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Laser photocoagulation for proliferative diabetic retinopathy (Review)

Evans JR, Michelessi M, Virgili G

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[Intervention Review]

Laser photocoagulation for proliferative diabetic retinopathy

Jennifer R Evans[1], Manuele Michelessi[2], Gianni Virgili[3]

[1]Cochrane Eyes and Vision Group, ICEH, London School of Hygiene & Tropical Medicine, London, UK. [2]Ophthalmology, Fondazione G.B. Bietti per lo studio e la ricerca in Oftalmolologia-IRCCS, Rome, Italy. [3]Department of Translational Surgery and Medicine, Eye Clinic, University of Florence, Florence, Italy

Contact: Jennifer R Evans, Cochrane Eyes and Vision Group, ICEH, London School of Hygiene & Tropical Medicine, Keppel Street, London, WC1E 7HT, UK. jennifer.evans@lshtm.ac.uk.

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ABSTRACT

Background

Diabetic retinopathy is a complication of diabetes in which high blood sugar levels damage the blood vessels in the retina. Sometimes new blood vessels grow in the retina, and these can have harmful effects; this is known as proliferative diabetic retinopathy. Laser photocoagulation is an intervention that is commonly used to treat diabetic retinopathy, in which light energy is applied to the retina with the aim of stopping the growth and development of new blood vessels, and thereby preserving vision.

Objectives

To assess the effects of laser photocoagulation for diabetic retinopathy compared to no treatment or deferred treatment.

Search methods

We searched CENTRAL (which contains the Cochrane Eyes and Vision Group Trials Register) (2014, Issue 5), Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid MEDLINE Daily, Ovid OLDMEDLINE (January 1946 to June 2014), EMBASE (January 1980 to June 2014), the *meta*Register of Controlled Trials (*m*RCT) (www.controlled-trials.com), ClinicalTrials.gov (www.clinicaltrials.gov) and 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 3 June 2014.

Selection criteria

We included randomised controlled trials (RCTs) where people (or eyes) with diabetic retinopathy were randomly allocated to laser photocoagulation or no treatment or deferred treatment. We excluded trials of lasers that are no longer in routine use. Our primary outcome was the proportion of people who lost 15 or more letters (3 lines) of best-corrected visual acuity (BCVA) as measured on a logMAR chart at 12 months. We also looked at longer-term follow-up of the primary outcome at two to five years. Secondary outcomes included mean best corrected distance visual acuity, severe visual loss, mean near visual acuity, progression of diabetic retinopathy, quality of life, pain, loss of driving licence, vitreous haemorrhage and retinal detachment.

Data collection and analysis

We used standard methods as expected by the Cochrane Collaboration. Two review authors selected studies and extracted data.

Main results

We identified a large number of trials of laser photocoagulation of diabetic retinopathy (n = 83) but only five of these studies were eligible for inclusion in the review, i.e. they compared laser photocoagulation with currently available lasers to no (or deferred) treatment. Three studies were conducted in the USA, one study in the UK and one study in Japan. A total of 4786 people (9503 eyes) were included in

these studies. The majority of participants in four of these trials were people with proliferative diabetic retinopathy; one trial recruited mainly people with non-proliferative retinopathy. Four of the studies evaluated panretinal photocoagulation with argon laser and one study investigated selective photocoagulation of non-perfusion areas. Three studies compared laser treatment to no treatment and two studies compared laser treatment to deferred laser treatment. All studies were at risk of performance bias because the treatment and control were different and no study attempted to produce a sham treatment. Three studies were considered to be at risk of attrition bias.

At 12 months there was little difference between eyes that received laser photocoagulation and those allocated to no treatment (or deferred treatment), in terms of loss of 15 or more letters of visual acuity (risk ratio (RR) 0.99, 95% confidence interval (CI) 0.89 to 1.11; 8926 eyes; 2 RCTs, low quality evidence). Longer term follow-up did not show a consistent pattern, but one study found a 20% reduction in risk of loss of 15 or more letters of visual acuity at five years with laser treatment. Treatment with laser reduced the risk of severe visual loss by over 50% at 12 months (RR 0.46, 95% CI 0.24 to 0.86; 9276 eyes; 4 RCTs, moderate quality evidence). There was a beneficial effect on progression of diabetic retinopathy with treated eyes experiencing a 50% reduction in risk of progression of diabetic retinopathy (RR 0.49, 95% CI 0.37 to 0.64; 8331 eyes; 4 RCTs, low quality evidence) and a similar reduction in risk of vitreous haemorrhage (RR 0.56, 95% CI 0.37 to 0.85; 224 eyes; 2 RCTs, low quality evidence).

None of the studies reported near visual acuity or patient-relevant outcomes such as quality of life, pain, loss of driving licence or adverse effects such as retinal detachment.

We did not plan any subgroup analyses, but there was a difference in baseline risk in participants with non-proliferative retinopathy compared to those with proliferative retinopathy. With the small number of included studies we could not do a formal subgroup analysis comparing effect in proliferative and non-proliferative retinopathy.

Authors' conclusions

This review provides evidence that laser photocoagulation is beneficial in treating proliferative diabetic retinopathy. We judged the evidence to be moderate or low, depending on the outcome. This is partly related to reporting of trials conducted many years ago, after which panretinal photocoagulation has become the mainstay of treatment of proliferative diabetic retinopathy.

Future Cochrane Reviews on variations in the laser treatment protocol are planned. Future research on laser photocoagulation should investigate the combination of laser photocoagulation with newer treatments such as anti-vascular endothelial growth factors (anti-VEGFs).

PLAIN LANGUAGE SUMMARY

Laser photocoagulation for proliferative diabetic retinopathy

Review question

Is laser photocoagulation an effective treatment for diabetic retinopathy?

Background

Diabetic retinopathy (DR) is a common problem for people with diabetes and can lead to loss of vision. The back of the eye (retina) can develop problems because of diabetes, including the growth of harmful new blood vessels (proliferative DR, referred to here as 'PDR'). Laser photocoagulation is a commonly used treatment for DR in which the eye doctor uses a laser on the back of the eye to stop some of the harmful changes.

Study characteristics

We found five studies. The searches were done in April 2014. Three studies were done in the USA, one study in the UK and one study in Japan. A total of 4786 people (9503 eyes) were included in these studies. Most participants had PDR.

Key results

We found that moderate vision loss at 12 months was similar in eyes treated with laser and eyes that were not treated, but similar assessments made at a later date showed that eyes treated with laser were less likely to have suffered moderate vision loss. Treatment with laser reduced the risk of severe visual loss by over 50% at 12 months. There was a similar effect on the progression of DR. None of the studies reported patient-relevant outcomes such as pain or loss of driving licence.

Quality of the evidence

We did not find very many studies and those we found were done quite a long time ago when standards of trial conduct and reporting were lower. We judged the quality of the evidence to be low, with the exception of the results for severe visual loss, which we judged to be moderate quality evidence.

Summary of findings for the main comparison. Laser photocoagulation compared to control for diabetic retinopathy

Laser photocoagulation compared to no treatment (or deferred treatment) for diabetic retinopathy

Patient or population: people with diabetic retinopathy
Settings: Ophthalmology clinics
Intervention: laser photocoagulation
Comparison: no treatment or deferred treatment

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk*	Corresponding risk				
	No treatment or deferred treatment	Laser photocoagulation				
Loss of 15 or more letters BCVA Follow-up: 12 months	Low risk (non-proliferative DR)		RR 0.99 (0.89 to 1.11)	8926 (2 RCTs)	⊕⊕⊖⊖ LOW [1,2]	The pooled RR 0.99 (0.89 to 1.11) is derived from one study with mainly low risk population RR 1.07 (0.92 to 1.23) and one study with mainly high risk population 0.86 (0.71 to 1.04)
	100 per 1000	99 per 1000 (89 to 111)				
	High risk (proliferative DR)					
	250 per 1000	248 per 1000 (223 to 278)				
BCVA measured using logMAR acuity (0 = 6/6 visual acuity, higher score is worse visual acuity) Follow-up: 12 months	The mean BCVA at 12 months in the control group was 0.12 logMAR	The mean BCVA at 12 months in the intervention group was 0.02 logMAR units higher (worse; 0.23 lower to 0.27 higher)		36 (1 RCT)	⊕⊕⊖⊖ LOW [1,3]	
Severe visual loss (BCVA < 6/60) Follow-up: 12 months	Low risk (non-proliferative DR)		RR 0.46 (0.24 to 0.86)	9276 (4 RCTs)	⊕⊕⊕⊖ MODERATE [1,4]	
	10 per 1000	5 per 1000 (2 to 9)				
	High risk (proliferative DR)					
	50 per 1000	23 per 1000				

		(12 to 43)				
Progression of diabetic retinopathy Follow-up: 12 months	Low risk (non-proliferative DR)		RR 0.49 (0.37 to 0.64)	8331 (4 RCTs)	⊕⊕⊖⊖ LOW [1,5]	
	100 per 1000	49 per 1000 (37 to 64)				
	High risk (proliferative DR)					
	400 per 1000	196 per 1000 (148 to 256)				
Quality of life Follow-up: 12 months	See comment	See comment				No studies reported this outcome
Pain Follow-up: at time of treatment	See comment	See comment				No studies reported this outcome
Loss of driving licence Follow-up: within three months of treatment	See comment	See comment				No studies reported this outcome

*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; **DR**: diabetic retinopathy; **BCVA**: Best corrected visual acuity

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.

*Estimates of assumed risk are indicative only, as estimates at 12 months were not available in all studies. For the low risk populations they were estimated from ETDRS (but acknowledging that the control group received deferred laser) and for the high risk populations they were estimated from DRS and Hercules 1977.
[1]Downgraded for risk of bias (-1): studies were not masked and treatment groups different
[2]Downgraded for inconsistency (-1): I^2 = 69% and effect estimates were in different directions. See comments for details
[3]Downgraded for imprecision (-1): wide confidence intervals
[4] There was heterogeneity (I^2 = 70%) but all effect estimates favoured laser photocoagulation so we did not downgrade for inconsistency
[5]Downgraded for indirectness (-1): study results were reported at 1, 3, 4 and 5 years

BACKGROUND

Description of the condition

Diabetic retinopathy (DR) is a microvascular complication of diabetes in which high blood sugar levels damage the blood vessels in the retina (Davidson 2007). These blood vessels may become blocked, which leads to a reduction or cessation of blood supply to the retina (non-proliferative diabetic retinopathy). Sometimes the vessels swell up and leak fluid (macular oedema) and sometimes new vessels grow (neovascularisation) on the retina and vitreous (also called the vitreous humour); this is known as proliferative diabetic retinopathy (PDR).

In general, the early stages of the disease are not associated with any symptoms. Disease progression is associated with visual loss and blindness, if left untreated. DR is an important cause of visual impairment worldwide. An estimated 285 million people are visually impaired and of these approximately 39 million people are blind (Pascolini 2012). DR is believed to account for approximately 1% of visual impairment and blindness, meaning nearly three million people worldwide are visually impaired due to this condition. The total number of people with diabetes is projected to increase from 171 million people in 2000 to 366 million in 2030 (Wild 2004).

This Cochrane Review is concerned with the treatment of DR, both proliferative and non-proliferative, but not macular oedema which is addressed in another review (Jorge 2013).

Description of the intervention

Laser photocoagulation involves applying light energy to the retina. This is absorbed by the retinal pigments, which heat up and cause thermal damage to the retinal tissues. There are several types of laser: gas (argon, krypton), diode, dye and YAG (RCOphth 2012).

Type of laser	Wavelength in nm (colour)	Comments
Argon	488 (blue) 514 (green)	-
Krypton	568 (yellow) 647 (red)	-
Dye laser	570 to 630, 577 (yellow) often used	-
Diode laser	810 (infrared)	Micropulse mode available
Frequency-doubled yttrium aluminium garnet (YAG) laser	532 (green) often used	Pattern scan laser (PASCAL) often used

Laser application may focus on microaneurysms or be delivered in a grid-pattern around the centre of the macula in people with diabetic macular oedema (DMO). When delivered to the peripheral retina, it may be focal, directed to neovascular tufts, or more commonly scattered, which is also known as panretinal photocoagulation (PRP) and in which 1200 to 2000 burns are applied to the peripheral retina. Laser photocoagulation may be applied in one session or may be delivered over several sessions to reduce the risk of adverse effects.

Peripheral or panretinal laser treatment is commonly delivered to ischaemic areas (i.e. those with low oxygen levels) in the retinal periphery, with the aims of causing regression of retinal neovascularisation and prevention of visual loss due to vitreous haemorrhage, tractional retinal detachment, or neovascular glaucoma, which are the main causes of visual loss in patients with end-stage PDR. Panretinal peripheral laser treatment was also initially proposed as a treatment that might prevent the occurrence of PDR.

How the intervention might work

The aim of laser photocoagulation is to slow down the growth of new blood vessels in the retina and thereby prevent the progression of visual loss (Ockrim 2010). Focal laser photocoagulation uses the heat of light to seal or destroy abnormal blood vessels in the retina. Individual vessels are treated with a small number of laser burns.

PRP aims to slow down the growth of new blood vessels in a wider area of the retina. Many hundreds of laser burns are placed on the peripheral parts of the retina to stop blood vessels from growing (RCOphth 2012). It is thought that the anatomic and functional changes that result from photocoagulation may improve the oxygen supply to the retina, and so reduce the stimulus for neovascularisation (Stefansson 2001). Again the exact mechanisms are unclear, but it is possible that the decreased area of retinal tissue leads to improved oxygenation and a reduction in the levels of anti-vascular endothelial growth factor. A reduction in levels of anti-vascular endothelial growth factor may be important in reducing the risk of harmful new vessels forming.

Why it is important to do this review

Laser photocoagulation is a well-established common treatment for DR and there are many different potential strategies for delivery of laser treatment that are likely to have different effects. A systematic review of the evidence for laser photocoagulation will provide important information on benefits and harms to guide treatment choices. With the advent of new treatments, especially the anti-vascular endothelial growth factor (anti-VEGF) agents, laser photocoagulation may become less commonly used in higher income countries, but may still have relevance as a potentially cost-effective treatment in other parts of the world. This review should be read in conjunction with related Cochrane Reviews of treatment of DR, including laser photocoagulation for diabetic macular oedema (Jorge 2013), anti-VEGF for proliferative

retinopathy (Martinez-Zapata 2014), anti-VEGF for diabetic macular oedema (Virgili 2012), and steroids for diabetic macular oedema (Grover 2008).

This is the first in a series of planned reviews on laser photocoagulation. Future reviews will compare different photocoagulation techniques.

OBJECTIVES

To assess the effects of laser photocoagulation for diabetic retinopathy compared to no treatment or deferred treatment.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) irrespective of the language in which they were published, or publication status (published or unpublished).

Types of participants

People with pre-proliferative (DR) or proliferative diabetic retinopathy (PDR). We excluded trials where the primary aim was to treat diabetic macular oedema as this is covered in a separate Cochrane Review (Jorge 2013).

Types of interventions

We considered trials of peripheral laser photocoagulation with any ophthalmic laser at any wavelength, either focal or panretinal. We compared this to no treatment, sham treatment or deferred treatment.

We included studies using any type of laser, but not studies using xenon arc photocoagulation or ruby laser, since these lasers have not been used for decades because of an observed increase in the risk of side-effects, such as peripheral field damage and macular traction (DRS 1981).

We excluded trials that compared different types (wavelength) of laser, laser application at different powers or for different exposure times, and trials that compared different regimens for the application of the laser (e.g. compared the number, pattern or location of burns, or compared different numbers of treatment sessions) as these will be considered in future Cochrane Reviews.

This review should be read in conjunction with related Cochrane Reviews that address the comparison between laser photocoagulation and other treatments such as anti-VEGF (Martinez-Zapata 2014; Virgili 2012), and steroids (Grover 2008).

Types of outcome measures

Primary outcomes

- Proportion of people who lose 15 or more letters (3 lines) of best-corrected visual acuity (BCVA) as measured on a logMAR chart.

Secondary outcomes

1. Mean distance visual acuity (BCVA).
2. Mean near visual acuity (NVA).
3. Severe visual loss (BCVA < 6/60).
4. Progression of diabetic retinopathy, as defined by trial investigators.
5. Quality of life measured using any validated questionnaire.
6. Adverse events: pain, loss of driving licence, vitreous haemorrhage, retinal detachment.

With the exception of adverse events, we aimed to collect data on these outcomes at one year after initiation of treatment, which we defined as the period between six and 18 months. We considered adverse events at any time point, but these are most likely to occur within three months of treatment. We also planned to report the primary outcome at longer time periods - two to five years - in order to comment on whether any effects observed are sustained in the long term.

We made some amendments to the outcomes from the protocol. See Differences between protocol and review.

Search methods for identification of studies

Electronic searches

We searched CENTRAL (which contains the Cochrane Eyes and Vision Group Trials Register) (2014, Issue 5), Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid MEDLINE Daily, Ovid OLDMEDLINE (January 1946 to June 2014), EMBASE (January 1980 to June 2014), the *meta*Register of Controlled Trials (*m*RCT) (www.controlled-trials.com), ClinicalTrials.gov (www.clinicaltrials.gov) and 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 3 June 2014.

See: Appendices for details of search strategies for CENTRAL (Appendix 1), MEDLINE (Appendix 2), EMBASE (Appendix 3), *m*RCT (Appendix 4), ClinicalTrials.gov (Appendix 5) and the ICTRP (Appendix 6).

Searching other resources

We searched the reference lists of included studies and other reviews identified by the searches.

Data collection and analysis

Selection of studies

Two review authors (JE, MM) independently screened the search results and selected trials for inclusion. We resolved disagreements through discussion.

We screened the list of citations and abstracts and classified records into 'possibly relevant' and 'definitely not relevant'. For the records we identified as 'possibly relevant' we obtained the full-text articles. Following the Criteria for considering studies for this review we classified trials into 'to be included' or 'to be excluded'. We documented excluded trials in the category in the Characteristics of excluded studies section.

Data extraction and management

Two authors (JE, MM) independently extracted data from trial reports and entered the data into Review Manager (RevMan 2014). We resolved any differences in opinion through discussion. We used a data collection spreadsheet. We obtained English translations of

any trial reported in a language other than English before extracting data.

We collected data on trial characteristics as detailed in Appendix 7.

We obtained the following data on outcomes specified in Types of outcome measures: for dichotomous outcomes, we collected data on the number of events and total participants followed up in each trial arm; for continuous outcomes, we collected data on the mean and standard deviation in each trial arm.

We did not attempt to obtain further information from trialists.

Assessment of risk of bias in included studies

We assessed risk of bias using the Cochrane Collaboration's tool for assessing the risk of bias as described in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Measures of treatment effect

We calculated the risk ratio (RR) for all dichotomous variables. This was a variation on the protocol - see Differences between protocol and review.

For continuous variables (only data on distance visual acuity were available) we calculated the mean difference.

All measures of effect were reported with 95% confidence intervals (CIs).

Unit of analysis issues

Four of the five studies were within-person studies but were reported as unmatched. We have used these data as reported, which is a conservative analysis. One trial considered one eye per person only, but it was not clear how that eye was selected for inclusion in the trial.

Dealing with missing data

We documented follow-up by intervention group. We aimed to collect data on reasons for loss to follow-up, but this information was not usually available. We documented when loss to follow-up was high (over 20%), or unbalanced between treatment groups, as a potential source of attrition bias. We planned to conduct an intention-to-treat (ITT) analysis if this was reported by the trialists, but we have conducted an available case analysis because the majority of trials did not report an ITT and the one small trial that did only reported one outcome as an ITT analysis (Sato 2012). An available case analysis makes the assumption that the treatment effect in people lost to follow-up was the same as that in people who were observed (assessed).

Assessment of heterogeneity

We assessed heterogeneity by visual inspection of the forest plots and by calculating the I^2 value (Higgins 2002). We also considered the Chi^2 test for heterogeneity, but this may have low power as few trials met the inclusion criteria.

Assessment of reporting biases

We were unable to look at small trial effects as we had planned because there were only five included trials.

We considered selective outcome reporting bias as part of the assessment of risk of bias in the individual studies (see Assessment of risk of bias in included studies section).

Data synthesis

We pooled data using a random-effects model, unless there were three or fewer trials, in which case we used a fixed-effect model.

There was considerable heterogeneity, and for many analyses the I^2 statistic was over 50%. In most analyses all effect estimates were in the same direction and we report a pooled value. The exception was Analysis 1.1, but as the effect estimates were relatively close to 1 we have reported a pooled estimate. This is a variation from our protocol - see Differences between protocol and review.

Subgroup analysis and investigation of heterogeneity

We did not plan any subgroup analysis at the protocol stage, but there was considerable heterogeneity in terms of baseline risk in participants with non-proliferative retinopathy and those with proliferative retinopathy.

There was not enough evidence to do subgroup analysis based on these groups, and new trials in future are unlikely.

Sensitivity analysis

We planned to repeat the analyses excluding studies at high risk of selection, or detection bias, or both. In most analyses trials were similar with respect to these risk of bias domains and so a sensitivity analysis was not possible. We did one sensitivity analysis for the outcome progression of DR.

Summary of findings

We report absolute risks and measures of effect in a 'Summary of findings' table, providing an overall assessment of the quality of the evidence for each outcome using the GRADE system (Guyatt 2011). Two review authors (JE, GV) independently performed the GRADE assessment.

Our pre-specified outcome measures were:

1. proportion of people who lose 15 or more letters (3 lines) of BCVA as measured on a logMAR chart;
2. mean logMAR visual acuity;
3. averse event: loss of driving licence;
4. adverse event: severe visual loss (BCVA < 6/60);
5. adverse event: pain;
6. quality of life measured using a validated questionnaire.

We planned to report outcomes 1, 2 and 6 at one year, outcomes 3 and 4 within three months of treatment and outcome 5 at time of treatment.

We modified the protocol to include severe visual loss as an effectiveness outcome measured at one year. See Differences between protocol and review.

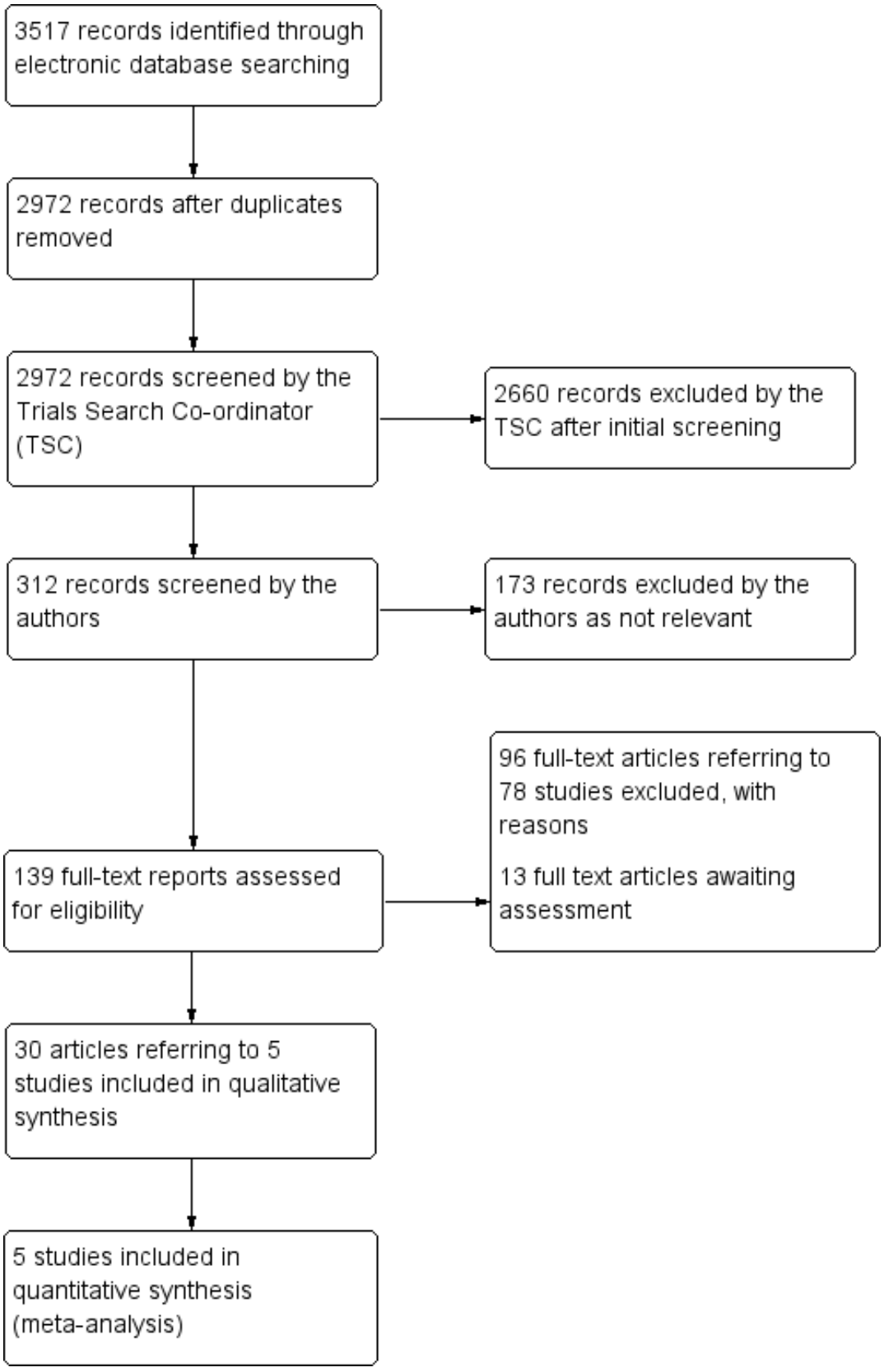
RESULTS

Description of studies

Results of the search

The electronic searches yielded a total of 3517 references (Figure 1). The Trials Search Co-ordinator removed 545 duplicate records, screened the remaining 2972 records and removed 2660 references that were not relevant to the scope of the review. We screened a total of 312 references and discarded 173 reports as these were not relevant to the scope of the review. We reviewed 139 full-text reports and included 30 reports of five studies that were eligible for inclusion in the review. We were unable to assess 13 reports, either because the full-text copy was unavailable or because a translation was needed. These reports are listed in the Studies awaiting classification section, but are unlikely to be eligible trials. We also excluded 96 reports that referred to 78 trials, see Characteristics of excluded studies for details.

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



Included studies

We identified five studies that compared laser photocoagulation to a control. Three studies were conducted in the USA (DRS 1978; ETDRS 1991; Yassur 1980), one study in the UK (Hercules 1977), and one study in Japan (Sato 2012).

Four studies were within-person RCTs i.e. one eye was randomly allocated to laser photocoagulation and the other eye to the control (DRS 1978; ETDRS 1991; Hercules 1977; Yassur 1980). Sato 2012 randomly allocated people to treatment and only one eye was included in the study; it was unclear how the eye was selected.

The number of participants enrolled ranged from 45 in Yassur 1980 to 3711 in ETDRS 1991. The average age of participants ranged from 41 years in Hercules 1977 to 60 years in Sato 2012. Most studies recruited participants aged approximately 18 to 70 years with an average age of around 45 years. The percentage of women enrolled ranged from 25% in Sato 2012 to 48% in Yassur 1980, but on average between 40% and 45% of the participants in each trial were women.

Two studies enrolled people with PDR only (Hercules 1977; Yassur 1980); two studies enrolled people either with moderate or severe non-proliferative DR or PDR (DRS 1978; ETDRS 1991); and one study enrolled participants with pre-proliferative DR (Sato 2012). In the DRS 1978 study approximately 80% of participants had PDR; in the ETDRS 1991 study approximately 20% of participants had PDR.

Most studies used PRP with argon laser (Table 1). The exception was Sato 2012, which evaluated selective photocoagulation of non-perfusion areas. Three studies compared laser to no treatment (DRS 1978; Hercules 1977; Yassur 1980); two studies compared laser to deferred laser treatment (ETDRS 1991; Sato 2012; i.e. control participants received laser when severe non-proliferative (ETDRS 1991) or PDR (ETDRS 1991; Sato 2012) developed).

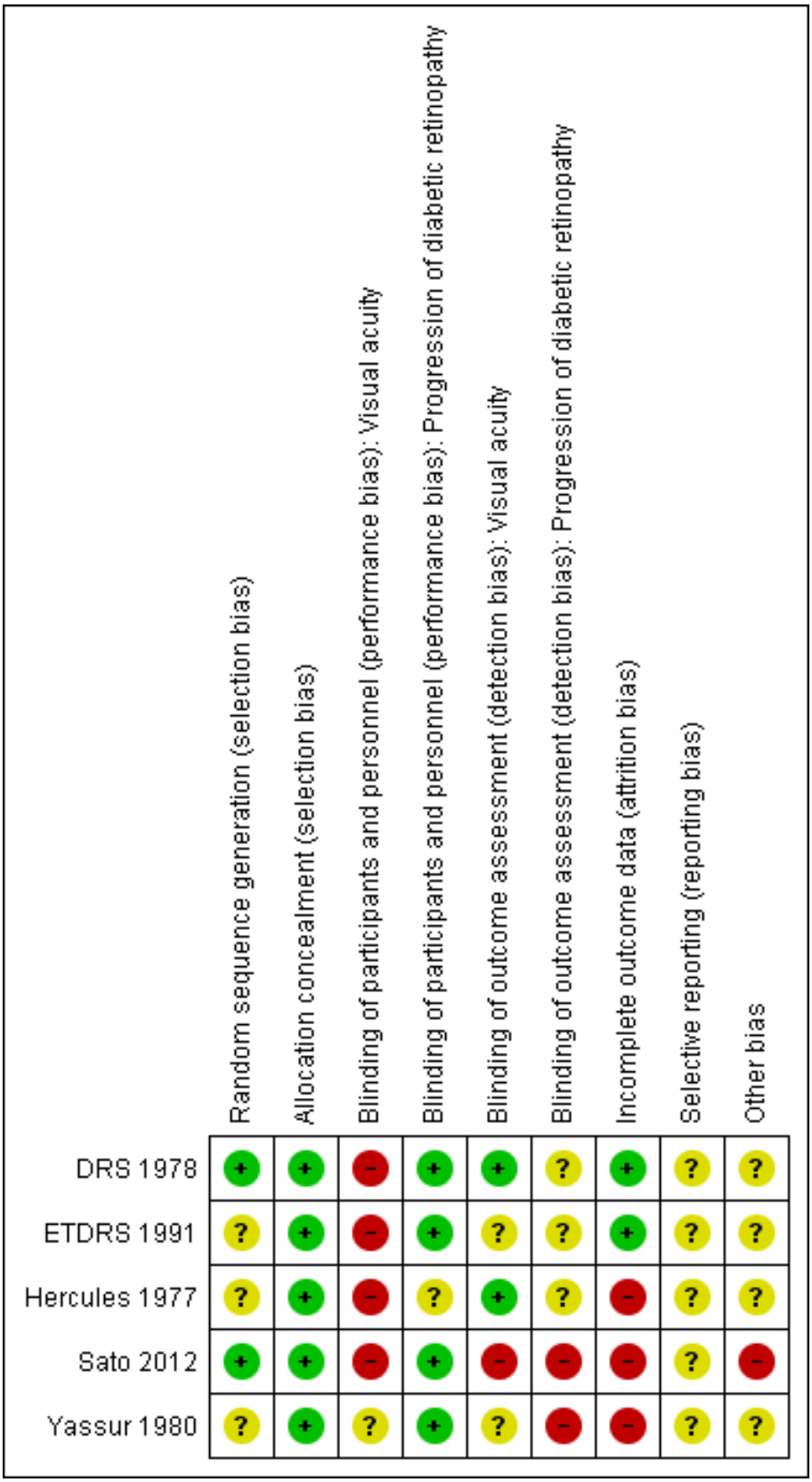
Excluded studies

See Characteristics of excluded studies.

Risk of bias in included studies

See Figure 2.

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



Allocation

Generation of the allocation sequence was considered adequate in two trials (DRS 1978; Sato 2012) and was not clearly described in the rest. As most of the studies were within-person studies, allocation concealment was not judged to be a problem (as all participants received both intervention and control). In the one parallel group study the allocation was clearly described and judged to be at low risk of bias (Sato 2012).

Blinding

We judged the studies that measured and reported visual acuity to be at a high risk of bias because the treatment and control groups were obviously different and patient knowledge of intervention could affect the measurement of visual acuity. However, the extent of the bias is difficult to judge, and some studies had specific protocols to improve the accuracy of the measurement of vision, such as encouraging patients to read as far down the chart as possible (DRS 1978). In general, we judged that patient and carer knowledge of assignment would not affect the progression of DR.

Incomplete outcome data

We judged within-person studies to be at low risk of attrition bias by definition because, although there may be attrition in patient follow-up, the follow-up between intervention and control groups, i.e. between eyes, will always be equal. However, two studies selectively removed participants who received treatment in the control eye (Hercules 1977; Yassur 1980), which we considered to be a potential source of bias for the effect estimate. The one parallel group study had considerable loss to follow-up (Sato 2012).

Selective reporting

In general reporting bias was difficult to judge with the information available. None of the studies reported all our review outcomes.

Other potential sources of bias

The Sato 2012 study was stopped early.

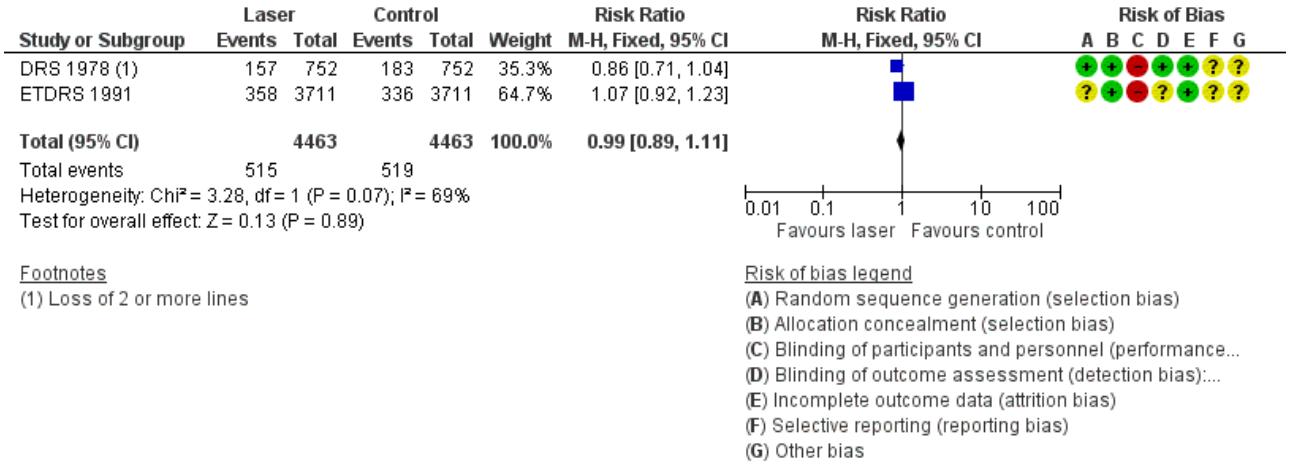
Effects of interventions

See: **Summary of findings for the main comparison** Laser photocoagulation compared to control for diabetic retinopathy

1.1 Loss of 15 or more letters BCVA at 12 months

For this outcome we found two relevant trials (DRS 1978; ETDRS 1991: n = 8926; Figure 3; Analysis 1.1). One of these studies reported loss of 10 or more letters rather than loss of 15 or more letters (DRS 1978). There was considerable heterogeneity of effect (I^2 = 69%; P value = 0.07). In the DRS 1978 study fewer eyes given laser photocoagulation lost 10 or more letters compared to untreated eyes, but there was uncertainty and the confidence intervals included 1 (RR 0.86, 95% CI 0.71 to 1.04). In the ETDRS 1991 study more eyes treated with laser photocoagulation lost 15 or more letters over 12 months compared to eyes given deferred treatment, but again there was uncertainty and the confidence intervals included 1 (RR 1.07, 95% CI 0.92 to 1.23).

Figure 3. Forest plot of comparison: 1 Laser photocoagulation versus control, outcome: 1.1 Loss of 15 or more letters BCVA at 12 months



1.2 Loss of 15 or more letters BCVA at longer follow-up times

Two trials reported this outcome at two years (DRS 1978; ETDRS 1991: n = 8306; Analysis 1.2). Fewer eyes given laser photocoagulation lost 15 (or 10) or more lines of visual acuity at two years compared to untreated (DRS 1978), or deferred treatment eyes (ETDRS 1991; RR 0.88, 95% CI 0.80 to 0.97). There was considerable heterogeneity I^2 = 73%, P value = 0.06). However, as both effect estimates were in the same direction (0.74 and 0.92) we have reported a pooled estimate.

Two trials reported this outcome at three years (ETDRS 1991; Sato 2012: n = 7458; Analysis 1.3). More eyes receiving laser photocoagulation lost 15 or more letters BCVA at three years compared to eyes with deferred treatment, but there was uncertainty in the result and the confidence intervals included 1 (RR 1.07, 95% CI 0.93 to 1.23). The results of the two trials were reasonably consistent I^2 = 14%.

No trials reported this outcome at four years.

One study reported this outcome at five years (ETDRS 1991; n = 7422). Eyes receiving laser photocoagulation were less likely to lose

15 or more letters compared to eyes receiving deferred treatment (RR 0.79, 95% CI 0.72 to 0.85).

1.3 Mean BCVA at 12 months

One study reported mean logMAR BCVA at three years (Sato 2012). The difference between the groups was small and uncertain (MD 0.02, 95% CI -0.23 to 0.27; n = 36).

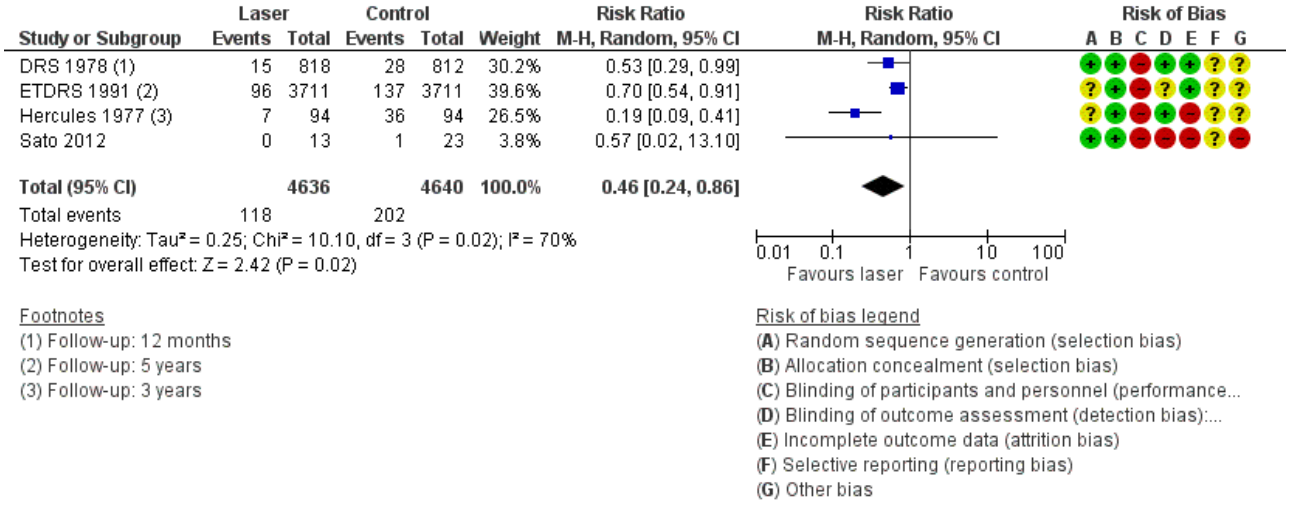
2 Mean NVA at 12 months

None of the studies reported near visual acuity.

3 Severe visual loss (BCVA < 6/60)

For the outcome of severe visual loss (BCVA < 6/60) we found four relevant trials (DRS 1978; ETDRS 1991; Hercules 1977; Sato 2012: n = 9276; Figure 4; Analysis 1.4). Eyes receiving laser photocoagulation were less likely to experience severe visual loss compared to untreated eyes or eyes that received deferred treatment (RR 0.46, 95% CI 0.24 to 0.86). This outcome had high levels of heterogeneity (I^2 = 70%, P value = 0.02), but as all the effect estimates were in the same direction we report a pooled estimate. Such heterogeneity seemed due to Hercules 1977, a small study including only patients with proliferative retinopathy, which recorded the largest benefit with laser.

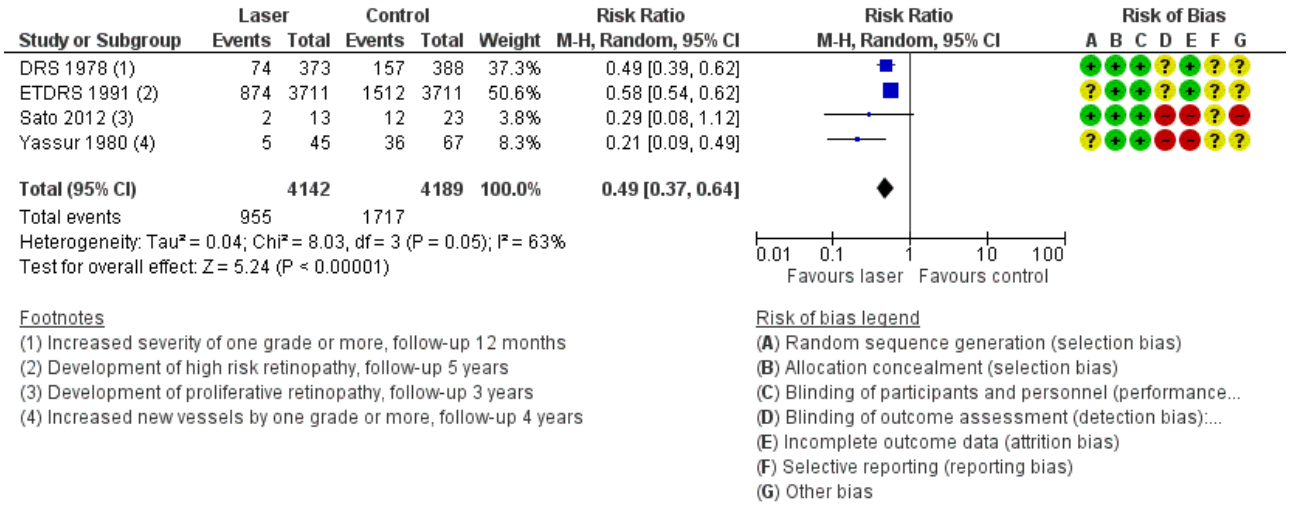
Figure 4. Forest plot of comparison: 1 Laser photocoagulation versus control, outcome: 1.4 Severe visual loss (BCVA < 6/60)



4 Progression of diabetic retinopathy

For the outcome of progression of DR we found four relevant trials (DRS 1978; ETDRS 1991; Sato 2012; Yassur 1980: n = 8331; Figure 5; Analysis 1.5).

Figure 5. Forest plot of comparison: 1 Laser photocoagulation versus control, outcome: 1.5 Progression of diabetic retinopathy



In the DRS 1978 study progression was based on grading of fundus photographs. Eyes were graded for new vessels and severity was graded by comparison with standard images. The following categories were used and progression was defined as change of one or more grades from no new vessels to moderate or severe NVD (NVD means new vessels on or within 1 disc diameter of the optic disc; NVE means new vessels elsewhere):

1. no new vessels;
2. mild NVE, no NVD;
3. moderate or severe NVE, no NVD;
4. mild NVD;
5. moderate or severe NVD.

In the ETDRS 1991 study progression was defined as the development of 'high risk proliferative diabetic retinopathy'. This was defined as PDR with high risk characteristics as defined by DRS 1978. These were new vessels on or within 1 disc diameter of the optic disc worse than a standard photograph, with or without vitreous or preretinal haemorrhage; or vitreous or preretinal haemorrhage accompanied by new vessels, either NVD (less than standard photograph) or NVE greater than or equal to a quarter of the disc area.

In Sato 2012 progression was defined as the development of PDR, i.e. the growth of new vessels (detected by ophthalmoscopy or fluorescein angiography), or preretinal/vitreous haemorrhage.

Yassur 1980 considered only new vessels on or near the optic disc. These were graded into five grades of severity based on the number of involved disc quadrants, calibre of the new vessels, density of neovascularisation (NVD) or fibrous proliferation at the disc (FPD), total area of NVD or FPD proliferation, plane of NVD or FPD proliferation, and fluorescein leakage from NVD. Progression was defined as increase in severity of one or more grades.

The time frames at which these outcomes were reported were different - ranging from 12 months to five years, and these are indicated on the figure.

DR was less likely to progress in eyes that received laser photocoagulation (RR 0.49, 95% CI 0.37 to 0.64). There was considerable heterogeneity I^2 = 63%, P value = 0.05) but all effect estimates were in the same direction, so we report a pooled estimate.

5 Quality of life

None of the included studies reported quality of life.

6.1 Adverse events: pain

None of the included studies reported pain.

6.2 Adverse events: loss of driving licence

None of the included studies reported patient outcomes such as loss of driving licence.

6.3 Adverse events: vitreous haemorrhage

For this outcome of vitreous haemorrhage we found two relevant trials (Hercules 1977; Sato 2012: n = 224; Analysis 1.6). People receiving laser photocoagulation were less likely to develop vitreous haemorrhage (RR 0.56, 95% CI 0.37 to 0.85; I^2 = 0%).

6.4 Adverse events: retinal detachment

None of the studies reported retinal detachment by intervention group.

Sensitivity analysis

For Analysis 1.5 progression of diabetic retinopathy, exclusion of two trials at high risk of selection or detection bias resulted in a RR of 0.55 (95% CI 0.48 to 0.64; participants = 8183; studies = 2; I^2 = 41%; Sato 2012; Yassur 1980). This is not dissimilar to the analysis of all four trials (RR 0.49, 95% CI 0.37 to 0.64; participants = 8331; studies = 4; I^2 = 63%).

DISCUSSION

Summary of main results

See Summary of findings for the main comparison.

We identified five trials. In the majority of these studies (4 trials, 99% of all participants) the intervention was panretinal photocoagulation (PRP) using an argon laser. There were differences in the patient population included in these studies. Two trials included 94% of the participants in this review (DRS 1978; ETDRS 1991). These two studies were conducted in the US population and were complementary: DRS 1978 assessed whether PRP is effective compared to no treatment in people mostly affected by proliferative diabetic retinopathy (PDR); ETDRS 1991 assessed whether earlier peripheral laser treatment of diabetic retinopathy (DR) in its non-proliferative or early proliferative stage is beneficial, compared to a strategy in which laser is used at a later stage, in high-risk PDR. Thus, any benefit in ETDRS 1991 should have been less than that seen in DRS 1978 as laser is also part of the control strategy in the former. In most of the analyses the effects observed in ETDRS 1991 were indeed lower than DRS 1978 but not significantly so. Even though there was evidence for statistical heterogeneity, effects were generally in the same direction, so we pooled the results to obtain (approximate) overall estimates of effect.

At 12 months there was little difference between eyes receiving laser photocoagulation and those allocated to no treatment (or deferred treatment), in terms of loss of 15 or more letters of visual acuity. Longer term follow-up did not show a consistent pattern, but ETDRS 1991 reported a 20% reduction in risk of loss of 15 or more letters of visual acuity at five years.

Treatment with laser reduced the risk of severe visual loss by over 50% at 12 months.

There was a beneficial effect on progression of DR with treated eyes experiencing a 50% reduction in risk of progression and a similar reduction in risk of vitreous haemorrhage.

None of the studies reported near visual acuity, quality of life, pain, or patient relevant outcomes such as loss of driving licence or adverse effects such as retinal detachment.

Overall completeness and applicability of evidence

Overall there is not a large amount of evidence from randomised controlled trials (RCTs) on laser photocoagulation compared to no treatment or deferred treatment. The evidence is dominated by two large studies conducted in the US population (DRS 1978; ETDRS 1991).

Reflecting the fact that the studies were conducted some time ago, there was a lack of data reported for many of our current pre-specified review outcomes, in particular patient-relevant outcomes such as quality of life.

We did not consider lasers that are not commonly used today but the treatment parameters used in the included trials were different to those in current use, in particular, smaller size and shorter duration burns are now used (RCOphth 2012).

Overall the evidence is applicable to people presenting with moderate to severe pre-proliferative and PDR, however, the fact that relatively few trials were identified, and that these were all conducted some time ago in high-income countries leaves a lack of evidence for lower- and middle-income countries and different parts of the world. However, we have no reason to suppose that the effectiveness of these treatments would be different in lower-income countries.

The introduction of anti-vascular endothelial growth factor (anti-VEGF) therapy for treating several chorioretinal vascular diseases has made it possible to achieve a rapid, but transient, regression of new vessels in PDR, especially to try to clear vitreous haemorrhage, but also to limit side effects of PRP regarding the occurrence of diabetic macular oedema in patients at risk. Moreover, anti-VEGF therapy is sometimes used in preparation of vitrectomy - which includes use of an endolaser - in advanced PDR. However, use of anti-VEGF in PDR may have adverse effects and requires multiple treatments. Other Cochrane Reviews compare the effectiveness of anti-VEGF and laser treatment for PDR (Martinez-Zapata 2014), and diabetic macular oedema (Virgili 2012).

Quality of the evidence

Overall there is not a large amount of evidence from RCTs on the effects of laser photocoagulation compared to no treatment or deferred treatment. The evidence is dominated by two large studies conducted in the US population (DRS 1978; ETDRS 1991). These two studies were generally judged to be at low or unclear risk of bias, with the exception of inevitable unmasking of patients due to differences between intervention and control.

Four of the studies were within-person (i.e. pair-matched), but none of the studies reported the results taking into account the matching. This means that the results will be conservative (confidence intervals wider than if matching had been taken into account). One study reported that they had repeated the analyses taking into account the pair-matching and that ignoring the pair-matching was indeed a conservative approach (ETDRS 1991).

Overall we judged the quality of the evidence to be moderate or low (Summary of findings for the main comparison), reflecting the fact that the studies contributing to the review were conducted some time ago, when standards of trial conduct and reporting were lower; heterogeneity was also present.

Potential biases in the review process

We followed standard methods expected by the Cochrane Collaboration. All changes from protocol are documented in Differences between protocol and review.

Agreements and disagreements with other studies or reviews

In current clinical guidelines, e.g. RCOphth 2012, PRP is recommended in high-risk PDR. The recommendation is that *"as retinopathy approaches the proliferative stage, laser scatter treatment (PRP) should be increasingly considered to prevent progression to high risk PDR"* based on other factors such as patients' compliance or planned cataract surgery.

These recommendations need to be interpreted while considering the risk of visual loss associated with different levels of severity

of DR, as well as the risk of progression. Since PRP reduces the risk of severe visual loss, but not moderate visual loss that is more related to diabetic maculopathy, most ophthalmologists judge that there is little benefit in treating non-proliferative DR at low risk of severe visual damage, as patients would incur the known adverse effects of PRP, which, although mild, include pain and peripheral visual field loss and transient DMO. The results of this review would confirm this approach.

AUTHORS' CONCLUSIONS

Implications for practice

This review provides evidence that laser photocoagulation is beneficial in treating diabetic retinopathy. There was not enough evidence to judge whether the effect of treatment is different in non-proliferative and PDR, but based on the baseline risk of progression of the disease, and risk of visual loss, the current approach of caution in treating non-proliferative DR with laser would appear to be justified.

By current standards the quality of the evidence is not high, however, the effects on risk of progression and risk of severe visual loss are reasonably large (50% relative risk reduction).

Implications for research

Future Cochrane Reviews will examine specific questions regarding the treatment protocol for laser photocoagulation.

Future trials on laser photocoagulation should focus on the combination with, and comparison to, newer interventions, such as anti-vascular endothelial growth factor (anti-VEGF) treatment.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

DRS 1978

Methods	Within-person RCT; both eyes included in study, eyes received different treatments
Participants	Country: USA Number of participants (eyes): 867 (1734) % women: 44% Average age (range): 43 years (15-69) Inclusion criteria: • BCVA 20/100 or better in each eye • PDR in at least one eye or severe non-proliferative DR in both eyes Exclusion criteria: • Unilateral aphakia • One or both lenses removed within 3 months of initial visit • Anticoagulant therapy that could not be discontinued during treatment • High or low blood pressure • Myocardial infarction within 6 months of initial visit

DRS 1978 *(Continued)*

	• Active tuberculosis or history of hemoptysis within 12 months of initial visit
Interventions	Intervention (n= 867 eyes) • argon laser Comparator (n= 867 eyes) • no treatment This trial also considered xenon arc laser but this has not been considered in this review
Outcomes	Primary outcome: • visual acuity Secondary outcomes: • visual fields • morphologic changes in the retina and vitreous Follow-up: every 4 months for 5 years
Notes	Date conducted: April 1972-September 1975 Sources of funding: NIH Declaration of interest: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	*"One eye of each patient was randomly assigned to immediate photocoagulation and the other to follow-up without treatment . . ."* Page 583, report number 8 Further details of sequence generation are on page 158 of report number 6
Allocation concealment (selection bias)	Low risk	*"The sealed envelope containing the assigned treatment was not to be opened in the clinic until a final determination had been made of the patient's eligibility and the patient had signed the consent form at the second initial visit"* Page 158, report number 6
Blinding of participants and personnel (performance bias) Visual acuity	High risk	Patients and personnel will have known which eye was treated
Blinding of participants and personnel (performance bias) Progression of diabetic retinopathy	Low risk	We judged it unlikely that patient or carer knowledge of treatment assignment would impact on the progression of diabetic retinopathy
Blinding of outcome assessment (detection bias) Visual acuity	Low risk	*" . . . measurement of best corrected visual acuity by examiners who did not know the identify of the treated eye and who attempted to reduce patient bias by urging the patient to read as far down the chart as possible with each eye, guessing at letters until more than one line was missed".* Page 584, report number 8

DRS 1978 *(Continued)*

Blinding of outcome assessment (detection bias) Progression of diabetic retinopathy	Unclear risk	-
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition in patients but not in unit of analysis (eyes)
Selective reporting (reporting bias)	Unclear risk	No access to protocol
Other bias	Unclear risk	-

ETDRS 1991

Methods	Within-person RCT; both eyes included in study, eyes received different treatments

Participants	Country:USA
	
	Number of participants (eyes): 3711 (7422)
	
	% women: 44%
	
	Average age 48 years (estimated; range 18-70)
	
	Inclusion criteria:
	
	• aged 18-70 years
	• DR in both eyes
	• each eye either:
	  ◦ no macular oedema, visual acuity 20/40 or better and moderate or severe nonproliferative or early PDR, or
	  ◦ macular oedema, visual acuity of 20/200 or better and mild, moderate or severe nonproliferative or early PDR
	
	Exclusion criteria:

Interventions	Intervention (n = 3711 eyes) • early argon laser Comparator (n = 3711 eyes) • deferred argon laser For the intervention group, eyes were also randomly allocated to 'full' or 'mild' PRP. For the comparator group, argon laser was applied if high risk PDR was detected
Outcomes	Primary outcome: • development of severe visual loss which was defined as visual acuity < 5/200 at two consecutive follow-up visits. Follow-up visits were 4 months apart. Visual acuity was measured using an ETDRS chart at a distance of 4 metres and at 1 metre if visual acuity < 20/100 Secondary outcomes: • visual fields • colour vision

ETDRS 1991 *(Continued)*

	• severity of retinopathy and macular oedema Follow-up: every 4 months for an unknown number of years
Notes	Date conducted: April 1980 to June 1985 Sources of funding: NEI Declaration of interest: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	*"The randomization schedules were designed to provide balance in: . . . the number of right and left eyes assigned to early photocoagulation".* Page 746, report number 7
Allocation concealment (selection bias)	Low risk	*"At the randomization visit, the Clinical Center ophthalmologist and staff reviewed the patient's . . . eligibility. . . The sealed mailer from the Coordinating Center containing the description of the photocoagulation strategy . . . was then opened."* Page 746, report number 7
Blinding of participants and personnel (performance bias) Visual acuity	High risk	Treatments were quite different and patients' perception of treatment may well have affected assessment of visual acuity
Blinding of participants and personnel (performance bias) Progression of diabetic retinopathy	Low risk	We judged it unlikely that patient or carer knowledge of treatment assignment would impact on the progression of diabetic retinopathy
Blinding of outcome assessment (detection bias) Visual acuity	Unclear risk	*"The protocol specified that visual acuity examiners be trained and certified, that they be masked from treatment assignment; that they follow standard procedures for encouraging patients to make the maximum effort to read as many letters as possible with each eye".* Page 747, report number 7
Blinding of outcome assessment (detection bias) Progression of diabetic retinopathy	Unclear risk	*"Fundus Photograph Reading Center staff, without knowledge of treatment assignments and clinical data, followed a standardized procedure to grade fundus photographs and fluorescein angiograms for individual lesions of diabetic retinopathy*" Page 748, report number 7
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition in patients but not in unit of analysis (eyes)
Selective reporting (reporting bias)	Unclear risk	No access to protocol
Other bias	Unclear risk	-

Hercules 1977

Methods	Within-person RCT; botheyes included in study, eyes received different treatments

Hercules 1977 *(Continued)*

Participants	Country: UK Number of participants (eyes): 94 (188 eyes) % women: 40% Average age (range): 41 years (18-65) Inclusion criteria: • both eyes of participant were similarly affected by a proliferative diabetic process involving the optic disc • observable features of the retinopathy had to be within the same grade when each eye was classified • visual acuity at initial assessment did not differ by more than two lines on the Snellen chart and was at least 6/24 in the worse eye Exclusion criteria: • 70 years or older • life expectancy was possibly too short for subsequent assessments • previous pituitary ablation • either eye had received previous xenon arc photocoagulation • presence of intercurrent ocular disease • visual acuity was adversely affected by opacities of the media and visual pathways, making retinal photography and treatment unsatisfactory • proliferation in the retina had reached the late cicatricial stage with localised traction detachment
Interventions	Intervention (n = 94) • argon laser Comparator (n = 94) • no treatment
Outcomes	Outcomes: • visual acuity: BCVA • appearance of the optic discs 6 months after treatment and yearly from that point (colour photographs and fluorescein angiograms) • vitreous haemorrhage and other complications including uveitis, glaucoma, and retinal detachment • blindness: PDR and/or vitreous haemorrhage involving reduction in visual acuity to less than 6/60 on the Snellen chart on at least two consecutive visits Follow-up: 6 months
Notes	Date conducted: not reported but trial 'initiated' in 1973 Sources of funding: not reported Declaration of interest: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported

Hercules 1977 *(Continued)*

Allocation concealment (selection bias)	Low risk	Not mentioned, but unlikely to be a problem in a within-person study
Blinding of participants and personnel (performance bias) Visual acuity	High risk	Treatments are quite different and patients' perception of treatment may well affect assessment of visual acuity
Blinding of participants and personnel (performance bias) Progression of diabetic retinopathy	Unclear risk	-
Blinding of outcome assessment (detection bias) Visual acuity	Low risk	*"... best corrected visual acuities were obtained at each visit, on subjective testing, by a refractionist who was not aware of the previous visual acuity nor the treated eye"* Page 557
Blinding of outcome assessment (detection bias) Progression of diabetic retinopathy	Unclear risk	-
Incomplete outcome data (attrition bias) All outcomes	High risk	*"Eight patients subsequently receiving treatment to the 'control' eye were removed from the study at that point."* Page 556
Selective reporting (reporting bias)	Unclear risk	No access to protocol
Other bias	Unclear risk	-

Sato 2012

Methods	Parallel group RCT. One eye per person enrolled; unclear how eye selected
Participants	Country: Japan Number of participants (eyes): 69 (69) % women: 25% Average age: 60 years Inclusion criteria: • preproliferative diabetic retinopathy • no previous photocoagulation • multiple non perfusion areas larger than one disc area on fluorescein angiography images Exclusion criteria: • clear fluorescein angiography images could not be obtained due to opaque media • fluorescein angiography could not be performed (e.g. due to allergy) • past history of intraocular surgery (except if 3 or more years after cataract surgery) • PRP indicated

Sato 2012 *(Continued)*

Interventions	Intervention (n = 32) • selective photocoagulation of nonperfusion areas Comparator (n = 37) • deferred panretinal laser photocoagulation For the comparator group: *"Whenever PDR developed, PRP was performed. The development of PDR was defined as the detection of any of the following: neovascularization detected by ophthalmoscope or FA and preretinal hemorrhage or vitreous hemorrhage. Therefore, in this study, PDR includes not only high-risk PDR but also early PDR as described by the Early Treatment Diabetic Retinopathy Study Research Group (ETDRS)"* Page 53 In both intervention and comparator groups: *". . . photocoagulation for macular edema was permitted when the ophthalmologist in charge of this study considered it necessary"*. Page 53/54
Outcomes	Primary outcome: • development of proliferative diabetic retinopathy Secondary outcomes: • high risk PDR • severe visual loss (BCVA < 0.025) • vitreous haemorrhage Follow-up: 3 years
Notes	Date conducted: February 2004-December 2008 Sources of funding: *"This study was supported by a Grant-in-Aid for Scientific Research C (no. 17591856), 2005, from the Japan Society for the Promotion of Science. The following authors have indicated that they have received grants from the Japanese Government: Sadao Hori and Naohito Yamaguchi."* Page 59 Declaration of interest: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	*"Patient data and FA images in those patients considered to be appropriate subjects by the ophthalmologists in charge of this study at each institution were sent to the Data Center in the Department of Public Health, Tokyo Women's Medical University. At the Data Center, a designated ophthalmologist confirmed whether each patient's data and FA images were appropriate. After confirmation, the patients were randomly assigned to either the nonphotocoagulation group (non-PC group) or to the photocoagulation group (PC group) using random number tables, and the ophthalmologists in charge of this study were informed of the groups into which their patients had been randomized."* Page 53
Allocation concealment (selection bias)	Low risk	*"Patient data and FA images in those patients considered to be appropriate subjects by the ophthalmologists in charge of this study at each institution were sent to the Data Center in the Department of Public Health, Tokyo Women's Medical University. At the Data Center, a designated ophthalmologist confirmed whether each patient's data and FA images were appropriate. After confirmation, the patients were randomly assigned to either the nonphotocoagulation group (non-PC group) or to the photocoagulation group (PC group) using random number tables, and the ophthalmologists in charge of this study were informed of the groups into which their patients had been randomized."* Page 53

Sato 2012 *(Continued)*

Blinding of participants and personnel (performance bias) Visual acuity	High risk	Not reported and treatments different
Blinding of participants and personnel (performance bias) Progression of diabetic retinopathy	Low risk	We judged it unlikely that patient or carer knowledge of treatment assignment would impact on the progression of diabetic retinopathy
Blinding of outcome assessment (detection bias) Visual acuity	High risk	Not reported and treatments different
Blinding of outcome assessment (detection bias) Progression of diabetic retinopathy	High risk	Not reported and treatments different
Incomplete outcome data (attrition bias) All outcomes	High risk	*"When we discontinued the study in December 2009, the courses of 17 patients (8 in the non-PC group and 9 in the PC group) had not yet been observed for the whole 36 months, although these patients could potentially continue to be observed for the 36 months. Of the 69 patients, 36 (23 in the non-PC group and 13 in the PC group) completed the 36-month follow-up in December 2009. Another 16 patients (6 in the non-PC group and 10 in the PC group) had dropped out of the study for the following reasons: 10 stopped coming to the hospital, 3 switched hospitals, 1 developed severe visual loss due to central retinal artery occlusion, 1 died, and 1 developed an allergy to fluorescein. As the number of patients who dropped out of the study was somewhat larger in the PC than in the non-PC group, we conducted the analysis using the intent-to-treat method in all 69 patients, as well as the treatment method in 36 patients".* Page 54 Outcomes of relevance to this review were largely reported on the 36 patients followed-up to three years. Development of PDR was reported in all 69 patients as well.
Selective reporting (reporting bias)	Unclear risk	No access to protocol
Other bias	High risk	*"The study was discontinued in December 2009. An analysis performed in October 2009 revealed a significantly higher incidence of PDR in the non-PC group. Thus, the Data Monitoring Committee suggested that continuing the study without providing the results to the public would be a major disadvantage to the patients randomized to the non-PC group."* Page 54

Yassur 1980

Methods	Within-person RCT; both eyes included in study, eyes received different treatments
Participants	Country: USA Number of participants (eyes): 45 (90) % women: 48% Average age (range): not reported (16-72)

Yassur 1980 *(Continued)*

	Inclusion criteria: not reported but participants had "neovascularisation of the disc" i.e. PDR Exclusion criteria: not reported
Interventions	Intervention (n = 45) • argon laser Comparator (n = 45) • no treatment
Outcomes	Primary outcome: • new proliferation on the disc Follow-up: 4 years
Notes	Date conducted: 1973-1974 Sources of funding: not reported Declaration of interest: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	*"... only one eye was randomly assigned to treatment"* Page 78
Allocation concealment (selection bias)	Low risk	Not mentioned, but unlikely to be a problem in a within-person study
Blinding of participants and personnel (performance bias) Visual acuity	Unclear risk	-
Blinding of participants and personnel (performance bias) Progression of diabetic retinopathy	Low risk	We judged it unlikely that patient or carer knowledge of treatment assignment would impact on the progression of diabetic retinopathy
Blinding of outcome assessment (detection bias) Visual acuity	Unclear risk	-
Blinding of outcome assessment (detection bias) Progression of diabetic retinopathy	High risk	Masking not mentioned and treatments quite different
Incomplete outcome data (attrition bias) All outcomes	High risk	*"Initially we reviewed the records of 83 consecutive patients assigned for a 4-year follow-up, but 16 patients dropped out at various stages because of death, inadequate follow-up, or because the 'control' eye was also treated."* Page 78
Selective reporting (reporting bias)	Unclear risk	No access to protocol

Yassur 1980 *(Continued)*

Other bias	Unclear risk	-

Abbreviations
BCVA: best corrected visual acuity
DR: diabetic retinopathy
ETDRS: Early Treatment Diabetic Retinopathy Study Research Group
FA: fluorescein angiography
NEI: National Eye Institute
NIH: National institutes for Healh
PDR: proliferative diabetic retinopathy
PRP: panretinal photocoagulation
RCT: randomised controlled trial

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

Study	Reason for exclusion
Al-Hussainy 2008	No untreated or deferred laser control group
Atmaca 1995	No untreated or deferred laser control group
Bandello 1993	No untreated or deferred laser control group
Bandello 1996	No untreated or deferred laser control group
Bandello 2001	No untreated or deferred laser control group
Bandello 2012	Not an RCT
Beetham 1969	Laser no longer in use
Birch-Cox 1978	Not RCT
Blankenship 1987	No untreated or deferred laser control group
Blankenship 1989	No untreated or deferred laser control group
Brancato 1990	No untreated or deferred laser control group
Brancato 1991	No untreated or deferred laser control group
British Multicentre Study Group 1975	Laser no longer in use
Buckley 1992	No untreated or deferred laser control group
Canning 1991	No untreated or deferred laser control group
Capoferri 1990	No untreated or deferred laser control group
Chaine 1986	No untreated or deferred laser control group
Chen 2013	No untreated or deferred laser control group
Crick 1978	No untreated or deferred laser control group

Study	Reason for exclusion
Doft 1982	No untreated or deferred laser control group
Doft 1992	No untreated or deferred laser control group
Dong 1997	Not an RCT
Elsner 2005	No untreated or deferred laser control group
Emi 2009	Not an RCT
Fankhauser 1972a	No untreated or deferred laser control group
Fankhauser 1972b	No untreated or deferred laser control group
Francois 1977	No untreated or deferred laser control group
Gerke 1985	No untreated or deferred laser control group
Haas 1999	No untreated or deferred laser control group
Hamilton 1981	No untreated or deferred laser control group
Ivanisevic 1992	No untreated or deferred laser control group
KARNS 1988	No untreated or deferred laser control group
Khosla 1994	No untreated or deferred laser control group
Klemen 1985	No untreated or deferred laser control group
Kovacic 2007	No untreated or deferred laser control group
Kovacic 2012	No untreated or deferred laser control group
Li 1986	No untreated or deferred laser control group
Liang 1983	No untreated or deferred laser control group
Lim 2009	Not an RCT
Lopez 2008	No untreated or deferred laser control group
MAPASS 2010	No untreated or deferred laser control group
McLean 1972	Unable to locate reference
Menchini 1990	No untreated or deferred laser control group
Menchini 1995	No untreated or deferred laser control group
Mirkiewicz-Sieradzka 1988	Not an RCT
Mirshahi 2013	No untreated or deferred laser control group
Misra 2013	Not an RCT

Study	Reason for exclusion
Mody 1983	No untreated or deferred laser control group
Muraly 2011	No untreated or deferred laser control group
Nagpal 2010	No untreated or deferred laser control group
Neira-Zalentein 2011	Not an RCT
Okuyama 1995	No untreated or deferred laser control group
Pahor 1998	No untreated or deferred laser control group
Pahor 1999	Not an RCT
Peng 2013	No untreated or deferred laser control group
Perez 2008	No untreated or deferred laser control group
PETER PAN Study 2013	No untreated or deferred laser control group
Plumb 1982	No untreated or deferred laser control group
Salman 2011	No untreated or deferred laser control group
Schiodte 1983	No untreated or deferred laser control group
Seiberth 1986	Not an RCT
Seiberth 1987	Not an RCT
Seiberth 1993	No untreated or deferred laser control group
Seymenoglu 2013	No untreated or deferred laser control group
Shimura 2003	No untreated or deferred laser control group
Shimura 2009	Not an RCT
Stanga 2010	No untreated or deferred laser control group
Tewari 2000	No untreated or deferred laser control group
Theodossiadis 1990	No untreated or deferred laser control group
Townsend 1980	Laser no longer in use
Uehara 1993	No untreated or deferred laser control group
Vera-Rodriguez 2008	No untreated or deferred laser control group
Wade 1990	No untreated or deferred laser control group
Wiznia 1985	Not an RCT
Wroblewski 1991	No untreated or deferred laser control group

Study	Reason for exclusion
Wroblewski 1992	No untreated or deferred laser control group
Zaluski 1986	No untreated or deferred laser control group

Abbreviation
RCT: randomised controlled trial

Characteristics of studies awaiting assessment *[ordered by study ID]*

Francois 1971

Methods	
Participants	
Interventions	
Outcomes	
Notes	Currently unable to source a copy of the article

Gaudric 1987

Methods	
Participants	
Interventions	
Outcomes	
Notes	Currently unable to source a copy of the article

Guo 2014

Methods	
Participants	
Interventions	
Outcomes	
Notes	Awaiting a translation of the report of the study

Kaluzny 1985

Methods	

Kaluzny 1985 *(Continued)*

Participants	
Interventions	
Outcomes	
Notes	Awaiting a translation of the report of the study

Krill 1971

Methods	
Participants	
Interventions	
Outcomes	
Notes	Currently unable to source a copy of the article

Leuenberger 1975

Methods	
Participants	
Interventions	
Outcomes	
Notes	Currently unable to source a copy of the article

Li 1987

Methods	
Participants	
Interventions	
Outcomes	
Notes	Awaiting a translation of the report of the study

Lund 1971

Methods	

Lund 1971 *(Continued)*

Participants	
Interventions	
Outcomes	
Notes	Awaiting a translation of the report of the study

Mella 1976

Methods	
Participants	
Interventions	
Outcomes	
Notes	Awaiting a translation of the report of the study

Mirzabekova 2004

Methods	
Participants	
Interventions	
Outcomes	
Notes	Awaiting a translation of the report of the study

Okun 1968

Methods	
Participants	
Interventions	
Outcomes	
Notes	Currently unable to source a copy of the article

Pahor 1997

Methods	

Pahor 1997 *(Continued)*

Participants	
Interventions	
Outcomes	
Notes	Awaiting a translation of the report of the study

Palacz 1988

Methods	
Participants	
Interventions	
Outcomes	
Notes	Awaiting a translation of the report of the study

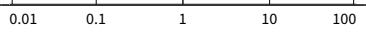
DATA AND ANALYSES

Comparison 1. Laser photocoagulation versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Loss of 15 or more letters BCVA at 12 months	2	8926	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.89, 1.11]
2 Loss of 15 or more letters BCVA at 2 years	2	8306	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.80, 0.97]
3 Loss of 15 or more letters BCVA at 3 years	2	7458	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.93, 1.23]
4 Severe visual loss (BCVA < 6/60)	4	9276	Risk Ratio (M-H, Random, 95% CI)	0.46 [0.24, 0.86]
5 Progression of diabetic retinopathy	4	8331	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.37, 0.64]
6 Vitreous haemorrhage	2	224	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.37, 0.85]

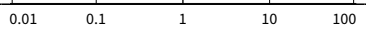
Analysis 1.1. Comparison 1 Laser photocoagulation versus control, Outcome 1 Loss of 15 or more letters BCVA at 12 months.

Study or subgroup	Laser n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
DRS 1978	157/752	183/752		35.26%	0.86[0.71,1.04]
ETDRS 1991	358/3711	336/3711		64.74%	1.07[0.92,1.23]
Total (95% CI)	**4463**	**4463**		**100%**	**0.99[0.89,1.11]**
Total events: 515 (Laser), 519 (Control)					
Heterogeneity: Tau^2=0; Chi^2=3.28, df=1(P=0.07); I^2=69.47%					
Test for overall effect: Z=0.13(P=0.89)					



Analysis 1.2. Comparison 1 Laser photocoagulation versus control, Outcome 2 Loss of 15 or more letters BCVA at 2 years.

Study or subgroup	Laser n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
DRS 1978	117/442	159/442		22.36%	0.74[0.6,0.9]
ETDRS 1991	507/3711	552/3711		77.64%	0.92[0.82,1.03]
Total (95% CI)	**4153**	**4153**		**100%**	**0.88[0.8,0.97]**
Total events: 624 (Laser), 711 (Control)					
Heterogeneity: Tau^2=0; Chi^2=3.65, df=1(P=0.06); I^2=72.59%					
Test for overall effect: Z=2.62(P=0.01)					

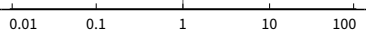


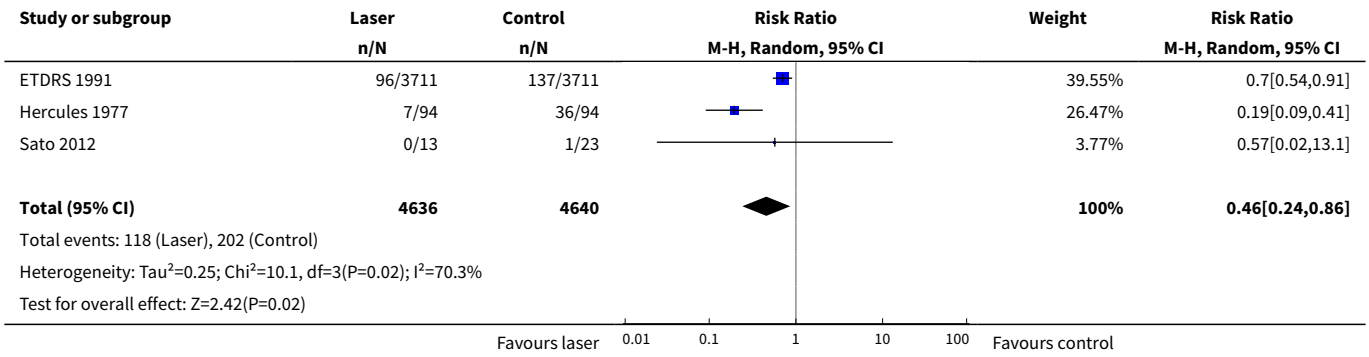
Analysis 1.3. Comparison 1 Laser photocoagulation versus control, Outcome 3 Loss of 15 or more letters BCVA at 3 years.

Study or subgroup	Laser n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
ETDRS 1991	358/3711	336/3711		99.57%	1.07[0.92,1.23]
Sato 2012	3/13	2/23		0.43%	2.65[0.51,13.89]
Total (95% CI)	**3724**	**3734**		**100%**	**1.07[0.93,1.23]**
Total events: 361 (Laser), 338 (Control)					
Heterogeneity: Tau^2=0; Chi^2=1.16, df=1(P=0.28); I^2=13.77%					
Test for overall effect: Z=0.97(P=0.33)					

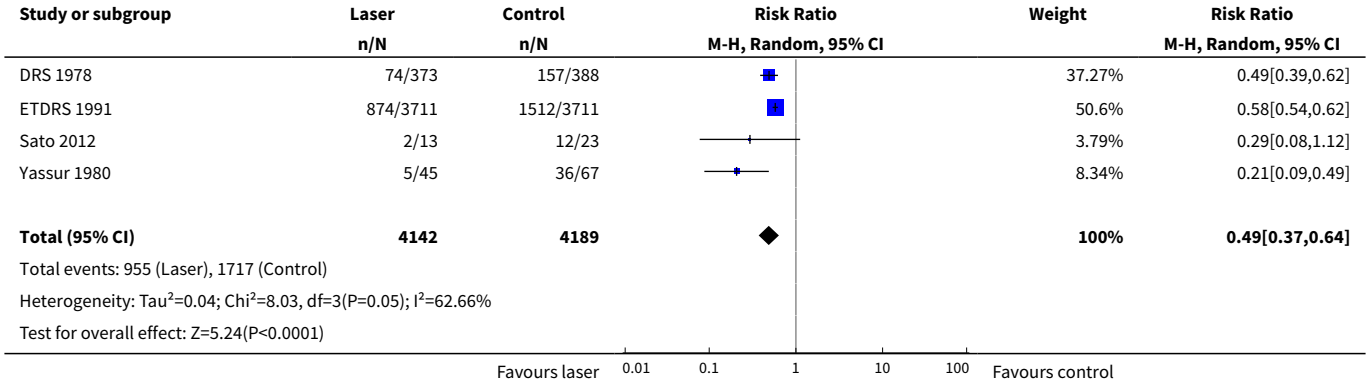
Analysis 1.4. Comparison 1 Laser photocoagulation versus control, Outcome 4 Severe visual loss (BCVA < 6/60).

Study or subgroup	Laser n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
DRS 1978	15/818	28/812		30.21%	0.53[0.29,0.99]

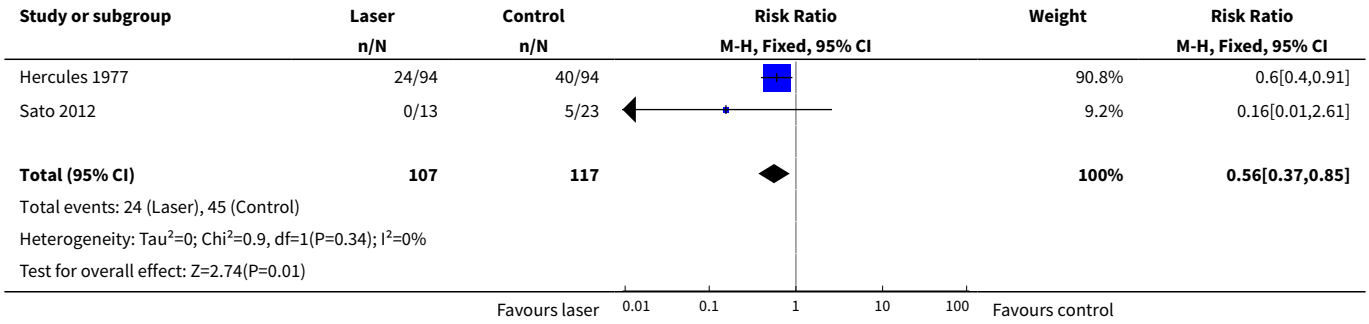




Analysis 1.5. Comparison 1 Laser photocoagulation versus control, Outcome 5 Progression of diabetic retinopathy.



Analysis 1.6. Comparison 1 Laser photocoagulation versus control, Outcome 6 Vitreous haemorrhage.



ADDITIONAL TABLES

Table 1. Characteristics of laser photocoagulation

Study	Type of laser	Type of photocoagulation	Number (size) of burns	Intensity	Exposure time (seconds)	Number of sessions

Table 1. Characteristics of laser photocoagulation *(Continued)*

DRS 1978	Argon	Panretinal Focal treatment of new vessels	800-1600 (500 µm) or 500-1000 (1000 µm)	Not reported	0.1	1 (usually)
ETDRS 1991	Argon	Panretinal	Full: 1200-1600 (500 µm) Mild: 400-650 (500 µm)	Moderate	0.1	Full: 2 or more Mild: 1
Hercules 1977	Argon	Panretinal	800 to 3000 (200 µm and 500 µm)	Minimal retinal blanching	Not reported	Up to 6
Sato 2012	Not reported	Selective photocoagulation of non-perfusion areas	(400 µm-500 µm)	Not reported	Not reported	
Yassur 1980	Argon	Panretinal	As for DRS 1978	As for DRS 1978	As for DRS 1978	As for DRS 1978

APPENDICES

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor: [Diabetic Retinopathy] explode all trees
#2 diabet* near/3 retinopath*
#3 proliferat* near/3 retinopath*
#4 diabet* near/3 maculopath*
#5 neovasculari?ation
#6 #1 or #2 or #3 or #4 or #5
#7 MeSH descriptor: [Light Coagulation] explode all trees
#8 photocoagulat*
#9 photo next coagulat*
#10 (focal or grid) near/3 laser*
#11 coagulat* or argon or krypton or YAG or diode or micropulse or panretinal
#12 #7 or #8 or #9 or #10 or #11
#13 #6 and #12

Appendix 2. MEDLINE (OvidSP) 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$ adj3 retinopath$).tw.
15. (proliferat$ adj3 retinopath$).tw.
16. (diabet$ adj3 maculopath$).tw.

17. neovasculari?ation.tw.
18. or/13-17
19. exp light coagulation/
20. photocoagulat$.tw.
21. (photo adj1 coagulat$).tw.
22. ((focal or grid) adj3 laser$).tw.
23. (coagulat$ or argon or krypton or YAG or diode or micropulse or panretinal).tw.
24. or/19-23
25. 18 and 24
26. 12 and 25

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. EMBASE (OvidSP) 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$).tw.
29. or/25-28
30. 29 not 10
31. 30 not (11 or 23)
32. 11 or 24 or 31
33. exp diabetic retinopathy/
34. (diabet$ adj3 retinopath$).tw.
35. (proliferat$ adj3 retinopath$).tw.
36. (diabet$ adj3 maculopath$).tw.
37. neovasculari?ation.tw.
38. or/33-37
39. exp laser coagulation/
40. argon laser/
41. photocoagulat$.tw.
42. (photo adj1 coagulat$).tw.
43. ((focal or grid) adj3 laser$).tw.
44. (coagulat$ or argon or krypton or YAG or diode or micropulse or panretinal).tw.
45. or/39-44
46. 38 and 45
47. 32 and 46

Appendix 4. *meta*Register of Controlled Trials search strategy

diabetic retinopathy AND (laser OR photocoagulation OR coagulation OR argon OR krypton OR YAG OR diode micropulse OR panretinal)

Appendix 5. ClinicalTrials.gov search strategy

diabetic retinopathy AND (laser OR photocoagulation OR coagulation OR argon OR krypton OR YAG OR diode micropulse OR panretinal)

Appendix 6. ICTRP search strategy

diabetic retinopathy = Condition AND laser OR photocoagulation OR coagulation OR argon OR krypton OR YAG OR diode micropulse OR panretinal = Intervention

Appendix 7. Data extraction sheet on trial characteristics

Table heading in RevMan 2014	**Subheadings for CEVG reviews**	**Comment**
Methods	Trial design	Parallel group RCT (i.e. people randomised to treatment) Paired eye or intra-individual RCT (i.e. eyes randomised to treatment) Cluster RCT (i.e. communities randomised to treatment) Cross-over RCT Other, specify
	Eyes	One eye included in trial - Specify how eye selected Both eyes included in trial, eyes received same treatment - Briefly specify how analysed (best/worst/average/both and adjusted for within-person correlation/both and not adjusted for within-person correlation) - Specify if mixture one eye and two eye Both eyes included in trial, eyes received different treatments (pair matched) - Specify if correct pair-matched analysis done
Participants	Country	
	Number of participants	
	% women	
	Average age	
	Age range	
	Inclusion criteria	
	Exclusion criteria	
Interventions	Intervention	Including number of participants randomly allocated to each
	Comparator	

(Continued)

Outcomes	List	Outcomes reported in methods and results, identify primary outcome if specified
Notes	Date conducted	Dates of recruitment of participants month/year to month/year
	Sources of funding	If reported
	Declaration of interest	If reported

WHAT'S NEW

Date	Event	Description
7 August 2015	Amended	Edits made to the Summary of findings table and additional source of support added

CONTRIBUTIONS OF AUTHORS

JE prepared a first draft of the protocol, which was revised by GV.

JE and MM screened search results and extracted data. GV and MM reviewed and commented on various drafts of the review.

DECLARATIONS OF INTEREST

JE: none known
MM: none known
GV: none known

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Internal sources

- No sources of support supplied

External sources

- Italian Ministry of Health and Fondazione Roma, Italy.

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  - The NIHR also funds the CEVG Editorial Base in London.
  - The Cochrane Review Incentive Scheme provided funding for Jennifer Evans to assist with completion of this review.

  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

Title

On the recommendation of a clinical peer reviewer we changed the title of this review from "laser photocoagulation for diabetic retinopathy" to "laser photocoagulation for proliferative diabetic retinopathy". The reviewer felt that clinicians seeing the broader title

would expect to see diabetic macular oedema (DMO) included in this review but this is specifically excluded as there is a separate review looking at laser for DMO (Jorge 2013).

Outcomes

We changed 'distance corrected near visual acuity' to 'near visual acuity'. We did not find any data on near visual acuity, either distance corrected or not.

We moved the outcome 'severe visual loss' out of adverse effects and further up the list, refecting the use of this outcome generally as a measure of effect rather than an adverse effect as originally defined in our protocol. We considered this outcome at one year follow-up as for the other effectiveness outcomes (and not, as originally planned, within three months of treatment).

We removed the outcome 'secondary choroidal neovascularisation' for future updates. This outcome is more of a concern after treatment for diabetic macular oedema. We did not find any data on this outcome.

Measures of effect

We planned to calculate the risk ratio for dichotomous variables where the event risk was greater than 10%, the odds ratio for dichotomous variables where the event risk was less than 10% and for very rare events (less than 1%) the Peto odds ratio. In fact for most analyses the event risk in the control group was greater than, or approximately, 10% and we felt that it would be confusing to report an odds ratio for only one outcome (severe visual loss) where the event rate was 4%. We have therefore only used the risk ratio as the measure of effect for dichotomous variables. This decision has not affected the conclusions drawn. For the outcome of severe visual loss the reported risk ratio was 0.46 (95% CI 0.24 to 0.86) and this is similar to the odds ratio of 0.40 (95% CI 0.18 to 0.88).

Data synthesis

We planned that, in cases of substantial heterogeneity, for example differences in direction of effect, or where the I^2 statistic was greater than 50% and the Chi^2 statistic less than 0.1, such that the pooled result did not summarize the individual trial results adequately, we would not provide a pooled estimate, unless visual inspection of the forest plot indicated it might be appropriate to do so (for example, if all effect estimates were in the same direction). For one analysis, Analysis 1.1, the effect estimates were reasonably close to 1 and we report a pooled estimate even though the effect estimates were not in the same direction.

INDEX TERMS

Medical Subject Headings (MeSH)

Diabetic Retinopathy [*surgery]; Disease Progression; Laser Coagulation [*methods]; Randomized Controlled Trials as Topic; Time Factors; Vision Disorders [etiology]; Visual Acuity; Vitreoretinopathy, Proliferative [*surgery]; Watchful Waiting

MeSH check words

Humans