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[Intervention Review]

Cyclodestructive procedures for refractory glaucoma

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ABSTRACT

Background

Cyclodestructive procedures are often used in patients with refractory glaucoma who have failed to achieve lower intraocular pressure (IOP) from filtration procedures and maximal medical therapy. Destruction of the ciliary body helps to lower IOP by reducing aqueous humor formation. Of the many types of cyclodestructive procedures, laser cyclophotocoagulation (CPC) has become the most common surgical method for reducing aqueous inflow. Options for CPC are wide-ranging: they can be performed using a neodymium:yttrium-aluminum-garnet (Nd:YAG) or diode laser and laser energy can be delivered by either the contact or non-contact method. Another cyclodestructive procedure is endoscopic cyclophotocoagulation (ECP), which the ophthalmologist can use selectively to target the ciliary epithelium and ablate ciliary body tissue. There is debate regarding which cyclodestructive method is best and how they compare to other glaucoma surgeries.

Objectives

To assess the relative effectiveness and safety of cyclodestructive procedures compared with other procedures in people with refractory glaucoma of any type and to assess the relative effectiveness and safety of individual cyclodestructive procedures compared with each other.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (which contains the Cochrane Eyes and Vision Trials Register) (2018, Issue 9); Ovid MEDLINE; Embase.com; PubMed; LILACS BIREME; ClinicalTrials.gov and the WHO ICTRP. The date of the search was 21 September 2018.

Selection criteria

We included randomized controlled trials or quasi-randomized trials in which participants underwent a secondary procedure for refractory glaucoma. We included trials with any laser type, route of administration, and laser settings. The primary comparison was any cyclodestructive procedure versus another glaucoma treatment, and the secondary comparisons were individual cyclodestructive procedures versus another cyclodestructive procedure.

Data collection and analysis

Two review authors independently reviewed the titles and abstracts from the database searches, and after retrieving the full-text reports of those that were potentially relevant, classified the full-text articles as included or excluded. Two review authors independently extracted data from the included studies and assessed the risk of bias. Discrepancies were resolved by discussion or by consultation with a third review author when necessary.

Main results

We included five trials reporting data for 330 eyes (326 participants). One study to had a low risk of bias for most domains and the other studies had an overall unclear risk of bias. This review includes four different comparisons: 1) ECP versus Ahmed implant, 2) micropulse CPC versus continuous-wave CPC; 3) CPC with a diode versus Nd:YAG laser; and 4) CPC with an Nd:YAG laser emitting 8J versus 4J.

No study reported data for our primary outcome, change from baseline in pain severity as reported by the participant or change in number of pain medications.

For our primary comparison, we included one trial that compared ECP with the Ahmed implant. At 12-month follow-up, the mean difference (MD) in IOPs between groups was -1.14 mmHg (95% confidence interval (CI) -4.21 to 1.93; 58 participants; low-certainty evidence (LCE)). At 24 months postintervention, we found very LCE suggesting that visual acuity may be better among participants in the ECP group than in the Ahmed implant group (MD -0.24 logMAR, 95% CI -0.52 to 0.04; 54 participants), and the difference in the mean number of glaucoma medications used by participants in each group was unclear (MD -0.50, 95% CI -1.17 to 0.17; 54 participants; very LCE). Reported adverse events in the ECP group (34 participants) were one case each of hypotony, phthisis bulbi, retinal detachment, and choroidal detachment; in the Ahmed implant group (34 participants) there was one case of endophthalmitis, two cases of retinal detachment, and six cases of choroidal detachment.

Three types of comparisons from four included studies provided data for our secondary comparisons. In the study that compared micropulse with continuous-wave CPC, median IOP was reported to be similar between the two groups at all time points. At 18 months postintervention, the median number of IOP-lowering medications was reduced from two to one in both groups. One participant in the micropulse and two in the continuous group exhibited worsened visual acuity. One case of prolonged inflammation was seen in the micropulse group (23 participants). Seven cases of prolonged inflammation, five cases of hypotony, and one case of phthisis bulbi were seen in the continuous group (23 participants).

Two studies compared CPC using a semiconductor diode versus an Nd:YAG laser. At 12 months postintervention, the MD in IOP was 1.02 mmHg (95% CI -1.49 to 3.53) in one study (LCE). The second study did not report mean IOP beyond three months of follow-up. Neither study reported the mean change in best-corrected visual acuity or number of glaucoma medications. Both studies reported hypotony as an adverse event in three participants in each study.

One study compared different energy settings of the same Nd:YAG laser. At 12-month follow-up, visual acuity was unchanged or improved in 21 of 33 participants in the 8J group and 20 of 27 participants in the 4J group (risk ratio 0.86, 95% CI 0.61 to 1.21; very LCE). More participants in the 8J group reduced the number of medications taken compared with the 4J group (RR 1.49, 95% CI 0.76 to 2.91; 50 participants; very low-certainty evidence). The presence of fibrin or hyphema were seen in five participants who received 8J and none who received 4J. There was a severe anterior chamber reaction in 11 of 26 (42%) participants who received 8J of energy and 2 of 21 (10%) participants who received 4J of energy.

Authors' conclusions

Evidence from five studies included in this review was inconclusive as to whether cyclodestructive procedures for refractory glaucoma result in better outcomes and fewer complications than other glaucoma treatments, and whether one type of cyclodestructive procedure is better than another. The most commonly reported adverse events across all five studies were hypotony and phthisis bulbi. Large, well-designed randomized controlled trials are needed. Patient-reported outcomes such as pain and quality of life should be considered as primary outcomes or important secondary outcomes of future trials.

PLAIN LANGUAGE SUMMARY

Laser surgery that lowers eye pressure by destroying a part of the eye that produces fluid inside the eye for people with uncontrolled glaucoma

What is the aim of this review?

The aim of this Cochrane Review was to find out how laser procedures compare to other approaches for lowering the pressure in the eye for people with glaucoma that has not responded to other types of treatment. We collected and analyzed all relevant studies of cyclodestructive procedures to answer this question and found five studies.

Key messages

There was not enough information to compare the different surgery options to each other. We were unable to conclude which type of surgery worked the best and was the safest.

What was studied in this review?

Some people who have glaucoma (damage to the optic nerve in the back of the eye) also have a buildup of pressure within the eye. This pressure may be because the eye has difficulty draining the fluid. If the ciliary body is destroyed, it can no longer produce too much fluid. Doing this may reduce the pressure within the eye and provide pain relief to people with glaucoma. There are several ways to destroy the ciliary body, which is known as cyclodestruction. Doctors can use a laser to destroy cells in the ciliary body, or they can freeze the cells. We wanted to compare these types of surgeries with more traditional surgeries for glaucoma. The laser surgery can be done in many different

ways because there are different types of lasers and methods for using them. We also aimed to compare these laser surgeries with each other to see whether any method worked better than others.

What are the main results of this review?

We found five studies that examined procedures to destroy the ciliary body. One compared using a laser to destroy the cells to another type of surgery that involved implanting a tube in the eye to carry away extra fluid. Four of the studies compared different types of lasers or different methods of applying the laser to the eye. We wanted to find out whether these surgeries helped reduce pain in people with glaucoma, but only two of the five studies asked participants about pain.

Two of the studies compared the same two types of lasers; we combined their data to help us understand the overall results. The two studies reported on the level of pressure in the eye after the surgeries. We found that both types of laser surgeries caused about the same amount of drop in pressure. We had only low confidence in these results because one of the studies had many participants lost to follow-up and did not report what had happened to them.

We were interested in learning how participants felt after the surgery, however none of the included studies asked participants this question. Future studies should ask this important question of participants. We also believe that future studies should ask participants about whether their pain was less after having the surgery.

How up-to-date is the review?

We searched for studies published up to 21 September 2018.

Summary of findings for the main comparison. Endoscopic cyclophotocoagulation compared with the Ahmed drainage implant for refractory glaucoma

Endoscopic cyclophotocoagulation compared with the Ahmed drainage implant for refractory glaucoma

Patient or population: adults with refractory glaucoma

Intervention: endoscopic cyclophotocoagulation (ECP)

Comparison: Ahmed drainage implant

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	ECP	Ahmed implant				
Pain control change from baseline 12 months postintervention	This outcome was not reported in the included studies.					
Mean change in IOP measured in mmHg 12 months postintervention	See comment	-	-	58 (1 RCT)	⊕⊕⊖⊖ **low**[1,2]	This study reported IOP at 12 months postintervention rather than the mean change in IOP from baseline. At 12 months postintervention, the MD was -1.14 mmHg (95% CI -4.21 to 1.93) when comparing ECP with the Ahmed implant.
Mean change in best-corrected visual acuity measured by logMAR 12 months postintervention	See comment	-	-	54 (1 RCT)	⊕⊖⊖⊖ **very low**[1,2,3]	Mean change in visual acuity at 12 months postintervention was not reported. At 24 months postintervention, visual acuity was better among participants in the ECP group than in the Ahmed implant group (MD -0.24 logMAR, 95% CI -0.52 to 0.04).
Mean change in mean deviation in study eyes	This outcome was not reported in the included studies.					

12 months postintervention						
Mean number of glaucoma medications 12 months postintervention	See comment	-	-	54 (1 RCT)	⊕⊝⊝⊝ **very low[1,2,3]**	The mean number of glaucoma medications used by participants in each group was reported at 24 months rather than at 12 months (MD -0.50, 95% CI -1.17 to 0.17).
Adverse events 12 months postintervention	See comment	-	-	68 (1 RCT)	⊕⊝⊝⊝ **very low[1,2,3]**	Adverse events were reported up to 24 months postintervention. In the ECP group (34 participants), there was 1 case each of hypotony, phthisis bulbi, retinal detachment, and choroidal detachment. In the Ahmed implant group (34 participants), there was 1 case of endophthalmitis, 2 cases of retinal detachment, and 6 cases of choroidal detachment.
Mean change in quality of life scores 12 months postintervention	This outcome was not reported in the included studies.					

*The basis for the **assumed risk** is the control group risk. 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; **IOP:** intraocular pressure; **MD:** mean difference; **RCT:** randomized controlled trial

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

[1]Downgraded due to high risks of bias (selection bias, performance bias, and attrition bias).
[2]Downgraded due to imprecision (wide confidence intervals).
[3]Downgraded due to indirectness (outcome assessed at a different time point).

Summary of findings 2. Micropulse versus continuous-wave cyclophotocoagulation for refractory glaucoma

Micropulse versus continuous-wave cyclophotocoagulation for refractory glaucoma

Patient or population: adults with refractory glaucoma

Intervention: micropulse cyclophotocoagulation (CPC)

Comparison: continuous-wave CPC

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Micropulse CPC	Continuous-wave CPC				
Pain control change from baseline 12 months postintervention	See comment	-	-	44 (1 RCT)	-	Pain control at 12 months was not assessed. The study investigators asked participants to rate their pain levels as "no pain," "mild," "moderate," or "severe" before and 1 week after surgery; however, these assessments were attributed to pain related to the surgery itself rather than pain due to glaucoma.
Mean change in IOP measured in mmHg 12 months postintervention	See comment	-	-	48 (1 RCT)	-	The study reported median IOP at a time point rather than mean change in IOP from baseline. Median IOP was reported to be similar between the 2 groups at all time points.
Mean change in best-corrected visual acuity measured by logMAR 12 months postintervention	See comment	-	-	48 (1 RCT)	-	1 participant in the micropulse CPC group and 2 participants in the continuous-wave CPC group exhibited worsened visual acuity.
Mean change in the mean deviation in study eyes change from baseline 12 months postintervention	This outcome was not reported in the included studies.					
Mean number of glaucoma medications	See comment	-	-	46 (1 RCT)	-	At 18 months postintervention, the median number of IOP-lowering medications was reduced from 2 to 1 in both groups.

12 months postintervention					
Adverse events 12 months postintervention	See comment -	-	46 (1 RCT)	-	Fewer complications were observed in the micropulse CPC group than in the continuous-wave CPC group up to 18 months postintervention. In the micropulse CPC group (23 participants), there was 1 case of prolonged inflammation. In the continuous-wave CPC group (23 participants), there were 7 cases of prolonged inflammation, 5 cases of hypotony, and 1 case of phthisis bulbi.
Mean change in quality of life scores 12 months postintervention	This outcome was not reported in the included studies.				

*The basis for the **assumed risk** is the control group risk. 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; **IOP:** intraocular pressure; **RCT:** randomized controlled trial

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

Summary of findings 3. Comparison of two cyclophotocoagulation lasers for refractory glaucoma

Cyclophotocoagulation using a semiconductor diode laser compared with cyclophotocoagulation using an Nd:YAG laser for refractory glaucoma

Population: adults with refractory glaucoma

Intervention: semiconductor diode laser

Comparison: Nd:YAG laser

Outcomes	Illustrative comparative risks* (95% CI)	Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments

	Assumed risk	Corresponding risk				
	Nd:YAG laser	Semiconductor diode laser				
Pain control change from baseline 12 months postintervention	This outcome was not reported in the included studies.					
Mean change in IOP measured in mmHg 12 months postintervention	See comment	-	-	95 (1 RCT)	⊕⊕⊖⊖ **low**[1,2]	1 study reported mean IOP at 12 months postintervention rather than the mean change in IOP from baseline. At 12 months postintervention, the MD was 1.02 mmHg (95% CI -1.49 to 3.53) when comparing the semiconductor diode laser with the Nd:YAG laser. The second study did not report mean IOP beyond 3 months of follow-up.
Mean change in best-corrected visual acuity measured by logMAR 12 months postintervention	See comment	-	-	127 (2 RCTs)	⊕⊖⊖⊖ **very low**[1,2,3]	1 study reported that evaluations of visual acuity measurements were inconclusive due to the poor visual function of eyes at entry, and the other study reported that at the last follow-up visit, 25 of 34 participants in the semiconductor diode group and 25 of 30 participants in the Nd:YAG group showed increased corrected visual acuity of more than 2 lines on the Snellen chart (or 1 line on the low-vision category) or no change in corrected visual acuity (RR 0.88, 95% CI 0.68 to 1.14).
Mean change in the mean deviation in study eyes change from baseline 12 months postintervention	This outcome was not reported in the included studies.					
Mean number of glaucoma medications	This outcome was not reported in the included studies.					

12 months postintervention					
Adverse events 12 months postintervention	See comment	-	-	-	1 study reported adverse events at 12 months follow-up, and the other reported only adverse events that occurred the day following surgery, so data could not be combined. Hypotony was reported in both studies and occurred in 3 participants in each study.
Mean change in quality of life scores 12 months postintervention	This outcome was not reported in the included studies.				

*The basis for the **assumed risk** is the control group risk. 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; **IOP:** intraocular pressure; **MD:** mean difference; **Nd:YAG:** neodymium:yttrium-aluminum-garnet; **RCT:** randomized controlled trial; **RR:** risk ratio

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

[1]Downgraded due to unclear or high risks of bias (selection bias, performance bias, and attrition bias).
[2]Downgraded due to imprecision (wide confidence intervals).
[3]Downgraded due to indirectness (outcome assessed at a different time point).

Summary of findings 4. Comparison of two cyclophotocoagulation energy levels for refractory glaucoma

Cyclophotocoagulation using an Nd:YAG at 4 J versus 8 J for refractory glaucoma

Patient or population: adults with refractory glaucoma

Intervention: 4 J

Comparison: 8 J

Outcomes	Illustrative comparative risks* (95% CI)	Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments

	Assumed risk	Corresponding risk				
	4 J	8 J				
Pain control change from baseline 12 months postintervention	See comment	-	-	50 (1 RCT)	⊕⊖⊖⊖ **very low[1,2,3]**	1 study reported levels of pain 1 day postintervention in a subset of participants: 8/26 participants in the 8-joule group reported no pain on the day after surgery compared with 12/24 participants in the 4-joule group (RR 0.62, 95% CI 0.31 to 1.24).
Mean change in IOP measured in mmHg 12 months postintervention	See comment	-	-	89 (1 RCT)	-	Change in IOP was only measured at the 2-hour and 1-day postintervention examinations.
Mean change in best-corrected visual acuity measured by logMAR 12 months postintervention	See comment	-	-	60 (1 RCT)	⊕⊖⊖⊖ **very low[1,2,3]**	Visual acuity was unchanged or improved in 21/33 participants in the 8-joule group and 20/27 participants in the 4-joule group (RR 0.86, 95% CI 0.61 to 1.21).
Mean change in the mean deviation in study eyes change from baseline 12 months postintervention	This outcome was not reported in the included studies.					
Mean number of glaucoma medications 12 months postintervention	See comment	-	-	50 (1 RCT)	⊕⊖⊖⊖ **very low[1,2,3]**	17/31 (54.8%) participants in the 8-joule group and 7/19 (36.8%) participants in the 4-joule group reduced the number of medications they were taking, though the time point of this assessment was not reported (RR 1.49, 95% CI 0.76 to 2.91).
Adverse events 12 months postintervention	See comment	-	-	50 (1 RCT)	-	Severe reactions, defined as the presence of fibrin or hyphema, were seen in 5 participants who received 8 J of energy and none who received 4 J of energy 2 hours after the intervention. 1 day after surgery, there was a severe an-

				terior chamber reaction in 11/26 (42%) participants who received 8 J of energy and 2/21 (10%) participants who received 4 J of energy.
Mean change in quality of life scores 12 months postintervention	This outcome was not reported in the included studies.			

*The basis for the **assumed risk** is the control group risk. 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; **IOP:** intraocular pressure; **Nd:YAG:** neodymium:yttrium-aluminum-garnet; **RCT:** randomized controlled trial; **RR:** risk ratio

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

[1]Downgraded due to unclear or high risks of bias (selection bias, performance bias, and attrition bias).
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BACKGROUND

Description of the condition

Glaucoma is a chronic progressive optic neuropathy associated with structural damage to the optic nerve and associated visual field loss, which can lead to vision loss and blindness if left undiagnosed and untreated (Foster 2002). Glaucoma is a heterogeneous group of conditions with multiple etiologies. The two main types are open-angle glaucoma (OAG) and angle-closure glaucoma (ACG). Neovascular glaucoma is a severe form of secondary glaucoma that results from occlusion of the trabecular meshwork and secondary closure of the angle by fibrovascular tissue proliferation.

Known risk factors that contribute to damage to the optic nerve include elevated intraocular pressure (IOP), older age, positive family history of glaucoma, African ancestry, high myopia, high cup-to-optic disk ratios, exfoliation syndrome, and decreased central corneal thickness (Coleman 2008; Gordon 2002; Landers 2002; Medeiros 2003; Quigley 2011). However, IOP remains the only modifiable risk factor for glaucoma and prognostic factor for glaucoma outcomes. Therapies for glaucoma, regardless of disease mechanism, thus target IOP reduction (Coleman 2012). Normally, the rate of aqueous humor production by the ciliary body equals the rate of its outflow. Intraocular pressure increases when part or all of the aqueous humor drainage system is blocked (Pan 2011). Increased IOP due to resistance to outflow is the presumed mechanism of OAG, the most common type of glaucoma.

Randomized clinical trials of participants with glaucoma have shown that there is a clear benefit to lowering IOP with medications, laser procedures, and incisional surgery to prevent further optic nerve damage and visual field deterioration (Burr 2012; CNTGS 1998; Heijl 2002; Leske 2003; Lichter 2001; VanVeldhuisen 2000; Vass 2007).

Epidemiology

Glaucoma is an increasingly critical public health problem due to the aging world population. Glaucoma is the leading cause of irreversible blindness and the second leading cause of blindness worldwide (Quigley 2011). Tham 2014 reported that the global prevalence of glaucoma for people aged 40 to 80 years is 3.54%. Tham 2014 also projected that by 2040 the number of people with glaucoma worldwide will increase to 111.8 million. Open-angle glaucoma is the most common type of glaucoma and accounts for 74% of cases worldwide (Quigley 1996). Worldwide, of people over 40 years old, 2% are estimated to have OAG, 0.7% to have ACG, and 0.4% to have neovascular glaucoma (Quigley 1996; Quigley 2006). In OAG, incidence by gender is similar; however, people of African ancestry have almost three times the age-adjusted prevalence than white people (Friedman 2004). There also are considerable differences in prevalence by ethnicity in ACG. The highest rates of ACG have been reported in Chinese, Inuit, and other Asian populations (He 2006; Van Rens 1988).

Symptoms and diagnosis

Open-angle glaucoma is often called the 'silent thief of sight' because it can cause irreversible damage without any symptoms at all. People with glaucoma typically do not notice visual field loss until central vision is affected in a late stage of the disease; 50% to 90% of people with glaucoma are unaware that they have glaucoma (Weinreb 2014).

Angle-closure glaucoma can be categorized into acute and chronic cases. Acute ACG requires immediate management to avoid blindness. People with acute ACG present with a painful red eye, blurred vision, headache, nausea, and vomiting (Weinreb 2014). People with chronic ACG present with similar symptoms as those with OAG. Glaucoma is diagnosed using tonometry, gonioscopy, optic nerve examination and imaging, corneal pachymetry, pupil examination, and visual field assessment.

Description of the intervention

Cyclodestructive procedures, first introduced by Vogt in the 1930s (Vogt 1936), are traditionally used in eyes with refractory glaucoma for whom filtration procedures have failed to lower IOP or slow disease progression; eyes with elevated IOP and limited useful vision on maximal medical therapy; and eyes with no visual potential in need of pain relief (Ansari 2007; Bloom 1997; Liu 2008; Pastor 2001). The goal of treatment is to reduce aqueous humor formation through ablation or destruction of the ciliary body epithelium. A number of different modalities have been used to achieve this aim including diathermy, cryotherapy, laser, ultrasound, and surgical excision (Beckman 1972; Bietti 1950; Coleman 1985; Shields 1985; Vogt 1936). Laser cyclophotocoagulation (CPC) and endoscopic cyclophotocoagulation (ECP) are the most commonly used procedures. Laser cyclophotocoagulation, first introduced in the 1970s by Beckman (Beckman 1973), has become the most common surgical method for reducing aqueous inflow. It can be performed using a neodymium:yttrium-aluminum-garnet (Nd:YAG) or diode laser (Lin 2004; Martin 2001), and laser energy can be delivered by either the contact or non-contact method (Lin 2002). Although CPC has been used to treat refractory glaucoma successfully, significant postoperative complications (i.e. visual loss, phthisis, loss of light perception) and discomfort have been reported by people undergoing this procedure (Lin 2004). Endoscopic cyclophotocoagulation, a newer method that specifically targets the ciliary process under direct viewing, is also used to treat refractory glaucoma. Since ECP can be used to ablate ciliary body tissue selectively, it has a lower incidence of vision-threatening complications (Lin 2002).

Other commonly used glaucoma surgeries include trabeculectomy and insertion of aqueous shunts. Trabeculectomy is typically used in eyes in which medications and laser therapy are insufficient to control disease (Prum 2016). Trabeculectomy is typically a filtering surgery where a block of eye filtration tissue is removed to decrease resistance to the outflow filtration of aqueous. While trabeculectomy lowers eye pressure and is considered by many ophthalmologists to be the gold-standard glaucoma operation, it is associated with significant postoperative complications. Complications include hyphema, shallow or flat anterior chamber, hypotony, choroidal detachment, blebitis, endophthalmitis, cataract formation, and hypotony maculopathy (Eldaly 2014). Aqueous shunts are traditionally used to manage medically uncontrolled glaucoma when trabeculectomy has failed to control IOP or is unlikely to succeed (Prum 2016). Aqueous shunts consist of a tube that diverts aqueous humor to an end plate (Minckler 2006). Complications include hypotony, diplopia, strabismus, proptosis, tube erosion, failure, corneal

decompensation, endophthalmitis, and visual loss (Sarkisian 2009).

How the intervention might work

When part or all of the aqueous humor drainage system is reduced or blocked, IOP increases (Pan 2011; Turkoski 2012). Aqueous humor is produced by the ciliary body epithelium. In cyclodestructive surgery, the laser energy that targets the ciliary body epithelium induces coagulative necrosis of these tissues and results in reduction of aqueous humor production, and thus reduced IOP (Liu 1994).

Why it is important to do this review

Although cyclodestructive procedures are not new, uncertainty exists regarding which cyclodestructive method is best and how they compare to other glaucoma surgeries. Additionally, much of the literature reports only small non-comparative case series; such study designs cannot demonstrate a benefit of one therapy over another. A systematic review, ideally incorporating meta-analysis, would be beneficial to compile information from individual studies and to estimate the relative effects of different procedures on IOP control.

OBJECTIVES

To assess the relative effectiveness (i.e. reduction of pain) and safety of cyclodestructive procedures (i.e. CPC and ECP) compared with other procedures (i.e. aqueous shunts) in people with refractory glaucoma of any type and to assess the relative effectiveness and safety of individual cyclodestructive procedures compared with each other.

METHODS

Criteria for considering studies for this review

Types of studies

We included only randomized controlled trials (RCTs) and quasi-RCTs (e.g., studies where the method of allocation is not considered strictly random such as by alternation, date of birth, or medical record number).

Types of participants

We included RCTs in which participants underwent a secondary procedure for refractory glaucoma (medically uncontrolled glaucoma for which other surgeries have failed). We included all types of glaucoma (i.e. primary open-angle glaucoma (OAG), angle-closure glaucoma (ACG), and secondary glaucoma such as neovascular, pigmentary, and exfoliation glaucoma). There were no restrictions based on participant age, gender, ethnicity, or comorbidity.

Types of interventions

We included all trials that compared cyclodestruction with aqueous shunts or another cyclodestructive procedure (CPC or ECP). We included trials with all types of lasers (i.e. ruby, Nd:YAG, diode), routes of administration (non-contact, contact), and laser settings. The primary comparison of interest was any cyclodestructive procedure versus another glaucoma treatment (aqueous shunts); the secondary comparisons were individual cyclodestructive procedures versus another cyclodestructive procedure.

Types of outcome measures

Primary outcomes

1. Change from baseline in pain severity as reported by the participant or change in number of pain medications prescribed from baseline to 12 months postintervention.

Secondary outcomes

1. Mean change in intraocular pressure (IOP) from baseline (immediate preoperative IOP) in study eyes at one week, one month, three months, six months, 12 months, and last follow-up after the procedure, measured using Goldmann tonometry, Tono-Pen, or another standard device. If sufficient information was available from the included studies, we planned to examine IOP in time-to-event analysis. When mean change in IOP from baseline was not reported, we used the mean IOP values at a time point to estimate the between-group treatment effects.
2. Mean change in best-corrected visual acuity in study eyes at 12 months postintervention, measured by logarithm of the minimum angle of resolution (logMAR) chart or equivalent.
3. Mean change in mean deviation in study eyes from baseline at 12 months postintervention as measured by automated perimetry.
4. Mean number of prescribed glaucoma medications, both topical and systemic, at 12 months postintervention.
5. Proportion of study eyes requiring additional glaucoma surgery by 12 months postintervention.

Adverse outcomes

We documented adverse outcomes reported by the included studies (i.e. prolonged inflammation, hypotony, phthisis, fibrin exudates). Since cyclodestructive surgeries are intraocular procedures, we also documented reports of endophthalmitis, retinal detachment, and choroidal hemorrhage.

Quality of life data

We planned to describe and compare quality of life outcomes by procedure if available.

Search methods for identification of studies

Electronic searches

The Cochrane Eyes and Vision Information Specialist searched the following electronic databases for RCTs and controlled clinical trials. We imposed no language or publication year restrictions.

- Cochrane Central Register of Controlled Trials (CENTRAL; 2018, Issue 9) (which contains the Cochrane Eyes and Vision Trials Register) in the Cochrane Library (searched 21 September 2018) (Appendix 1).
- MEDLINE Ovid (1946 to 21 September 2018) (Appendix 2).
- Embase.com (1947 to 21 September 2018) (Appendix 3).
- PubMed (1948 to 21 September 2018) (Appendix 4).
- LILACS BIREME (Latin American and Caribbean Health Science Information Database) (1982 to 21 September 2018) (Appendix 5).
- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov; searched 21 September 2018) (Appendix 6).

- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp; searched 21 September 2018) (Appendix 7).

Searching other resources

We searched the references of reports from included studies for additional relevant studies without restrictions regarding language or date of publication.

Data collection and analysis

Selection of studies

Two review authors independently reviewed the titles and abstracts of all records identified through electronic and manual searches. Each of these review authors classified titles and abstracts as either 'definitely relevant,' 'possibly relevant,' or 'definitely not relevant.' We retrieved the full-text reports of all records classified as 'definitely relevant' or 'possibly relevant.' The same two review authors reviewed the full-text articles, classifying the reported studies as either 'definitely include' or 'definitely exclude.' Any disagreements between the two review authors were resolved by discussion at each stage of selection, or by consulting a third review author when necessary. We excluded those studies labeled as 'definitely exclude' and documented the reasons for exclusion in the Characteristics of excluded studies table. When information needed to include or exclude a study from the review was unclear or unavailable from the study reports, we attempted to contact the study authors to clarify eligibility.

Data extraction and management

Two review authors independently extracted data from the included studies using internet-based data abstraction forms developed in collaboration with Cochrane Eyes and Vision (CEV) in the Systematic Review Data Repository (srdr.ahrq.gov). We extracted data from reports from each study relevant to the study design and methods, participant characteristics, interventions, and outcomes. Any discrepancies were resolved between the two review authors by discussion or by consulting a third review author when necessary. One review author entered data into Review Manager 5 (RevMan 5) (Review Manager 2014), and a second review author verified the entered data.

Assessment of risk of bias in included studies

Two review authors independently assessed each included study for risk of bias using the tools described in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2017). We assessed the following 'Risk of bias' parameters.

1. Sequence generation.
2. Allocation concealment before randomization.
3. Masking of participants, personnel, and outcome assessors.
4. Incomplete outcome data reporting.
5. Selective outcome reporting.
6. Other potential sources of bias (e.g. funding source).

We assessed each trial for each criterion and judged the trial as being at either 'high,' 'low,' or 'unclear' risk of bias (lack of information or uncertainty regarding the potential for bias).

Measures of treatment effect

Dichotomous outcomes

We analyzed the need for additional glaucoma surgery using summary risk ratios (RRs) with 95% confidence intervals (CIs) when data were available.

Continuous outcomes

We summarized mean reduction from baseline in IOP, mean change in logMAR visual acuity, mean deviations from visual field tests, number of glaucoma medications, and any potential scale used to quantify pain (as reported by the participants) would be accepted using summary mean differences (MDs) with 95% CIs. Whenever the included studies measured continuous outcomes using different scales, we calculated standardized mean differences (SMDs).

Unit of analysis issues

The participant was the unit of analysis. The optimal study design included one study eye per participant. We recorded whether studies enrolled one or two study eyes per participant. For trials that had included both eyes per participant, we planned to account, when possible, for intraperson correlation of outcomes as outlined in Chapter 16 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We planned to use paired analysis whenever included studies used a paired-eye design, however none of the included studies used a paired-eye design.

Dealing with missing data

We contacted study authors to request missing details including but not limited to study methods, effect estimates, and standard deviations. Whenever study authors did not respond within two weeks, we used the data available.

Assessment of heterogeneity

We assessed both clinical and methodological heterogeneity of included studies by examining variations in participant characteristics, inclusion/exclusion criteria, and assessments of primary and secondary outcomes. We used the I^2 statistic (%) to determine the proportion of variation in outcomes attributable to heterogeneity rather than chance. We deemed an I^2 statistic value of greater than 50% as reflecting substantial heterogeneity. In addition, we examined the overlap of effect estimates and CIs among individual studies, with poor overlap interpreted as indicating heterogeneity.

Assessment of reporting biases

We planned to use funnel plots in Review Manager 5 to examine signs of asymmetry to evaluate small-study effects and potential for publication bias if we included 10 or more studies in a meta-analysis (Review Manager 2014). However, the only possible meta-analyses included outcomes from only two studies, so we did not perform this investigation. We assessed the potential for selective outcome reporting as part of the 'Risk of bias' assessment.

Data synthesis

We planned to combine the results in a meta-analysis using a random-effects model, as long as we did not detect any substantial heterogeneity. However, we could combine outcome data from only two included studies in meta-analysis, so we used a fixed-effect model. When clinical, methodological, and statistical (I^2

statistic value of greater than 50%) characteristics suggested substantial heterogeneity, we presented the results in a narrative summary and did not conduct a meta-analysis.

Subgroup analysis and investigation of heterogeneity

We planned to perform subgroup analyses to compare effect estimates for different administration of procedures (non-contact versus contact) and underlying causes of glaucoma (open-angle, angle-closure, neovascular), but there were not enough included studies to create these subgroups.

Sensitivity analysis

We planned to conduct sensitivity analyses to determine the impact of excluding studies with high risk of bias, with industry funding, or without full-length reports, but as we could include only two studies in any meta-analyses, sensitivity analyses were not possible.

'Summary of findings' table

We followed the GRADE classification approach and used the reporting of effect estimates, imprecision, indirectness, inconsistency, and risk of bias to grade the strength of evidence for each outcome as very low, low, moderate, or high (GRADEpro 2015).

We included the following outcomes in the 'Summary of findings' tables for each comparison.

1. Change from baseline in pain severity as reported by the participant or change in number of pain medications prescribed from baseline to 12 months postintervention.
2. Mean change in IOP from baseline (immediate preoperative IOP) in study eyes at 12 months postintervention.
3. Mean change in logMAR best-corrected visual acuity in study eyes at 12 months postintervention.
4. Mean change in mean deviation in study eyes from baseline at 12 months postintervention.
5. Mean number of prescribed glaucoma medications, both topical and systemic, at 12 months postintervention.
6. Proportion of participants with an adverse event.
7. Change from baseline in quality of life scores at 12 months postintervention.

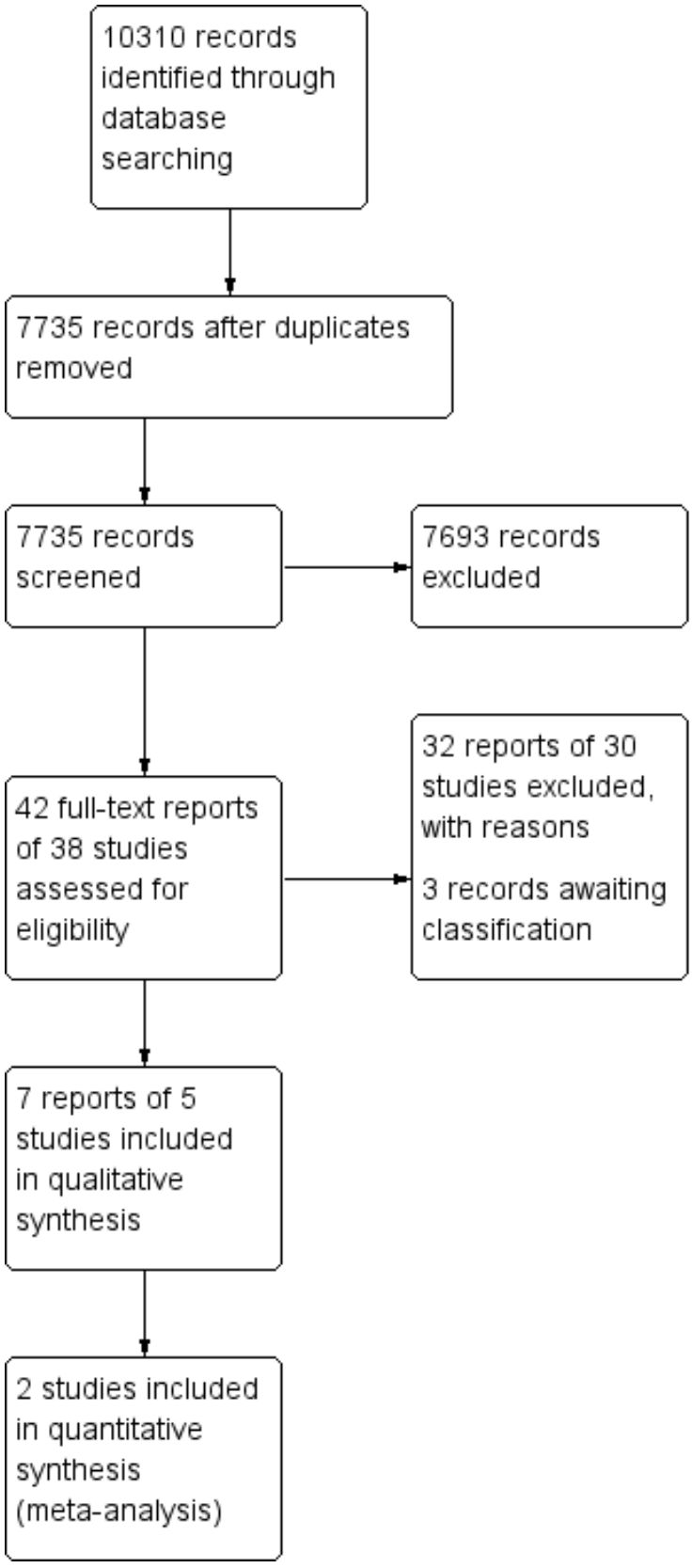
RESULTS

Description of studies

Results of the search

We performed the electronic database searches on 21 September 2018, and they are up-to-date as of that day. The searches identified 10,310 references including articles and trial registry records (Figure 1). We removed 2575 duplicate references, and two review authors independently screened the remaining 7735 references. We obtained the full-text reports for 42 references. We identified 5 studies published as 7 reports that met the inclusion criteria for this review. We identified 3 studies on ClinicalTrials.gov, which we tagged as awaiting classification because sufficient information to make a decision about their inclusion or exclusion is currently not available. We excluded 32 references. We have reported the reasons for exclusion in the Characteristics of excluded studies tables.

Figure 1. Study flow diagram.



Included studies

We included 5 studies in this review reporting outcomes for 330 eyes of 326 participants. The studies are described here in summary and in more detail in the Characteristics of included studies tables.

Types of participants

Participants in all included studies had refractory glaucoma requiring a cyclodestructive procedure. Shields 1993, Ulbig 1995, and Youn 1998 enrolled participants for whom traditional surgical approaches had failed or were not possible or inappropriate. Lima 2004 enrolled participants who had at least one previous trabeculectomy; Aquino 2015 allowed participants "with or without previous surgical intervention." The studies were conducted in four countries: one in Brazil (Lima 2004), one in Singapore (Aquino 2015), one in the United Kingdom (Ulbig 1995), and two in the United States (Shields 1993; Youn 1998).

Types of interventions

The included studies used a variety of different types of cyclodestructive surgeries. Only one of the included studies compared a cyclodestructive procedure with another glaucoma treatment, our primary comparison of interest. The other included studies compared two types of cyclodestructive procedures, our secondary comparison of interest. Each of the included studies had two study arms.

For our primary comparison of a cyclodestructive procedure versus another glaucoma treatment, Lima 2004 compared endoscopic cyclophotocoagulation (ECP) with insertion of the Ahmed tube, a drainage implant device.

Among the four studies that compared two types of cyclodestructive procedure, all used cyclophotocoagulation (CPC) as the cyclodestructive procedure in both study arms. Aquino 2015 compared two types of contact CPC. Some participants were randomized to micropulse mode of laser delivery, with repetitive, short pulses of energy separated by rest periods, while others were randomized to conventional continuous-wave CPC, in which continuous high energy was delivered. Shields 1993 compared non-contact CPC using two energy levels from the same type of laser: 4 J or 8 J of laser energy from an Nd:YAG laser, while Ulbig 1995 compared non-contact CPC using the Nd:YAG with another laser, a continuous-wave semiconductor diode, which emitted at 810 nm rather than the 1064 nm of the Nd:YAG laser. Youn 1998 also compared the Nd:YAG laser with a semiconductor laser, but a different one from the one used in Ulbig 1995. Youn 1998 and Ulbig 1995 were the only two studies from which outcome data could be combined in meta-analyses, as they both compared the Nd:YAG laser with a semiconductor laser. The study arms in the other two studies that randomized participants to two types of CPC were too different to justify combining their outcomes.

Types of outcomes

Primary outcome

No study reported on our primary outcome, change from baseline in pain severity as reported by the participant or change in number of pain medications. However, Aquino 2015 asked participants to rate their pain levels as "no pain," "mild," and "severe" before and one week after laser treatment. In Shields 1993, pain was described by participants on the day after surgery as "none," "moderate," or "severe." These pain ratings were regarded as equivalent to discomfort related to the laser treatment and not related to disease.

Secondary outcomes

Four studies reported mean IOP at various postoperative time points (Lima 2004; Shields 1993; Ulbig 1995; Youn 1998). Aquino 2015 reported median IOP rather than mean IOP. None of the studies reported mean change in visual acuity from baseline to 12 months postintervention. In Shields 1993, visual acuity changes were reported only for the participants who did not require further surgery; Lima 2004 commented on mean change in visual acuity postoperatively and incidence of visual acuity worsening at 24 months; and Youn 1998 reported number of participants with decreased visual acuity, no change, and increased corrected visual acuity. No study reported the mean number of glaucoma medications prescribed at 12 months. Lima 2004 reported the mean number of glaucoma medications at 24 months; Aquino 2015 reported the median number of medications at 18 months; and Shields 1993 reported the number of participants who were taking fewer medications than at baseline. Youn 1998 and Shields 1993 reported the proportion of participants who required additional surgeries. However, Youn 1998 did not note the time point of assessment, and neither Youn 1998 nor Shields 1993 specified whether participants required non-cyclodestructive glaucoma surgeries. All studies reported adverse outcomes, but none of the studies reported any visual field or quality of life data.

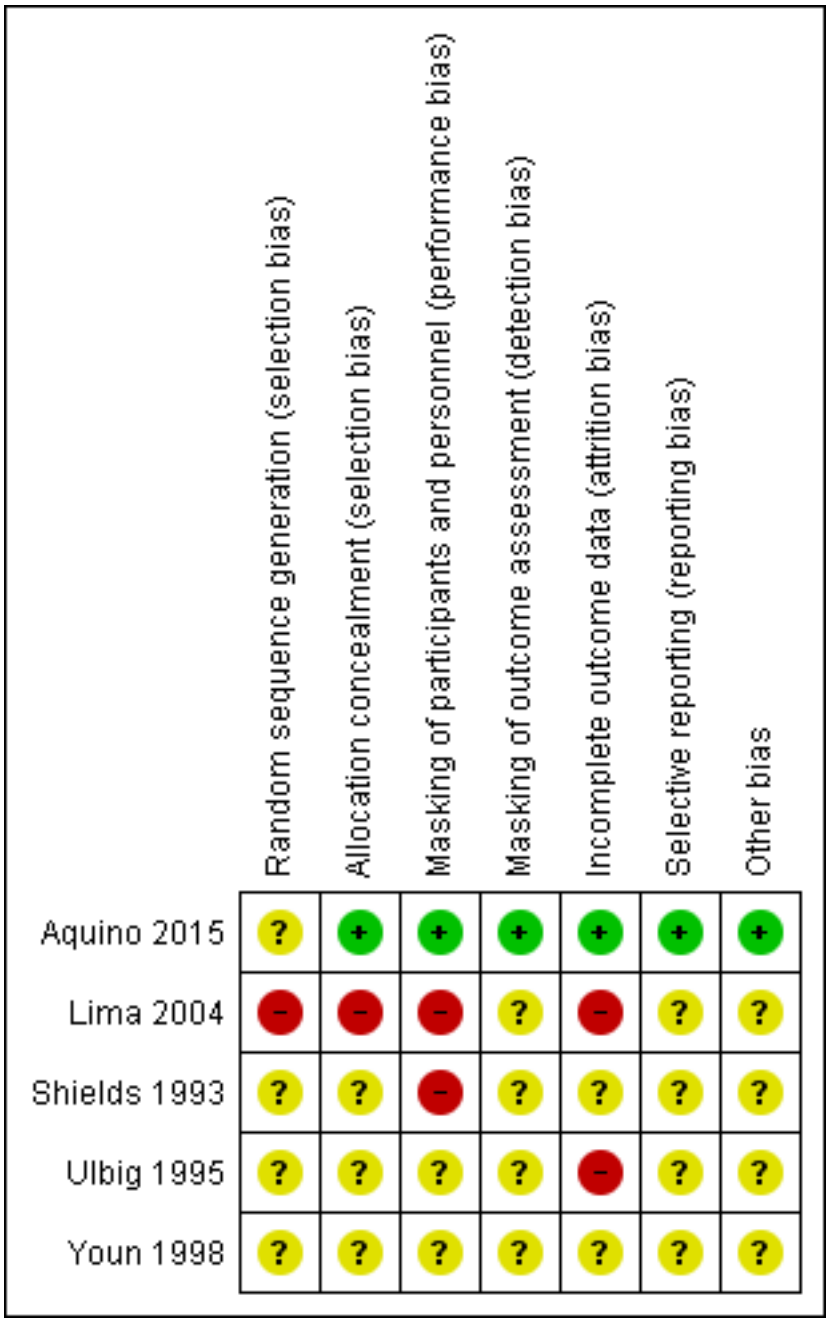
Excluded studies

We excluded 25 studies published in 27 reports after full-text review. The majority were excluded because they were the wrong study design, that is they were not RCTs (n = 20, 74%) (Alves Júnior; Benitez Del Castillo Sanchez 1996; Bloom 2013; Chalam 1999; Chalam 2001; Chen 2013; Cyrlin 1999; Fankhauser 1993; Goldenberg-Cohen 2005; Kaushik 2008; Koraszewska-Matuszewska 2004; Noureddin 1992; Radax 1992; Shukla 1981; Suzuki 1989; Walland 1998; Wei 1999; Xu 2007; Yu 2008; Zhang 2010). We excluded five studies because participants did not meet our criteria for refractory glaucoma (medically uncontrolled glaucoma for which other surgeries have failed) (n = 7, 26%) (Agarwal 2004; Egbert 2001; Liu 2008; Tzamalis 2011). We excluded five additional studies because they had been reported in abstracts (Brooks 1993a; Korte 2002a; Marcus 1992a; Miller-Meeks 1994a; Zweifach 1997a).

Risk of bias in included studies

We judged one included study to have low risk of bias for most domains (Aquino 2015). We classified the other four studies as having unclear risk of bias for the majority of the domains, with high risk for some domains in Lima 2004 and Shields 1993 . See Figure 2 for details.

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



Allocation

We judged selection bias in two parts: random sequence generation and allocation concealment before assignment.

We judged all included studies to have unclear risk of selection bias based on random sequence generation, largely due to lack of information. Aquino 2015 did not specify that computer randomization was used, but stated that randomization codes were obtained from opaque, sealed envelopes. Ulbig 1995 and Youn 1998 did not report sequence generation. Shields 1993 reported that participants were randomized using a series of random numbers, but did not clarify how the numbers were generated. The authors of Lima 2004 stated that their participants were not truly randomized, as they randomized only the first participant and thereafter alternated between the two interventions. We judged this study to be at high risk for selection bias, although the authors stated that they believed their method was a way to assign the same number of eyes to each group; that there were no biases in the eligibility criteria; and their method "did not influence the distribution" of the participants.

We judged only one study to have low risk of bias based on allocation concealment: Aquino 2015 reported the use of opaque, sealed envelopes. Allocation concealment before assignment was not mentioned in the reports of the rest of the included studies.

Masking (performance bias and detection bias)

We judged Aquino 2015 to have low risk of both performance and detection bias, as it was stated that participants and outcome assessors were masked. The report authors noted that it was not possible to mask the surgeon due to the need to use different probes in the two interventions.

In Lima 2004, masking of participants or study personnel was not possible due to the nature of the interventions (cyclodestructive procedure or drainage device implantation), therefore we judged this study to be at high risk of performance bias. Similarly, in Shields 1993, the CPC procedures were performed by unmasked surgeons, resulting in a judgement of high risk of performance bias. Neither of these studies reported whether outcomes assessors were masked, thus we judged both to have an unclear risk of detection bias.

Two studies did not mention masking; we judged them to have unclear risk of both performance and detection bias (Ulbig 1995; Youn 1998).

Incomplete outcome data

We judged one of the included studies to have low risk of attrition bias: Aquino 2015 reported no participants lost to follow-up at the one-year visit. In two studies, participants who were excluded or lost to follow-up were simply excluded from the final analysis (45% and 14.7% for Ulbig 1995 and Lima 2004, respectively, three months after intervention). We rated both studies as having a high risk of attrition bias. We judged Youn 1998 to have unclear risk of attrition bias because the number of participants who were excluded and/or lost to follow-up, if any, was not reported. We judged Shields 1993 to have an unclear risk of attrition bias because the length of follow-up varied among participants after the four-week mark.

Selective reporting

Four included studies had no protocol available, thus it was unclear whether there was selective reporting bias (Lima 2004; Shields 1993; Ulbig 1995; Youn 1998). We judged only included study to have low risk of selective reporting, as all outcomes for which data had been collected were reported (Aquino 2015).

Other potential sources of bias

We rated one study as at low risk of other potential sources of bias (Aquino 2015). We judged Lima 2004, Shields 1993, Ulbig 1995, and Youn 1998 to have unclear risk of bias for this domain because financial sources and conflicts of interest were not reported.

Effects of interventions

See: **Summary of findings for the main comparison** Endoscopic cyclophotocoagulation compared with the Ahmed drainage implant for refractory glaucoma; **Summary of findings 2** Micropulse versus continuous-wave cyclophotocoagulation for refractory glaucoma; **Summary of findings 3** Comparison of two cyclophotocoagulation lasers for refractory glaucoma; **Summary of findings 4** Comparison of two cyclophotocoagulation energy levels for refractory glaucoma

Primary comparison: cyclodestructive procedure versus another glaucoma treatment

Only one of the included studies compared a cyclodestructive procedure with another type of glaucoma treatment (Lima 2004). The Ahmed tube shunt was implanted in a standard fashion and tube secured 8 mm from the limbus in the superior temporal quadrant and positioned 2 to 3 mm into the anterior chamber. The ECP was performed by a superior temporal pars plana incision, 3.5 mm from the limbus with a power of 0.5 W, continuous mode for approximately 2 seconds to 210 degrees of the ciliary body.

Primary outcome: change from baseline in pain control

Change in pain severity was not assessed.

Secondary outcome: mean change in intraocular pressure from baseline

Lima 2004 reported mean IOP at various time points rather than the mean change in IOP from baseline. Because baseline IOP was similar in both groups (41.61 mmHg in the ECP group and 41.32 mmHg in the Ahmed implant group), we used the mean difference (MD) in mean IOPs to estimate the between-group treatment effects (Analysis 1.1). At one-week follow-up, the group that received ECP had higher IOP compared with the group that received the Ahmed implant (MD 4.12 mmHg, 95% confidence interval (CI) 1.79 to 6.45). At one month postoperatively, the mean IOPs in the two groups were similar (MD 0.56 mmHg, 95% CI -2.50 to 3.62). At three months, the group that received ECP had lower IOP compared with the group that received the Ahmed implant (MD -6.83 mmHg, 95% CI -9.73 to -3.93). At six months, the group that received ECP still had lower IOP compared with the group that received the Ahmed implant, although there was less of difference than at three months (MD -3.78 mmHg, 95% CI -6.18 to -1.38). At 12 and 24 months, the mean IOPs were again similar in both groups (MD -1.14 mmHg, 95% CI -4.21 to 1.93 and MD -0.66 mmHg, 95% CI -4.30 to 2.98, respectively). It was noted that reduced IOP from baseline stabilized after two months in eyes treated with ECP, but gradually rose, then reduced, in the Ahmed implant group. We assessed the certainty of evidence for IOP outcomes as low, downgrading for risk of bias (-1) and imprecision (-1).

Secondary outcome: mean change in best-corrected visual acuity in study eyes at 12 months postintervention

Mean change in visual acuity at 12 months postintervention was not reported; however, mean logMAR visual acuity at 24 months postintervention was reported. At 24 months postintervention, visual acuity in logMAR was 0.74 ± 0.42 for 28 participants in the ECP group and 0.98 ± 0.61 for 26 participants in the Ahmed implant group (MD -0.24 logMAR, 95% CI -0.52 to 0.04). In addition, at 24 months postoperatively, fewer participants in the ECP group (16%) were classified as having worse visual acuity from baseline than in the Ahmed implant group (37.5%). The authors did not define how much worse than baseline they used for classifying "visual acuity worsening," nor did the authors report the numerator or denominators for these proportions. We assessed the certainty of evidence for visual acuity outcomes as very low, downgrading for risk of bias (-1), imprecision (-1), and indirectness (-1).

Secondary outcome: mean change in the mean deviation in study eyes from baseline at 12 months postintervention

This outcome was not assessed in Lima 2004.

Secondary outcome: mean number of glaucoma medications at 12 months postintervention

Mean number of glaucoma medications was reported at 24 months rather than at 12 months. The mean number of glaucoma medications was 2.0 ± 1.2 in the ECP group (n = 28) and 2.5 ± 1.3 in the Ahmed drainage implant group (n = 26) (MD -0.50, 95% CI -1.17 to 0.17). We assessed the certainty of evidence for number of glaucoma medications as very low, downgrading for risk of bias (-1), imprecision (-1), and indirectness (-1).

Secondary outcome: proportion of study eyes requiring additional glaucoma surgery by 12 months postintervention

Lima 2004 did not report whether any eye required additional glaucoma surgery by 12 months postintervention.

Adverse events

Lima 2004 reported "complications during the study" rather than a specific follow-up time. Prolonged inflammation was not reported; one case of hypotony and one case of phthisis bulbi were identified in the ECP group (2.9% of 34 participants), but none in the Ahmed implant group. Conversely, one case of endophthalmitis was reported in the group that received the Ahmed drainage implant, compared with none in the ECP group (2.9% of 34 participants). Retinal detachment occurred in both study arms, in one participant in the ECP group (2.9%) and two participants in the Ahmed implant group (5.9%). No case of choroidal hemorrhage was reported; however, choroidal detachment occurred in one participant in the ECP group (2.9%) compared with six participants in the Ahmed implant group (17.6%). We assessed the certainty of evidence for adverse events as very low, downgrading for risk of bias (-1), imprecision (-1), and indirectness (-1).

Quality of life

This outcome was not assessed or reported by Lima 2004.

Secondary comparison: cyclodestructive procedure versus another cyclodestructive procedure

Micropulse cyclophotocoagulation versus continuous-wave cyclophotocoagulation

In micropulse CPC, the laser is used with repetitive, short pulses of energy (2 W) separated by a break period for a total of 62.5 J. This was compared with the conventional CPC method (1.4 to 2 W, 2 seconds per burn, 20 to 28 burns/eye; 60 to 112 J), which uses a continuous wave of high energy delivered to the eye, in Aquino 2015.

Primary outcome: change from baseline in pain control

Pain control at 12 months was not assessed in Aquino 2015. However, before treatment and one week after treatment, the study investigators asked participants to rate their pain levels as "no pain," "mild," "moderate," or "severe." Before surgery the numbers of participants who rated their pain as "mild" and "moderate" were six (27%) and one (5%), and seven (32%) and one (4%), in the micropulse CPC group (n = 22) and the continuous-wave CPC group (n = 22), respectively. No participant said they had "severe" pain before surgery. After surgery, all participants in the micropulse CPC group reported "no pain," while two (9%) and one (5%) in the continuous-wave CPC group rated pain as "mild" and "moderate," respectively. No participant in either group said they had "severe" pain at one week after surgery. It should be noted that the study authors interpreted pain ratings from the first week assessment as equivalent to discomfort related to the laser treatment and not to glaucoma.

Secondary outcome: mean change in intraocular pressure from baseline

Aquino 2015 did not present mean IOPs, but reported that the median IOP was not significantly different between the two groups at any time point. This study used survival analysis to show a significant difference in the number of participants who had achieved an IOP between 6 mmHg and 21 mmHg with at least 30% IOP reduction from baseline (the study's primary outcome) at one year: 75% of participants in the micropulse CPC group (n = 24) compared with 29% of participants in the continuous-wave CPC group (n = 24). By 18 months postoperatively, they reported no statistically significant difference.

Secondary outcome: mean change in best-corrected visual acuity in study eyes at 12 months postintervention

Mean change in visual acuity was not reported in Aquino 2015, but the report stated that one participant in the micropulse CPC group (n = 23) and two participants in the continuous-wave CPC group (n = 23) exhibited worsened visual acuity.

Secondary outcome: mean change in the mean deviation in study eyes from baseline to 12 months postintervention

This outcome was not reported in Aquino 2015.

Secondary outcome: mean number of glaucoma medications at 12 months postintervention

Aquino 2015 did not assess the number of glaucoma medications used by participants at 12 months postintervention. The study authors reported that at the 18-month follow-up, the median number of IOP-lowering medications was reduced from two to one in both the micropulse CPC group and the continuous-wave CPC group.

Secondary outcome: proportion of study eyes requiring additional glaucoma surgery by 12 months postintervention

This outcome was not reported in Aquino 2015.

Adverse events

The authors noted that they observed more complications in the continuous-wave CPC group than in the micropulse CPC group. Prolonged anterior chamber inflammation and phthisis bulbi occurred in more eyes treated with continuous-wave CPC compared with micropulse CPC (seven eyes or 30% versus one eye or 4% for prolonged inflammation and one eye or 4% versus no eyes for phthisis bulbi, for continuous-wave CPC and micropulse CPC, respectively). Hypotony was observed in five eyes treated with continuous-wave CPC but none treated with micropulse CPC. Other adverse events such as fibrin exudates, endophthalmitis, retinal detachment, and choroidal hemorrhage were not mentioned.

Quality of life

Aquino 2015 did not assess quality of life.

Cyclophotocoagulation using a semiconductor diode laser versus Nd:YAG laser

Two trials compared two types of cyclodestructive lasers (Ulbig 1995; Youn 1998). In both trials, a 810-nanometer diode laser was compared to a 1064-nanometer Nd:YAG laser; however, the two trials used different brands of diode lasers (Ulbig 1995 used the Microlase continuous-wave semiconductor diode laser, and Youn 1998 used the OcuLight SLx with a handheld fiber optic G-probe diode laser).

Primary outcome: change from baseline in pain control

Neither trial reported outcomes related to pain control.

Secondary outcome: mean change in intraocular pressure from baseline

Both trials reported mean IOP at one week and one month after surgery. There was uncertainty as to which intervention group had a lower IOP when comparing the semiconductor laser with the Nd:YAG laser at these time points (MD -1.45 mmHg, 95% CI -5.70 to 2.80 and MD -0.69 mmHg, 95% CI -4.29 to 2.90, for one week and one month, respectively) (Analysis 2.1). At three months, Ulbig 1995 reported an MD of -1.90 mmHg (95% CI -15.84 to 12.04) when comparing the group that received cyclodestructive surgery with a semiconductor diode laser versus with an Nd:YAG laser. However, many participants were not included in the three-month follow-up (40% in the semiconductor diode group and 50% in the Nd:YAG group). Youn 1998 reported the mean IOP at 6 months and 12 months postoperatively: MD -0.06 mmHg (95% CI -3.28 to 3.16) and MD 1.02 mmHg (95% CI -1.49 to 3.53), respectively. It should be noted that Youn 1998 did not provide the total number of participants analyzed for each time point; in our analysis, we used the number randomized into each intervention. The study did not provide details about missing data or loss to follow-up. We assessed the certainty of evidence for IOP outcomes as low, downgrading for risk of bias (-1) and imprecision (-1).

Secondary outcome: mean change in best-corrected visual acuity in study eyes at 12 months postintervention

Neither trial reported mean change in best-corrected visual acuity; however, both trials reported some information related to visual acuity. Ulbig 1995 reported that the evaluation of visual acuity measurements was "inconclusive owing to the very poor visual function in the majority of treated eyes at entry level." It was stated that there was no significant change in vision and no significant difference in the course of visual acuity based on the laser used, but quantitative data were not provided. Youn 1998 reported that at the last follow-up visit, 25 of 34 participants in the diode group and 25 of 30 participants in the Nd:YAG group showed increased corrected visual acuity of more than two lines on the Snellen chart (or one line on the low-vision category) or no change in corrected visual acuity (risk ratio (RR) 0.88, 95% CI 0.68 to 1.14). Thus, they also reported that visual acuity was decreased in nine participants in the diode group and five participants in the Nd:YAG group (RR 1.59, 95% CI 0.60 to 4.22). We assessed the certainty of evidence for visual acuity outcomes as very low, downgrading for risk of bias (-1), imprecision (-1), and indirectness (-1).

Secondary outcome: mean change in the mean deviation in study eyes from baseline at 12 months postintervention

Neither Ulbig 1995 nor Youn 1998 reported visual field outcomes.

Secondary outcome: mean number of glaucoma medications at 12 months postintervention

Neither Ulbig 1995 nor Youn 1998 reported on the number of glaucoma medications used by participants after the CPC procedure.

Secondary outcome: proportion of study eyes requiring additional glaucoma surgery by 12 months postintervention

Ulbig 1995 did not report on the number of participants who needed additional glaucoma surgery. Youn 1998 reported that 6/49 (12.2%) participants in the diode laser group and 4/46 (8.6%) in the Nd:YAG laser group underwent repeat CPC (RR 1.41, 95% CI 0.42 to 4.67). They did not note the assessment time point or whether other participants underwent other additional glaucoma surgeries. We assessed the certainty of evidence for this outcome as very low, downgrading for risk of bias (-1), imprecision (-1), and indirectness (-1).

Adverse events

We were unable to synthesize adverse event outcome data, as they were reported at different time points: three months in Ulbig 1995 and 12 months in Youn 1998.

Ulbig 1995 reported that one of 20 (5%) participants in the diode laser group had very mild anterior segment inflammatory response and conjunctival burns. Five of 20 (25%) participants in the Nd:YAG group experienced adverse events on the first day after surgery: hypotony occurred in three participants and hyphema and subconjunctival hemorrhage occurred in one participant each. The authors reported that all complications resolved within two weeks. No other adverse events were reported.

Youn 1998 reported that two of 49 (4%) participants in the diode laser group had hypotony; three (6%) had hyphema; and one participant had phthisis. One of 46 participants (2%) in the Nd:YAG laser group had hypotony, and one participant had hyphema. It was also noted that mild anterior segment inflammation was seen in all participants, especially following the CPC procedures.

Quality of life

Neither Ulbig 1995 nor Youn 1998 assessed quality of life.

Cyclophotocoagulation using an Nd:YAG laser at 8 J versus 4 J

One study compared CPC using two different energy settings (Shields 1993). Outcomes were reported at one day postintervention and at final follow-up (mean of 12.6 months in the 8-joule group and 12.7 in the 4-joule group).

Primary outcome: change from baseline in pain control

Shields 1993 did not assess the change from baseline in pain control at 12 months follow-up; however, data on pain, self reported as "none," "moderate," or "severe" on the day after surgery, were reported in a subset of participants. Fewer participants in the 8-joule group (8/26) reported no pain on the day after surgery than in the 4-joule group (12/24) (RR 0.62, 95% CI 0.31 to 1.24). Thus, more participants in the 8-joule group (18/26) than in the 4-joule group (12/24) reported moderate or severe pain (RR 1.38, 95% CI 0.86 to 2.23). We assessed the certainty of evidence for pain outcomes as very low, downgrading for risk of bias (-1), imprecision (-1), and indirectness (-1).

Secondary outcome: mean change in intraocular pressure from baseline

Change in IOP was measured only at the two-hour and one-day postoperative examinations. Among participants who had the same or lower IOP at one day postoperatively compared with baseline (96% in the 8-joule group and 88% in the 4-joule group), the mean reductions in IOP were 15.5 mmHg and 14.5 mmHg for the 8-joule and 4-joule groups, respectively. The variation in means (e.g. standard deviation) was not reported, thus we did not calculate the between-group mean difference. One participant in the 8-joule group and three participants in the 4-joule group had a rise in pressure (increase of 1 mmHg in the 8-joule group and 6 to 23 mmHg in the 4-joule group).

Secondary outcome: mean change in best-corrected visual acuity in study eyes at 12 months postintervention

In Shields 1993, visual acuity changes were reported for the participants who did not require further surgery up to final follow-up: 33 (75%) of the 8-joule group and 27 (60%) of the 4-joule group. Visual acuity was unchanged or improved in 21/33 participants in the 8-joule group and 20/27 participants in the 4-joule group (RR 0.86, 95% CI 0.61 to 1.21). Thus, visual acuity was reduced in 12/33 participants in the 8-joule group and 7/27 participants in the 4-joule group (RR 1.40, 95% CI 0.64 to 3.06). We assessed the certainty of evidence for visual acuity outcomes as very low, downgrading for risk of bias (-1), imprecision (-1), and indirectness (-1).

Secondary outcome: mean change in the mean deviation in study eyes from baseline at 12 months postintervention

This outcome was not reported by Shields 1993.

Secondary outcome: mean number of glaucoma medications at 12 months postintervention

Shields 1993 did not report the mean number of glaucoma medications at 12 months postintervention, but stated that 17/31 (54.8%) participants in the 8-joule group and 7/19 (36.8%) participants in the 4-joule group reduced the number of medications they were taking, though the time point of this assessment was not reported (RR 1.49, 95% CI 0.76 to 2.91). Again, only participants who did not require further surgery were assessed for this outcome. We assessed the certainty of evidence for this outcome as very low, downgrading for risk of bias (-1), imprecision (-1), and indirectness (-1).

Secondary outcome: proportion of study eyes requiring additional glaucoma surgery by 12 months postintervention

Shields 1993 reported that 33/44 (75%) and 27/45 (60%) participants treated with the 8-joule and 4-joule Nd:YAG laser, respectively, required no additional glaucoma surgery by the last follow-up time point in the study. Eleven of 44 (25%) participants in the 8-joule group compared with 18/45 participants (40%) in the 4-joule group required additional glaucoma surgery after the first CPC procedure (RR 0.63, 95% CI 0.33 to 1.17). We assessed the certainty of evidence for additional surgeries as very low, downgrading for risk of bias (-1), imprecision (-1), and indirectness (-1).

Adverse events

Severe reactions, defined as the presence of fibrin or hyphema, were seen in five participants who received 8 J of energy and were not observed in the group treated with 4 J of energy two hours after the intervention. One day after surgery, there were mild, medium, and severe anterior chamber reactions in one (3%), 14 (54%), and 11 (42%) of the 26 participants who received 8 J of energy during their Nd:YAG CPC, respectively. There was a mild anterior chamber reaction in four participants (19%), a moderate anterior chamber reaction in 15 participants (71%), and a severe reaction in two participants (10%) of 21 participants who received 4 J of energy.

Quality of life

Shields 1993 did not assess quality of life.

DISCUSSION

Summary of main results

We identified five trials that met the inclusion criteria for this review. These studies analyzed outcomes for 330 eyes of 326 participants. The studies were conducted in Brazil, Singapore, the United Kingdom, and the United States. We judged one study to have a low risk of bias for most 'Risk of bias' domains; we judged the other studies to be at unclear risk of bias overall. This review included four different comparisons:

1. ECP versus Ahmed implant (1 RCT, 68 eyes, Summary of findings for the main comparison);
2. micropulse CPC versus continuous-wave CPC (1 RCT, 48 eyes, Summary of findings 2);
3. CPC with a diode laser versus Nd:YAG laser (2 RCTs, 135 eyes, Summary of findings 3); and
4. CPC with an Nd:YAG laser emitting 8 J versus 4 J of energy (1 RCT, 89 eyes, Summary of findings 4).

No study reported data for our primary outcome, change from baseline in pain control as reported by the participant or change in number of pain medications. In two studies, participants were asked to rate their level of pain after surgery, but these pain ratings were regarded as equivalent to discomfort related to the treatment rather than related to disease control.

Our primary comparison was a cyclodestructive procedure versus another glaucoma treatment. The comparison identified for this review was ECP compared with an aqueous shunt implant. Pain was not assessed in this study. Intraocular pressure was higher in the group that received ECP at one week; similar at one month; higher in the group that received the Ahmed implant at three and six months; and similar at the 12- and 24-month follow-up. Visual acuity was not significantly different at 24 months postintervention, although it was noted that the aqueous shunt group had a greater incidence of eyes in which visual acuity had worsened.

Three types of comparisons from four included studies fit our secondary comparison. The study that compared micropulse with continuous-wave CPC did ask participants about pain, but indicated that any pain reported one week after surgery was due to the laser treatment and not glaucoma. This study reported median rather than mean IOPs, but stated that IOP was similar between the two groups at all time points. In addition, more complications were noted in the continuous-wave CPC group. Two studies compared a semiconductor diode versus an Nd:YAG laser for CPC. Pain was not an outcome in either study, but we were able to perform a meta-analysis on the IOPs at one week and one month postoperatively (MD -1.5, 95% CI -5.7 to 2.8 and MD -0.7, 95% CI -4.3 to 2.9,

respectively). The last comparison was a study comparing CPC using the same type of laser but with different energy settings. There were no significant differences in outcomes based on level of energy for IOP, visual acuity, and number of glaucoma medications required, however more serious adverse events occurred in the participants who were treated with CPC at a higher energy setting.

The most commonly reported adverse events across all five studies were hypotony and phthisis bulbi. There did not appear to be a statistically significant difference in the incidence of these events by type of surgery. Since adverse events were reported at various time points and sometimes only broadly as "during follow-up," only minimal synthesis of the data was possible.

Overall completeness and applicability of evidence

This review included five studies with very different interventions. Though each study included at least one arm that was a cyclodestructive procedure, meta-analysis of outcome data was limited to two studies. Our primary goal in this review was to compare cyclodestructive procedures with other glaucoma treatments. Unfortunately, only one study analyzed this type of comparison. That study compared ECP with an aqueous shunt. We did not identify any other studies that used ECP, so while we found a lack of conclusive evidence about the benefit of ECP versus an Ahmed implant, we were unable to compare ECP to other types of CPC or other cyclodestructive procedures. Among the studies that compared CPC with different parameters, many outcomes were not reported. While it may be useful to know whether outcomes are better with a certain type of laser (micropulse compared with continuous stream, for example), such studies do not provide insight into whether CPC in any form provides better outcomes for refractory glaucoma patients compared with other types of cyclodestructive surgery or traditional glaucoma surgeries.

Two of our outcomes of interest were not reported in any of the included studies. In addition to pain, we were interested in the quality of life of participants undergoing the various treatments and cyclodestructive procedures. Information for this outcome would be useful, as patient-reported outcomes can help support a surgery if efficacy and safety are similar between the two. Additionally, visual field data were not reported in any of the included studies. This outcome is clinically important as it evaluates vision loss due to glaucoma and can complement IOP measures for determining the severity of the disease. However, given that people with refractory glaucoma are at a very advanced stage of the disease with a very low acuity and advanced visual field defects, it may be difficult to properly assess the effect of treatment on quality of life or visual field loss.

There is also some concern about the differences in the types of participants included in this review. Most of the studies enrolled participants in which traditional surgical approaches had failed or were not possible/not appropriate. One study specified that they would only enroll participants who had at least one previous trabeculectomy, while another allowed participants "with or without previous surgical intervention." These differences in types of participants help cover the spectrum of 'real-world' glaucoma patients, but make it difficult to compare the results of one study to the results of another.

Certainty of the evidence

Due to the differences in interventions across our five included studies, we were able to conduct a meta-analysis using data from only two studies. Several of our outcomes of interest were not reported in these two studies. Intraocular pressure at a time point was the only outcome for which we were able to conduct meta-analysis. We graded the certainty of the evidence as low, downgrading for risk of bias because one of the trials had serious issues with potential attrition bias and imprecision of the effect estimates. For other outcomes in the review, we also downgraded for indirectness because outcomes were reported at shorter time points or at "final" follow-up visits, which were not consistent among all participants in a trial.

Potential biases in the review process

We followed Cochrane standards for this review with the hopes of minimizing bias. Two review authors independently screened the studies and made decisions on inclusion. Data were extracted independently by two review authors and then reconciled by a third review author. Potential bias could arise due to the fact that much of the trial reporting was unclear. At some points in this review we had to make decisions and assumptions about the number of participants in order to analyze the data in a meaningful way. Additonally, we chose to include one trial that was quasi-randomized based on the study authors reporting that their quasi-randomization process was as good as true randomization.

Agreements and disagreements with other studies or reviews

There are few large studies or other reviews examining cyclodestructive procedures. To our knowledge, there has been no systematic review that attempted to evaluate all types of cyclodestructive procedures that: (a) compared cyclodestructive procedures with other glaucoma surgeries and (b) compared cyclodestructive procedures with each other, as we have done in this review. We did identify a small number of publications to which we can compare our results. A retrospective cohort analysis of 5570 Medicare patients who underwent either cyclodestructive procedure or a drainage device procedure found that when repeat procedures were not included in the definition of an adverse outcome, eyes that received a drainage device procedure had 3.8 times higher odds of an adverse outcome than eyes that received a cyclodestructive procedure (odds ratio 3.8, 95% CI 3.07 to 4.67) (Topouzis 1998). The cyclodestructive procedures in the study included cyclodialysis, cyclodiathermy, cyclocryotherapy, and cyclophotocoagulation. In the one study we included that compared a cyclodestructive procedure to a drainage device (Lima 2004), there was an unclear difference in the risk of complications during the study. Another study published in 2001 reported that their aim was to evaluate the efficacy of contact diode laser CPC using different treatment parameters (Mistlberger 2001). As part of our secondary comparison, we included one study that used contact diode for CPC (Aquino 2015). Mistlberger 2001 examined 206 eyes treated between April 1991 and September 1997 with a diode laser through a contact probe. Mean IOP was reduced from 42.1 ± 11.0 mmHg to 17.3 ± 10.9 mmHg at 12 months. This is an approximately 60% reduction in IOP from baseline. We did not identify large cohort studies and systematic reviews on the other types of interventions included in this review.

AUTHORS' CONCLUSIONS

Implications for practice

Due to differences in interventions, the evidence from the five studies included in this review was inconclusive, and we cannot make any clinical recommendations regarding the use of cyclodestructive procedures. We were unable to answer our main questions as to whether cyclodestructive procedures for refractory glaucoma result in better outcomes or fewer complications than other glaucoma treatments and if so, if one type of cyclodestructive procedure is better than the others. Several of our comparisons had only one included study, and a new trial of the same comparison would be very likely to change the estimate. For the comparison that had two included studies, cyclophotocoagulation with a neodymium:yttrium-aluminum-garnet (Nd:YAG) laser compared to cyclophotocoagulation with a diode laser, we rated the certainty of the evidence as low for the treatments' effects on intraocular pressure, the only outcome we were able to synthesize. Our primary outcome of changes in pain was either not addressed at all or not addressed adequately for comparison in the included studies.

Implications for research

Large, well-designed randomized controlled trials comparing different types of cyclodestructive procedures with other glaucoma surgeries are needed. If cyclophotocoagulation is found to be the most effective and/or safest cyclodestructive procedure, other studies addressing the various parameters (Nd:YAG versus diode laser, contact versus non-contact, amount of energy, and micropulse versus continuous wave) are warranted. The types of participants should be addressed with care, as there may be differences in effectiveness among participants who have had previous surgical intervention and those who have not. Despite the fact that people with refractory glaucoma often have advanced disease, patient-reported outcomes such as pain and quality of life are needed and should be included in the primary outcomes of these trials.

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CHARACTERISTICS OF STUDIES

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

Aquino 2015

Methods	**Study design:** parallel-group RCT **Number randomized:** 48 total; 24 eyes of 24 participants in the MPCPC group, 24 eyes of 24 participants in the CWCPC group **Unit of analysis:** individual (1 eye per participant) **Number analyzed:** 48 total; 24 eyes of 24 participants in the MPCPC group, 24 eyes of 24 participants in the CWCPC group **Exclusions and losses to follow-up:** no exclusions, 1 participant in each group was lost to follow-up after 1 year of follow-up **How were missing data handled?:** excluded from analysis **Reported power calculation:** yes, power of 97% to distinguish between the two treatments in achieving the primary outcome (IOP between 6 and 21 mmHg and at least a 30% reduction with or without anti-glaucoma medications after 12 months).
Participants	**Country:** Singapore **Age:** median 63.5 years in the MPCPC group and 66 years in the CWCPC group **Gender:** 17 (71%) men and 7 (29%) women in the MPCPC group; 14 (58%) men and 10 (42%) women in the CWCPC group **Inclusion criteria:** aged 21 years old and above, with refractory glaucoma defined as IOP > 21 mmHg unresponsive to maximal tolerated medical therapy with or without previous surgical intervention, who were poor candidates for a filtration procedure and who had best-corrected visual acuity of 6/60 or worse **Exclusion criteria:** ocular infection, inflammation or eye surgery in the study eye in the 2 months prior to enrollment

Aquino 2015 *(Continued)*

	Equivalence of baseline characteristics: yes
Interventions	**Intervention 1:** micropulse cyclophotocoagulation **Intervention 2:** continuous-wave cyclophotocoagulation **Length of follow-up:** mean follow-up 17.5 ± 1.6 months, range 16 to 19 months
Outcomes	**Primary outcome, as defined in study reports:** success defined as IOP between 6 and 21 mmHg and at least 1 30% reduction in IOP at the final follow-up with or without IOP-lowering medications **Secondary outcomes, as defined in study reports:** visual acuity; number of repeat treatments; number of IOP-lowering medications at 18 months **Adverse events reported:** yes **Intervals at which outcomes assessed:** 1 day, 1 week, 1 month, 3 months, 6 months, 12 months, and 18 months
Notes	**Trial registration:** NCT00349414 **Funding sources:** "No stated funding sources" **Disclosures of interest:** "No stated conflict of interest" **Study period:** between January 2007 and December 2008 **Reported subgroup analyses:** no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	After informed consent, a randomization code was obtained from 1 of the sequentially numbered, opaque, sealed envelopes.
Allocation concealment (selection bias)	Low risk	After informed consent, a randomization code was obtained from 1 of the sequentially numbered, opaque, sealed envelopes.
Masking of participants and personnel (performance bias)	Low risk	Laser treatment was performed by a single surgeon (AMT). It was not possible to mask the surgeon performing the laser procedure because different probes were used for MPCPC and CWCPC, but participants were masked regarding the type of laser intervention received.
Masking of outcome assessment (detection bias)	Low risk	Quote: "IOP was measured using Goldmann applanation tonometry (GAT) by an ophthalmologist masked to the treatment group"
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 participant from each group missed the final follow-up at 18 months; all participants were followed for at least 1 year.
Selective reporting (reporting bias)	Low risk	All outcomes collected were reported.
Other bias	Low risk	No other source of bias

Lima 2004

Methods	**Study design:** parallel-group quasi-RCT

Lima 2004 *(Continued)*

	Number randomized: 68 participants total, 34 eyes of 34 participants in the ECP group, 34 eyes of 34 participants in the Ahmed group **Unit of analysis:** individual (1 eye per participant was included) **Number analyzed:** 58 eyes of 58 participants at 12 months; 54 eyes of 54 participants at 24 months. Per group: 31 eyes of 31 participants in the ECP group and 27 eyes of 27 participants in the Ahmed group; 28 in the ECP group and 26 in the Ahmed group at 24 months **Exclusions and losses to follow-up:** no exclusions, 10 participants at 12 months; 14 participants at 24 months **How were missing data handled?:** not reported **Reported power calculation:** no **Unusual study design:** "The first eligible patient was randomized either to ECP or Ahmed drainage implantation, and then alternated consecutively with both techniques"; "Patients who reached a failure end point were censored from further analyses. However, their IOP was included in the average IOP calculation at this time"
Participants	**Country:** Brazil **Age:** mean 53.76 years in the ECP group and 56.64 years in the Ahmed group **Gender:** 20 (59%) men and 14 (41%) women in the ECP group; 19 (56%) men and 15 (44%) women in Ahmed group **Inclusion criteria:** all pseudophakic with an IOP greater than or equal to 35 mmHg on maximum tolerated therapy, with at least 1 previous trabeculectomy with antimetabolite, and a visual acuity better than light perception **Exclusion criteria:** eyes that had previous glaucoma drainage device implantation or a cyclodestructive procedure; eyes that did not perceive light; eyes that had a retinal or choroidal detachment; or eyes with a failed corneal graft **Equivalence of baseline characteristics:** yes
Interventions	**Intervention 1:** endoscopic cyclophotocoagulation **Intervention 2:** Ahmed drainage implant **Length of follow-up:** 21.29 ± 6.42 (from 2 to 24) months for the ECP eyes; 19.82 ± 8.35 (from 2 to 24) months for the Ahmed group (P = 0.4)
Outcomes	**Primary outcome, as defined in study reports:** success defined as an IOP greater than 6 mmHg and below 21 mmHg at 24 months of follow-up with or without maximum tolerated therapy **Secondary outcomes, as defined in study reports:** number of medications used, visual acuity **Adverse events reported:** yes **Intervals at which outcomes assessed:** 7 days, 1, 2, 3, 4, 5, 6, 12, 18, and 24 months
Notes	**Funding sources:** not reported **Disclosures of interest:** not reported **Study period:** recruitment from January 1998 to April 2000 **Reported subgroup analyses:** no
Risk of bias	

Lima 2004 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quote: "The first eligible patient was randomized either to ECP or Ahmed drainage implantation, and then alternated consecutively with both techniques. Although our patients were not truly randomized, they followed an alternating sequence that was established before the beginning of the study, attempting to assign the same number of eyes in each group. We believe that there were no biases in the eligibility criteria, which means we did not influence the distribution of our patients."
Allocation concealment (selection bias)	High risk	Allocation by alternating assignment
Masking of participants and personnel (performance bias)	High risk	Not reported, but masking was not possible due to the nature of the interventions
Masking of outcome assessment (detection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	10 (14.7%) participants at 12 months and 14 (20.6%) participants at 24 months were not included in the final analysis.
Selective reporting (reporting bias)	Unclear risk	Protocol not available
Other bias	Unclear risk	Funding source and interest was not reported.

Shields 1993

Methods	**Study design:** parallel-group RCT **Number randomized:** 89 eyes of 89 participants; 45 eyes of 45 participants in 4-joule group, 44 eyes of 44 participants in 8-joule group **Exclusions after randomization:** none **Number analyzed:** not reported **Unit of analysis:** individual (1 eye per participant was randomly selected) **Losses to follow-up:** not reported **How were missing data handled?:** not reported **Reported power calculation:** no **Unusual study design?:** no
Participants	**Country:** United States **Age:** mean 65.8, range 32 to 89 years in the 4-joule group; mean 60.1, range 11 to 86 years in the 8-joule group **Gender:** 18 (40%) men and 27 (60%) women in the 4-joule group; 22 (50%) men and 22 (50%) women in the 8-joule group

Shields 1993 *(Continued)*

	Inclusion criteria: medically uncontrolled glaucoma for which more traditional surgical approaches such as laser trabeculoplasty, iridotomy, and filtering surgery had failed, were not possible, or were felt to have a low chance of success **Exclusion criteria:** people were excluded who were not sufficiently mature to tolerate retrobulbar anesthesia and laser treatment by slit-lamp delivery **Equivalence of baseline characteristics:** yes
Interventions	**Intervention 1:** transscleral Nd:YAG cyclophotocoagulation with 4 J of laser energy **Intervention 2:** transscleral Nd:YAG cyclophotocoagulation with 8 J of laser energy **Length of follow-up:** mean 12.7 months, range 5 to 21 months in the 4-joule group; 12.6 months, range 5 to 20 months in the 8-joule group
Outcomes	**Primary outcome, as defined in study reports:** Snellen visual acuity; IOP; number of medications used; time from initial to additional surgery **Secondary outcomes, as defined in study reports:** not distinguished **Adverse events reported:** yes **Intervals at which outcomes assessed:** 2 hours, 1 day, 2 to 4 weeks, and thereafter as required
Notes	**Trial registration:** none **Funding sources:** not reported **Disclosures of interest:** not reported **Study period:** not reported **Reported subgroup analyses:** no

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "qualified patients were randomized (by a series of random numbers) into one of two treatment groups: group A or group B"
Allocation concealment (selection bias)	Unclear risk	Not reported
Masking of participants and personnel (performance bias)	High risk	All transscleral Nd:YAG CPC procedures were performed by the authors in an unmasked fashion, no information about participant blinding.
Masking of outcome assessment (detection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Follow-up length varied among participants after 4 weeks.
Selective reporting (reporting bias)	Unclear risk	Protocol not available
Other bias	Unclear risk	Financial support and interest unclear

Ulbig 1995

Methods	**Study design:** RCT
	Number randomized: 40 eyes of 40 participants, 20 eyes in each group
	Exclusions after randomization: 0
	Number analyzed: 40 total, 20 per group
	Unit of analysis: 1 eye per individual
	Losses to follow-up: 18 total losses at 3 months after the intervention
	How were missing data handled?: not reported
	Reported power calculation: no
	Unusual study design?: no
Participants	**Country:** United Kingdom
	Age: mean 55 years (21 to 89 range)
	Gender: 24 men and 16 women
	Inclusion criteria: glaucoma not adequately controlled by topical drugs or laser trabeculoplasty, and for which drainage surgery was not thought to be appropriate
	Exclusion criteria: none
	Equivalence of baseline characteristics: yes
Interventions	**Intervention 1:** cyclophotocoagulation using a continuous wave diode (810 nm)
	Intervention 2: cyclophotocoagulation using a free-running Nd:YAG laser (1064 nm)
	Length of follow-up: 3 months
Outcomes	**Primary outcome, as defined in study reports:** IOP, visual acuity, anterior chamber inflammatory activity
	Secondary outcomes, as defined in study reports: not distinguished
	Adverse events reported: yes
	Intervals at which outcomes assessed: 1 hour, 1 day, 1 week, 1 month, and 3 months
Notes	**Trial registration:** not reported
	Funding sources: "This work was supported by European Science Exchange Programme, the Royal Society, London, grant no 623008.F621/DJHG/LM (MWU), and Deutsche
	Forschungsgemeinschaft (DFG), Bonn, Germany, grant no Ul 109/1-1 (MWU)"
	Disclosures of interest: not reported
	Study period: unclear
	Reported subgroup analyses: no

Risk of bias

Bias	Authors' judgement	Support for judgement

Ulbig 1995 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Masking of participants and personnel (performance bias)	Unclear risk	Not reported
Masking of outcome assessment (detection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	Participants who were excluded or lost to follow-up were not included in the final analysis: 8 (40%) in the diode group and 10 (50%) in the Nd:YAG group at month 3.
Selective reporting (reporting bias)	Unclear risk	Protocol not available
Other bias	Unclear risk	Financial interest not reported; the mean preoperative IOP was lower in the diode laser group (32.1 mmHg, range 12 to 55) compared with the Nd:YAG laser group (39.2 mmHg, range 19 to 67), although it was not statistically significant.

Youn 1998

Methods	**Study design:** parallel-group RCT **Number randomized (total and per group):** 95 eyes of 91 participants; 46 eyes of 46 participants to the Nd:YAG group, 49 eyes of 49 participants to the diode group **Exclusions after randomization:** not reported **Number analyzed:** not reported **Unit of analysis:** eyes **Losses to follow-up:** not reported **How were missing data handled?:** not reported **Reported power calculation:** no **Unusual study design?:** for 4 participants, both eyes of a single participant were separately assigned into intervention groups, and it is unclear if the analysis took into account non-independence of the eyes.
Participants	**Country:** United States **Age:** mean 65.67 years, range 21 to 92 years in total; 65.23 years, range 21 to 92 years in the Nd:YAG group; 66.06 years, range 24 to 92 years in the diode group **Gender:** 51 (54%) men and 44 (46%) women in total; 22 (48%) men and 24 (52%) women in the Nd:YAG group, 29 (59%) men and 20 (41%) women in the diode group **Inclusion criteria:** medically uncontrolled glaucoma for which conventional surgical approaches had failed or were believed to have a poor likelihood of success **Exclusion criteria:** not reported

Youn 1998 *(Continued)*

	Equivalence of baseline characteristics: yes
Interventions	**Intervention 1:** transscleral cyclophotocoagulation using Nd:YAG laser **Intervention 2:** transscleral cyclophotocoagulation using semiconductor diode laser **Length of follow-up:** 10.42 ± 3.16 months
Outcomes	**Primary outcome, as defined in study reports:** corrected visual acuity, IOP, type of glaucoma **Secondary outcomes, as defined in study reports:** not distinguished **Adverse events reported:** yes **Intervals at which outcomes assessed:** 1 week, 1, 6, and 12 months postoperatively
Notes	**Trial registration:** none **Funding sources:** not reported **Disclosures of interest:** not reported **Study period:** not reported **Reported subgroup analyses:** yes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Masking of participants and personnel (performance bias)	Unclear risk	Not reported
Masking of outcome assessment (detection bias)	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Number of participants who were excluded or lost to follow-up was unclear.
Selective reporting (reporting bias)	Unclear risk	Protocol not available
Other bias	Unclear risk	Financial source and interest was not reported; for 4 participants, both eyes of a single participant were separately assigned into intervention groups, and it is unclear if the analysis took into account non-independence of the eyes.

CPC: cyclophotocoagulation
CWCPC: continuous-wave cyclophotocoagulation
ECP: endoscopic cyclophotocoagulation
IOP: intraocular pressure
MPCPC: micropulse cyclophotocoagulation
Nd:YAG: neodymium:yttrium-aluminum-garnet

RCT: randomized controlled trial

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

Study	Reason for exclusion
Agarwal 2004	Patient population not eligible
Alves Júnior	Not RCT or quasi-RCT
Benitez Del Castillo Sanchez 1996	Not RCT or quasi-RCT
Bloom 2013	Not RCT or quasi-RCT
Brooks 1993	Conference abstract
Chalam 1999	Not RCT or quasi-RCT
Chalam 2001	Not RCT or quasi-RCT
Chen 2013	Not RCT or quasi-RCT
Cyrlin 1999	Not RCT or quasi-RCT
Egbert 2001	Patient population not eligible
Fankhauser 1993	Not RCT or quasi-RCT
Goldenberg-Cohen 2005	Not RCT or quasi-RCT
Kaushik 2008	Not RCT or quasi-RCT
Koraszewska-Matuszewska 2004	Not RCT or quasi-RCT
Korte 2002	Conference abstract
Liu 2008	Patient population not eligible
Marcus 1992	Conference abstract
Miller-Meeks 1994	Conference abstract
Noureddin 1992	Not RCT or quasi-RCT
Radax 1992	Not RCT or quasi-RCT
Shukla 1981	Not RCT or quasi-RCT
Suzuki 1989	Not RCT or quasi-RCT
Tzamalis 2011	Patient population not eligible
Walland 1998	Not RCT or quasi-RCT
Wei 1999	Not RCT or quasi-RCT
Xu 2007	Not RCT or quasi-RCT

Study	Reason for exclusion
Yildirim 2009	Patient population not eligible
Yu 2008	Not RCT or quasi-RCT
Zhang 2010	Not RCT or quasi-RCT
Zweifach 1997	Conference abstract

RCT: randomized controlled trial

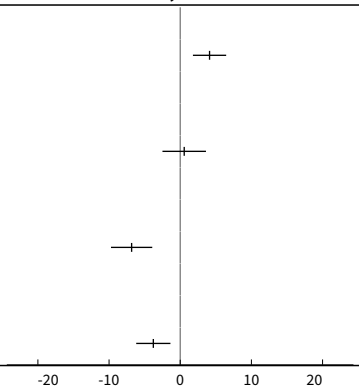
DATA AND ANALYSES

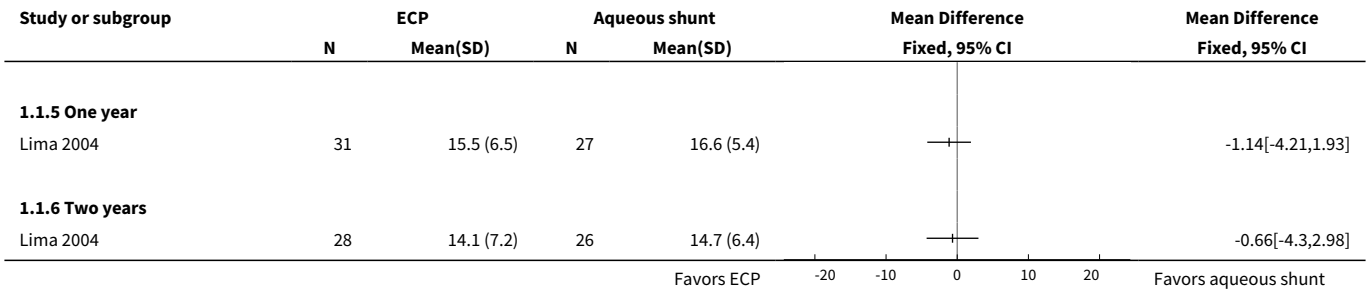
Comparison 1. Endoscopic cyclophotocoagulation versus aqueous shunt

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean intraocular pressure at a time point	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.1 One week	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 One month	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 Three months	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.4 Six months	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.5 One year	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.6 Two years	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 1.1. Comparison 1 Endoscopic cyclophotocoagulation versus aqueous shunt, Outcome 1 Mean intraocular pressure at a time point.

Study or subgroup	ECP N	ECP Mean(SD)	Aqueous shunt N	Aqueous shunt Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
1.1.1 One week						
Lima 2004	34	9.5 (5.2)	34	5.4 (4.6)		4.12[1.79,6.45]
1.1.2 One month						
Lima 2004	34	11.4 (5)	34	10.8 (7.6)		0.56[-2.5,3.62]
1.1.3 Three months						
Lima 2004	33	13.6 (6.2)	32	20.4 (5.7)		-6.83[-9.73,-3.93]
1.1.4 Six months						
Lima 2004	31	14 (3.6)	28	17.8 (5.5)		-3.78[-6.18,-1.38]

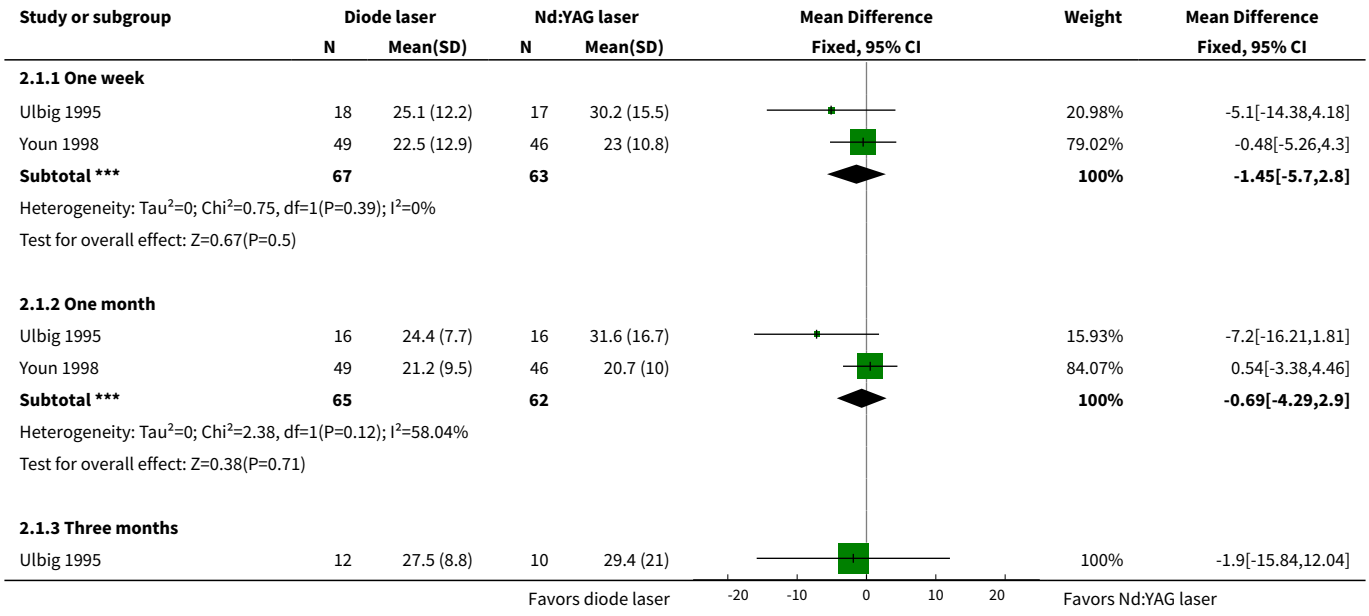


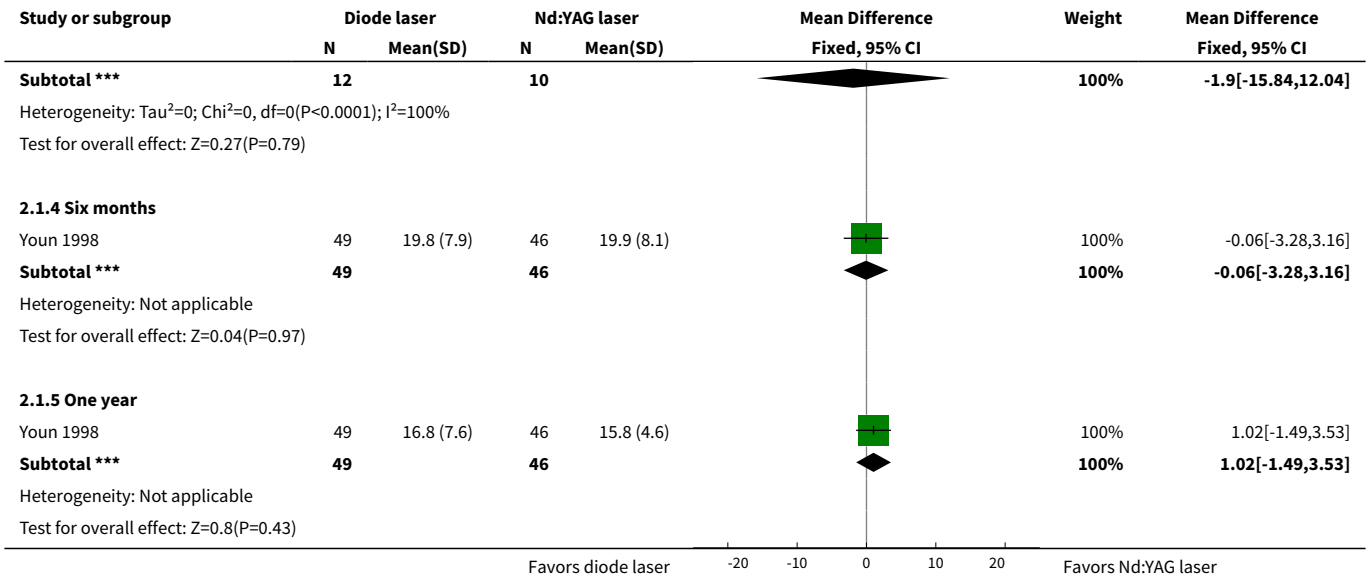


Comparison 2. Cyclophotocoagulation using a semiconductor diode laser versus Nd:YAG laser

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean intraocular pressure at a time point	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 One week	2	130	Mean Difference (IV, Fixed, 95% CI)	-1.45 [-5.70, 2.80]
1.2 One month	2	127	Mean Difference (IV, Fixed, 95% CI)	-0.69 [-4.29, 2.90]
1.3 Three months	1	22	Mean Difference (IV, Fixed, 95% CI)	-1.90 [-15.84, 12.04]
1.4 Six months	1	95	Mean Difference (IV, Fixed, 95% CI)	-0.06 [-3.28, 3.16]
1.5 One year	1	95	Mean Difference (IV, Fixed, 95% CI)	1.02 [-1.49, 3.53]

Analysis 2.1. Comparison 2 Cyclophotocoagulation using a semiconductor diode laser versus Nd:YAG laser, Outcome 1 Mean intraocular pressure at a time point.





APPENDICES

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor: [Glaucoma] explode all trees
#2 MeSH descriptor: [Intraocular Pressure] explode all trees
#3 MeSH descriptor: [Ocular Hypertension] explode all trees
#4 glaucom*
#5 (intra*ocular or ocular) near/3 (hypertension* or tension* or pressur*)
#6 IOP
#7 {or #1-#6}
#8 MeSH descriptor: [Lasers] explode all trees
#9 laser*
#10 MeSH descriptor: [Laser Coagulation] explode all trees
#11 MeSH descriptor: [Light Coagulation] explode all trees
#12 photocoagulat* or cyclocoagulat*
#13 coagulat* or argon* or diode*
#14 ND* YAG or Neodymium* YAG or ND*YAG or Neodymium*YAG or YAG*ND OR YAG*Neodymium
#15 cyclophotocoagulat* or cyclodestruct* or cycloablat* or endocyclophotocoagulat* or cryotherap*
#16 ciliary near/3 (destruct* or ablat)
#17 MeSH descriptor: [Diathermy] explode all trees
#18 MeSH descriptor: [Electrolysis] explode all trees
#19 diatherm* or ultrasonic* or electrolys* or beta irradiat*
#20 {or #8-#19}
#21 #7 and #20

Appendix 2. MEDLINE Ovid search strategy

1. Randomized Controlled Trial.pt.
2. Controlled Clinical Trial.pt.
3. (randomized or randomised).ab,ti.
4. placebo.ab,ti.
5. drug therapy.fs.
6. randomly.ab,ti.
7. trial.ab,ti.
8. groups.ab,ti.
9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10. exp animals/ not humans.sh.

11. 9 not 10
12. exp glaucoma/
13. glaucom*.tw.
14. exp intraocular pressure/
15. ((intra?ocular or ocular) adj3 (hypertension* or tension* or pressur*)).tw.
16. Ocular Hypertension/
17. IOP.tw.
18. or/12-17
19. exp lasers/
20. laser*.tw.
21. laser coagulation/
22. exp Light Coagulation/
23. limit 22 to yr="1966 - 1992"
24. (photocoagulat* or cyclocoagulat*).tw.
25. (coagulat* or argon* or diode*).tw.
26. ((ND* adj1 YAG) or (Neodymium* adj1 YAG) or ND*YAG or Neodymium*YAG or YAG*ND or YAG*Neodymium).tw.
27. (cyclophotocoagulat* or cyclodestruct* or cycloablat* or endocyclophotocoagulat* or cryotherap*).tw.
28. (ciliary adj3 (destruct* or ablat*)).tw.
29. exp diathermy/
30. exp electrolysis/
31. (diatherm* or ultrasonic* or electrolys* or beta irradiat*).tw.
32. or/19-21,23-31
33. 18 and 32
34. 11 and 33

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

Appendix 3. Embase.com search strategy

#1 'randomized controlled trial'/exp
#2 'randomization'/exp
#3 'double blind procedure'/exp
#4 'single blind procedure'/exp
#5 random*:ab,ti
#6 #1 OR #2 OR #3 OR #4 OR #5
#7 'animal'/exp OR 'animal experiment'/exp
#8 'human'/exp
#9 #7 AND #8
#10 #7 NOT #9
#11 #6 NOT #10
#12 'clinical trial'/exp
#13 (clin* NEAR/3 trial*):ab,ti
#14 ((singl* OR doubl* OR trebl* OR tripl*) NEAR/3 (blind* OR mask*)):ab,ti
#15 'placebo'/exp
#16 placebo*:ab,ti
#17 random*:ab,ti
#18 'experimental design'/exp
#19 'crossover procedure'/exp
#20 'control group'/exp
#21 'latin square design'/exp
#22 #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21
#23 #22 NOT #10
#24 #23 NOT #11
#25 'comparative study'/exp
#26 'evaluation'/exp
#27 'prospective study'/exp
#28 control*:ab,ti OR prospectiv*:ab,ti OR volunteer*:ab,ti
#29 #25 OR #26 OR #27 OR #28
#30 #29 NOT #10
#31 #30 NOT (#11 OR #23)
#32 #11 OR #24 OR #31
#33 'glaucoma'/exp

#34 'intraocular pressure'/exp
#35 'intraocular pressure abnormality'/de
#36 'ocular ischemic syndrome'/exp
#37 glaucom*:ab,ti
#38 ((intra*ocular OR ocular) NEAR/3 (hypertension* OR tension* OR pressur*)):ab,ti
#39 iop:ab,ti
#40 #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39
#41 'lasers'/exp
#42 laser*:ab,ti
#43' laser coagulation'/exp
#44 photocoagulat*:ab,ti OR cyclocoagulat*:ab,ti
#45 coagulat*:ab,ti OR argon*:ab,ti OR diode*:ab,ti
#46 (nd* NEAR/1 yag):ab,ti OR (neodymium* NEAR/1 yag):ab,ti OR nd*yag:ab,ti OR neodymium*yag:ab,ti OR yag*nd:ab,ti OR yag*neodymium:ab,ti
#47 cyclophotocoagulat*:ab,ti OR cyclodestruct*:ab,ti OR cycloablat*:ab,ti OR endocyclophotocoagulat*:ab,ti OR cryotherap*:ab,ti
#48 ('ciliary body' NEAR/3 destruct*):ab,ti OR (ciliary NEAR/3 ablat*):ab,ti
#49 'diathermy'/exp
#50 'electrolysis'/exp
#51 diatherm*:ab,ti OR ultrasonic*:ab,ti OR electrolys*:ab,ti OR (beta NEXT/1 irradiat*):ab,ti
#52 #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51
#53 #40 AND #52
#54 #32 AND #53

Appendix 4. PubMed search strategy

#1 ((randomized controlled trial[pt]) OR (controlled clinical trial[pt]) OR (randomised[tiab] OR randomized[tiab]) OR (placebo[tiab]) OR (drug therapy[sh]) OR (randomly[tiab]) OR (trial[tiab]) OR (groups[tiab])) NOT (animals[mh] NOT humans[mh])
#2 glaucom*[tw]
#3 ((intraocular[tw] OR intracocular[tw] OR ocular[tw]) AND (hypertension*[tw] OR tension*[tw] OR pressur*[tw]))
#4 IOP[tw]
#5 #2 OR #3 OR #4
#6 laser*[tw]
#7 photocoagulat*[tw] OR cyclocoagulat*[tw]
#8 (coagulat*[tw] OR argon*[tw] OR diode*[tw])
#9 (ND YAG[tw] OR Neodymium YAG[tw] OR YAG ND[tw] OR YAG Neodymium[tw])
#10 (cyclophotocoagulat*[tw] OR cyclodestruct*[tw] OR cycloablat*[tw] OR endocyclophotocoagulat*[tw] OR cryotherap*[tw])
#11 ciliary[tw] AND (destruct*[tw] OR ablat*[tw])
#12 (diatherm*[tw] OR ultrasonic*[tw] OR electrolys*[tw] OR beta irradiat*[tw])
#13 #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12
#14 #5 AND #13
#15 #1 AND #14
#16 Medline[sb]
#17 #15 NOT #16

Appendix 5. LILACS search strategy

(MH:C11.525$ OR glaucom$ OR MH:G14.440$ OR IOP OR (intraocular hypertension$) OR (intraocular tension$) OR (intraocular pressure $) OR (ocular hypertension$) OR (ocular tension$) OR (ocular pressure$)) **AND (**Laser$ OR MH:E07.632.490$ OR MH:E07.710.520$ OR MH:SP4.011.087.698.384.075.166.027$ OR MH:VS2.006.002.009$ OR MH:E02.520.745.410$ OR MH:E02.594.530$ OR MH:E04.014.520.530$ OR MH:E04.350.750.410$ OR MH:E04.540.630.410$ OR photocoagulat$ OR MH:E02.520.745$ OR MH:E04.350.750$ OR MH:E04.540.630$ OR Coagulat$ OR argon$ OR diode$ OR ND$YAG OR Neodymium$YAG OR Cyclophotocoagulat$ OR Cyclocoagulat$ OR cyclodestruct$ OR cycloablat$ OR endocyclophotocoagulat$ OR cryotherap$ OR Diatherm$ OR MH:E02.565.280$ OR MH:E02.779.496.280$ OR Electrolys$ OR MH:E05.301.250$ OR MH:SP4.011.097.057$ OR ultrasonic$ OR (ciliary destruct$) OR (ciliary ablat$) OR (beta irradiat$))

Appendix 6. ClinicalTrials.gov search strategy

(glaucoma OR hypertension OR intraocular pressure) AND (Laser OR cyclophotocoagulation OR cyclodestruction OR photocoagulation OR cryotherapy OR diathermy OR electrolysis OR cyclocoagulation OR coagulation OR argon OR diode OR ultrasonic OR ciliary ablation OR ciliary destruction OR "beta irradiation")

Appendix 7. WHO ICTRP search strategy

glaucoma AND laser OR glaucoma AND cyclophotocoagulation OR glaucoma AND cyclodestruction OR glaucoma AND photocoagulation OR glaucoma AND cryotherapy OR glaucoma AND diathermy OR glaucoma AND electrolysis OR glaucoma AND cyclocoagulation OR

glaucoma AND coagulation OR glaucoma AND argon OR glaucoma AND diode OR glaucoma AND ultrasonic OR glaucoma AND ciliary ablation OR glaucoma AND ciliary destruction OR glaucoma AND beta irradiation OR hypertension AND laser OR hypertension AND cyclophotocoagulation OR hypertension AND cyclodestruction OR hypertension AND photocoagulation OR hypertension AND cryotherapy OR hypertension AND diathermy OR hypertension AND electrolysis OR hypertension AND cyclocoagulation OR hypertension AND coagulation OR hypertension AND argon OR hypertension AND diode OR hypertension AND ultrasonic OR hypertension AND ciliary ablation OR hypertension AND ciliary destruction OR hypertension AND beta irradiation OR intraocular pressure AND laser OR intraocular pressure AND cyclophotocoagulation OR intraocular pressure AND cyclodestruction OR intraocular pressure AND photocoagulation OR intraocular pressure AND cryotherapy OR intraocular pressure AND diathermy OR intraocular pressure AND electrolysis OR intraocular pressure AND cyclocoagulation OR intraocular pressure AND coagulation OR intraocular pressure AND argon OR intraocular pressure AND diode OR intraocular pressure AND ultrasonic intraocular pressure AND ciliary ablation OR intraocular pressure AND ciliary destruction OR intraocular pressure AND beta irradiation

CONTRIBUTIONS OF AUTHORS

MC and AC conceived and designed the review. MC coordinated the review. MC and CK screened the searches and extracted data. MC and members of the CEV editorial team entered the data. MC and members of the CEV team performed the data analysis. MC, CK, AC, and members of the CEV editorial team interpreted the data and wrote the review.

DECLARATIONS OF INTEREST

MC has no known conflicts of interest.
CK has no known conflicts of interest.
AC has no known conflicts of interest.

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

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In the protocol, we stated that we would only include randomized controlled trials. In a deviation from the protocol, we chose to include one study that self defined as "not truly randomized." This study randomized only the first participant to one study arm, and then assigned consecutive participants to an intervention in an alternating format. We considered this to be a quasi-randomized controlled trial. The trial authors stated that they believed there to be "no biases in the eligibility criteria" and concluded that they did not influence the distribution of their participants into the study groups.

INDEX TERMS

Medical Subject Headings (MeSH)

*Glaucoma Drainage Implants [adverse effects]; Aqueous Humor; Ciliary Body [*surgery]; Endoscopy; Glaucoma [*surgery]; Intraocular Pressure; Laser Coagulation [adverse effects] [*methods]; Lasers, Solid-State [therapeutic use]; Randomized Controlled Trials as Topic; Visual Acuity

MeSH check words

Humans