatively) has been proposed as an intervention to reduce the incidence of POVCH.

Search date

The evidence is up to date to May 2015.

Key results

The electronic database searches identified 12 randomised controlled trials that met the inclusion criteria. We performed a number of analyses that suggest that pre- or intraoperative anti-VEGF may reduce the incidence of early POVCH. The effect on late POVCH was unclear. We are currently unable to comment on the effect of anti-VEGF treatment on postoperative visual acuity due to significant differences in the studies' design and outcomes.

The risk of adverse events when using preoperative anti-VEGF appears small.

Quality of evidence

We are reasonably certain that anti-VEGF reduces the incidence of early POVCH (high-quality evidence) but less certain about its effects on late POVCH and risk of adverse effects.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Anti-VEGF compared with control for prevention of postoperative vitreous cavity haemorrhage after vitrectomy for proliferative diabetic retinopathy

Patient or population: People with proliferative diabetic retinopathy undergoing vitrectomy
Settings: Hospital
Intervention: Anti-VEGF
Comparison: No anti-VEGF

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Anti-VEGF				
Early POVCH 4 weeks	**182 per 1000**	**52 per 1000** (15 to 175)	**RR 0.28** (0.08 to 0.96)	144 (2)	⊕⊕⊕⊕ high	POVCH grade 2 or worse
Early POVCH 4 weeks	**310 per 1000**	**109 per 1000** (71 to 164)	**RR 0.35** (0.23 to 0.53)	512 (9)	⊕⊕⊕⊕ high	POVCH all grades
Late POVCH 6 months	**198 per 1000**	**143 per 1000** (60 to 341)	**RR 0.72** (0.30 to 1.72)	196 (3)	⊕⊕◯◯ **low**[1]	POVCH all grades
Visual acuity logMAR acuity 6 months	The mean visual acuity ranged across control groups from 0.51 to 2.07 logMAR	Due to substantial heterogeneity between studies (I^2 = 88%), we could not estimate a treatment effect and hence a corresponding risk	Mean differences ranged from 1.31 logMAR in favour of anti-VEGF to 0.14 logMAR in favour of control	289 (5)	We did not GRADE this as we do not have an estimate of effect	
Vitreous cavity washout 6 months	**70 per 1000**	**15 per 1000** (3 to 74)	**RR 0.19** (0.06 to 0.67)	291 (5)	⊕⊕◯◯ **low**[2]	

Adverse effects: retinal detachment at any time	**91 per 1000**	**42 per 1000** (18 to 99)	**RR 0.46** (0.19 to 1.08)	372 (7)	⊕⊕◯◯ **low**[3]	Other adverse events considered included: raised intraocular pressure, rubeosis, neovascular glaucoma, cataract progression, systemic adverse events. Not much data available/reported
Quality of life 6 months	Not reported					

*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; **MD:** Mean difference; **RR:** Risk ratio; **POVCH:** Postoperative vitreous cavity haemorrhage; **VEGF:** Vascular endothelial growth factor.

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

[1]Downgraded for imprecision (confidence intervals include 1 (no effect)) and indirectness (the analysis includes all grades of POVCH, but we planned to consider only grade 2 or worse).
[2]Downgraded for risk of bias (none of the trials contributing to this analysis reported methods of sequence generation and allocation concealment in enough detail to judge risk of bias) and imprecision (confidence intervals include 1 (no effect)).
[3]Downgraded for risk of bias (all except one of the trials contributing to this analysis reported methods of sequence generation and allocation concealment in enough detail to judge risk of bias) and imprecision (confidence intervals include 1 (no effect)).

BACKGROUND

Description of the condition

Pars plana vitrectomy is an established and successful treatment for the complications of proliferative diabetic retinopathy (PDR) (Ho 1992; McLeod 1991). Up to 10% of people presenting with PDR require the treatment within one year (Kaiser 2000). The most common indication for surgery is non-clearing vitreous haemorrhage (Ho 1992; McLeod 1991). Unfortunately, postoperative vitreous cavity haemorrhage (POVCH) is a significant complication occurring in approximately 20% to 30% of cases, although the reported range is large: 5% to 80% of cases (Benson 1988; Blankenship 1986; Liggett 1987; Novak 1984; Tolentino 1989; Virata 2001; Yorston 2008).

Although there can be overlap, POVCH occurs in two main forms.

1. Early POVCH, being present from the first few postoperative days and delaying visual recovery by non-clearance.
2. Late POVCH, occurring later during follow-up, commonly at two to six months postoperatively, after a postoperative period during which the vitreous cavity was clear.

Aetiology of POVCH

Persistent haemorrhage can result from operative and postoperative oozing of the remnants of new vessels or dissected tissue, or directly from the sclerostomies used to perform surgery. It can also occur from clot lysis in the first few postoperative days. Leaching of red blood cells can occur from retained old haemorrhages in residual anterior vitreous, causing apparent POVCH (McLeod 1991; Novak 1984; Tolentino 1989).

Recurrent haemorrhage can result from late haemorrhage from dissected tissue, recurrent traction on residual new vessels, or indeed postoperative new vessel growth in the posterior retina. Recent studies have shown that a common cause of recurrent haemorrhage is new anterior vessel growth at the inner sclerostomy sites associated with fibrous traction (Bhende 2000; Hershberger 2004; Hotta 2000; Kreiger 1993; Sawa 2000; Steel 2008; West 2000). Termed 'entry site neovascularisation' (ESNV) (McLeod 2000), this is thought to be an aberrant wound-healing response related to the presence of retinal and pars plana ischaemia (Kreiger 1993; Yeh 2005). The presence of ESNV is difficult to observe clinically because of the extreme anterior location, but can be confirmed at the time of revision surgery with deep scleral indentation or endoscopic techniques (West 2000). It can also be localised, with anterior segment high-resolution ultrasonography of the inner sclerostomy sites (Bhende 2000; Hershberger 2004; Hotta 2000; Steel 2008).

Consequences and management of POVCH after occurrence

People with POVCH suffer a delay in their visual recovery which, in some cases, results in a worse level of visual acuity than preoperatively. Intraocular pressure can become raised from trabecular meshwork obstruction. If maculopathy is present, then additional laser treatment cannot be applied, with the risk of worsening foveal function in the long term.

The initial treatment for POVCH is observation (Tolentino 1989). Spontaneous clearance occurs in many cases. Because they are no longer trapped in the gel structure of the vitreous, red blood cells can circulate and clear more freely from the vitreous cavity. Clearance is related to the amount of haemorrhage, its frequency, and the degree of communication between anterior and posterior segments, allowing red blood cells to enter the anterior chamber and be cleared via the trabecular meshwork (McLeod 2000).

Non-clearing POVCH necessitates revision surgery in approximately one-third to one-half of those who experience POVCH and approximately 10% of all patients undergoing surgery (Blankenship 1986; Blumenkranz 1986; Brown 1992; Han 1991; Martin 1992; Novak 1984; Schachat 1983; Tolentino 1989). Non-clearing POVCH is treated with surgery to remove haemorrhage and to treat any underlying cause that may have been identified. The timing of the surgery will depend on a variety of factors, including social situation, fellow-eye status, maculopathy needing treatment, intraocular pressure, etc.

In some patients, spontaneous clearing or revision surgery is followed by further haemorrhage, frustrating visual rehabilitation further, especially if this occurs in the better eye.

Description of interventions to reduce the incidence of POVCH and how the interventions may work

At the time of the initial vitrectomy surgery, several strategies may have been used to prevent POVCH and avoid the need for repeat surgery. We can divide these into two main groups.

1. Established surgical interventions that are generally regarded as standard clinical practice.

i) Ensuring adequate haemostasis at the time of vitrectomy with laser or intraocular bipolar coagulation to reduce postoperative oozing of dissected blood vessels.

ii) Removal of peripheral haemorrhagic vitreous to reduce leaching of sequestered red blood cells postoperatively into the vitreous cavity.

iii) Identification and removal of all posterior vitreoretinal traction. Vitreoschisis is also known to occur in people with PDR, and identification of this and dissection in the true vitreoretinal plane are important in order to avoid recurrent traction and postoperative bleeding from neovascular tissue (Schwatz 1996).

iv) Applying supplementary posterior panretinal photocoagulation if required.

2. Other strategies to prevent POVCH that have been reported but not routinely adopted.

Surgical

- Applying additional anterior retinal photocoagulation up to the ora serrata to ablate retro-oral ischaemic retina and reduce the production of postoperative neovascular growth factors (Liggett 1987; Mason 1978; Yeh 2005).
- Direct treatment to the sclerostomy sites themselves with either cryotherapy or laser (Yeh 2005). This is thought to reduce the occurrence of entry site neovascularisation by inhibiting cellular migration through the sclerostomy wounds and causing focal atrophy of the ciliary epithelia.
- Removal of Wieger's ligament and thorough anterior vitrectomy, especially around the inner sclerostomy wounds (McLeod 2000; McLeod 2003). This may be effective by:
    - increasing the egress of red blood cells and growth factors from the posterior segment to the anterior segment for rapid clearance of any POVCH;
    - reducing any putative concentration of growth factors around the sclerostomy sites themselves;
    - removing the vitreous scaffold along which anterior new vessels could grow.

Some clinicians advocate simultaneous or even pre-emptive cataract surgery to achieve these aims and reduce the risk of POVCH (Schiff 2007).

- Agents with physical actions thought to possibly reduce the rate of POVCH inserted into the eye during surgery, such as air (Joondeph 1989), gas (Koutsandrea 2001; Yang 2007), or viscoelastic substances (Packer 1989).

Pharmacologic

Preoperative

- The vascular endothelial growth factor (VEGF) inhibitor bevacizumab has been used preoperatively to reduce vascular proliferation and reduce the vascularity of neovascular tissue (Romano 2009a; Yang 2008).

Intraoperative

- Triamcinolone has been used intraoperatively by intraocular injection to reduce inflammation and vascular proliferation (Faghihi 2008).
- Bevacizumab has been used intraoperatively to reduce vascular proliferation following surgery (Romano 2009b).

Postoperative

- Oral tranexamic acid, which inhibits fibrinolysis and hence clot dissolution, administered to the patient postoperatively (Laatikainen 1987; Ramezani 2005).

Why it is important to do this review

Diabetes mellitus is an increasing health problem. It is estimated that 6% (3.2 million) of the UK population are currently diabetic and that this will increase to 5 million by 2025. Ten per cent (10 billion UK pounds) of the total NHS budget is spent treating the acute costs of diabetes and its complications and this is predicted to increase to 17 billion by 2035 (Diabetes UK 2014). Diabetic retinopathy is one of the leading cause of blindness in the working age group in the UK accounting for 14.4% of blind and partially sighted registrations (Liew 2014).

Within 20 years of diagnosis nearly all people with Type 1 and almost two thirds of people with Type 2 diabetes have some degree of retinopathy (Scanlon 2008) and after 15 years, 30% and 10% of type 1 and type 2 diabetics respectively develop PDR (Klein 1984a; Klein 1984b). These patients are at risk of severe visual loss resulting from the complications of PDR. A study of patients at a large eye unit in the USA suggested that approximately 10% of patients presenting with PDR require vitrectomy surgery within one year (Kaiser 2000). Estimates based upon data from our region (Vaideanu 2014) suggest that approximately 4000 vitrectomies for the complications of PDR are currently performed annually in the UK. If 10% require revision surgery, this equates to 400 patients per annum in the UK. POVCH after vitrectomy surgery is certainly a significant problem and its occurrence is distressing for patients as well as delaying visual recovery. Repeat interventions expose the patient to further operative risk and anxiety and add to the overall cost of care. The use of anti-VEGF treatment is becoming increasingly common for many ophthalmic conditions and has significant revenue consequences. The result of anti-VEGF use, both preoperatively and intraoperatively, to reduce the occurrence of POVCH is uncertain, and a review of the literature will aid in optimum patient management and design of future studies.

The use of anti-VEGF treatment is becoming increasingly common for many ophthalmic conditions and has significant revenue consequences. However, the effectiveness of anti-VEGF use, both preoperatively and intraoperatively, in reducing the occurrence of POVCH is uncertain. A review of the literature will aid in optimum patient management and in the design of future studies.

OBJECTIVES

This review aimed to summarise the effects of anti-VEGF use to reduce the occurrence of POVCH after vitrectomy surgery for PDR.

METHODS

Criteria for considering studies for this review

Types of studies

This review aimed to include all randomised controlled trials (RCTs) and quasi-RCTs. If we had not found any RCTs that met our inclusion criteria, we would have provided a description of the evidence for current practice from non-randomised comparative trials along with the nature of evidence on which the review was based. We imposed no language or date restrictions.

Types of participants

Participants in the trials had to be people with PDR undergoing vitrectomy for the complications of diabetic retinopathy for the first time.

Types of interventions

Intervention: any use of anti-VEGF designed to reduce POVCH. We considered the following anti-VEGF treatments when given pre- or intraoperatively.

- Bevacizumab 1.25 mg/0.05 ml
- Ranibizumab 0.5 mg/0.05 ml
- Pegaptanib 0.3 mg/0.05 ml
- Aflibercept 2.0 mg/0.05 ml

Comparator: no treatment, sham treatment, or any other anti-VEGF.

Types of outcome measures

As the aim of this review was to look at the prevention of POVCH, we excluded studies that did not report POVCH.

Primary outcomes

1. The incidence of early POVCH after surgery. We defined early POVCH as haemorrhage present from the first postoperative day or recurrent within four weeks postoperatively, either being at least grade 2 in severity as measured by the Diabetic Retinopathy Vitrectomy Study criteria (Anonymous 1985).
2. The incidence of late POVCH after surgery. We defined late POVCH as haemorrhage occurring more than four weeks postoperatively after a period during which the vitreous cavity was clear. The minimum length of follow-up for this outcome was six months.

Secondary outcomes

1. Visual acuity at six months following the primary vitrectomy.
2. The incidence of vitreous cavity washout or revision vitrectomy at six months.
3. Adverse effects of intervention including cataract, iris rubeosis and rubeotic glaucoma, retinal detachment, increased inflammation and systemic side effects.
4. Quality of life measures performed at least six months following vitrectomy.
5. Density of POVCH, as measured by the Diabetic Vitrectomy Study criteria (Anonymous 1985).

Follow-up

Follow-up for the reviewed studies' outcome measures varied from 1 month to 12 months postvitrectomy. We looked at studies with any follow-up period, using six-month follow-up data as a minimum for late POVCH and visual acuity. Follow-up periods for the remaining secondary outcomes varied and are described in the Characteristics of included studies section.

Search methods for identification of studies

Electronic searches

We searched CENTRAL (which contains the Cochrane Eyes and Vision Group Trials Register) (2015, Issue 4), Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid MEDLINE Daily, Ovid OLDMEDLINE (January 1946 to May 2015), PubMed (January 1966 to May 2015), EMBASE (January 1980 to May 2015), Latin American and Caribbean Health Sciences (LILACS) (January 1982 to May 2015), the ISRCTN registry (www.isrctn.com/editAdvancedSearch), ClinicalTrials.gov (www.clinicaltrials.gov), and the the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/search/en). We did not use any date or language restrictions in the electronic searches for trials. We last searched the electronic databases on 26 May 2015.

See: Appendices for details of search strategies for CENTRAL (Appendix 1), MEDLINE (Appendix 2), PubMed (Appendix 3), EMBASE (Appendix 4), LILACS (Appendix 5), ISRCTN (Appendix 6), ClinicalTrials.gov (Appendix 7), and the ICTRP (Appendix 8).

We ran the initial searches both with and without RCT search filters, as we wished to identify as much literature as possible on POVCH. For subsequent updates, however, we will only run searches with RCT filters, as the review is focusing on evidence from RCTs only.

After editorial input, we decided to revise and broaden the search strategies for the review. The searches were constructed of terms

for the following four components: diabetic retinopathy, vitrectomy, haemorrhage, anti-VEGF drugs. The searches have now been amended whereby the terms for vitrectomy and for haemorrhage have been combined into one search set of terms. This has made the search broader and will help us to identify additional relevant studies.

Searching other resources

We manually searched the reference lists of the trials included in the review for additional trials. We did not specifically handsearch journals or conference proceedings for this review.

Data collection and analysis

Selection of studies

Both review authors independently assessed abstracts to ascertain which studies met the inclusion criteria for the review. We labelled the abstracts as included, unclear, or excluded. We obtained full-text copies of all included and unclear studies, and we independently determined which studies met the inclusion criteria. We again labelled each study as included, unclear, or excluded. We discussed any unclear articles and contacted the authors of the relevant article for further details when necessary.

Data extraction and management

Both review authors independently extracted data using standard methodological procedures expected by Cochrane. We compared each data set and resolved any discrepancies by discussion. We independently entered data into Review Manager and then rechecked the data (RevMan 2014).

Assessment of risk of bias in included studies

We structured the criteria for assessment of risk of bias per Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We assessed each domain area, giving a judgement of 'low' risk of bias, 'high' risk of bias, or 'unclear' risk of bias. A judgement of 'unclear' indicated we were uncertain of the risk of bias. We looked specifically at the following domain areas:

- Methods used to generate the study groups.
- Methods used to conceal the allocation of the study groups.
- Methods used to mask (blind) study participants and personnel.
- Review of the study outcome data, looking specifically at the completeness of each study group outcome and selective outcome reporting.

Measures of treatment effect

We presented dichotomous outcomes as risk ratios and continuous outcomes as mean difference.

The review's primary outcomes included dichotomous data on the incidence of persistent or early POVCH and the incidence of late POVCH following the primary surgery. The secondary outcome data contained dichotomous data on the incidence of vitreous cavity washout or revision vitrectomy at six months and the adverse effects of the intervention. We intended to analyse visual acuity at six months following the primary vitrectomy as continuous data. POVCH density is graded into four categories: grades 0 to 3. Rather than analysing the data as ordinal outcomes, we proposed to group together grade 0 with grade 1 POVCH and grade 2 with grade 3 POVCH in order to generate two larger groups, which we planned to analyse as dichotomous data in a meta-analysis.

Unit of analysis issues

Ahn 2011 and Manabe 2015 included a small number of participants who had both eyes randomised. We included these participants in the analysis. Due to the number being small, we considered that the effect of interpersonal variance on any outcome would be negligible.

Dealing with missing data

Where data were missing in the included studies, we contacted the authors of the trials to request the missing data. In studies for which the trial authors could not provide missing data, we assessed whether the missing data were of 'low' or 'high' risk of bias, as per Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

We intended to include studies missing data considered to be of 'low' risk of bias in a meta-analysis. We would also have included studies thought to be at 'high' risk of bias in the meta-analysis, but we would have performed a sensitivity analysis in order to assess their impact on the outcome of the meta-analysis.

Assessment of heterogeneity

We assessed clinical heterogeneity by careful review of the study papers and presented a descriptive summary of results. We assessed heterogeneity between studies included in the meta-analysis using the I^2 statistic. We took an I^2 result of more than 50% as an indication of high study heterogeneity.

Assessment of reporting biases

To avoid the presence of reporting biases within the review, we searched trial registry databases, which allowed us to identify all registered trials, published and unpublished. We contacted investigators of registered trials that were listed as having completed

participant recruitment to ask for any unpublished data that may be relevant to the review outcomes.

Data synthesis

We performed analysis of data from the included RCTs for the two primary outcomes, secondary outcomes 1 and 2, and also for rate of postoperative retinal detachment. We used a random-effects model for any analysis containing three or more RCTs.

Sensitivity analysis

We excluded trials that included participants with silicone oil tamponade because we felt that the tamponade could affect the assessment of the outcomes.

Summary of findings table

We prepared a 'Summary of findings' table presenting relative and absolute risks. We graded the overall quality (certainty) of the evidence for each outcome using the GRADE classification (GRADEpro 2014). We included the following outcomes in the 'Summary of findings' table.

1. Early POVCH (four weeks)
2. Late POVCH (six months)
3. Visual acuity, logMAR (six months)
4. Vitreous cavity washout (six months)
5. Adverse events: retinal detachment (at any time)
6. Quality of life

These outcomes were not defined a priori because the original protocol and first edition of this review were published before the summary of findings methodology was adopted by the Cochrane Eyes and Vision Group.

RESULTS

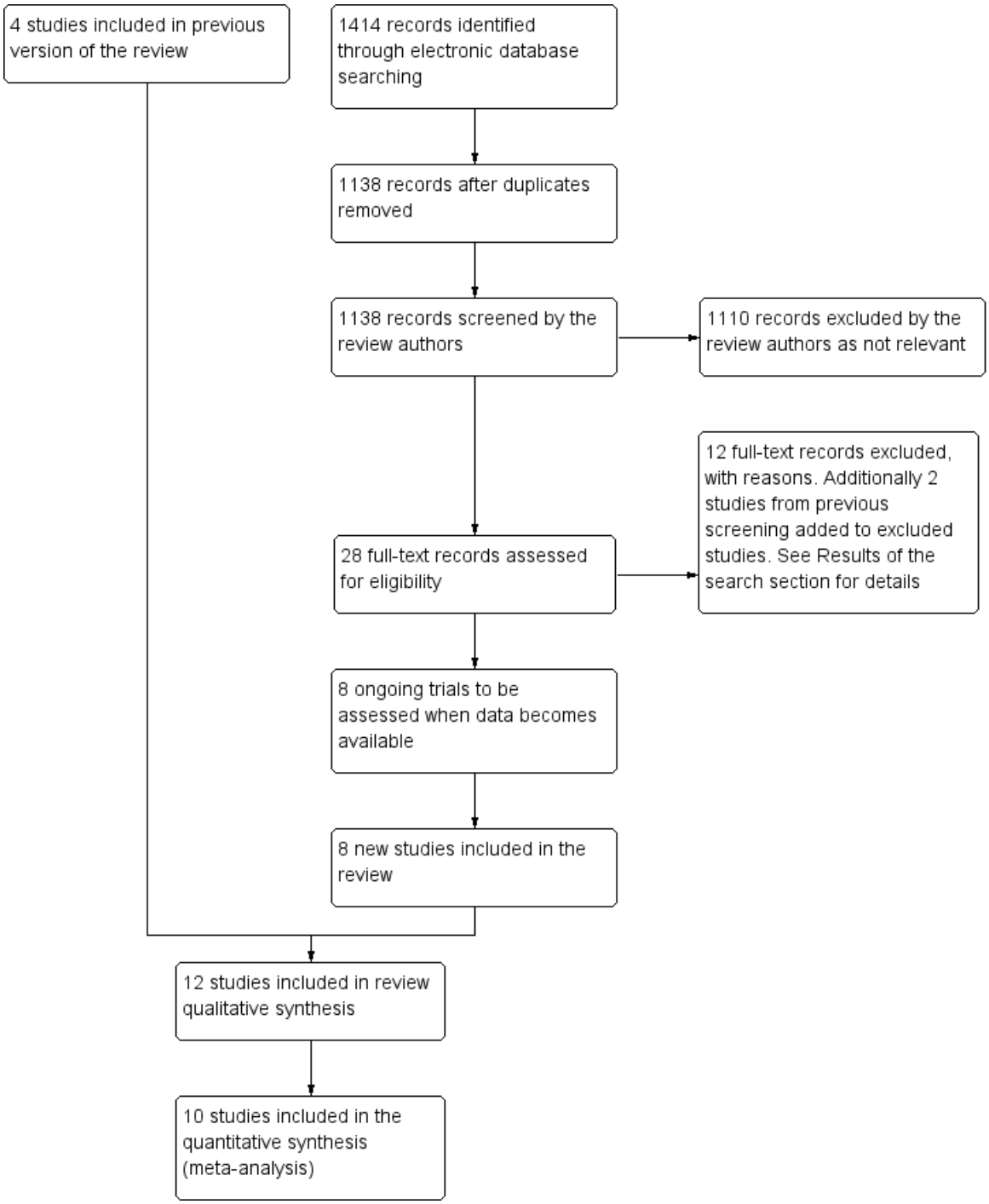
Description of studies

Results of the search

The electronic searches yielded a total of 472 titles and abstracts and 9 reports of ongoing studies. After deduplication, the Trials Search Co-ordinator scanned 397 records and discarded 311 records that were not relevant to the scope of the review. We screened the titles and abstracts of the remaining 86 references. We rejected 70 abstracts as not eligible for inclusion in the review. We obtained and screened full-text copies of 16 references, of which we included 4 studies and excluded 12 studies from the review.

The amended searches run in May 2015 retrieved a total of 1414 records (Figure 1). After removing duplicate records, we screened 1138 references and excluded 1110 records that were not relevant to the scope of the review. We assessed 28 full-text reports of studies for potential inclusion in the review. In addition to the four previously included studies (Ahmadieh 2009; di Lauro 2009; Modarres 2009; Rizzo 2008), we have now included eight new studies (Ahn 2011; El Batarny 2008; Elwan 2013; Farahvash 2011; Hernández-Da Mota 2010; Manabe 2015; Sohn 2012; Zaman 2013). We excluded 12 studies (Berk Ergun 2014; Bhavsar 2014; Demir 2013; Goncu 2014; Gupta 2008; Gupta 2012a; Gupta 2012b; Jirawison 2012; Li 2010; Pakzad-Vaezi 2014; Pokroy 2011; Sato 2013). We previously excluded da R Lucena 2009 and Yeh 2009 at the initial stage of screening abstracts. However, these two studies have been included in a meta-analysis by Zhao 2011, so in the interests of transparency we have now added these studies to our list of excluded trials with reasons for exclusion.

Figure 1. Results from searching for studies for inclusion in the review.



We also added the following eight reports of ongoing trials, which we will assess for potential inclusion in the review when data becomes available (ISRCTN79120387; NCT00931125; NCT01091896; NCT01151722; NCT01306981; NCT01589718a; NCT01805297 NCT01854593).

Included studies

We identified 12 completed studies from the electronic database searches that met our inclusion criteria; see the Characteristics of included studies table for details.

Setting and participants

The included studies were conducted in a number of countries. Three were from Iran, two were from Italy, two were from Egypt, and the remaining were from South Korea, USA, Mexico, Pakistan, and Japan. The included studies randomised a total of 654 eyes. Sample size varied from 20, in Sohn 2012, to 107, in Ahn 2011. The mean age of the participants included was 54.2 years.

Intervention

The majority of included studies gave 1.25 mg intravitreal bevacizumab (IVB) (0.05 ml) within one week of pars plana vitrectomy. The studies with a different protocol were the following.

- Ahn 2011 had an intervention group in which 1.25 mg IVB was given at the end of surgery (37 participants).
- di Lauro 2009 had an intervention group that received 1.25mg IVB three weeks before vitrectomy.
- Hernández-Da Mota 2010 gave 1.25 mg IVB 48 hours before surgery.
- Manabe 2015 gave 0.16 mg (0.05 ml) IVB one day before surgery.
- Modarres 2009 gave 2.5 mg IVB three to five days before surgery.

Outcomes

The main outcomes in the trials included best-corrected visual acuity (BCVA), feasibility of surgery (operating time, intraoperative bleed, and type of surgical steps required), and postoperative complications. The main postoperative complications were rate of POVCH, iris rubeosis, and retinal detachment. Follow-up varied significantly across the trials, ranging from one month, in Ahmadieh 2009 and Manabe 2015, to one year, in Elwan 2013. The majority of trials had a final follow-up visit at six months.

A number of trials reporting the incidence of POVCH have included participants who received silicone oil endotamponade, which has made interpretation of the trial results difficult. The presence of silicone oil within the vitreous cavity precludes an accurate diagnosis of POVCH, as any blood would be localised to the far periphery of the posterior chamber. Grading of POVCH is not possible with silicone endotamponade present. In light of this, we have carried out sensitivity analyses on the incidence of POVCH excluding participants with silicone oil endotamponade. Two trials excluded participants who received silicone oil and gave an accurate grading system for POVCH (Ahmadieh 2009; Ahn 2011).

In addition, we identified nine ongoing RCTs and have provided details in the Characteristics of ongoing studies table. We cannot comment on whether the these studies' characteristics meet the inclusion criteria until they are published and we can undertake a review of their methodology.

Excluded studies

We excluded 26 studies identified by the search that were either non-randomised prospective studies or retrospective studies; see the Characteristics of excluded studies table. We excluded two trials that did not collect data on POVCH (da R Lucena 2009; Pakzad-Vaezi 2014).

Risk of bias in included studies

See also Figure 2 and Figure 3.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

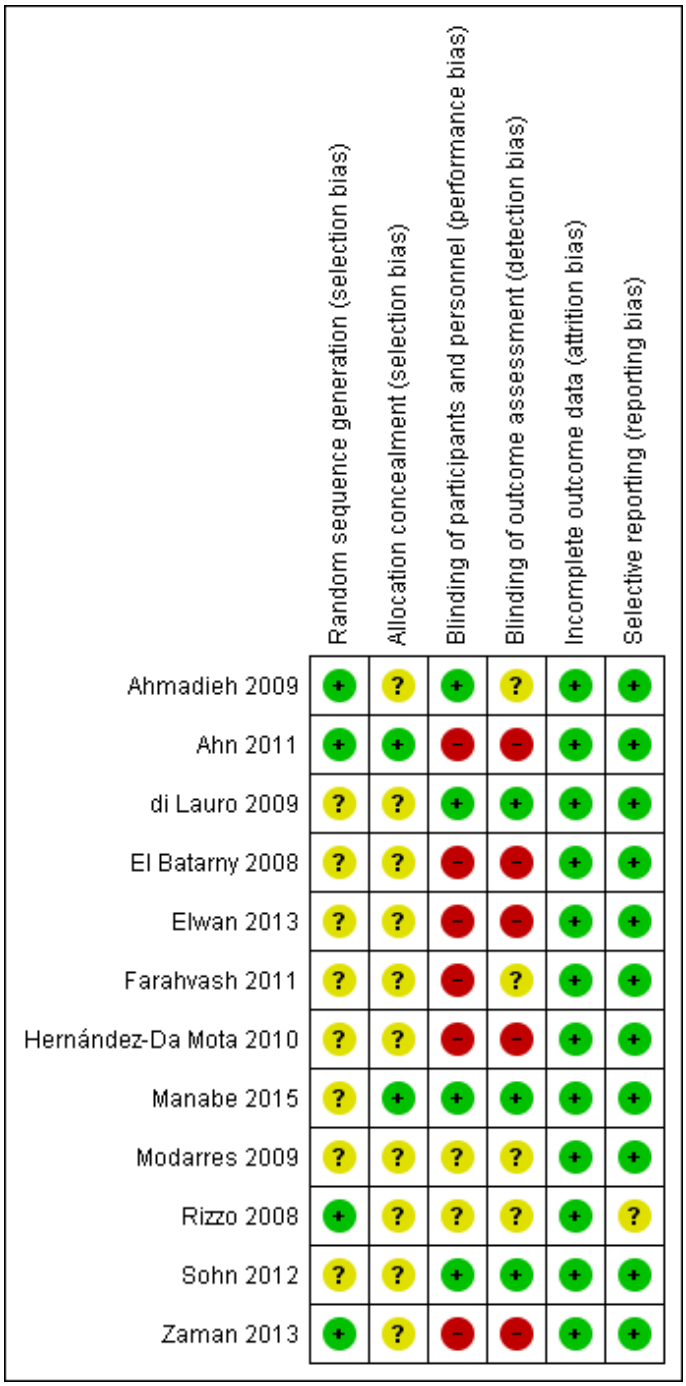
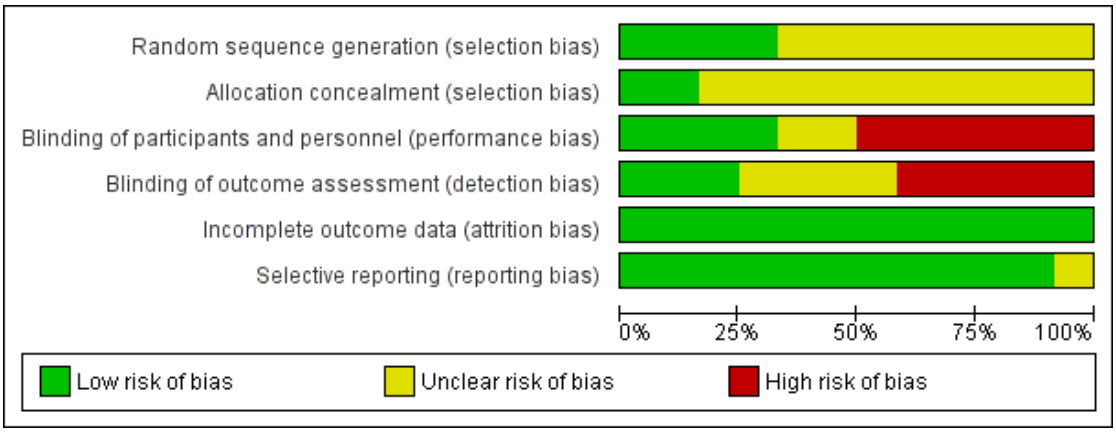


Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Allocation

Ahmadieh 2009 and Ahn 2011 clearly stated how the random sequence generation was performed. In both studies, a biostatistician was used to allocate participants and ensure that investigators were unaware of the series details. We graded the methods as 'low' risk for randomisation and allocation. di Lauro 2009 stated that participants were randomly assigned into the three groups, but provided no description on how the randomisation or sequence allocation was performed. El Batarny 2008, Elwan 2013, Farahvash 2011, Hernández-Da Mota 2010, Modarres 2009, Sohn 2012, and Zaman 2013 did not state how participants were allocated into each group and provided no details about the randomisation methods. Rizzo 2008 used a table of random numbers to assign each study participant to group one or group two, but provided no details of the sequence generation. We graded the methods used for allocation as 'unclear' for di Lauro 2009, El Batarny 2008, Elwan 2013, Farahvash 2011, Hernández-Da Mota 2010, Modarres 2009, Rizzo 2008, Sohn 2012, and Zaman 2013. In Manabe 2015, the allocation was done by the "envelop" methods, but the generation of the allocation sequence was not clearly described.

Blinding

We assessed Ahmadieh 2009 and Sohn 2012 as at 'low' risk of bias for masking (blinding), as a clear description of how this process was performed was provided. We graded Ahn 2011, El Batarny 2008, Elwan 2013, Farahvash 2011, and Hernández-Da Mota 2010, which had an open-label design, as 'high' risk. We graded di Lauro 2009, Rizzo 2008, Modarres 2009, and Zaman 2013, which did not comment on the masking of participants or investigators, as 'unclear'.

Incomplete outcome data

Ahmadieh 2009, Ahn 2011, Farahvash 2011, and Sohn 2012 clearly accounted for each participant who failed to complete the study protocol. It should be noted that in Ahmadieh 2009, less than half the participants (16 of 35) within the treatment group failed to complete the protocol, and only 18 of 35 participants within the control group completed the protocol. Manabe 2015 reported participant flow; all participants were followed up to 1 month. Although the remaining included RCTs did not comment directly on the attrition rate, it is clear from the results that all participants completed follow-up.

Selective reporting

All the included studies reported the stated primary and secondary outcomes.

Other potential sources of bias

Ahmadieh 2009 recorded a high number of participants who failed to complete the trial in both the control and treatment groups: 15 of 35 in the control group and 19 of 35 in the treatment

group. The main reasons for failing to complete follow-up were vitreous haemorrhage reabsorption, silicone oil endotamponade, gas tamponade, and lost to follow-up.

Ahn 2011 included 107 eyes of 91 participants. The 16 bilateral participants were included in the data analysis; no comment was made as to whether adjustment for within-person correlation was performed during statistical analysis.

In the IVB group of Manabe 2015, participants with bilateral proliferative diabetic retinopathy (PDR) received IVB in one eye only, and the other eye was excluded from the study. The authors considered that IVB injected in one eye may pass to the contralateral eye. In the control group, both eyes of bilateral cases were included in the study.

Effects of interventions

See: **Summary of findings for the main comparison**

We have described the effect of each intervention in order of outcome type.

Primary outcomes

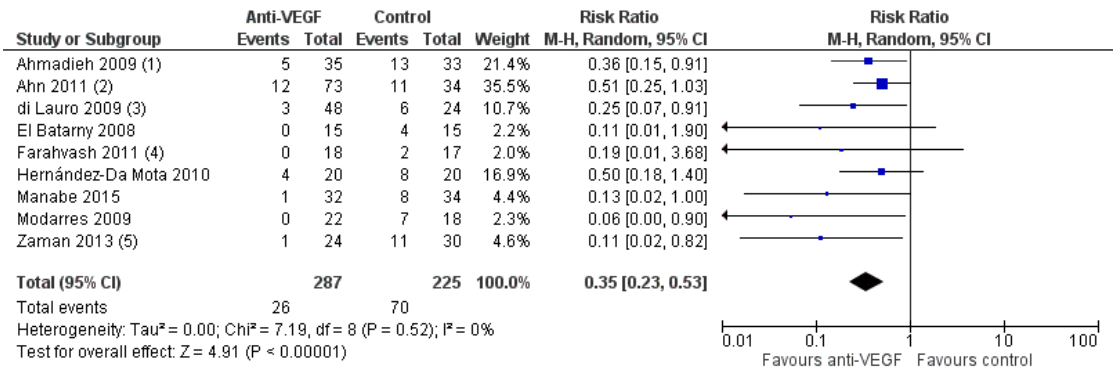
1. The incidence of early POVCH after surgery

Eight included RCTs commented on the incidence of early POVCH following pre- or intraoperative anti-VEGF administration (Ahmadieh 2009; Ahn 2011; di Lauro 2009; El Batarny 2008; Farahvash 2011; Hernández-Da Mota 2010; Modarres 2009; Zaman 2013). As many of the RCTs included participants who received silicone oil endotamponade in their results, making it difficult to establish the true incidence and grade of POVCH, we have performed a number of sensitivity analyses for this outcome excluding trials that included silicone oil cases. They are as follows.

- Analysis 1.1: Contained only data from Ahmadieh 2009 and Ahn 2011, as these two RCTs excluded participants who received silicone oil and gave an accurate grading system for POVCH. The analysis included only grade 2 POVCH or worse. The use of pre- or intraoperative IVB was shown to reduce the incidence of early POVCH (risk ratio (RR) 0.28, 95% confidence interval (CI) 0.08 to 0.96). This analysis contained 144 participants, 89 in the intervention arm and 55 in the control arm.

- Analysis 1.2: Included all trials that reported the incidence of POVCH (all grades). The use of pre- or intraoperative IVB was shown to reduce the incidence of POVCH (RR 0.35, 95% CI 0.23 to 0.53; eyes = 512; studies = 9; I^2 = 0%) (Figure 4). Thirty-seven participants in the intervention group received intraoperative IVB.

Figure 4. Forest plot of comparison: 1 Anti -VEGF vs control, outcome: 1.2 Early POVCH (all grades).



Footnotes

(1) 1.25mg IVB one week before surgery; follow-up 4 weeks after surgery
(2) 1.25mg IVB one day to two weeks before surgery or during surgery; follow-up 4 weeks after surgery
(3) 1.25mg IVB one week or three weeks before surgery; follow-up 4 weeks after surgery
(4) Note from JE: could not find these data in paper: 1.25mg IVB one week before surgery; follow-up 4 weeks after surgery
(5) 1.25mg IVB one week before surgery; follow-up 4 weeks after surgery

- Analysis 1.3: Included all trial results that reported the incidence of POVCH (all grades) with participants who received silicone oil endotamponade excluded. The use of pre- or intraoperative IVB was shown to reduce the incidence of

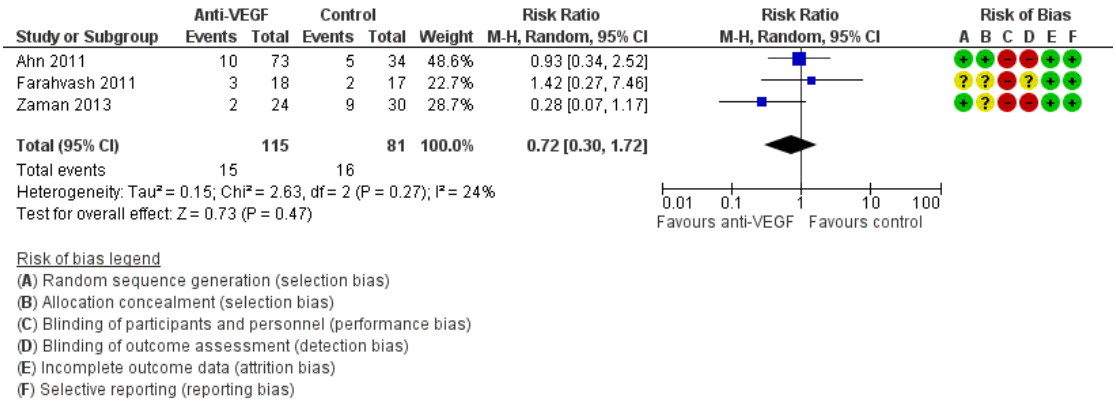
POVCH (RR 0.34, 95% CI 0.19 to 0.60; eyes = 302; studies = 6; I^2 = 7%).

Sohn 2012 did comment on one case of POVCH found at three-month follow-up in the control group. The corresponding author could not provide a clear definition of early or late POVCH. We have therefore not included this result within the above analyses.

2. The incidence of late POVCH after surgery

Three included studies commented on the effect of IVB on the incidence of late POVCH (Ahn 2011: Farahvash 2011; Zaman 2013). Only Ahn 2011 gave a grade for the severity of late POVCH. Analysis 1.4 contained the reported data from all the trials that commented on late POVCH (any grade) and found no reportable effect of pre- or intraoperative IVB on late POVCH (RR 0.72, 95% CI 0.30 to 1.72). This analysis contained 196 participants, 115 in the intervention arm and 81 in the control arm (Figure 5).

Figure 5. Forest plot of comparison: 1 Anti-VEGF versus control, outcome: 1.4 Late POVCH (all grades).



Ahn 2011 found no statistical difference between the rate of late POVCH in the control group and combined pre- and intraoperative IVB groups, P = 0.813.

Hernández-Da Mota 2010 included "recurrent haemorrhage" as an outcome, however provided no definition. We attempted to contact the corresponding author, but received no reply. These data are therefore currently excluded.

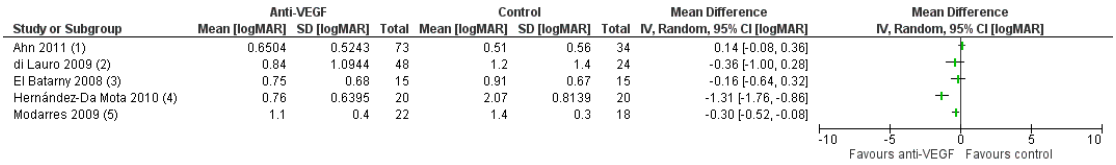
Secondary outcomes

1. Visual acuity at six months following the primary vitrectomy

Seven included studies commented on BCVA at six months or longer (Ahn 2011; di Lauro 2009; El Batarny 2008; Elwan 2013; Modarres 2009; Rizzo 2008; Zaman 2013). Six of the studies used LogMAR method for measuring acuity, while Elwan 2013 reported decimal acuity. Zaman 2013 provided a comparison of pre- and postoperative BCVA; the study provided no specific values.

We found considerable heterogeneity between studies (I^2 = 88%) with mean difference in acuity ranging from 1.31 logMAR units better vision in the anti-VEGF group, Hernández-Da Mota 2010, to 0.14 logMAR units better vision in the control group, Ahn 2011 (Analysis 1.5) (Figure 6). This means that a pooled estimate of effect may not be informative.

Figure 6. Forest plot of comparison: 1 Anti -VEGF vs control, outcome: 1.5 Visual acuity at six months or longer [logMAR].



Footnotes
(1) Follow-up: 6 months
(2) Follow-up: 6 months
(3) Follow-up: 12 months (range 7-18 months)
(4) Follow up: 6 months
(5) Follow-up: 6 months

2. The incidence of vitreous cavity washout or revision vitrectomy at six months

Five RCTs commented on the rate of vitreous cavity washout within six months (di Lauro 2009; El Batarny 2008; Elwan 2013; Manabe 2015; Modarres 2009). Analysis 1.6 showed that people receiving IVB were less likely to receive vitreous cavity washout (RR 0.19, 95% CI 0.06 to 0.67; eyes = 291; studies = 5; I^2 = 0%).

3. Adverse effects of intervention including cataract, iris rubeosis and rubeotic glaucoma, retinal detachment, increased inflammation and systemic side effects

We have provided all reported adverse events in detail in Table 1. No systemic complications of IVB use were reported.

As many of the included RCTs commented on the rate of postoperative retinal detachment, we elected to analyse this data. We did not list this analysis on the review protocol and undertook it at the update stage. Analysis 1.7 showed the risk of postoperative retinal detachment was lower within the intervention arm, but the result was not statistically significant, the confidence intervals were wide and include 1 (no effect) (RR 0.46, 95% CI 0.19 to 1.08). This analysis contained 372 participants, 208 in the intervention arm and 164 in the control arm.

4. Quality of life measures performed at least six months following vitrectomy

There are currently no studies that comment on this outcome.

5. Density of POVCH, as measured by the Diabetic Vitrectomy Study criteria

Ahmadieh 2009 clearly stated the grading for the density of POVCH within the results section. Four participants had grade 2 or 3 POVCH in the treatment group at one-week follow-up (4/16 (25%)), while 10 participants had grade 2 or 3 POVCH at the same follow-up within the control group (10/18 (55.5%)). At one-month follow-up this had changed to two participants within the treatment group (2/16 (12.5%)) and nine within the control group (9/18 (50%)).

Ahn 2011 defined POVCH in a similar manner to the Diabetic Vitrectomy Study criteria. At one month following surgery, 2/36 (5.6%), 0/37, and 1/34 (2.9%) of participants had grade 2 or worse POVCH in study group 1 (preoperative IVB), group 2 (intraoperative IVB), and group 3 (control), respectively.

The incidence of late POVCH (grade 2 or worse) occurred in 3/36 (8.3%) in the preoperative IVB group, 3/37 (8.1%) in the intraoperative IVB group, and 3/34 (8.8%) in the control group.

di Lauro 2009 commented that grade 3 POVCH (no fundal view) occurred in 6/24 (25%) of eyes in the control group and 1/24 (4%) and 2/24 (8.3%) of eyes that received bevacizumab 7 and 20 days preoperatively, respectively, when assessed three months postoperatively.

El Batarny 2008, Farahvash 2011, Hernández-Da Mota 2010, Modarres 2009, and Zaman 2013 did not clearly state the grading of POVCH.

DISCUSSION

Summary of main results

The aim of this review was to establish whether the use of anti-VEGFs as an adjunct to pars plana vitrectomy, either pre- or intraoperatively, is of benefit. Currently the review includes 12 RCTs, all of which look at the use of IVB. The main outcomes were the effect of IVB on early and late POVCH, BCVA, vitreous cavity washout rates, and postoperative complications. We summarised the effect of IVB by outcome type.

Primary outcomes

1. The incidence of early POVCH after surgery

Nine RCTs commented on the effect of IVB on the incidence of early POVCH. Analysis 1.1, Analysis 1.2, and Analysis 1.3 all showed a beneficial effect of IVB in reducing the rate of early POVCH following vitrectomy. The inclusion of participants who received silicone oil endotamponade may well have biased the true incidence of early POVCH, and so we advise caution when interpreting the results of Analysis 1.2 and Analysis 1.3. However, as silicone oil is commonly used following complex delamination surgery, the inclusion of this group is important and may provide a more practical guide to the effect of IVB.

2. The incidence of late POVCH after surgery (defined as occurring more than four weeks postoperatively after a period during which the vitreous cavity was clear)

Three RCTs reported the effect of IVB on late POVCH. Analysis 1.4 found no evidence of an effect of pre- or intraoperative IVB on the rate of late POVCH. This analysis contained two RCTs that included participants with silicone oil endotamponade in their results. Again, this may bias the true incidence of late POVCH. Ahn 2011 was the only study that excluded these participants before reporting their results, and found no effect of IVB on late POVCH.

Secondary outcomes

1. Visual acuity at six months following the primary vitrectomy

The current analysis (Analysis 1.5, Figure 6) suggested that use of IVB has no significant effect on average BCVA at six months. However, due to substantial heterogeneity between studies, we could not estimate an accurate pooled effect.
Many factors could affect BCVA within this heterogenous group of participants, particularly clarity of the media and vitreous cavity. The presence of silicone oil within the vitreous cavity will ensure it is clear in situations when potential recurrent haemorrhage may well have caused reduced vision. Further RCTs that exclude silicone oil participants are needed before a more accurate result can be reported.

2. The incidence of vitreous cavity washout or revision vitrectomy within six months

Two of the five studies within this analysis (Analysis 1.6) had no estimable effect. The incidence of vitreous cavity washout was reduced with the use of IVB.

3. Adverse effects of intervention including cataract, iris rubeosis and rubeotic glaucoma, retinal detachment, increased inflammation and systemic side effects

All included RCTs reported the adverse effects of preoperative IVB (Table 1). The results suggested that the risk of complications and adverse side effects appears to be small.

4. Quality of life measures performed at least six months following vitrectomy

There are currently no studies that comment on this outcome.

5. Density of POVCH, as measured by the Diabetic Vitrectomy Study criteria

Ahmadieh 2009, Ahn 2011, and di Lauro 2009 commented on the density of POVCH. Five other studies that commented on the density of POVCH did not clearly state the grading of POVCH, and the trial authors were unable to provide further information when contacted. We can draw no conclusion about the relative density of POVCH using preoperative IVB compared with controls.

Overall completeness and applicability of evidence

This review included 12 trials conducted in Europe, North America, Africa, and Asia. The results of these trials are likely to be applicable to standard clinical practice. The trials consistently showed that IVB applied around the time of vitrectomy to reduce the occurrence of complications of proliferative diabetic retinopathy decreased the risk of POVCH. However, the evidence was less complete with respect to other outcomes; for example the effect of IVB on visual acuity and adverse effects was less certain.
All the trials used IVB and most trials used a similar dose of (1.25 mg), but a variety of regimens were used in terms of whether the dose was given before, immediately before, or during surgery. No data were available on other anti-VEGF agents.
A number of ongoing RCTs are currently looking at the effects of ranibizumab, pegaptanib sodium, and aflibercept on POVCH and BCVA (see Characteristics of ongoing studies). The results of these trials will help clarify the effect of anti-VEGF on late POVCH and BCVA.

Quality of the evidence

The design of RCTs looking at the effect of adjunctive use of anti-VEGF in diabetic vitrectomy is difficult. There are a number of indications for vitrectomy in proliferative retinopathy. These vary from non-clearing vitreous haemorrhage in older patients with previously treated inactive proliferative diabetic retinopathy,

through to younger patients with active untreated proliferative diabetic retinopathy and severe tractional changes. Many of the included RCTs had a heterogenous group of participants, as above, and the effect of IVB on POVCH and BCVA may differ depending on the patient type.

Five of the included trials appear to be or state that they are 'open label'. This is a significant proportion and may limit confidence in the estimation of the treatment effect of IVB.

We restricted the meta-analysis to published RCT data, and it may be possible that bias exists if smaller trials not accepted for publication found no effect on early POVCH. A number of the included trials had a low number of participants, which reduces the power of the current analysis.

Potential biases in the review process

The review authors followed the key criteria listed within the Assessment of risk of bias in included studies section of the review to ensure that risk of bias was minimised during trial selection.

Agreements and disagreements with other studies or reviews

Zhao 2011 performed a systematic review looking at the potential benefits of preoperative IVB on both intraoperative (including intraoperative bleeding, endodiathermy, iatrogenic retinal tears, and mean surgical time) and postoperative (including BCVA, recurrent vitreous haemorrhage, reabsorption time of blood and other complications) outcomes.

Data analysis of included studies within the Zhao 2011 review, which looked at the incidence of early POVCH, showed an almost statistically significant result in favour of the treatment group (odds ratio (OR) 5.48, 95% CI 0.97 to 31.02; P = 0.05). This result is in agreement with the data analysis of this review. However, it should be noted that many of the included studies within the Zhao 2011 data analysis contained participants who received silicone oil endotamponade, which may be a significant source of bias. Also, the Zhao 2011 authors commented that due to varying definitions of POVCH, study heterogeneity within the data analysis was high (I^2 = 93.6%), and so the results should be interpreted with caution.

Zhang 2013 reported similar outcomes in a meta-analysis of the reported data on preoperative IVB use in vitrectomy for proliferative diabetic retinopathy. The study reported a beneficial effect of IVB on the rate of early POVCH (OR 0.35, 95% CI 0.21 to 0.58) and no effect on the rate of late POVCH (OR 0.55, 95% Cl 0.25 to 1.21).

Veliz 2014 summarised the results of a previously published version of this review. Zhang 2013, Zhao 2011, and Veliz 2014 concluded that bevacizumab probably decreased intraoperative bleeding, but its effect on visual acuity is uncertain. They concluded that it might increase the risk of cardiovascular events, but this was based on a RR of 2.2 with 95% CIs from 0.11 to 44.3, so there is some uncertainty with this estimate as well.

AUTHORS' CONCLUSIONS

Implications for practice

This review provides support for the use of perioperative IVB to prevent POVCH after vitrectomy for proliferative diabetic retinopathy. The current analysis suggests that pre- or intraoperative IVB reduces the risk of early POVCH, but the effect on late POVCH is uncertain. The number of reported severe complications from IVB use was low.

Implications for research

Further randomised studies looking at the effect of anti-VEGF agents on the incidence and management of POVCH will strengthen the current evidence base. These studies need to address the effect on both early and late POVCH, while ensuring that the use of endotamponade, which may be required during the postoperative period, is clearly stated within the results and allowed for in the power calculations prior to the study. Furthermore, the spontaneous clearance of vitreous haemorrhage or clearance following the injection of an anti-VEGF should be factored in for the power calculation. A minimum follow-up period of at least six months is important to ensure that late POVCH can be recognised. Visual acuity should be analysed at defined time points and measured before and after further surgery to remove POVCH. We recommend grading of POVCH using the criteria within the Diabetic Retinopathy Vitrectomy Study, making the outcome of RCTs more comparable and easier to subject to further analysis.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Ahmadieh 2009

Methods	Prospective, randomised, double-masked clinical trial Country: Iran
Participants	Number: 68 eyes of 68 participants undergoing PPV Age: Mean (± SD) age was 55.2 ± 11.1 years (range 21 to 76 years) Sex: 34 (50%) males; 34 (50%) females Inclusion criteria: 1. Non-clearing vitreous haemorrhage 2. Tractional retinal detachment involving or threatening the macula 3. Active progressive PDR Exclusion criteria: 1. BCVA of 20/40 or better 2. Pregnancy 3. History of IVB injection 4. Intraoperative use of long-acting gas or silicone oil 5. Simultaneous intraocular surgery such as cataract extraction 6. Monocular participants
Interventions	Intervention: • IVB injection (1.25 mg) 1 week before surgery (n = 35) Comparator: • Sham injection (n = 33)
Outcomes	Primary outcome measure: • Incidence of early (≤ 4 weeks) postoperative vitreous haemorrhage Secondary outcome measures: • Mean change in BCVA • IVB-related adverse events Follow-up: 1 day, 1 week, and 1 month after surgery
Notes	Trial registration number: NCT00524875 Date study conducted: January 2007 to December 2007 Funding: not reported Conflict of interest: reported that there were none

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was performed by random block permutation according to a computer-generated randomisation list

Ahmadieh 2009 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants were masked to the treatment method
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Visual acuity was measured by an optometrist who was masked to the groups. All pre- and postoperative examinations were performed by one of the authors (NS) , who was also masked to the study group identification
Incomplete outcome data (attrition bias) All outcomes	Low risk	A flow chart included within the results section accounted for all participants who failed to complete the study protocol
Selective reporting (reporting bias)	Low risk	All primary and secondary outcomes were reported, based on both the intention-to-treat analysis and per-protocol analysis

Ahn 2011

Methods	Prospective, randomised, open-label trial Country: South Korea
Participants	Number: 107 Age: Mean age (± SD). Preoperative IVB group 51.0 (± 9.5), intraoperative IVB group 55.6 (± 10.6), and control 55.0 (± 11.4) Sex: (Male/female). Preoperative IVB group 23/13, intraoperative IVB group 21/16, and control 16/18 Inclusion criteria: 1. Non-clearing vitreous haemorrhage 2. Macula-involving or macula-threatening TRD or fibrovascular proliferation with vitreoretinal adhesions Exclusion criteria: 1. Intraoperative use of long-acting gas or silicone oil 2. Repeat vitrectomy after first vitrectomy for retinal diseases other than vitreous haemorrhage 3. Previous history of vitrectomy 4. Uncontrolled hypertension 5. History of blood coagulopathy
Interventions	Intervention: • IVB injection (1.25 mg/0.05 ml) 1 to 14 days before PPV • IVB injection (1.25 mg/0.05 ml) at the end of PPV Comparator: • No IVB injection

Ahn 2011 (*Continued*)

Outcomes	Primary outcome measures: • Incidence of early (< 4 weeks) POVCH • Incidence of late (> 4 weeks) POVCH Secondary outcome measures: • Initial time of vitreous clearing • BCVA at 6 months after surgery Follow-up: 1 day, 1 week, 1, 3, and 6 months after surgery if there were no postoperative events
Notes	A total of 107 eyes of 91 participants, of which there were 16 bilateral participants, were included for analysis Trial registration number: NTC00745498 Date study conducted: June 2008 to October 2010 (from trials registry entry) Funding: not reported Conflict of interest: reported that there were none

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation was carried out using a permuted block analysis
Allocation concealment (selection bias)	Low risk	Allocation was performed by a biostatistician
Blinding of participants and personnel (performance bias) All outcomes	High risk	The study was open label
Blinding of outcome assessment (detection bias) All outcomes	High risk	The study was open label
Incomplete outcome data (attrition bias) All outcomes	Low risk	The distribution and attrition rate of study participants was clearly described in a flow chart
Selective reporting (reporting bias)	Low risk	All outcomes were reported

di Lauro 2009

Methods	Prospective interventional randomised controlled trial Country: Italy
Participants	Number: 72 eyes of 68 participants Age: Not given Sex: Not given

	Inclusion criteria: • Vitreous haemorrhage • TRD Exclusion criteria: • Neovascular glaucoma or cataract, or both • Combined traction and rhegmatogenous retinal detachment (diagnosed either before or during the surgery)
Interventions	Intervention: • IVB injection (1.25 mg) 1 week before the vitrectomy (n = 24) • IVB injection (1.25 mg) 3 weeks before the vitrectomy (n = 24) Comparator: • Sham injection: subconjunctival injection of 0.05 ml of balanced salt solution 3 weeks before the vitrectomy (n = 24)
Outcomes	Primary outcome measures: • Clearing of vitreous haemorrhage • Incidence of adverse effects and the need for other procedures during the surgery Secondary outcome measures: • Change in BCVA • Duration of surgery Follow-up: 1, 6, 12, and 24 weeks after surgery, and ultrasonography was performed before and 24 weeks after the injection
Notes	Trial registration number: NCT01025934 Date study conducted: October 2005 to May 2007 Funding: not reported Conflict of interest: reported that there were none

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"We randomly assigned eligible patients... " and "The patients were randomly divided into three treatment groups (A, B, C)"
Allocation concealment (selection bias)	Unclear risk	Not stated in the report
Blinding of participants and personnel (performance bias) All outcomes	Low risk	A sham injection was used in the control group
Blinding of outcome assessment (detection bias) All outcomes	Low risk	A sham injection was used in the control group

di Lauro 2009 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Not stated in the report, however clear from the results that all participants completed follow-up
Selective reporting (reporting bias)	Low risk	Data for all main outcomes were analysed and presented

El Batarny 2008

Methods	Prospective, randomised, open-label control trial Country: Egypt
Participants	Number: 30 Age: Mean (± SD). Control group 46 (± 12) and intervention group 44 (± 11) Sex: Not given Inclusion criteria: • TRD threatening or involving the macula • TRD with vitreous haemorrhage • Non-clearing vitreous haemorrhage (present for more than 1 month) • Massive preretinal/subhyaloid blood covering the posterior pole Exclusion criteria not stated
Interventions	Intervention: • IVB (1.25 mg) 5 to 7 days before surgery (n = 15) Comparator: • No treatment (n = 15)
Outcomes	Primary outcomes: • Feasibilty of surgery • Postoperative complications Follow-up: 1 day, 7 days, 2 weeks, 1 month, and then monthly until end of study (all participants completed a minimum of 6 months)
Notes	Trial registration number: not reported Date study conducted: not reported Funding: not reported Conflict of interest: reported that there were none

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Participants were randomised by diagnosis
Allocation concealment (selection bias)	Unclear risk	Not stated

El Batarny 2008 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants were not masked to their study group
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not mentioned, and treatment groups were different
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed follow-up
Selective reporting (reporting bias)	Low risk	All outcomes were reported

Elwan 2013

Methods	Prospective, randomised, open-label study Country: Egypt
Participants	Number: 100 Age: Mean (± SD). Control group 61.42 (± 5.49) and intervention group 61.94 (± 5.96) Sex: 61 male and 39 female Inclusion criteria: • Complications of PDR Exclusion criteria: • Previous vitreoretinal surgery • Participants with diabetes and other conditions that may cause vitreous haemorrhage • Diabetic participants undergoing vitrectomy for persistent macular oedema • Participants with BCVA of less than hand movements vision
Interventions	Intervention: • IVB (1.25 mg/0.05 ml) 1 week before vitrectomy (n = 50) Comparator: • No IVB (n = 50)
Outcomes	Primary outcomes: • Feasibility of surgery • Postoperative complications (postoperative vitreous haemorrhage, iris rubeosis, and retinal detachment) • BCVA at 12 months Follow-up: 1 day, 1 week, 1, 3, 6, 9 months, and 1 year
Notes	No response from authors to correspondence asking for clarification of POVCH definitions Trial registration number: not reported Date study conducted: November 2008 to November 2010 Funding: not reported

Elwan 2013 (*Continued*)

	Conflict of interest: reported that there were none

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	High risk	No masking of participants
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not mentioned, and treatment groups were different
Incomplete outcome data (attrition bias) All outcomes	Low risk	No comment was made. However, it is clear from the results that all participants completed follow-up
Selective reporting (reporting bias)	Low risk	All outcomes were reported

Farahvash 2011

Methods	Randomised, single-masked (surgeon), controlled trial Country: Iran
Participants	Number: 35 Age: Mean (range) 58.5 (37 to 73) Sex: M/F. 18/17 Inclusion criteria: • Vitreous haemorrhage > 1 month in a participant with no history of panretinal photocoagulation • Non-clearing vitreous haemorrhage in a participant with complete panretinal photocoagulation • Vitreous haemorrhage with neovascularisation of the iris • Vitreous haemorrhage with glaucoma • Vitreous haemorrhage with retinal detachment Exclusion criteria: • Vitrectomy or any intraocular injection in the study eye • History of IVB in either eye • Previous myocardial infarction or thromboembolic event • Uncontrolled hypertension • Use of anticoagulation (except aspirin, which was discontinued 1 week before injection) or coagulation abnormalities

Interventions	Intervention: • IVB (1.25 mg) 7 days before surgery (n = 18) Comparator: • No IVB (n = 17)
Outcomes	Primary outcomes: • Severity of intraoperative bleeding and break formation Secondary outcomes • Visual acuity at month 3 postsurgery • Complications of surgery: retinal detachment, neovascular glaucoma • Early and late postoperative vitreous haemorrhage Follow-up: 1 day, 1 week, every 3 months (minimum follow-up 3 months)
Notes	We contacted the authors to further discuss the severity of POVCH in each arm of the study. Although no formal grading scale was used to assess the POVCH, the authors described the clinical findings as follows: "We had two cases of early vitreous cavity haemorrhage (within 4 weeks of surgery), both in non injection group. The haemorrhage was dense and fundus obscuring, but resolved spontaneously during follow up. Both of them have been undergone vitrectomy for vitreous haemorrhage without TRD, with no air, SF6 or silicone as a tamponade We had five cases of late vitreous cavity haemorrhage before writing of paper (occurring after more than 4 weeks), two in non injection group and three in injection group. Only in one participant in injection group, vitreous cavity haemorrhage was dense and fundus obscuring. In other participants, it presented as recurrent bouts of non fundus obscuring vitreous cavity haemorrhage" Trial registration number: not reported Date study conducted: January 2008 to January 2009 Funding: not reported Conflict of interest: reported that there were none

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Participants were randomly assigned to injection of bevacizumab (injection group) or not (control group), within each subgroup
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	High risk	Study participants were not masked to which group they had been randomised to
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	All surgeons were masked regarding treatment group, but it was unclear if the outcome assessors were masked

Farahvash 2011 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Participants who failed to complete the study follow-up are clearly accounted for in the results
Selective reporting (reporting bias)	Low risk	All outcomes were reported

Hernández-Da Mota 2010

Methods	Prospective, randomised, open-label study Country: Mexico
Participants	Number: 40 Age: Mean 55.7 (both groups) Sex: Not given Inclusion criteria: • Presence of advanced PDR • Presence of TRD threatening the macula • $HbA_{1c} < 7$ Exclusion criteria: • Macular involvement of retinal detachment • Iris rubeosis • Cataract - when precluding proper evaluation of the fundus • No perception of light vision • Macular ischaemia
Interventions	Intervention: • IVB (1.25 mg/0.05 ml), 48 hours before vitrectomy (n = 20) Comparator: • No IVB (n = 20)
Outcomes	Primary outcomes: • BCVA • Feasibility of surgery (intraoperative bleeding, break formation) • Postoperative complications (POVCH, iris rubeosis, and retinal detachment) Follow-up: 1 week, 3 and 6 months
Notes	No response from authors to correspondence asking for clarification of POVCH definitions Trial registration number: not reported Date study conducted: not reported Funding: reported none Conflict of interest: reported that there were none

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Hernández-Da Mota 2010 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	"Patients were randomly assigned into two groups"
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants were not masked to treatment group
Blinding of outcome assessment (detection bias) All outcomes	High risk	"For all patients, visual acuity and intraocular pressure were measured and recorded before PPV in a standardized, masked manner" However, not clearly stated whether outcome assessment was always masked and whether other outcomes, such as intraocular bleeding, were masked
Incomplete outcome data (attrition bias) All outcomes	Low risk	Although not directly stated, it is clear from the results that all participants completed the stated follow-up
Selective reporting (reporting bias)	Low risk	All outcomes were reported

Manabe 2015

Methods	Prospective, double-masked randomised controlled trial Country: Japan
Participants	Number: 62 people (66 eyes) Age: average 60 years (range 20 to 82) Sex: 82% male Inclusion criteria: • Diagnosed as having an indication for primary vitrectomy because of persistent vitreous haemorrhage for over 3 months and TRD caused by PDR; or fundus findings of proliferative changes or vitreous haemorrhage in people with iris neovascularisation or neovascular glaucoma Exclusion criteria: • Intraocular surgery or retinal photocoagulation within 3 months before the study • Intravitreal injection of drugs or sub-Tenon injection of steroids within 3 months before the study • Cerebrovascular infarction or myocardial infarction within 3 months before the study
Interventions	Intervention: • IVB 0.16 mg/0.05 ml) 1 day before vitrectomy (n= 32) Comparator: • Sham injection 1 day before vitrectomy (n=34)

Outcomes	Primary outcome: • Frequency of reoperation due to postoperative recurrent vitreous haemorrhage within 4 weeks after vitrectomy Secondary outcome measures: • Numbers of intraoperative laser and endodiathermy spots • Frequency of postoperative recurrent vitreous haemorrhage within 4 weeks after vitrectomy • Concentration of VEGF in vitreous at the beginning of surgery
Notes	Trial registration number: NCT01854593 Date study conducted: June 2012 to August 2013 Funding: not reported Conflict of interest: reported "none"

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Low risk	"...were randomised using the envelop method" "Both the investigators and patients were masked to the treatment assignment"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Both the investigators and patients were masked to the treatment assignment"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"All postoperative examinations were performed by three vitreoretinal surgeons (H. S., T.H., H.N.) who also were masked to the study group allocation"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised participants were followed up for 1 month
Selective reporting (reporting bias)	Low risk	All outcomes on trial registry entry reported

Modarres 2009

Methods	Prospective, single-masked (surgeon), randomised clinical trial Country: Iran
Participants	Number: 40 Age: Mean (± SD). Intervention group 55.8 (± 11.3) and control group 53.2 (± 11.7) Sex: Not given Inclusion criteria: • Diabetics who were candidates for vitrectomy Exclusion criteria: • Presence of significant cataract to cause impairment of vision • Previous IVB injection • Other vitreoretinal pathology: past history of uveitis, retinal artery or vein occlusion Follow-up: Mean follow-up 7 ± 3.6 months
Interventions	Intervention: • IVB injection (2.5 mg) 3 to 5 days before operation (n = 22) Comparator: • No treatment (n = 18)
Outcomes	Primary outcome measure: • Facilitation of surgery and decrease in complications Secondary outcome measure: • Anatomic and visual outcomes at 6 months Follow-up: Mean follow-up 7 ± 3.6 months
Notes	Trial registration number: not reported Date study conducted: not reported Funding: not reported Conflict of interest: reported that there were none

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"40 eyes of 40 diabetic participants who were candidates for vitrectomy were randomly assigned to receive ..."
Allocation concealment (selection bias)	Unclear risk	Not stated in report
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not stated in report
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"The surgeons were masked as to the injection", but not clear if the outcome assessors were masked

Incomplete outcome data (attrition bias) All outcomes	Low risk	Not stated in report, however clear from the results that all participants completed follow-up
Selective reporting (reporting bias)	Low risk	All data discussed within the primary outcome for facilitation of surgery were analysed

Rizzo 2008

Methods	Interventional, consecutive, randomised, prospective study Country: Italy
Participants	Number: 22 Age: Mean (range). 52 years (24 to 63) Sex: Not given Inclusion criteria: • TRD • Tractional rhegmatogenous retinal detachment • TRD complicated by vitreous haemorrhage Exclusion criteria: • History of vitrectomy • History of thromboembolic events • Major surgery in the 3 previous months or planned within 28 days • Uncontrolled hypertension • Known coagulation abnormalities or current use of anticoagulative medication other than aspirin
Interventions	Intervention: • IVB (1.25 mg) 5 to 7 days before PPV (n = 11) Comparator: • No IVB (n = 22)
Outcomes	Primary outcome measure: • Feasibility of the surgery Secondary outcome measure: • Visual and anatomic outcome at 6 months Follow-up: up to 6 months
Notes	Trial registration number: not reported Date study conducted: not reported Funding: not reported Conflict of interest: reported that there were none

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Rizzo 2008 (*Continued*)

Random sequence generation (selection bias)	Low risk	"We used a table of random numbers in order to assign each study participant to group 1 or 2"
Allocation concealment (selection bias)	Unclear risk	Not stated in report
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not stated in report
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated in report
Incomplete outcome data (attrition bias) All outcomes	Low risk	Not stated in report, however it is clear from the results that all participants completed follow-up
Selective reporting (reporting bias)	Unclear risk	Results for the feasibility of surgery were stated, but no analysis was performed

Sohn 2012

Methods	Prospective, double-masked, interventional study Country: USA
Participants	Number: 20 eyes of 19 participants Age: Median 52 years Sex: M/F. 12/7 Inclusion criteria: • TRD involving the macula • Combined tractional/rhegmatogenous detachments • Non-clearing or recurrent vitreous haemorrhage precluding panretinal photocoagulation, with tractional detachment not involving the macula Exclusion criteria: • History of vitrectomy • Dense vitreous haemorrhage preventing preoperative grading of fibrovascular membranes • Inability to return for PPV within 3 to 7 days after randomisation • History of stroke, thromboembolic event, or myocardial infarction within 6 months • Younger than 18 years • Pregnancy
Interventions	Intervention: • IVB (1.25 mg/0.05 ml) 3 to 7 days before vitrectomy (n = 10) Comparator: • No treatment (n = 10)

Sohn 2012 (*Continued*)

Outcomes	Clinical outcomes: • Median Visual acuity at 3 months postsurgery • Surgical complications: POVCH, cataract, neovascular glaucoma, and retinal detachment Follow-up: up to 3 months
Notes	We contacted the corresponding author to clarify if the POVCH was early or late. The author confirmed that the haemorrhage had occurred in the 3-month follow-up, but could not give more detail of when it occurred

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not stated in report
Allocation concealment (selection bias)	Unclear risk	Not stated in report
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants in the control group underwent a sham injection
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants in the control group underwent a sham injection
Incomplete outcome data (attrition bias) All outcomes	Low risk	The number of participants lost to follow-up was clearly stated
Selective reporting (reporting bias)	Low risk	All outcomes were reported

Zaman 2013

Methods	Randomised, open-label, controlled trial Country: Pakistan
Participants	Number: 54 Age: Mean (± SD). 52.07 (± 5.54). Range 39 to 67 Sex: M/F. 32/22 Inclusion criteria: • Non-clearing vitreous haemorrhage of at least 1 month • TRD involving or threatening the macula • Pre-retinal subhyaloid bleeding covering the macula Exclusion criteria: not stated

Interventions	Intervention: • IVB (1.25 mg/0.05 ml) 1 week prior to surgery (n = 24) Comparator: • No treatment (n = 30)
Outcomes	Primary outcome measures: • BCVA after surgery • Postoperative complications, including rate of early and late POVCH, frequency of hyphaema and rubeosis Follow-up: days 1, 7, 14 and then monthly for up to 6 months
Notes	We attempted to contact the corresponding author to clarify details in the methodology and results, but have received no response Trial registration number: not reported Date study conducted: September 2010 to August 2011 Funding: not reported Conflict of interest: not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Patients were randomised into two categories"
Allocation concealment (selection bias)	Unclear risk	Not commented on within the article
Blinding of participants and personnel (performance bias) All outcomes	High risk	Although no specific comment was made, the study appears to be open label
Blinding of outcome assessment (detection bias) All outcomes	High risk	Although no specific comment was made, the study appears to be open label
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed the study protocol
Selective reporting (reporting bias)	Low risk	All stated outcomes were presented in the results

BCVA: best-corrected visual acuity
IVB: intravitreal bevacizumab
PDR: proliferative diabetic retinopathy
PPV: pars plana vitrectomy
SD: standard deviation
TRD: tractional retinal detachment
VEGF: vascular endothelial growth factor

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

Study	Reason for exclusion
Abdelhakim 2011	This prospective case series included 20 eyes and found the following results: • Mean pre-injection BCVA (logMAR) was 1.460 +/- 0.439. • Mean BCVA on day 1, week 1, months 2 and 3 after surgery were 1.645 +/- 0.422, 1.300 +/- 0.413, 1.065 +/- 0.538, and 1.065 +/- 0.538 logMAR, respectively (P = 0.078, 0.123, 0.002, and 0.002, respectively). • Intraoperative bleedings were minimal in most cases (85%, n = 17). • Postoperatively, 16 participants had no bleeding (80%), 4 had minimal bleeding (20%), and 1 had recurrent fibrovascular proliferation (5%). The study was excluded as it was non-randomised
Berk Ergun 2014	This study was excluded as it is retrospective
Bhavsar 2014	Vitrectomy was an outcome rather than an intervention
Cheema 2010	This study was excluded as it is retrospective
da R Lucena 2009	Did not assess POVCH
Demir 2013	This study was excluded as it is retrospective
Doganay 2010	This prospective case-controlled study was excluded due to lack of randomisation. Participants were divided into two groups: Group 1 (n = 32) received 1.25 mg of IVB 1 week before surgery; Group 2 (n = 50) did not Results: • Recurrent vitreous haemorrhage was found in 4 participants (12.5%) from Group 1 and in 14 participants (28%) from Group 2. • An increase in the mean BCVA value was determined in 24 participants (75%) from Group 1 and in 32 participants (64%) from Group 2.
Goncu 2014	Excluded as not randomised.
Gupta 2008	Excluded as not randomised.
Gupta 2012a	This study was excluded due to its retrospective design
Gupta 2012b	Excluded as this is a retrospective observational study
Ishikawa 2009	This study was excluded because of small numbers and no control group. Also no comment made on POVCH
Jirawison 2012	Excluded as this is a retrospective observational study
Li 2010	This study was excluded due to its retrospective design
Lo 2009	This study was excluded due to its retrospective design

(*Continued*)

NCT01589718	Withdrawn prior to enrolment.
Oshima 2009	This study was excluded because of the retrospective enrolment of participants, the absence of randomisation, and the different study periods of the two groups
Pakzad-Vaezi 2014	Did not assess POVCH
Park 2010	This study was excluded due to its retrospective design
Pokroy 2011	This study was excluded due to its retrospective design
Romano 2009a	Found the following results: • No reduction in the rate of early grade 2 and 3 POVCH (2/32 (6%) at 7 days and 1 month) following preoperative bevacizumab. • Rates of late POVCH (grade 2 and 3): 2/32 (6%) at 3 months and 3/32 (9%) at 6 months. • A significant improvement in 29/32 eyes (mean BCVA 1.6 (SD 1.2) to 0.4 (SD 0.8) logMAR, P = 0.02) with surgery. There was no improvement secondary to POVCH (grade 2 to 3) in the remaining 3 eyes. • No clinically significant intraocular inflammation on the first postoperative day. Cataract formation occurred in 12/22 (54%). • The incidence of grade 2 and 3 POVCH at 1 day, 1 week, 1, 3, and 6 months was 9%, 6%, 6%, 6%, and 9%, respectively (n = 32). This prospective study was excluded due to the lack of a control group. Participants also received an additional dose of bevacizumab at the end of surgery, which makes interpretation of the effect of the preoperative bevacizumab on POVCH difficult
Romano 2009b	Found the following results: • The incidence of grade 2 and 3 POVCH in the initial postoperative period was 4/30 (14%) at 7 days and 11/30 (36%) at 1 month. • Rates of late POVCH (grade 2 and 3) were 9/30 (30%) at 3 and 6 months. • Visual improvement in 21/30 treated eyes (mean BCVA 1.00 (SD 0.9) to 0.4 logMAR). There was no improvement secondary to POVCH in the remaining eyes (9/30, P = 0.2). • No clinically significant intraocular inflammation on the first postoperative day. Cataract formation occurred in 9/22 (40%) of phakic participants during the 6-month follow-up. • The incidence of grade 2 and 3 POVCH to be 20%, 14%, 36%, 30%, and 30% (n = 30). This prospective study was excluded due to the lack of a control group
Sato 2013	This study was excluded due to its retrospective design
Yang 2008	Found the following results: • A significant reduction in the vitreous clear-up rate postoperatively in participants who received preoperative bevacizumab and C_3F_8 endotamponade, when compared with their historical control group (7.2 (SD 5.6) vs 15.2 (SD 11.4) days (P = 0.04)). No significant reduction in the rate of early POVCH (defined as recurrent haemorrhage that obscured the retinal vessels - grade 2 or above in the Diabetic Retinopathy Vitrectomy Study, for more than 1 week after vitreous clear-up) was observed between the treatment and control groups (0/16 vs 1/24 (P = 0.41)). • The rate of late POVCH in participants who received preoperative bevacizumab and C_3F_8 endotamponade was 1/16 (6.25%) and in the historical control group 1/24 (4%). This study was excluded due to the small numbers and lack of randomisation (participants in the control group

(*Continued*)

	were selected retrospectively). Also C_3F_8 was used in addition to preoperative anti-VEGF in all participants in the treatment group
Yeh 2009	Excluded as participants allocated by alternation
Yeoh 2008	Found the following results: • No significant reduction in the overall rate of POVCH (7/18 (38.8%)), in 18 cases treated with 1.25 mg of bevacizumab within 2 weeks of surgery. When the results are divided into early and late POVCH, 2/18 cases had early POVCH (11.1%) and 5/18 had late POVCH (27.7%). • A late rebleed rate of 27.7% (5/18). The authors suggested that this rate may be secondary to later reperfusion of fibrovascular tufts, once the effect of bevacizumab has worn off, which would not have been apparent at the time of surgery. • Visual acuity had improved in 14/18 treated eyes, was unchanged in 1/18, and was worse in 3/18. The mean improvement in postoperative visual acuity was not quantified because of the significant number of participants with hand movement vision preoperatively. Of the 3 participants who had reduced visual acuity, 2 had extensive macular ischaemia on fluorescein angiography, and the remaining eye still contained silicone oil. • 7/18 (38.8%) treated eyes had POVCH within the 6-month follow-up. 6 of the 7 eyes required surgical washout (6/18 (33.3%)). • No adverse events in any participant treated with bevacizumab, local or systemic. This study was excluded due to the lack of a control group.
Yeung 2010	This study was excluded as it is retrospective.

BCVA: best-corrected visual acuity
logMAR: logarithm of minimal angle of resolution
POVCH: postoperative vitreous cavity haemorrhage
SD: standard deviation
VEGF: vascular endothelial growth factor

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

ISRCTN79120387

Trial name or title	A randomised, single-masked, phase IV pilot study of the efficacy and safety of adjunctive intravitreal Avastin® (bevacizumab) in the prevention of early postoperative vitreous haemorrhage following diabetic vitrectomy
Methods	Randomised, single-masked, controlled trial
Participants	30
Interventions	Avastin® will be administered intravitreally in a single- or dual-dose regimen of 1.25 mg (in 0.05 ml) 2 weeks prior to vitrectomy and at the end of vitrectomy if internal tamponade (oil, air, or gas) was not used. No sham intravitreal injections will be given before or after vitrectomy if participant is randomised to the usual treatment group

ISRCTN79120387 (*Continued*)

Outcomes	Primary: Postoperative vitreous haemorrhage based on 2 masked clinical assessments at 6 weeks and 6 months Secondary: 1. Recruitment and drop-out rates 2. Rates of re-operation for recurrent vitreous haemorrhage 3. Rate of postoperative rubeosis and rubeotic glaucoma 4. Rate and severity of intraoperative bleed 5. Mean change in ETDRS acuity and MNRead acuity 6. Serum Avastin® and growth factor levels at 2 and 4 to 6 weeks after injection. Vitreous levels at 2 weeks after injection
Starting date	2007
Contact information	Mr Lyndon da Cruz Moorfields Eye Hospital, 162 City Road, London
Notes	No reply from lead investigator

NCT00516464

Trial name or title	Evaluation of ranibizumab on the ease of procedure and complication rate in proliferative diabetic retinopathy (PDR) requiring vitrectomy
Methods	Randomised, single-masked, controlled trial
Participants	40
Interventions	40 participants will be enrolled and randomised 3:1 to ranibizumab or vitrectomy alone. 30 consented, enrolled participants will receive 3 intravitreal injections of 0.5 mg ranibizumab administered 1 to 3 weeks pre-procedure, intraoperatively, and 1 month postvitrectomy
Outcomes	To evaluate the effect of ranibizumab on vitrectomy complications such as recurrent vitreous haemorrhage, postoperative retinal detachment rates, and development of intraoperative retinal breaks. (Time frame: 6 months)
Starting date	August 2007
Contact information	Retina Associates, PA. Shawnee Mission, Kansas, United States, 66204 Contact: Lexie Manning 913-831-7400 lmanning@kcretina.com
Notes	Principal Investigator: Gregory M Fox, MD. Contacted: Lead author clarified that they are unlikely to have any data relevant to this review and will probably not go on to publish data from this trial

NCT00931125

Trial name or title	Randomized, double blinded, controlled, two-center study assessing the safety and efficacy of intravitreal ranibizumab as a preoperative adjunct treatment before vitrectomy surgery in proliferative diabetic retinopathy (PDR) compared to vitrectomy alone
Methods	Randomised, double-masked, controlled trial
Participants	Active, not recruiting. Estimate 70
Interventions	This is a randomised, double-masked, controlled, 2-centre study assessing the feasibility, efficacy, and safety of intravitreal ranibizumab injection applied as a preoperative adjunct treatment before vitrectomy surgery in severe PDR. Comparator arm consists of participants receiving standard vitrectomy alone with sham intravitreal injection preoperatively
Outcomes	Primary outcome measures: 1. Efficacy of preoperative intravitreal ranibizumab [Time Frame: OP day] [Designated as safety issue: No] 2. Efficacy, measured by surgical time, number of intraoperative bleedings, intraoperative retinal breaks, required endodiathermy Secondary outcome measures: 1. Change in BCVA [Time Frame: 6 months] [Designated as safety issue: No] 2. Effect in anatomical changes [Time Frame: 3 ± 1 days after injection] [Designated as safety issue: No] 3. Safety [Time Frame: Over 6 months] [Designated as safety issue: Yes] 4. Retinal circulation integrity [Time Frame: Month 1, 3, 6] [Designated as safety issue: Yes]. Evaluating the circulation of original retinal vessels, evaluating the size of proliferative vessels (size of leaking areas and number of leaking points measured by fluorescein angiography)
Starting date	March 2009 Estimated study completion date: December 2013
Contact information	University of Debrecen, Medical and Health Science Center, Faculty of Medicine, Department of Ophthalmology
Notes	Debrecen, Hungary, H-4012

NCT01091896

Trial name or title	Adjuvant intravitreal bevacizumab in pars plana vitrectomy for vitreous hemorrhage secondary to diabetic retinopathy
Methods	Randomised, single-masked, controlled trial
Participants	Not stated
Interventions	No intervention: 1 - no bevacizumab. Participants will neither receive bevacizumab before nor during vitrectomy Experimental: 2 - bevacizumab before vitrectomy. Participants will receive intravitreal injection of 1.25 mg of bevacizumab (0.05 ml) 7 days before vitrectomy Experimental: 3 - bevacizumab after vitrectomy. Participants will receive intravitreal injection of 1.25 mg of

NCT01091896 (*Continued*)

	bevacizumab (0.05 ml) at the end of vitrectomy
Outcomes	Primary outcome measure: recurrent vitreous haemorrhage incidence after vitrectomy Secondary outcome measure: visual outcome
Starting date	2010 Estimated study completion date: March 2011
Contact information	felipeppalmeida@yahoo.com.br
Notes	Principal Investigator: Felipe Almeida

NCT01151722

Trial name or title	Adjuvant intravitreal bevacizumab in pars plana vitrectomy for diabetic vitreous hemorrhage (ABeVi)
Methods	Randomised, single-masked, controlled trial
Participants	Not stated
Interventions	No intervention: no injection, no bevacizumab Experimental 2: bevacizumab before vitrectomy Experimental 3: bevacizumab after vitrectomy
Outcomes	Primary outcome measure: vitreous haemorrhage recurrence [Time Frame: 3 months]
Starting date	2009 Estimated study completion date: December 2009
Contact information	felipeppalmeida@yahoo.com.br
Notes	Principal Investigator: Felipe Almeida, MD

NCT01306981

Trial name or title	A prospective, randomised controlled trial of ranibizumab pre-treatment in diabetic vitrectomy - a pilot study
Methods	Randomised, double-masked, controlled study
Participants	Not stated
Interventions	Participants will be randomised 1:1 to receive either ranibizumab intravitreal injection (0.5 mg in 0.05 ml) or saline subconjunctival injection at the time of surgery
Outcomes	Primary outcome measures: BCVA [Time Frame: 12 weeks post-op] Secondary outcome measures:

NCT01306981 (*Continued*)

	1. Ease of performing vitrectomy surgery 2. Incidence of postoperative vitreous haemorrhage [Time Frame: 6 weeks post-op] 3. Extent of retinal neovascularisation [Time Frame: 6 weeks post-op] 4. Extent of tractional retinal detachment [Time Frame: 1 week postinjection] 5. Extent of macular perfusion [Time Frame: 12 weeks post-op] 6. Vitreous and serum levels of ranibizumab and related cytokines [Time Frame: 1 week postinjection] 7. Incidence of postoperative vitreous haemorrhage [Time Frame: 12 weeks post-op] 8. Extent of retinal neovascularisation [Time Frame: 12 weeks post-op]
Starting date	2011 Estimated study completion date: March 2013
Contact information	Moorfields Eye Hospital NHS Foundation Trust
Notes	Principal Investigator: Mr James W Bainbridge MA, PhD, FRCOphth. Contacted: Currently the study is in the write-up stages. Unpublished data on the rate of POVCH are as follows: Vitreous cavity haemorrhage occurred in 4/15 in the ranibizumab (Lucentis®) arm and 6/15 in the control arm. At 12-weeks post-op persistent vitreous cavity haemorrhage was observed in 0/15 in the ranibizumab arm and 2/15 in the control arm

NCT01805297

Trial name or title	Intravitreal aflibercept injection as a surgical adjuvant in severe proliferative diabetic retinopathy
Methods	Randomised, open-label, controlled trial
Participants	12
Interventions	1. Vitrectomy with Aflibercept Injection Preoperative 2.0 mg intravitreal aflibercept and vitrectomy with intraoperative 2.0 mg intravitreal aflibercept injection 2. Standard Vitrectomy Preoperative 2.0 mg intravitreal aflibercept and standard of care vitrectomy
Outcomes	Primary outcome measures: 1. Rate of postoperative vitreous haemorrhage [Time Frame: 24 weeks] 2. Amount of postoperative vitreous haemorrhage [Time Frame: 24 weeks] Secondary outcome measures: 1. Mean change in visual acuity [Time Frame: 24 weeks] 2. Need for any additional surgical intervention [Time Frame: 24 weeks] 3. Changes in mean central retinal thickness [Time Frame: 24 weeks] 4. Changes in mean PDR grading [Time Frame: 24 weeks]
Starting date	2013 Estimated study completion date: April 2014
Contact information	Robert-Leonard@dmei.org

NCT01805297 (*Continued*)

Notes	Principal Investigator: Robert Leonard MD

NCT01854593

Trial name or title	Prospective randomized controlled study on the efficacy of 0.16 mg intravitreal bevacizumab injection for proliferative diabetic retinopathy
Methods	Randomised, double-masked, controlled trial
Participants	66 (recruitment completed August 2013)
Interventions	Control group: sham injection and 25 gauge vitrectomy Intervention group: 0.16 mg/0.05 ml bevacizumab (single injection 1 day before operation) and 25 gauge vitrectomy
Outcomes	1. VEGF concentration in vitreous after intravitreal bevacizumab injection [Time Frame: 1 year] 2. Early (within 4 weeks) postoperative vitreous haemorrhage 3. Re-operation due to vitreous haemorrhage
Starting date	May 2012
Contact information	Ayumu Manabe, Nihon University
Notes	Study results on ClinicalTrials.gov

BCVA: Best-corrected visual acuity
ETDRS: Early Treatment Diabetic Retinopathy Study
PDR: proliferative diabetic retinopathy
TRD: tractional retinal detachment
VEGF: vascular endothelial growth factor

DATA AND ANALYSES

Comparison 1. Anti-VEGF versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Early POVCH (grade 2 or worse)	2	144	Risk Ratio (M-H, Fixed, 95% CI)	0.28 [0.08, 0.96]
2 Early POVCH (all grades)	9	512	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.23, 0.53]
3 Early POVCH (all grades, excluding silicone oil cases)	6	302	Risk Ratio (M-H, Random, 95% CI)	0.34 [0.19, 0.60]
4 Late POVCH (all grades)	3	196	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.30, 1.72]
5 Visual acuity at six months or longer	5		Mean Difference (IV, Random, 95% CI)	Totals not selected
6 Vitreous cavity washout	5	291	Risk Ratio (M-H, Random, 95% CI)	0.19 [0.06, 0.67]
7 Retinal detachment	7	372	Risk Ratio (M-H, Random, 95% CI)	0.46 [0.19, 1.08]

Analysis 1.1. Comparison 1 Anti-VEGF versus control, Outcome 1 Early POVCH (grade 2 or worse).

Review: Anti-vascular endothelial growth factor for prevention of postoperative vitreous cavity haemorrhage after vitrectomy for proliferative diabetic retinopathy

Comparison: 1 Anti-VEGF versus control

Outcome: 1 Early POVCH (grade 2 or worse)

Study or subgroup	Anti VEGF n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Ahmadieh 2009 (1)	2/16	9/18		86.5 %	0.25 [0.06, 0.99]
Ahn 2011 (2)	1/73	1/37		13.5 %	0.51 [0.03, 7.88]
Total (95% CI)	**89**	**55**		**100.0 %**	**0.28 [0.08, 0.96]**
Total events: 3 (Anti VEGF), 10 (Control)					
Heterogeneity: Chi^2 = 0.20, df = 1 (P = 0.65); I^2 =0.0%					
Test for overall effect: Z = 2.02 (P = 0.044)					
Test for subgroup differences: Not applicable					

(1) Data included from this paper is the 'per protocol' outcomes

(2) Data in the experimental group includes both pre-operative and intraoperative administration of bevacizumab

Analysis 1.2. Comparison 1 Anti-VEGF versus control, Outcome 2 Early POVCH (all grades).

Review: Anti-vascular endothelial growth factor for prevention of postoperative vitreous cavity haemorrhage after vitrectomy for proliferative diabetic retinopathy

Comparison: 1 Anti-VEGF versus control

Outcome: 2 Early POVCH (all grades)

Study or subgroup	Anti-VEGF n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Ahmadieh 2009 (1)	5/35	13/33		21.4 %	0.36 [0.15, 0.91]
Ahn 2011 (2)	12/73	11/34		35.5 %	0.51 [0.25, 1.03]
di Lauro 2009 (3)	3/48	6/24		10.7 %	0.25 [0.07, 0.91]
El Batarny 2008	0/15	4/15		2.2 %	0.11 [0.01, 1.90]
Farahvash 2011 (4)	0/18	2/17		2.0 %	0.19 [0.01, 3.68]
Hern ndez-Da Mota 2010	4/20	8/20		16.9 %	0.50 [0.18, 1.40]
Manabe 2015	1/32	8/34		4.4 %	0.13 [0.02, 1.00]
Modarres 2009	0/22	7/18		2.3 %	0.06 [0.00, 0.90]
Zaman 2013 (5)	1/24	11/30		4.6 %	0.11 [0.02, 0.82]
Total (95% CI)	**287**	**225**		**100.0 %**	**0.35 [0.23, 0.53]**
Total events: 26 (Anti-VEGF), 70 (Control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 7.19$, df = 8 (P = 0.52); $I^2 = 0.0\%$					
Test for overall effect: Z = 4.91 (P < 0.00001)					
Test for subgroup differences: Not applicable					

(1) 1.25mg IVB one week before surgery; follow-up 4 weeks after surgery

(2) 1.25mg IVB one day to two weeks before surgery or during surgery; follow-up 4 weeks after surgery

(3) 1.25mg IVB one week or three weeks before surgery; follow-up 4 weeks after surgery

(4) Note from JE: could not find these data in paper: 1.25mg IVB one week before surgery; follow-up 4 weeks after surgery

(5) 1.25mg IVB one week before surgery; follow-up 4 weeks after surgery

Analysis 1.3. Comparison 1 Anti-VEGF versus control, Outcome 3 Early POVCH (all grades, excluding silicone oil cases).

Review: Anti-vascular endothelial growth factor for prevention of postoperative vitreous cavity haemorrhage after vitrectomy for proliferative diabetic retinopathy

Comparison: 1 Anti-VEGF versus control

Outcome: 3 Early POVCH (all grades, excluding silicone oil cases)

Study or subgroup	Anti VEGF n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Ahmadieh 2009	5/35	13/33		32.3 %	0.36 [0.15, 0.91]
Ahn 2011	12/73	11/34		48.6 %	0.51 [0.25, 1.03]
El Batarny 2008	0/12	4/6		4.1 %	0.06 [0.00, 0.96]
Farahvash 2011	0/15	2/15		3.6 %	0.20 [0.01, 3.85]
Manabe 2015	1/28	6/28		7.3 %	0.17 [0.02, 1.30]
Modarres 2009	0/12	7/11		4.1 %	0.06 [0.00, 0.97]
Total (95% CI)	**175**	**127**		**100.0 %**	**0.34 [0.19, 0.60]**

Total events: 18 (Anti VEGF), 43 (Control)

Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 5.37$, df = 5 (P = 0.37); $I^2 = 7\%$

Test for overall effect: Z = 3.72 (P = 0.00020)

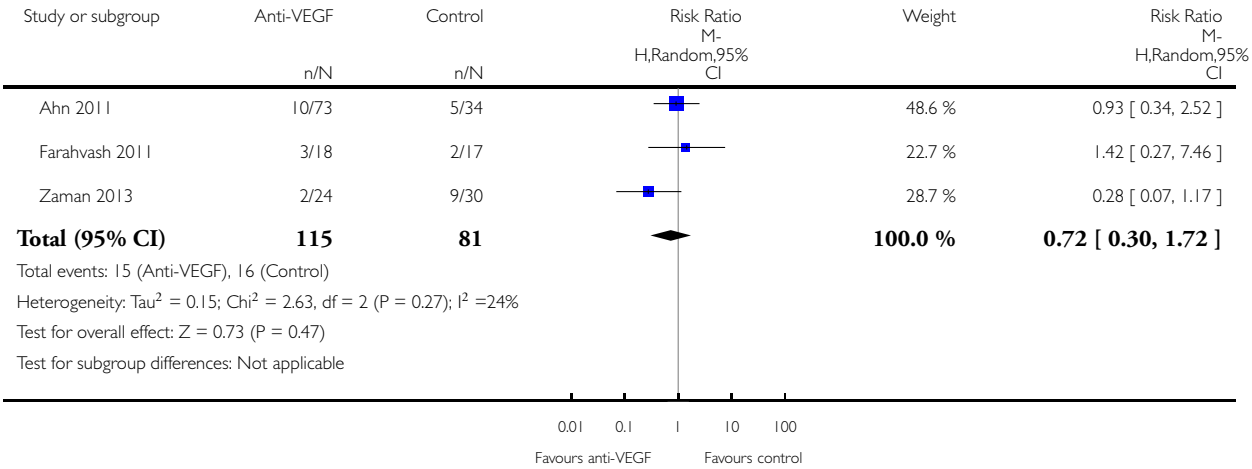
Test for subgroup differences: Not applicable

Analysis 1.4. Comparison 1 Anti-VEGF versus control, Outcome 4 Late POVCH (all grades).

Review: Anti-vascular endothelial growth factor for prevention of postoperative vitreous cavity haemorrhage after vitrectomy for proliferative diabetic retinopathy

Comparison: 1 Anti-VEGF versus control

Outcome: 4 Late POVCH (all grades)

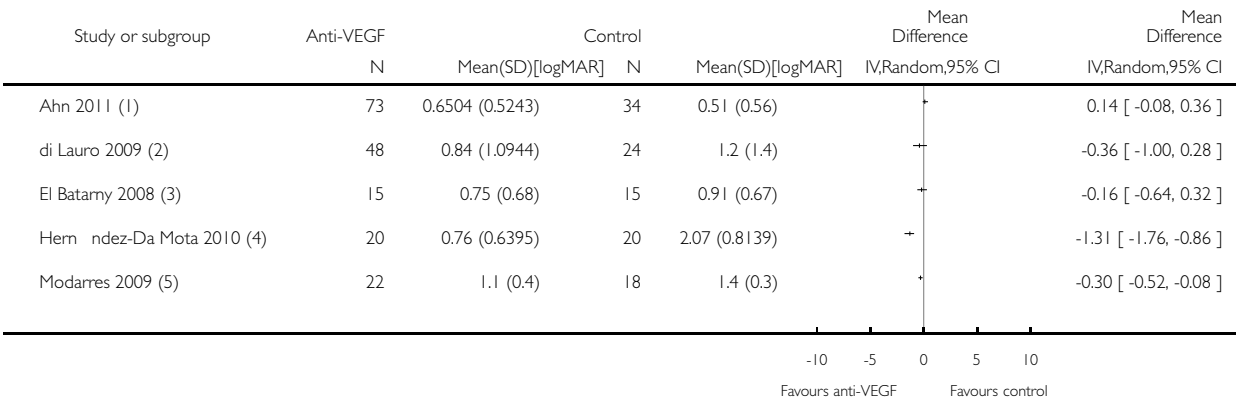


Analysis 1.5. Comparison 1 Anti-VEGF versus control, Outcome 5 Visual acuity at six months or longer.

Review: Anti-vascular endothelial growth factor for prevention of postoperative vitreous cavity haemorrhage after vitrectomy for proliferative diabetic retinopathy

Comparison: 1 Anti-VEGF versus control

Outcome: 5 Visual acuity at six months or longer



(1) Follow-up: 6 months

(2) Follow-up: 6 months

(3) Follow-up: 12 months (range 7-18 months)

(4) Follow up: 6 months

(5) Follow-up: 6 months

Analysis 1.6. Comparison 1 Anti-VEGF versus control, Outcome 6 Vitreous cavity washout.

Review: Anti-vascular endothelial growth factor for prevention of postoperative vitreous cavity haemorrhage after vitrectomy for proliferative diabetic retinopathy

Comparison: 1 Anti-VEGF versus control

Outcome: 6 Vitreous cavity washout

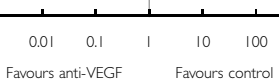
Study or subgroup	Anti-VEGF n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
di Lauro 2009	1/48	2/24		28.0 %	0.25 [0.02, 2.62]
El Batarny 2008	0/15	0/15			Not estimable
Elwan 2013	1/50	5/50		34.7 %	0.20 [0.02, 1.65]
Manabe 2015	1/32	7/34		37.2 %	0.15 [0.02, 1.17]
Modarres 2009	0/12	0/11			Not estimable
Total (95% CI)	**157**	**134**		**100.0 %**	**0.19 [0.06, 0.67]**

Total events: 3 (Anti-VEGF), 14 (Control)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.10$, df = 2 (P = 0.95); $I^2 = 0.0\%$

Test for overall effect: Z = 2.60 (P = 0.0094)

Test for subgroup differences: Not applicable

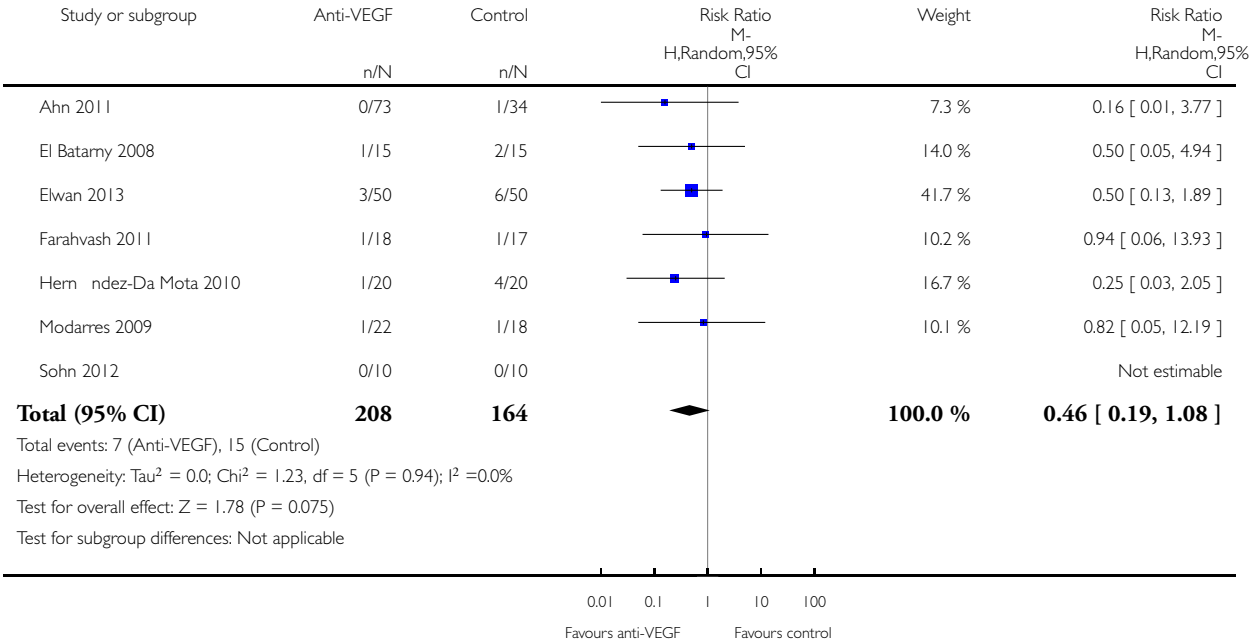


Analysis 1.7. Comparison 1 Anti-VEGF versus control, Outcome 7 Retinal detachment.

Review: Anti-vascular endothelial growth factor for prevention of postoperative vitreous cavity haemorrhage after vitrectomy for proliferative diabetic retinopathy

Comparison: 1 Anti-VEGF versus control

Outcome: 7 Retinal detachment



ADDITIONAL TABLES

Table 1. Adverse effects

Adverse effect / Study	Injection-related complications	Raised intraocular pressure	Iris neovascularisation	Neovascular glaucoma	Cataract progression	Retinal detachment	Systemic adverse effects	Other local effects
Ahmadieh 2009	No cases	1 person only	No cases	-	-	-	-	-
Ahn 2011	-	-	-	Anti-VEGF: 5/73 (7%) Control: 1/34 (3%)	Anti-VEGF: 5/60 (8%) Control: 5/32 (16%)	Anti-VEGF: 0/73 (0%) Control: 1/34 (3%)	No cases	-

Table 1. Adverse effects (*Continued*)

di Lauro 2009	-	-	-	-	-	3/72 (4%) but unclear which group	No cases	-
El Batarny 2008	-	-	Anti-VEGF: 0/20 Control: 1/15 (6.7%)	-	Anti-VEGF: 4/15 (26. 6%) Control: 7/15 (46. 7%)	Anti-VEGF: 1/15 (6.7%) Control: 2/15 (13. 3%)	No cases	-
Elwan 2013	-	-	Anti-VEGF: Regressed in 10/50 (20%) Control: Persisted in 6/50 (12%) No new post-op cases reported	-	-	Anti-VEGF: 3/50 (6%) Control: 6/ 50 (12%)	No cases	-
Farahvash 2011	-	-	No cases	No cases	"During the follow-up, all but 2 phakic patients with significant cataract and best-corrected visual acuity < 20/200 underwent cataract surgery"	Anti-VEGF: 1/18 (6%) Control: 1/17 (6%)	Mortality (range 3-15 months follow-up) Anti-VEGF: 1/18 (6%) Control: 1/17 (6%)	-
Hernandez-Da Mota 2010	-	Anti-VEGF: 4/20 (20%) Control: 0/20	-	Anti-VEGF: 0/20 Control: 2/20 (10%)	Anti-VEGF: 3/20 (15%) Control: 4/20 (20%)	Anti-VEGF: 1/20 (5%) Control: 4/20 (20%)	-	-
Manabe 2015	No cases	Anti-VEGF: 2/32 (6%) Control: 6/34 (18%)	-	Anti-VEGF: 0/32 Control: 3/34 (9%)	-	-	No cases	-

Table 1. Adverse effects (*Continued*)

Modarres 2009	-	-	-	-	-	Anti-VEGF: 1/22 (5%) Control: 1/18 (6%)	No cases	No cases
Sohn 2012	-	-	-	Anti-VEGF: 0/10 Control: 1/10 (10%)	Anti-VEGF: 1/10 (10%) Control: 1/10 (10%)	No cases	-	-
Zaman 2013	-	-	Anti-VEGF: 3/24 (13%) Control: 7/30 (23%)	-	-	-	-	-

VEGF: vascular endothelial growth factor

APPENDICES

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor: [Diabetic Retinopathy] explode all trees
#2 diabet*
#3r etinopath*
#4 #1 or #2 or #3
#5 MeSH descriptor: [Vitrectomy] explode all trees
#6 vitrectom*
#7 PPV*
#8 MeSH descriptor: [Sclerostomy] explode all trees
#9 sclerostom* or sclerectom*
#10 MeSH descriptor: [Vitreous Hemorrhage] this term only
#11 MeSH descriptor: [Vitreous Body] this term only
#12 hemorrhag* or haemorrhag*
#13 MeSH descriptor: [Postoperative Complications] explode all trees
#14 MeSH descriptor: [Recurrence] this term only
#15 #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14
#16 MeSH descriptor: [Angiogenesis Inhibitors] explode all trees
#17 MeSH descriptor: [Angiogenesis Inducing Agents] explode all trees
#18 MeSH descriptor: [Endothelial Growth Factors] explode all trees
#19 MeSH descriptor: [Vascular Endothelial Growth Factors] explode all trees
#20 macugen* or pegaptanib* or lucentis* or rhufab* or ranibizumab* or bevacizumab* or avastin or aflibercept
#21 anti near/2 VEGF
#22 endothelial near/2 growth near/2 factor
#23 #16 or #17 or #18 or #19 or #20 or #21 or #22

#24 #4 and #15 and #23

Appendix 2. MEDLINE (Ovid) search strategy

1. randomized controlled trial.pt.
2. (randomized or randomised).ab,ti.
3. placebo.ab,ti.
4. dt.fs.
5. randomly.ab,ti.
6. trial.ab,ti.
7. groups.ab,ti.
8. or/1-7
9. exp animals/
10. exp humans/
11. 9 not (9 and 10)
12. 8 not 11
13. exp diabetic retinopathy/
14. diabet$.tw.
15. retinopath$.tw.
16. or/13-15
17. exp vitrectomy/
18. vitrectom$.tw.
19. PPV$.tw.
20. sclerostomy/
21. (sclerostom$ or sclerectom$).tw.
22. vitreous hemorrhage/
23. vitreous body/
24. (hemorrhag$ or haemorrhag$).tw.
25. exp postoperative complications/
26. or/17-25
27. exp angiogenesis inhibitors/
28. exp angiogenesis inducing agents/
29. exp endothelial growth factors/
30. exp vascular endothelial growth factors/
31. (macugen$ or pegaptanib$ or lucentis$ or rhufab$ or ranibizumab$ or bevacizumab$ or avastin or aflibercept).tw.
32. (anti adj2 VEGF$).tw.
33. (endothelial adj2 growth adj2 factor$).tw.
34. or/27-33
35. 16 and 26 and 34
36. 12 and 35

The search filter for trials at the beginning of the MEDLINE strategy is from the published paper by Glanville et al (Glanville 2006).

Appendix 3. PubMed search strategy

((diabetic retinopathy[mesh]) OR (diabetes OR diabetic) OR (retinopathy)) AND ((vitrectomy[mesh]) OR (vitrectomy) OR (PPV) OR (sclerostomy[mesh]) OR (sclerostomy OR sclerectomy)) OR (vitreous hemorrhage[mesh]) OR (vitreous body[mesh]) OR (hemorrhage OR haemorrhage) OR (postoperative complications[mesh]) OR (recurrence[mesh])) AND ((angiogenesis inhibitors[mesh]) OR (angiogenesis inducing agents[mesh]) OR (endothelial growth factors[mesh]) OR (vascular endothelial growth factors[mesh]) OR (macugen OR pegaptanib OR lucentis OR rhufab OR ranibizumab OR bevacizumab OR avastin OR aflibercept) OR (endothelial growth factor) OR (anti VEGF))

Appendix 4. 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$).tw.
29. or/25-28
30. 29 not 10
31. 30 not (11 or 23)
32. 11 or 24 or 31
33. exp diabetic retinopathy/
34. diabet$.tw.
35. retinopath$.tw.
36. or/33-35
37. exp vitrectomy/
38. vitrectom$.tw.
39. PPV$.tw.
40. sclerostomy/
41. (sclerostom$ or sclerectom$).tw.
42. vitreous hemorrhage/

43. vitreous body/
44. (hemorrhag$ or haemorrhag$).tw.
45. exp postoperative complication/
46. recurrent disease/
47. or/37-46
48. exp angiogenesis/
49. exp angiogenesis inhibitors/
50. exp angiogenic factor/
51. exp endothelial cell growth factor/
52. exp vasculotropin/
53. (macugen$ or pegaptanib$ or lucentis$ or rhufab$ or ranibizumab$ or bevacizumab$ or avastin or aflibercept$).tw.
54. (anti adj2 VEGF$).tw.
55. (endothelial adj2 growth adj2 factor$).tw.
56. or/48-55
57. 36 and 47 and 56
58. 32 and 57

Appendix 5. LILACS search strategy

diabet$ or retinopath$ and vitrectom$ or PPV$ or sclerostom$ or sclerectom$ and vitreous or hemorrhag$ or haemorrhag$ or postoperat$ or recur$

Appendix 6. ISRCTN search strategy

retinopathy AND vitrectomy AND haemorrhage
retinopathy AND vitrectomy AND hemorrhage

Appendix 7. ClinicalTrials.gov search strategy

Retinopathy AND Vitrectomy AND (Haemorrhage or Hemorrhage)

Appendix 8. ICTRP search strategy

Vitrectomy OR Haemorrhage OR Hemorrhage OR Vitroretinal OR Vitreous = Title AND Diabetic Retinopathy = Condtion AND Macugen OR Pegaptanib OR Lucentis OR Rhufab OR Ranibizumab OR Bevacizumab OR Avastin OR Aflibercept = Intervention

WHAT'S NEW

Last assessed as up-to-date: 26 May 2015.

Date	Event	Description
22 October 2014	New citation required and conclusions have changed	Issue 8, 2015: Eight new RCTs (Ahn 2011; El Batarny 2008; Elwan 2013; Farahvash 2011; Hernández-Da Mota 2010; Manabe 2015; Sohn 2012; Zaman 2013) were identified that met the inclusion criteria

(*Continued*)

22 September 2014	New search has been performed	Issue 8, 2015: Electronic searches were updated

CONTRIBUTIONS OF AUTHORS

Jonathan Smith and David Steel were responsible for:

- Conceiving the review
- Designing the review
- Co-ordinating the review
- Screening search results
- Data management
- Screening retrieved papers against inclusion criteria
- Appraising quality of papers
- Abstracting data from papers
- Analysis of data
- Interpretation of data
- Entering data into RevMan
- Writing the review
- Updating the review

DECLARATIONS OF INTEREST

JS: Received money as an an unconditional grant by Novartis to cover the expense of accommodation for an international ophthalmology meeting in 2012.

DS: Acted as a consultant to Alcon, and my institution has received grant funding from Novartis.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- National Institute for Health Research (NIHR), UK.
- Richard Wormald, Co-ordinating Editor for the Cochrane Eyes and Vision Group (CEVG), acknowledges financial support for his CEVG research sessions from the Department of Health through the award made by the National Institute for Health Research to Moorfields Eye Hospital NHS Foundation Trust and UCL Institute of Ophthalmology for a Specialist Biomedical Research Centre for Ophthalmology.
- The NIHR also funds the CEVG Editorial Base in London.

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

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Due to the importance of postoperative retinal detachment, we included an additional analysis to enable patients and surgeons to make a more informed choice when deciding to use IVB as an adjunct to vitrectomy.

Our protocol specified that we would exclude participants who received silicone oil endotamponade in the review analysis. Peer review comments on our review questioned whether this would give rise to bias, and so we presented analyses of all participants and sensitivity analyses excluding silicone oil cases. These additional analyses were not originally planned within the protocol.

Our protocol specified that we would present odds or risk ratios. We have chosen to present risk ratios as they are easier to interpret.

INDEX TERMS

Medical Subject Headings (MeSH)

Angiogenesis Inhibitors [therapeutic use]; Antibodies, Monoclonal [therapeutic use]; Antibodies, Monoclonal, Humanized; Bevacizumab [therapeutic use]; Diabetic Retinopathy [*surgery]; Intravitreal Injections; Postoperative Hemorrhage [*prevention & control]; Preoperative Care; Randomized Controlled Trials as Topic; Vascular Endothelial Growth Factor A [antagonists & inhibitors]; Vascular Endothelial Growth Factors [*antagonists & inhibitors]; Vitrectomy [*adverse effects]; Vitreous Hemorrhage [*prevention & control]

MeSH check words

Humans