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[Intervention Protocol]

Different lasers and techniques for proliferative diabetic retinopathy

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To assess the effects of different techniques and types of laser photocoagulation treatment for PDR. We will compare different wavelengths; power and pulse duration; pattern, number and location of burns versus standard argon laser single spot treatment as defined by ETDRS.

BACKGROUND

Description of the condition

Diabetic retinopathy (DR) is a chronic progressive, potentially sight-threatening disease of the retinal microvasculature associated with prolonged hyperglycaemia. As the leading cause of blindness among working-aged adults around the world, DR is a major public health problem (Klein 2007). Its incidence is rising dramatically along with the incidence of type 2 diabetes, driven by greater longevity combined with sedentary lifestyles and increasing levels of obesity (Geiss 2011). Globally, there are approximately 93 million people with DR, including 17 million with proliferative DR, 21 million with diabetic macular oedema, and 28 million with vision-threatening diabetic retinopathy (VTDR) (Yau 2012). A pooled analysis from diabetic population-based studies around

the world found overall prevalence rates of 34.6% for any DR, 6.96% for proliferative DR, 6.81% for diabetic macular oedema and 10.2% for VTDR. All DR prevalence endpoints increased with diabetes duration, haemoglobin A(1c), and blood pressure levels and were higher in people with type 1 compared with type 2 diabetes (Yau 2012).

These data highlight the substantial worldwide public health burden of DR and the importance of tackling modifiable risk factors to reduce its occurrence. The Diabetes Control and Complications Trial (DCCT) showed that intensive glycaemic control was effective in delaying the onset, as well as slowing the progression, of DR in patients with type 1 diabetes (DCCT Research Group 1993). The UK Prospective Diabetes Study (UKPDS) showed the risk of complications in type 2 diabetics was independently and additively correlated with hyperglycaemia and hypertension,

with risk reductions of 21% per 1% decrease in HbA1c and 11% per 10 mmHg decrease in systolic blood pressure (Stratton 2006; UKPDS Group 1998). There are various classifications of diabetic retinopathy, but all recognise the two basic mechanisms leading to loss of vision: retinopathy (risk of developing new vessels) and maculopathy (risk of damage to the central fovea). For the purposes of this review, we are concerned with vision-threatening diabetic retinopathy, defined by the presence of abnormal new vessels. The differences between classifications relate mainly to levels of retinopathy and to terminology used. Severity is ranked into a stepwise scale from no retinopathy through various stages of non-proliferative or pre-proliferative disease to advanced proliferative disease (ETDRS Research Group 1991).

Proliferative diabetic retinopathy (PDR) is characterised by its location and its severity. With regard to location, there may be new vessels on the disc (NVD) or within 1 disc diameter (DD) of the margin of the disc; elsewhere in the retina (NVE) and associated with haemorrhage; or on the iris (NVI). Severity is classified as early PDR; PDR with high risk characteristics, such as NVD > 1/4 DD, any NVD or NVE associated vitreous haemorrhage; florid PDR; and gliotic PDR. 'Involutionary' PDR refers to new vessels that have regressed, usually in response to treatment but (rarely) spontaneously.

Description of the intervention

Laser photocoagulation reduces the oxygen demand of the outer layers of the retina and helps divert adequate oxygen and nutrients to the inner retinal layers, favourably altering the haemodynamics (Stefánsson 2001). Laser photocoagulation may also act by reducing the expression of vasoactive factors such as vascular endothelial growth factor (VEGF) and protein kinase C (PKC) in the retina (Ghosh 2005). Indeed, different landmark studies have supported the efficacy of laser pan-retinal photocoagulation (PRP) in preventing vision loss. The Diabetic Retinopathy Study (DRS) demonstrated that laser photocoagulation of the retina reduced severe visual loss (defined as visual acuity of 5/200 or less on two consecutive visits at least four months apart) (DRS Research Group 1978), and the Early Treatment Diabetic Retinopathy Study (ETDRS) addressed the question of the appropriate time for performing laser photocoagulation, showing that PRP was beneficial only in cases where proliferative changes were present or imminent (ETDRS Research Group 1985). It also showed that focal or grid photocoagulation was beneficial in reducing visual loss due to macular oedema (ETDRS Research Group 1985). Laser PRP is more beneficial when performed at an advanced stage of the disease, when proliferative changes have appeared and are threatening vision. This treatment is associated with its own morbidity, so as the disease progresses to the PDR stage the risk-benefit ratio is altered in favour of PRP. The visual loss due to PRP is much less debilitating at this stage compared with the high risk of severe

vision loss in the near future if the retinopathy were to remain untreated (Feman 2004).

How the intervention might work

Proliferative diabetic retinopathy (PDR) is the angiogenic response of the retina to extensive capillary closure. New vessels grow at the interface of perfused and non-perfused retina and are described as NVD or NVE. Other sites of new vessels include the iris (NVI), which suggest more advanced and widespread ischaemia. Peripheral retinal ischaemia, in the absence of surrogate markers or capillary drop out (blot haemorrhage, venous beading, intraretinal microvascular anomalies) may not always be readily discernible

clinically, and hence retinal angiography – especially wide field

retinal angiography – is useful in detecting ischaemic changes.

The aim of laser PRP treatment is to destroy the areas where there is capillary non-perfusion and retinal ischaemia. If there is an inadequate response without full regression of new vessels, then clinicians should repeat the treatment. Lasers act by inducing thermal damage after absorption of energy by tissue pigments. The three main retinal pigments are luteal pigment, haemoglobin and melanin, and the appropriate laser wavelength will be selectively absorbed in one of these pigments. The goal of PRP is to target the retinal pigment epithelium (RPE) with minimal photoreceptor damage and RPE cell loss, and barely visible scar formation within the outer retina.

Following the guidelines published by the DRS and ETDRS, argon laser photocoagulation has been the gold standard for the treatment of PDR. Level 1 evidence from the DRS recommended multisession PRP laser extending into far-peripheral zones in high-risk eyes (DRS Research Group 1981). Practitioners still widely follow this guideline as a frame of reference, generating peak energy production in the 514 nm wavelength. At the same time, reasonable modifications may be applied to different clinical scenarios, and the guidelines do not necessarily represent an absolute start or endpoint of therapy. In a practical sense, the clinical goal is to administer enough laser burns to ischaemic retina to induce regression of active neovascularisation, preventing new lesions or haemorrhage. This includes 360° treatment in the case of PDR, with adequate spacing to avoid excessive compromise of peripheral vision. There are no standard power settings, since burn adequacy is dependent on variables such as media clarity, fundus pigmentation, and method of delivery, but the goal is to achieve an adequate blanching of the outer neural retina with medium grey spots. Avoiding intense white spots will reduce the risk of inducing haemorrhage and foci for retinal breaks or choroidal neovascularisation. Dividing the PRP treatment into two or more sessions can help minimise the occurrence of adverse effects (Doft 1982).

Different laser strategies can also help reduce ocular side effects, such as laser burn scarring and visual field loss (Muqit 2010). Argon-dye laser photocoagulators produce optical radiations in

the visible spectrum. However the newer “yellow” wavelength lasers have the highest combined absorption in the melanin-oxyhemoglobin layers of the RPE/choriocapillaris complex and thought to induce less scatter with increased efficiency compared to green laser photocoagulators (Castillejos-Rios 1992).

MicroPulse is a tissue-sparing laser technology that can limit tissue thermal elevation to temperatures below the threshold of retinal tissue damage and induce beneficial intracellular biological effects without any visible laser-induced damage. Reported MicroPulse protocols have used both diode laser which produces energy in the invisible infrared band (810 nm), and the 577 nm (yellow) laser. Both these laser treatment strategies can be either continuous or subthreshold (MicroPulse) and target the melanin within the RPE for photothermal effects, with minimisation of functional and structural damage to the outer retina since there is no absorption by photoreceptors and haemoglobin (Pollack 1998). The lack of a bright flash provides more patient comfort, with minimal retinal bleaching and rapid recovery from the laser treatment. However, the resulting retinal laser burn may be more difficult to assess clinically. The MicroPulse laser has been adapted to fire in a rapid sequence micropulse mode where there are short applications of laser. A major issue for clinicians is that laser titration may be difficult in the absence of visible laser uptake, with risks of overlapping retreatment burns. Additionally, the subthreshold diode micropulse (SDM) laser burns are not visualised using fundus autofluorescence (FAF) or optical coherence tomography (OCT) techniques (Luttrull 2006).

Clinicians increasingly use the PASCAL (PAttern SCAn Laser) frequency-doubled neodymium-doped yttrium aluminium garnet solid-state laser with a wavelength of 532 nm. Power settings for PASCAL are generally double that of argon for comparable treatments. However, pulse duration is one-fifth that of conventional argon laser treatment so application of laser burns may be quicker and less painful (Muraly 2011). There are multispot laser delivery systems that allow a pulse duration of 10 to 30 ms compared with the 100 to 200 ms used with conventional laser. Additionally, the procedure can be semiautomated by delivering multiple laser burns to the retina with a single depression of the foot pedal. Multispot laser treatment for PDR has been shown to be safe and effective, preserving central visual acuity as well as peripheral visual field (Muqit 2010). Shorter duration of laser pulse has been demonstrated to be more favourable for pain (Al-Hussainy 2008; Muqit 2010). It is recognised that if laser treatment is applied using a shorter duration of pulse (e.g. 20 ms), a larger number of burns are needed to achieve control of PDR, either in a single session or multiple sessions (Muraly 2011).

Why it is important to do this review

Current NICE guidelines for the management of PDR recommend that an ophthalmologist promptly perform a course of full argon laser therapy and continue until regression of neovascular-

isation (Ghanchi 2013). However, most of the evidence base relies on the previously described landmark trials, which use older lasers from the 1980s, and it does not provide enough evidence to recommend newer laser techniques. There is growing evidence that treatment with newer laser machines may be equally effective but safer and less uncomfortable. We think that there should be a high quality review of alternative laser treatments, including modern lasers, to reduce harm from photocoagulation. This systematic review is designed to examine efficacy and safety in people with PDR treated with alternative types of laser. We will also assess the evidence base for alternative laser strategies such as a step-wise approach with an initial light-scattered PRP, with further laser if the retinopathy does not regress; and ischaemia-targeted laser to the peripheral retina as seen on fluorescein angiography with the aid of wide field imaging compared with standard argon laser. This review will follow on from the preliminary work carried out by Evans 2014 in a recent Cochrane review assessing the effects of laser photocoagulation for DR compared to no treatment or deferred treatment. Pan-retinal photocoagulation has been the mainstay of treatment of PDR for many years, but future Cochrane reviews on variations in the laser treatment protocol were recommended. A NIHR-HTA project (12/71/01) addressed a similar question but in different populations, with earlier disease than in our proposed review (Royle 2015).

OBJECTIVES

To assess the effects of different techniques and types of laser photocoagulation treatment for PDR. We will compare different wavelengths; power and pulse duration; pattern, number and location of burns versus standard argon laser single spot treatment as defined by ETDRS.

METHODS

Criteria for considering studies for this review

Types of studies

We will only include randomised controlled trials (RCTs) in this review.

Types of participants

We will include people with type 1 or 2 diabetes mellitus of all ages and both sexes with PDR as defined in the included studies. We will include a subgroup of trials where participants have received previous pharmacological treatments for diabetic eye disease. We

will not exclude studies that enrolled participants with other associated retinal diseases such as retinal vein occlusion as long as the diabetic subgroup with PDR is clearly identified and the reason for laser is PDR.

Types of interventions

We will include RCTs that consider the types of peripheral laser pan-retinal photocoagulation (PRP) for PDR described below, and we will only include studies with a comparator group of standard argon laser PRP.

Interventions

We will compare variations of the following parameters to the standard argon laser single spot treatment (comparator).

Wavelength

Any ophthalmic laser type (wavelength) including but not limited to:

- diode laser (810 nm);
- pattern scanning laser such as PASCAL (532 nm) or NAVILAS.

We will exclude studies that consider lasers that are not in common use, such as the xenon arc photocoagulation or ruby laser.

Laser burn application

Any laser burn application method including but not limited to:

- variations in total number of burns required to induce regression of neovascularisation, including number of laser sessions required;
- use of multispot pattern laser delivery;
- use of conventional slit lamp (PASCAL) or the fundus camera-navigated laser (NAVILAS) system.

Location of laser burns

Any laser burn target location including but not limited to ischaemia-targeted retinal location.

Laser combined with other treatments

We will include studies in which participants may have also received non-laser based therapies for other indications such as diabetic macular oedema (DMO), for example, anti-VEGF, intraocular steroid implants or traditional Chinese medicine; however, we will treat these as a separate subset.

We will exclude studies that compare laser versus laser plus another non-laser intervention for PDR, as this is covered in another Cochrane review.

Comparator

The comparator will be standard argon laser single spot treatment according to ETDRS guidelines. Specifically, the recommendations in the ETDRS are an initial treatment peripheral scatter laser treatment consisting of 1200 to 1600 burns of moderate intensity, 200 to 500 μm spot size, with one-half to one-spot diameter spacing. Argon pulse duration is 100 to 200 ms with power titrated to produce moderate-intensity burns but with full treatment divided over at least two sessions according to different clinical scenarios (ETDRS Research Group 1987).

Types of outcome measures

Primary outcomes

The primary outcome will be best-corrected visual acuity (BCVA). Specifically we will use the proportion of people who lost or gained at least 15 ETDRS letters (equivalent to 3 ETDRS lines) as measured on a LogMAR chart at the one and five year time point.

Secondary outcomes

We will look at the following secondary outcomes.

1. Change in mean BCVA (LogMAR) at 12 months and five years. We will collect data on final value if change is not available.
2. Change in mean best-corrected near visual acuity (NVA) at 12 months and five years. We will collect data on final value if change is not available.
3. Progression of diabetic retinopathy/maculopathy at 12 months and five years as defined by trial investigators, including OCT central macular thickness (CMT) where measured.
4. Visual field testing, including mean deviation (MD) and if failed, the Estermann standard driving test.
5. Patient-reported outcome measure (PROM) for pain associated with the treatment, and vision-related quality of life measured using any validated questionnaire, including loss of driving licence at 12 months and five years.
6. Resource use and costs.

Adverse events

Adverse events at any time: macular oedema, retinal detachment, vitreous haemorrhage, need for vitrectomy surgery, severe visual loss (BCVA < 6/60).

Search methods for identification of studies

Electronic searches

We will search CENTRAL (which contains the Cochrane Eyes and Vision Trials Register) (latest issue), Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid MEDLINE Daily, Ovid OLDMEDLINE (January 1946 to present), EMBASE (January 1980 to present), the ISRCTN registry (www.isrctn.com/editAdvancedSearch), ClinicalTrials.gov (www.clinicaltrials.gov) and the WHO International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/search/en). We will not use any date or language restrictions in the electronic search for trials.

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

Searching other resources

We will search the reference lists of potentially includable studies to identify any additional trials. We do not intend to handsearch conference proceedings for this review.

Data collection and analysis

Selection of studies

Two authors will independently review all the titles and abstracts identified from the electronic and manual searches against the inclusion criteria using web-based review management software (covidence.org). We will obtain full-text copies of all potentially or definitely relevant articles. We will contact trial investigators for further information if required. We will resolve discrepancies between authors as to whether or not studies meet inclusion criteria by discussion. We will document the excluded studies and the reasons for exclusion.

Data extraction and management

We will extract the following participant and trial characteristics and report them in a table format (Appendix 7).

- Participant characteristics (age, sex, glycated haemoglobin (HbA1c), cholesterol, blood pressure, diagnostic criteria used for PDR, baseline visual acuity, OCT-determined CMT, and areas of ischaemic retinal tissue according to fluorescein angiography).
- Intervention (laser agent, laser settings, number of spots delivered, treatment interval and number, retinal target location).
- Methodology (group size, randomisation, blinding).
- Outcomes data as specified above.

We will contact trial investigators for key unpublished information that is missing from reports of included studies. Two review authors will independently extract the data, entering data into web-

based review management software ([Covidence 2015](#)), and using pre-piloted data extraction templates. Covidence will enable us to compare discrepancies, which we will resolve by discussion. We will directly import data from Covidence into Review Manager 5 ([RevMan 2014](#)).

Assessment of risk of bias in included studies

Two review authors will independently assess the risk of bias of the included trials according to Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)). We will consider the following main criteria.

- Selection bias: random sequence generation, allocation concealment.
- Performance bias: blinding of participants, researchers and outcome assessors.
- Attrition bias: loss to follow-up, rates of adherence.
- Reporting bias: selective outcome reporting. We will report each parameter as being at high, low, or unclear risk of bias, resolving any discrepancies between the authors by discussion. We will contact study authors to clarify study details relating to any unclear risk of bias. If there is no response from the authors, we will classify the trial based on available information.

See [Table 1](#) for additional information on assessment of risk of bias.

Measures of treatment effect

We will measure treatment effect according to the data types described in Chapter 9 of the *Cochrane Handbook for Systematic Reviews of Interventions* ([Deeks 2011](#)). These include the following.

Dichotomous data

Variables in this group include the primary outcome and the proportion of participants experiencing an adverse event during follow-up. We will report dichotomous variables as risk ratios (RRs) with 95% confidence intervals (CIs).

Continuous data

We will report continuous variables including mean change in visual acuity as mean difference with 95% CI (if normally distributed) or median and interquartile range (if not normally distributed).

Counts and rates data

We will measure the number of adverse events experienced by each participant as counts and rates data. If these adverse events occur commonly, we will analyse them as dichotomous variables. If the adverse events occur rarely, we will use the Peto odds ratio.

Qualitative data

We will report the types of adverse event, resource use and quality of life data qualitatively as a narrative description of qualitative data.

Unit of analysis issues

The unit of analysis for efficacy of treatment and ocular safety will be the eye for which authors have reported the data. Trials may randomise one or both eyes to the intervention or comparator. If people are randomly allocated to treatment but only one eye per person is included in the trial, then there will not be a unit of analysis issue. In these cases, we will document how investigators selected the eye. If people are randomly allocated to treatment but both eyes are included and reported, we will analyse as clustered data and adjust for within-person correlation. We may have to contact the trial investigators for further information to do this. If the study is a within-person study, that is, if one eye is randomly allocated to intervention and the other eye receives the comparator, then we will analyse as paired data. We may have to contact the trial investigators for further information to do this. The unit of analysis for economic and quality of life measures will be the individual.

Dealing with missing data

We will seek key unpublished information that is missing from reports of included studies by contacting study authors. If possible, we will conduct an intention-to-treat (ITT) analysis. We will use imputed data if computed by the trial investigators using an appropriate method but will not impute missing data ourselves. If ITT data are not available, we will do an available case analysis. This assumes that data are missing at random. We will assess whether this assumption is reasonable by collecting data from each included trial on the number of participants excluded or lost to follow-up and reasons for loss to follow-up by treatment group, if reported.

Assessment of heterogeneity

We will examine the overall characteristics of the studies, in particular the type of participants and types of interventions, to assess the extent to which the studies are similar enough to make pooling study results sensible. We will look at the forest plots of study results to see how consistent the results of the studies are, in particular looking at the size and direction of effects. We will assess heterogeneity between trial results using the I^2 value (Higgins 2011). We will consider I^2 values of greater than 50% to represent substantial inconsistency but will also consider the Chi^2 P value. As this may have low power when there are few studies, we will consider P values less than 0.1 to indicate statistical significance of the Chi^2 test.

Assessment of reporting biases

If we find 10 studies or more, we will create a funnel plot and interpret asymmetry as indicating possible publication bias.

Data synthesis

If there is no substantial clinical or statistical heterogeneity between the trials, we will combine the results in a meta-analysis using a random-effects model. We will use a fixed-effect model if there are three trials or fewer. In case of substantial clinical or statistical heterogeneity, we will not combine study results but present a narrative or tabulated summary. An exception where pooling of data would still take place is if we detect substantial statistical heterogeneity but examination of the forest plot indicates the individual trial results are all consistent in their direction of effect (i.e. the risk ratios or mean differences largely fall on one side of the null line).

Subgroup analysis and investigation of heterogeneity

We will consider clinical sources of heterogeneity including the type of diabetes, stability of glycaemic, lipid and blood pressure control, baseline visual acuity, baseline central macular thickness, and previous treatments for PDR. We will conduct subgroup analyses to investigate clinical heterogeneity. When parameters are available, we will stratify data according to baseline visual acuity worse than 6/24 Snellen equivalent (55 LogMAR letters), baseline CMT as measured by OCT greater than 400 μm , and type 1 or 2 diabetes. We will only perform these subgroup analyses for the primary outcome of this review.

Sensitivity analysis

We will conduct sensitivity analyses to determine the impact of exclusion of studies with lower methodological quality (defined as being at high risk of bias in one or more domains), unpublished data and industry-funded studies. We will only perform the sensitivity analyses for the primary review outcomes.

Summary of findings table

A 'Summary of findings' table will provide key information concerning the certainty of the evidence, the magnitude of effect of the interventions examined, and the sum of available data on all specified review primary and secondary outcomes for a given comparison. If data are not available in suitable format, we will provide a narrative summary in the table.

The 'Summary of findings' table will include the following six key outcomes.

1. Loss of vision of three lines at one and five years.
2. Progression of diabetic retinopathy at one and five years as defined by trial investigators, including OCT central macular thickness (CMT) where measured.

3. Adverse events at any time: macular oedema, retinal detachment, vitreous haemorrhage, need for vitrectomy surgery, severe visual loss (BCVA < 6/60).

4. Visual field loss, including failed Estermann standard driving test.

5. PROM: significant pain during the laser procedure.

6. PROM: vision-related quality of life measure using any validated questionnaire at one and five years.

Two review authors will independently use the GRADE approach to assess the certainty of the evidence in the included studies using GRADEpro GDT software (GRADEpro 2014). We will resolve discrepancies by discussion.

We will calculate the assumed risk from the median risk in the

comparator group of the included studies, unless there are compelling reasons to suggest that this is not the best estimate, in which case we will provide a rationale for the source.

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CEV will create and execute the electronic search strategies.

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* Indicates the major publication for the study

ADDITIONAL TABLES**Table 1. Risk of bias**

Item	Low	Unclear	High
Sequence generation	Computer generated list, random table, other method of generating random list	Not reported how list was generated. Trial may be described as 'randomised' but with no further details	Alternate allocation, date of birth, records (review authors should exclude these RCTs)
Allocation concealment	Central centre (web/telephone access), sealed opaque envelopes	Not reported how allocation administered. Trial may be described as 'randomised' but with	Investigator involved in treatment allocation or treatment allocation clearly not masked

Table 1. Risk of bias (Continued)

		no further details	
Blinding (masking) of participants and personnel	Clearly stated that participants and personnel (apart from doctor) not aware of which lens received	Described as 'double-masked' with no information on who was masked	No information on masking. As lenses different we will assume that in absence of reporting on this participants and personnel were not masked
Blinding (masking) of outcome assessors	Clearly stated that outcome assessors were masked	Described as 'double-masked' with no information on who was masked	No information on masking. As lenses different we will assume that in absence of reporting on this outcome assessors were not masked
Incomplete outcome data	Missing data less than 20% (i.e. more than 80% follow-up) <i>and</i> equal follow-up in both groups <i>and</i> no obvious reason why loss to follow-up should be related to outcome	Follow-up not reported or missing data > 20% (i.e. follow-up < 80%) but follow-up equal in both groups	Follow-up different in each group and related to outcome
Selective outcome reporting	All outcomes in protocol, trials registry entry or both are reported	No access to protocol or trials registry entry	Outcomes in protocol or trials registry entry selectively reported

APPENDICES

Appendix I. 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 MeSH descriptor: [Lasers, Gas] this term only
- #9 photocoagulat*
- #10 photo next coagulat*
- #11 (focal or grid or scatter) near/3 laser*
- #12 coagulat* or argon or krypton or YAG or diode or micropulse or Pascal or panretinal
- #13 #7 or #9 or #10 or #11 or #12
- #14 #6 and #13

Appendix 2. MEDLINE (Ovid) search strategy

1. randomized controlled trial.pt.
2. (randomized or randomised).ab,ti.
3. placebo.ab,ti.
4. dt.fs.
5. randomly.ab,ti.
6. trial.ab,ti.
7. groups.ab,ti.
8. or/1-7
9. exp animals/
10. exp humans/
11. 9 not (9 and 10)
12. 8 not 11
13. exp diabetic retinopathy/
14. (diabet\$ 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. lasers, gas/
21. photocoagulat\$.tw.
22. (photo adj1 coagulat\$).tw.
23. ((focal or grid or scatter) adj3 laser\$).tw.
24. (coagulat\$ or argon or krypton or YAG or diode or micropulse or Pascal or panretinal).tw.
25. or/19-24
26. 18 and 25
27. 12 and 26

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

Appendix 3. EMBASE (Ovid) search strategy

1. exp randomized controlled trial/
2. exp randomization/
3. exp double blind procedure/
4. exp single blind procedure/
5. random\$.tw.
6. or/1-5
7. (animal or animal experiment).sh.
8. human.sh.
9. 7 and 8
10. 7 not 9
11. 6 not 10
12. exp clinical trial/
13. (clin\$ adj3 trial\$).tw.
14. ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj3 (blind\$ or mask\$)).tw.
15. exp placebo/
16. placebo\$.tw.
17. random\$.tw.
18. exp experimental design/
19. exp crossover procedure/
20. exp control group/

21. exp latin square design/
22. or/12-21
23. 22 not 10
24. 23 not 11
25. exp comparative study/
26. exp evaluation/
27. exp prospective study/
28. (control\$ or prospectiv\$ or volunteer\$).tw.
29. or/25-28
30. 29 not 10
31. 30 not (11 or 23)
32. 11 or 24 or 31
33. 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 or scatter) adj3 laser\$).tw.
44. (coagulat\$ or argon or krypton or YAG or diode or micropulse or Pascal or panretinal).tw.
45. or/39-44
46. 38 and 45
47. 32 and 46

Appendix 4. ISRCTN search strategy

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

Appendix 5. ClinicalTrials.gov search strategy

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

Appendix 6. ICTRP search strategy

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

Appendix 7. Data on study characteristics

Mandatory items		Optional items
Methods		
Study design	Parallel group RCT (<i>i.e. people randomised to treatment</i>) Within-person RCT (<i>i.e. eyes randomised to treatment</i>) Cluster RCT (<i>i.e. communities randomised to treatment</i>) Cross-over RCT Other, specify	Exclusions after randomisation Losses to follow-up Number randomised/analysed How were missing data handled? (<i>e.g. available case analysis, imputation methods</i>) Reported power calculation (Y/N), <i>if yes, sample size and power</i> Unusual study design/issues
Eyes or Unit of randomisation/unit of analysis	One eye included in study , <i>specify how eye selected</i> Two eyes included in study, both eyes received same treatment , <i>briefly specify how analysed (best/worst/average/both and adjusted for within person correlation/both and not adjusted for within person correlation) and specify if mixture one eye and two eye</i> Two eyes included in study, eyes received different treatments , <i>specify if correct pair-matched analysis done</i>	
Participants		
Country		Setting
Total number of participants	<i>This information should be collected for total study population recruited into the study. If these data are only reported for the people who were followed up only, please indicate.</i>	Ethnic group
Number (%) of men and women		Equivalence of baseline characteristics (Y/
Average age and age range		
Inclusion criteria		
Exclusion criteria		
Interventions		
Intervention (n =) Comparator (n =) See MECIR 65 and 70	Number of people randomised to this group Drug (or intervention) name Dose Frequency Route of administration	

(Continued)

Outcomes		
Primary and secondary outcomes <i>as defined in study reports</i> <i>See MECIR R70</i>	List outcomes Adverse events reported (Y/N) Length of follow-up and intervals at which outcomes assessed	Planned/actual length of follow-up
Notes		
Date conducted	Specify dates of recruitment of participants mm/yr to mm/yr	Full study name: <i>(if applicable)</i> Reported subgroup analyses (Y/N) Were trial investigators contacted?
Sources of funding		
Declaration of interest <i>See MECIR 69</i>		

CONTRIBUTIONS OF AUTHORS

All the authors have made a substantial contribution to the review from conception and design of study, to drafting and commenting on the review including data analysis.

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