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Article (Accepted version) (Refereed)

Original citation:
Jackson, Timothy L., Nicod, Elena, Angelis, Aris, Grimaccia, Federico, Pringle, Edward and Kanavos, Panos (2016) *Pars plana vitrectomy for diabetic macular edema: a systematic review, meta-analysis, and synthesis of safety literature.* Retina. ISSN 1539-2864

DOI: 10.1097/IAE.0000000000001280

Pars plana vitrectomy for diabetic macular edema: a systematic review, meta-analysis, and synthesis of safety literature

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Abbreviated title: Vitrectomy for diabetic macular edema

Financial support: T. Jackson is an advisor to Bausch & Lomb, and DORC, and consultant to ThromboGenics, and his employer received research grant from Novartis and Ophthotech for unrelated projects. E. Nicod, A. Angelis, F. Grimaccia and P. Kanavos received an unrestricted educational grant from ThromboGenics for an unrelated project.

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Meetings: The paper has not been presented at any meetings.

Acknowledgments: We thank Dr Dhanes Thomas who provided anonymized participant-level data for meta-analysis.

Key words: complications; diabetic macular edema; efficacy; meta-analysis; optical coherence tomography central retinal thickness; pars plana vitrectomy; safety; systematic review; visual acuity.

Summary statement: A meta-analysis of vitrectomy for diabetic macular edema found no significant difference in visual outcome compared to laser or observation. Retinal thickness was better than with laser/observation at 6 months, but this benefit had reversed by 12 months. Intraoperative retinal breaks occurred in 7.1%, and postoperative retinal detachment in 1.2%

Abstract

Purpose. To assess the risk and benefit of pars plana vitrectomy for diabetic macular edema (DME).

Methods. We conducted a systematic literature review using PubMed, EMBASE, Web of Science, and Cochrane Central Database of Controlled Trials until September 2014. The population was patients with DME, intervention vitrectomy, comparator macular laser or observation, and efficacy outcome visual acuity and central retinal thickness (CRT). Safety outcomes were intra- and postoperative surgical complications. The efficacy meta-analysis included only randomized controlled trials. The safety analysis included prospective, retrospective, controlled and uncontrolled studies.

Results. Five studies were eligible for the efficacy meta-analysis (n = 127 eyes) and 40 for the safety analysis (n = 1,562 eyes). Combining follow up intervals from 6 to 12 months, the meta-analysis found a non-significant 2 letter visual acuity difference favoring vitrectomy, and a significant 102 micron greater reduction in CRT favoring vitrectomy, but a post-hoc subgroup analysis found that a 6 month CRT benefit reversed by 12 months. The most frequent complications were retinal break (7.1%), elevated intraocular pressure (5.2%), epiretinal membrane (3.3%), and vitreous hemorrhage (2.4%). Cataract developed in 68.6% of 121 phakic eyes.

Conclusions. Vitrectomy produces structural and functional improvements in select eyes with DME, but the visual gains are not significantly better than with laser or observation. No major safety concerns were identified.

Introduction

Diabetic macular edema (DME) is a leading cause of visual loss in developed nations,[1, 2] and as the population with diabetes expands,[3] the burden of DME will increase. For many years the standard therapy for DME has been focal macular photocoagulation laser. The Early Treatment of Diabetic Retinopathy Study (ETDRS) established that laser approximately halves the risk of moderate vision loss in patients with clinically significant macular edema.[4] More recently, several randomized controlled trials (RCTs) have demonstrated the safety and efficacy of intravitreal steroid injections and implants.[5-9] Vascular endothelial growth factor (VEGF), by increasing vascular permeability, plays an important role in the pathogenesis of DME.[10, 11] Studies investigating the intravitreal use of the anti-VEGF agents ranibizumab,[12-16] aflibercept,[2, 17] and bevacizumab[18] have also shown favorable results.[19]

There are a number of clinical studies suggesting that an attached vitreous may adversely affect the clinical course of DME, or possibly contribute to its pathogenesis. Sivaprasad *et al* found that posterior vitreous detachment (PVD) was less common in eyes with DME, and that vitreous attachment appeared to reduce the benefit of intravitreal steroid therapy.[20] A synthesis of the literature by Jackson *et al* found that some degree of vitreomacular traction (VMT) was present in 12% of eyes with DME, and up to 24% in surgical series.[21] Vitreomacular traction may aggravate any underlying tendency for DME, and if severe, VMT can cause macular edema in its own right. It therefore seems reasonable to assume that relief of VMT would be beneficial.

Several authors have advocated the use of pars plana vitrectomy (PPV) to treat DME. Whilst PPV is well established for the treatment of persistent vitreous hemorrhage[22] and tractional retinal detachment,[23, 24] its use as a treatment for DME has not been supported by large randomized controlled trials (RCTs).

Laboratory studies provide a theoretical basis to support the use of PPV. Several animal studies[25-27] and some human studies[28] reported that PPV increases vitreous oxygenation in the context of ischemia, and increased oxygen tension is likely to reduce VEGF. It has been estimated that vitreous viscosity is 300 to 2000 times greater than aqueous,[29] and following vitrectomy diffusion coefficients of intravitreal molecules, including VEGF, should increase by a similar magnitude.[30] Therefore, following PPV, VEGF and other pro-inflammatory cytokines would be expected to diffuse away from the macula more easily.[31] Conversely, the post-vitrectomy decrease in the viscosity of the vitreous cavity has the possible disadvantage of interfering with intraocular pharmacokinetics and reducing the half-life of intravitreal drugs.[32]

In the absence of large RCTs of PPV for DME we aimed to undertake a systematic review and meta-analysis to assess if PPV is an appropriate surgical intervention. Specifically, we aimed to determine the benefit of PPV in terms of the mean change in visual acuity (VA) and reduction in optical coherence tomography (OCT) central retinal thickness (CRT), and the risk in terms of intra- and postoperative complications. An analysis of risk and benefit is particularly important in the context

of new intravitreal drug treatments that have proven efficacy and favorable safety profiles - interventions that do not expose patients to the risks of PPV.

Methods

Study design, population, intervention, comparison and outcome

We aimed to estimate the risk and benefit of PPV for DME. To estimate the potential benefit of PPV we used a meta-analysis of efficacy outcomes, selecting only RCTs. To estimate the risks of PPV, in terms of surgical complications, we undertook a systematic review, to encompass a wider range of literature and increase the likelihood of detecting rare events. The population was patients with DME, the intervention was PPV, and the comparison was traditional standard care,[4] namely focal macular photocoagulation laser or observation. The two main efficacy outcomes were visual acuity (VA), and optical coherence tomography (OCT) central retinal thickness (CRT). Safety outcomes included all reported intra- or postoperative surgical complications, or other adverse events attributed to PPV or local or general anesthesia. The study protocol was registered with the international prospective register of systematic reviews (registration number CRD42014013646, National Institute of Health Research Centre for Reviews and Dissemination, University of York, UK) and conducted in accordance with Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidance (http://www.prisma-statement.org/, accessed 21 January 2015).

Eligibility

To be eligible for the meta-analysis RCTs had to recruit patients with DME, and compare PPV to traditional standard care (observation or macular photocoagulation laser), for the treatment of DME. Outcome data had to include change in VA and change in CRT at least 6 months after enrolment, and safety at any time point. The data had to be of sufficient quality, in terms of clear eligibility, defined efficacy and safety outcomes, and data completeness, and in particular studies had to report any complications that occurred, or state that there were none. Only English, French and German language articles in peer-reviewed journals were eligible. Studies that failed to provide pre- and post-operative VA were excluded, as were those appearing as abstract only, and studies where patients received adjunctive therapy such as intravitreal steroids and anti-VEGF drugs, as these could confound the analysis of vitrectomy versus laser/observation. Editorials, expert opinions, and articles in non-peer reviewed journals were excluded. Articles using intravitreal vital stains to assist with peeling of the internal limiting membrane (ILM) were not excluded.[33-36] Similar eligibility criteria were applied to the safety analysis, except that studies did not need to be RCTs or have a control group, the minimum VA follow up did not apply, and they need not report CRT. Prospective, retrospective, controlled and uncontrolled studies, including case reports, were eligible for the safety analysis.

Literature review

An Ovid MEDLINE database search from 1946 to 23 September 2014 was undertaken using Boolean operators with the following keywords (and corresponding MESH headings if they were available): vitrectomy; diab*; macula*; oedema or

edema; maculopathy; vitreomacular traction; vitreomacular adhesion; taut posterior hyaloid. The search was not restricted by adding terms such as adverse events, complications, or safety, but rather each eligible article was reviewed for safety data. Searches were repeated using EMBASE™ (Ovid), and the Cochrane Central Database of Controlled Trials (CENTRAL, Cochrane library). An example search is shown in eAppendix 1 (see Supplement).

The retrieved abstracts were then reviewed by two senior retinal experts (TJ, EP) who selected articles for full review if they appeared to meet the eligibility criteria. Further articles were identified in the bibliographies of retrieved articles. Where necessary, authors were contacted to obtain unpublished raw data from RCTs.

Data extraction

Three independent reviewers (FG, AA, EN) entered data from each article into an electronic data capture form. Any discrepancy was resolved by consensus or, if necessary, by arbitration of a senior retinal specialist (TJ). The protocol for data collection included the following information for each article: 1) general information about the study (aim, summary, key findings); 2) methodological details (study design, study population, entry criteria, methods, study period); 3) primary and secondary outcomes; 4) presenting and final VA; 5) whether or not eyes underwent peeling of the ILM at the time of PPV; 6) safety outcomes (adverse events and serious adverse events, including surgical complications and reoperations).

Assessment of bias

The risk of bias was assessed using the Cochrane Risk of Bias Assessment tool which grades risk of bias as low, unclear or high risk. Seven domains of risk where assessed including assessments for selection bias, performance bias, detection bias, attrition bias and reporting bias.

Data analysis

To analyse visual outcome across studies the mean VA data were converted to logarithm of the minimum angle of resolution (LogMAR) units.[37] Counting fingers vision was assigned a LogMAR acuity of 1.6, hand movements 1.9, light perception 2.2, and no light perception 2.5.[38-40] Meta-analysis was used to pool comparisons of the mean change in LogMAR VA and change in CRT comparing PPV and control (observation or laser). The fixed effect method with inverse variance weighting was used. Statistical analysis was performed using RevMan 5.2 available from the Cochrane Collaboration.[41] Safety data were pooled across all studies, including non-RCTs.

Results

Meta-analysis of efficacy:

Six RCTs were identified that provided mean change in LogMAR VA and mean change in retinal thickness, comparing patients having undergone PPV with controls.[42-47] One study was excluded, as it was not possible to obtain raw data or summary statistics for the outcomes in question, despite contacting the author (eAppendix 2, see supplement).[47] Additional, anonymous participant-level data were

obtained from two study authors, such that their reports could be included in the meta-analysis.[45, 46] Of the five RCTs included, four used a laser control group[42, 43, 45, 46] and one used an untreated control group[44]. We identified possible duplicate reporting in two studies[43, 44], but concluded these were different populations given the different eligibility criteria and control groups. Follow up duration was 6 months in 3 studies[42, 44, 46] and 12 months[45, 46] in 2 (one study reported both outcomes[46]) (Table 1). One study[46] reported results at 6 and 12 months, where 5 patients were double counted for the LogMAR results and 6 patients for the CRT. Sensitivity analysis was performed to test the effect on the results by excluding the 6 month or 12 month outcome. This resulted in similar magnitude and precision of results. We preferred to report the combined results (at 6 and 12 months) due to the greater sample size. This summarizing error was considered acceptable as sensitivity analysis testing showed it did not affect the conclusion.

All RCTs appeared to be at low risk of reporting bias (Figures 1A and 1B). It is not possible to effectively mask patients to the intervention, vitrectomy, observation or control, and as such all studies are at risk of introducing performance bias. Detection bias may have been minimized by using masked assessors for VA outcome collection, although only 2 out of 5 studies explicitly stated doing this.[44, 48] It was felt that the collection of automated OCT central retinal thickness data was unlikely to introduce bias whether masked assessors were used or not. Randomization methodology and allocation concealment were not always explicitly reported across the trials (see eAppendix 3 in the Supplement).

Table 1. Randomized controlled study characteristics included in the meta-analysis, showing visual acuity and central retinal thickness before and after pars plana vitrectomy

	Thomas 2005	**Yanyali 2005**	**Yanyali 2006**	**Patel 2006**	**Kumar 2007**
Patient population	**33 eyes of 33 patients with DME, VA of 0.3 logMAR or worse, after one or more macular laser treatments**	**24 eyes of 12 patients with DME in both eyes. One eye used as control.**	**20 eyes of 10 patients with DME in both eyes. One eye used as contol. Patients were unresponsive to grid laser photocoagulation**	**12 eyes from 12 patients with persistent clinically significant DME despite previous macular laser.**	**24 eyes of 24 patients with diffuse DME.**
Males (%)	70	41.7	40	58	91.7
Mean follow-up period (months)	12	6	12	6 and 12	6
Intervention	**PPV + ILM peeling**	**PPV + ILM peeling**	**PPV + ILM peeling**	**Standard three-port PPV with elevation and the removal of the posterior vitreous cortex (no ILM peeling)**	**PPV + ILM peeling**
Treated eyes (number)	15	12	10	7	12
Mean age (years)	64.3	64.4	61.5	63 (all)	57.25
LogMAR VA ± 1SD before (Snellen)	0.67 ± 0.30 (20/94)	0.75 ± 0.40 (20/112)	0.72 ± 0.43 (20/105)	0.55 ± 0.18 (20/71)	1.11 ± 0.09 (20/258)
LogMAR VA ± 1SD after (Snellen)	0.71 ± 0.33 (20/103)	0.54 ± 0.40 (20/69)	0.55 ± 0.45 (20/71)	0.5 ± 0.22 (20/63) (6 eyes/6 months) 0.57 ± 0.18 (20/74) (6 eyes/12 months)	0.92 ± 0.10 (20/166)
CRT ± 1SD before (µl)	426.2 ± 111.2	439.3 ± 102.0	391.3 ± 91.6	375.3 ±144.8	567.5 ± 147.9
CRT ± 1SD after (µl)	347.1 ± 202.9	219.8 ± 60.6	225.5 ± 49.5	318.2 ± 114.8 (6 eyes/6 months)	266.6 ± 69.4

				334.17 ± 112.0 (6 eyes/12 months)	
Control	**Macular laser**	**Modified grid laser photocoagulation**	**Untreated controls**	**Laser**	**Modified grid laser photocoagulation**
Control eyes (number)	18	12	10	8	12
Mean age (years)	64	64	62	63 (all)	57
LogMAR VA ± 1SD before (Snellen)	0.62 ± 0.23 (20/83)	0.59 ± 0.26 (20/78)	0.44 ± 0.44 (20/55)	0.50 ± 0.25 (20/63)	1.07 ± 0.06 (20/235)
LogMAR VA ± 1SD after (Snellen)	0.57 ± 0.32 (20/74)	0.50 ± 0.26 (20/63)	0.60 ±0.56 (20/80)	0.42 ± 0.22 (20/53) (8 eyes/6 months) 0.31 ±0.13 (20/40) (6 eyes/12 months)	0.97 ± 0.09 (20/186)
CRT ± 1SD before (µl)	440.3 ± 172.8	407.1 ± 96.0	356.2 ± 140.1	404.5 ± 145.8	463.6 ± 92.4
CRT ± 1SD after (µl)	330.0 ± 117.7	378.5 ± 135.6	318.4 ± 111.1	320.63 ± 114.0 (8 eyes/6 months) 308.2 ± 123.1 (6 eyes/12 months)	357.0 ± 77.21

Footnote: VA: visual acuity; CRT: central retinal thickness; DME: diabetic macular edema; ILM peel: internal limiting membrane peeling; PPV: pars plana vitrectomy; SD: standard deviation; VA: visual acuity.

Figure 1. Risk of bias summary and graph.

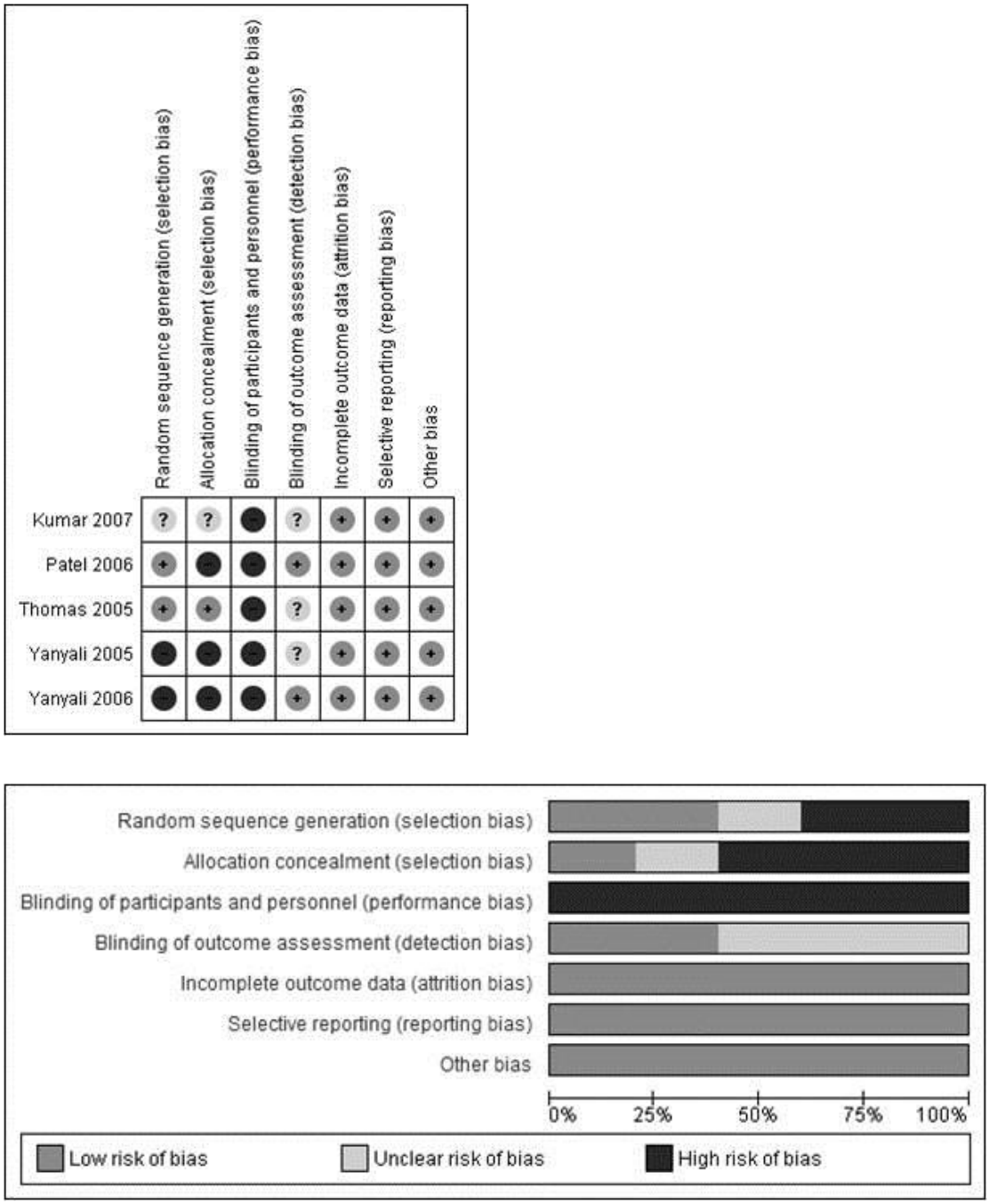

Figure 1 illustrates the risk of bias summary (A) and the risk of bias graph (B). The review is based on the authors' judgements about each risk of bias item for each included study. The risk of bias in each paper was evaluated for across seven domains. Each domain was rated as either Low Risk, Unclear Risk or High Risk of introducing bias.

Abbreviations: + low risk; ? unclear risk; - high risk.

Figure 2 shows a forest plot of the vision outcome (mean change in VA in LogMAR units) from the meta-analysis of the five RCTs, comparing PPV with control. Overall there was a 2 letter (0.04 logMAR units) difference favoring PPV over control but this was not significant (95% confidence interval [CI] -0.02 to 0.1 logMAR units, p=0.18).

As part of the iterative process and in accordance with PRISMA guidance, the original analysis protocol was adapted to accommodate the variability in the follow up interval reported (6 or 12 months) and control group (observation or laser). Specifically, we undertook a post-hoc analysis of the main efficacy outcome measures (change in mean VA and CRT) in three subgroups: 1) studies reporting outcomes at 6 months with laser control; 2) studies reporting at 12 months with laser control; and 3) studies reporting at 12 months with untreated controls. In the laser controlled studies, using mean VA at 6 months there was an almost significant (p=0.05) benefit from vitrectomy compared to laser, however this reversed at 12 months, with an almost significant result favoring laser (p=0.07). The subgroup analyses are shown in Figure 2. Within each subgroup the results were similar, however on combining all 3 subgroups there was moderate heterogeneity (I^2 of 60%).

Figure 2. Meta-analysis of vision outcome comparing pars plana vitrectomy to standard care

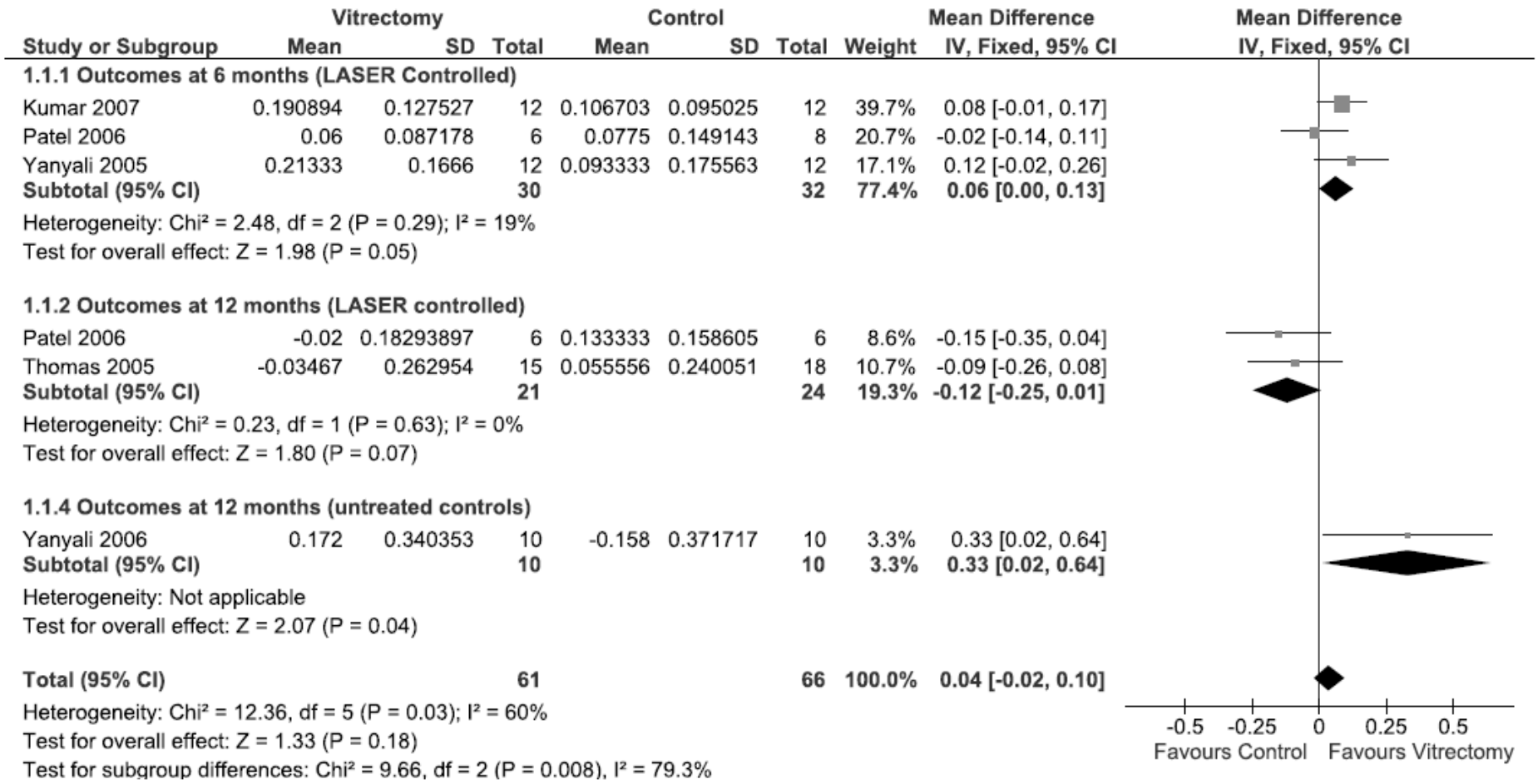

Figure 3. Meta-analysis of change in optimal coherence tomography macular thickness comparing pars plana vitrectomy to standard care

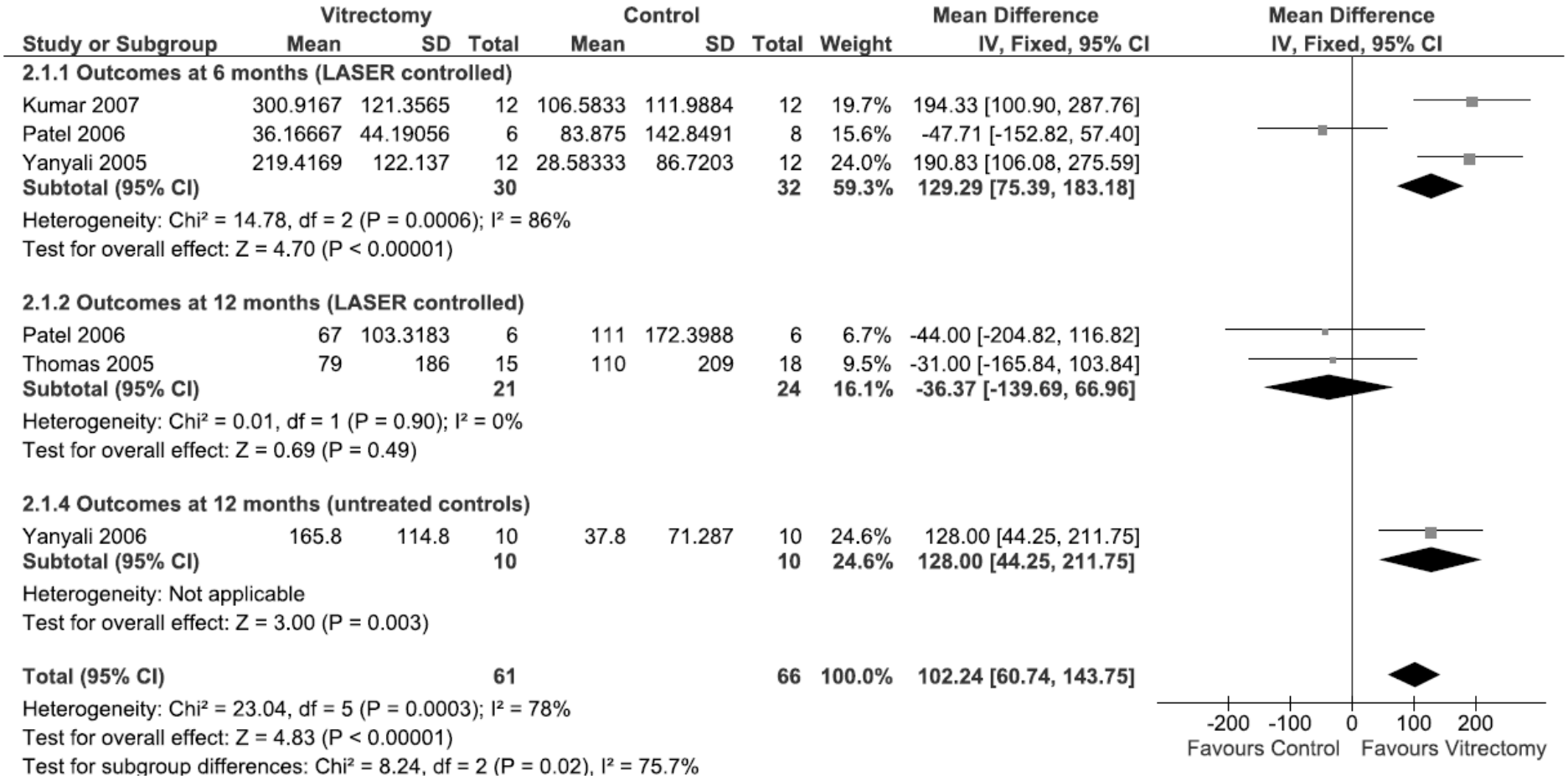

Figure 2 shows a meta-analysis of vision outcome (change in mean logarithm of the minimum angle of visual acuity), comparing pars plana vitrectomy to standard care (observation or macular laser). The overall analysis of the five RCTs showed a better visual outcome in the vitrectomy group, but this was not quite significant and there was heterogeneity amongst the trials.

Abbreviations: CI = confidence interval; IV = Inverse variance method used; Fixed= Fixed effect model used; SD = standard deviation.

Figure 3 presents a meta-analysis of change in optical coherence tomography macular thickness, comparing pars plana vitrectomy or standard care (observation or macular laser). The overall analysis showed that vitrectomy resulted in a significantly greater reduction in macular thickness than standard care.

Abbreviations: CI = confidence interval; IV = Inverse variance method used; Fixed= Fixed effect model used; SD = standard deviation.

Figure 3 presents a forest plot of the meta-analysis of the same five RCTs, with respect to change in CRT. Overall there was a significant, 102 μm (95% CI 61 to 144μm, p<0.00001) greater reduction in macular thickness in the pooled vitrectomy group compared with the control group (I^2 of 78%). However, as can be seen in Figure 3, the subgroup analysis suggested that the advantage of PPV over laser at 6 months was not evident at 12 months.

Safety:

A total of 425 abstracts were retrieved. Of these 106 potentially eligible articles were reviewed in full, of which 40 were eligible for the safety analysis. Although the literature search extended back to 1946, the first eligible report was published in 1992,[3] and 38 of 40 were published after 2000 (eAppendix 4, see supplement).

In 40 studies, intra- and postoperative complications were reported (Table 2).[3, 42-44, 46, 48-82] The most frequent intraoperative surgical complications were peripheral retinal break (7.08% of 1,469 eyes), iatrogenic tears (0.68% of 1,469 eyes), and focal, petechial spontaneously resolving retinal hemorrhage (0.34% of 1,469 eyes). The most frequent postoperative complications were raised intraocular pressure (5.19% of 1,562 eyes), epiretinal membrane (3.27% of 1,562 eyes), vitreous hemorrhage (2.43% of 1,562 eyes), neovascular glaucoma (1.60% of 1,562 eyes), glaucoma (1.41% of 1,562 eyes), macular hard exudates (1.34% of 1562 eyes) and retinal detachment (1.22% of 1,562 eyes).

Table 2. Intra- and postoperative complications[3,42-44,46,48-82]

Intra-operative complications	Number of eyes	Number of eyes affected	Eyes affected (%)
Peripheral retinal break	1469	104	7.08%
Iatrogenic tears	1469	10	0.68%
Focal, petechial, spontaneously resolving retinal hemorrhage	1469	5	0.34%
Retinal detachment	1469	2	0.14%
Entry site break	1469	1	0.07%
post-operative complications			
Cataract*	1562	40	2.56%
Cataract surgery	1562	19	47.50%
Intraocular pressure	1562	81	5.19%
Epiretinal membrane	1562	51	3.27%
Vitreous hemorrhage	1562	38	2.43%
Neovascular glaucoma	1562	25	1.60%
Glaucoma	1562	22	1.41%
Hard exudate deposits in the center of the macula	1562	21	1.34%
Retinal detachment	1562	19	1.22%
Mild progression of nuclear sclerosis	1562	12	0.77%
Rhematogenous retinal detachment	1562	10	0.64%
Cystoid macular edema	1562	6	0.38%
Macular retinal pigment epithelium abnormalities	1562	5	0.32%
Ocular hypertension	1562	4	0.26%
Neovascularisation of the angle	1562	3	0.19%
Secondary Glaucoma	1562	3	0.19%
APE atrophy of the macula	1562	3	0.19%
Unusual refex of the retinal surface	1562	3	0.19%
Ischemic optic neuropathy	1562	3	0.19%
Endophthalmitis	1562	3	0.19%
Lipid deposit in the centre of the macula	1562	3	0.19%
Central retinal vein occlusion	1562	2	0.13%
Full-thickness macular hole	1562	1	0.06%
Dissociated optic nerve fiber layer appearance	1562	1	0.06%
Posterior vitreous detachment	1562	1	0.06%
Lamellar macular hole	1562	1	0.06%
Choroidal neovascularization	1562	1	0.06%
Deterioration of existing cataract	1562	1	0.06%
Partial thickness macular hole	1562	1	0.06%
Retinal hemorrhage	1562	1	0.06%

*Cataract developed in 68.6% of 121 phakic eyes

The rate of post-vitrectomy cataract was not reliably reported and many reports did not detail the proportion of phakic eyes. Cataract was reported to develop in only 40 of 1,562 eyes (2.56%), of which 47.5% (19 of 40 eyes) underwent subsequent cataract surgery. Four studies provided the post-vitrectomy cataract rate in 121 phakic eyes, and 83 (68.6%) of these eyes developed cataract over a mean of 31.0 months.[57, 65, 67, 70]

A post hoc safety analysis was undertaken using the data from the RCTs included in the efficacy meta-analysis, to assess if the complication rates differed from those reported in the main safety analysis (which included uncontrolled and retrospective studies). The complication rates appeared similar in the 46 participants with detailed safety reporting, in that the most common complication was progression of nuclear sclerosis (23.9%) followed by raised intraocular pressure (6.5%). The only other complication reported was rhegmantogenous retinal detachment in one patient (2.1%).[42-44, 46]

Discussion

Our meta-analysis of RCTs suggests that the visual benefits following vitrectomy for DME were not significantly better than those achieved using conventional management with laser and observation. The RCTs indicated that PPV was associated with a significantly greater reduction in macular thickness than laser and observation, but there was heterogeneity in this overall result, and our subgroup analysis may be

more informative. This showed a trend for better OCT results than with laser at 6 months, but this trend had reversed by 12 months.

The VA gain in the RCTs was equivalent to 2 ETDRS letters (0.04 LogMAR). The Ranibizumab for Edema of the mAcula in Diabetes (READ-2) study randomized patients with DME to receive ranibizumab, macular laser, or both.[14] In the group receiving only ranibizumab, vision improved by an average of 7.4 letters at 6 months. Another RCT compared ranibizumab alone, and in combination with macular laser, and reported a mean gain of 6.1 letters at 12 months in the group that only received ranibizumab.[15] Yet another study showed a 5.8 letter gain following ranibizumab and deferred laser.[16] As such the PPV RCT results do not compare favorably with those of anti-VEGF therapy in terms of the mean VA change (or in relation to the comparison with a laser control group). However, ddirect comparison between the anti-VEGF studies and our meta-analysis is difficult for several reasons. Key amongst these is that vitrectomy is often reserved for patients who have failed other treatments, whereas anti-VEGF agents are often used as a first-line treatment. Ideally, there would be RCTs directly comparing PPV and anti-VEGF treatments.

No major safety concerns were identified. Retinal breaks were the most common complication. A database study of 8,257 PPVs also found that retinal breaks were the most common intraoperative complication.[83] In the subset of eyes undergoing epiretinal membrane surgery, a PPV of similar complexity, iatrogenic retinal breaks occurred in 3.0% of cases, whereas the present series incorporated studies that used somewhat varying terminology, with those describing ‘peripheral retinal breaks’

averaging a 7.1% rate, and those reporting 'iatrogenic tears' averaging 0.7%. Retinal detachment occurred in 1.5% of the epiretinal membrane cases, compared with 1.2% in the present analysis. The incidence of post-vitrectomy hemorrhage and neovascular glaucoma were higher in the present series, consistent with an underlying diagnosis of diabetes. Although the safety of PPV for DME appears comparable to other studies of PPV, the complication rates are higher than those seen following intravitreal anti-VEGF injections for DME.[13, 15, 16]

The main strength of the present meta-analysis is that it provides a pooled estimate of treatment effect across several RCTs, and the safety analysis considers an even larger pool of patients that may be better able to detect rare events. There is a risk that publication or reporting bias may favor the selection of reports describing positive surgical outcomes.[84, 85] Also, post-vitrectomy lens changes may be a confounding variable. It was not possible to determine the lens status in many studies, or to reliably determine the proportion of eyes that underwent cataract surgery. It is well known that PPV causes cataract and this is likely to reduce the mean visual gain, and this is possibly suggested by the worse VA outcome at 12 months compared to 6 months, as shown in Figure 2 (this would not however explain a worsening of the OCT outcome over this timeframe). Conversely, removal of preexisting lens opacity during initial combined phakovitrectomy, or subsequently as a result of post-vitrectomy cataract, will tend to improve the mean VA of the PPV group. Although laser or observation remain the standard of care for many patient, anti-VEGF therapy is now emerging as a standard of care for many other patients. Our results suggest that PPV is not superior to laser or observation, and the pivotal anti-VEGF trials in turn show that anti-VEGF treatment is superior to laser; this might appear to indicate that anti-VEGF

therapy is superior to PPV, that analysis requires direct comparison of PPV versus anti-VEGF therapy, and is not proven by our analysis.

Another intrinsic difficulty of studies involving PPV is that masking is not possible, as sham surgery would not be practical. However most of the RCTs provided relatively robust VA assessment and lack of masking is unlikely to materially influence CRT measurement, which relies on automated computer software analysis.

Interventional case series recruit patients in whom surgery is considered clinically reasonable, and those with milder disease may have been excluded.[86] Therefore the results may not be representative of all patients with DME, or comparable with studies investigating intravitreal injections. Also, even if the overall functional benefit was no better than macular laser, it is possible that a subgroup of patients with DME and significant vitreomacular traction may benefit from PPV. Vitreomacular traction or taut posterior hyaloid is reported to be present in 17% of DME cases undergoing PPV.[21]

In summary, this study found that PPV produced both structural and functional benefit in eyes with DME, but the functional benefit was not significantly better than that obtained using macular laser, and the structural benefits appeared to decline, or possibly reverse, with time. Like previous reviews,[21] we identified a lack of high quality evidence, and the need for large RCTs comparing PPV to the latest gold standard, in particular intravitreal anti-VEGF drugs. Given the favorable results with these newer treatments, the need to justify PPV becomes even greater.

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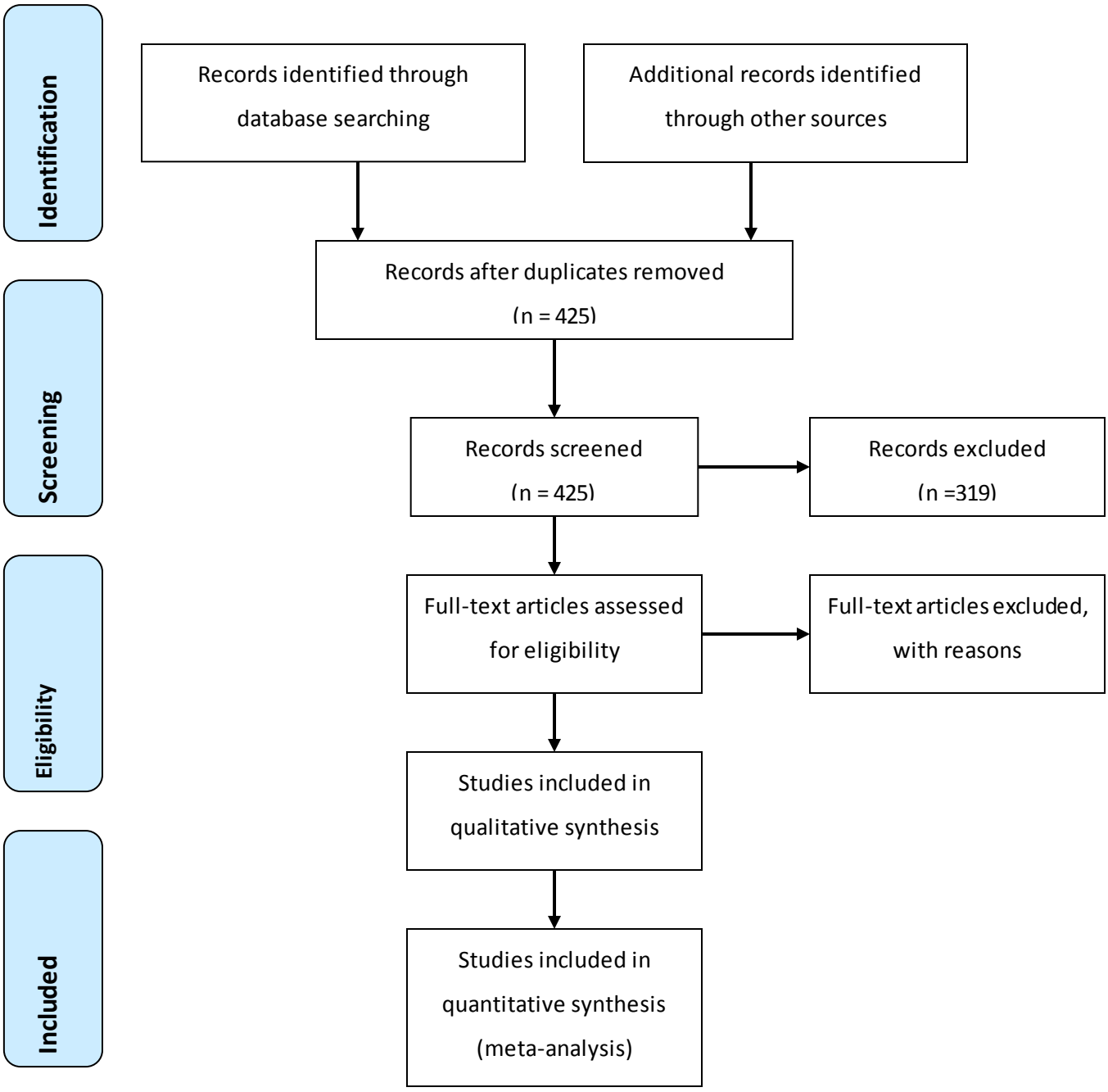
Appendix 1 Search Strategy

Illustrative literature search using OvidSP (EMBASE) to retrieve studies of pars plana vitrectomy for the treatment of diabetic macular edema.

	Searches	Results
1	edema.mp. or edema/	225,844
2	oedema.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	27,735
3	1 or 2	23,4960
4	retina macula lutea/ or macula*.mp.	57,065
5	3 and 4	13,297
6	macular edema.mp. or retina macula edema/	10,492
7	macular oedema.mp.	1,441
8	5 or 6 or 7	13,297
9	diabetes mellitus/or diabet*.mp.	722,041
10	8 and 9	5,351
11	diabetic macular edema/	2,040
12	10 or 11	5,351
13	vitrectomy.mp. or vitrectomy/	18,637
14	12 and 13	950

Appendix 2. PRISMA 2009 Flow Diagram (Efficacy Analysis)



Appendix 3. Risk of Bias Summary of Included Studies

Study: Kumar 2007

Methods	Randomized controlled trial
Participants	24 Eyes. Visual acuity ≤ 6/60, diffuse macular edema, HbA1C > 7.5%, study based in India. Excluded patients with fundus fluorescein angiogram (FFA) evidence of macular ischemia, vitreomacular traction, cataract surgery within 1 year, previous vitrectomy, previous panretinal photocoagulation (PRP) in 12months, previous grid laser in 6 months, uncontrolled diabetes, hypertension or chronic renal failure
Interventions	Pars plana vitrectomy (PPV) with dye-assisted internal limiting membrane (ILM) peel or grid LASER. No triamcinolone used
Outcomes	Early Treatment of Diabetic Retinopathy Study (ETDRS) visual acuity (VA), macular thickness, macular volume at 6 months

Bias	Authors judgement	Support for judgement
Random sequence generation (selection bias)	Unclear	Randomisation method not mentioned
Allocation concealment (selection bias)	Unclear	Randomisation concealed by sealed envelop
Blinding of participants and personnel (performance bias)	High risk	Patients not masked (vitrectomy or laser)
Blinding of outcome assessment (detection bias)	Unclear	No mention if assessors were masked
Incomplete outcome data (attrition bias)	Low risk	25 patients assessed, 24 eyes analysed
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Low risk	

Study: Patel 2006

Methods	Randomized controlled trial
Participants	20 patients recruited, 7 vitrectomy patients, 8 laser patients Clinically significant macular edema (CSME) depsite previous macular laser (less than 2years), Snellen acuity 6/15- 6/60 (65- 35 letters) Excluded macular ischemia
Interventions	Vitrectomy (ILM not peeled) (7 patients) or macular laser (8 patients)
Outcomes	ETDRS VA, optical coherence tomography (OCT), and FFA at baseline and 12 months

Bias	Authors judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation performed by separate department in same hospital. Comment: Probably done
Allocation concealment (selection bias)	High risk	Concealment method not described
Blinding of participants and personnel (performance bias)	High risk	Patients can not be masked to intervention
Blinding of outcome assessment (detection bias)	Low risk	Masked observers
Incomplete outcome data (attrition bias)	Low risk	20 patients recruited, 15 analysed- similar attrition in each group
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Low risk	

Study: Thomas 2005

Methods	Randomized controlled trial
Participants	Diabetic macular edema with no macular traction Previous macular laser VA 6/12 or worse Excluded ischemic maculopathy
Interventions	19 patients randomised to vitrectomy with ILM peel compared to 21 control patients undergoing further macular laser
Outcomes	Best corrected logarithm of the minimum angle of resolution (LogMAR) VA and mean OCT central macular thickness

Bias	Authors judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization prepared by independent medical statistician
Allocation concealment (selection bias)	Low risk	Sealed, numbered opaque envelopes used: probably adequate
Blinding of participants and personnel (performance bias)	High risk	Unable to mask patients
Blinding of outcome assessment (detection bias)	Unclear risk	No mention if assessors were masked
Incomplete outcome data (attrition bias)	Low risk	Similar loss to follow up in both groups (vitrectomy group loss 4/19, laser control group loss 3/18)
Selective reporting (reporting bias)	Low risk	All outcomes reported Intention to treat analysis used
Other bias	Low risk	

Study: Yanyali 2005

Methods	Randomised controlled trial
Participants	12 patients, 24 eyes Bilateral diabetic macular edema Type 2 diabetes No vitreomacular traction No previous laser
Interventions	12 eyes vitrectomy with ILM peeling Fellow 12 eyes undergo macular laser
Outcomes	Best corrected LogMAR VA and mean OCT central macular thickness

Bias	Authors judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Method of randomisation not explained
Allocation concealment (selection bias)	High risk	Method of concealment not explained
Blinding of participants and personnel (performance bias)	High risk	Participant not masked
Blinding of outcome assessment (detection bias)	Unclear risk	No mention if assessors were masked
Incomplete outcome data (attrition bias)	Low risk	Full follow up
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Low risk	

Study: Yanyali 2006

Methods	Randomized controlled trial
Participants	10 patients, 20 eyes Bilateral diabetic macula edema Type 2 diabetes All had previous grid laser and now considered 'unresponsive to further laser' No vitreomacular traction
Interventions	10 eyes underwent vitrectomy with ILM peeling 10 fellow eyes followed observation alone
Outcomes	OCT retinal thickness and visual acuity

Bias	Authors judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Method of randomization not explained
Allocation concealment (selection bias)	High risk	Method of concealment not explained
Blinding of participants and personnel (performance bias)	High risk	Unable to mask patients
Blinding of outcome assessment (detection bias)	Low risk	Assessor was masked to treatment groups
Incomplete outcome data (attrition bias)	Low risk	No patients lost to follow up
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Low risk	

Appendix 4. PRISMA 2009 Flow Diagram (Safety Analysis).