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Device-modified trabeculectomy for glaucoma

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[Intervention Review]

Device-modified trabeculectomy for glaucoma

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ABSTRACT

Background

Glaucoma is an optic neuropathy that leads to vision loss and blindness. It is the second most common cause of irreversible blindness worldwide. The main treatment for glaucoma aims to reduce intraocular pressure (IOP) in order to slow or prevent further vision loss. IOP can be lowered with medications, and laser or incisional surgeries. Trabeculectomy is the most common incisional surgical procedure to treat glaucoma. Device-modified trabeculectomy is intended to improve drainage of the aqueous humor to lower IOP. Trabeculectomy-modifying devices include Ex-PRESS, Ologen, amniotic membrane, expanded polytetrafluoroethylene (E-PTFE) membrane, Gelfilm and others. However, the effectiveness and safety of these devices are uncertain.

Objectives

To assess the relative effectiveness, primarily with respect to IOP control and safety, of the use of different devices as adjuncts to trabeculectomy compared with standard trabeculectomy in eyes with glaucoma.

Search methods

We searched CENTRAL (which contains the Cochrane Eyes and Vision Trials Register) (2014, Issue 12), Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid MEDLINE Daily, Ovid OLDMEDLINE (January 1946 to December 2014), EMBASE (January 1980 to December 2014), PubMed (1948 to December 2014), Latin American and Caribbean Literature on Health Sciences (LILACS) (January 1982 to December 2014), the *meta*Register of Controlled Trials (*m*RCT) (www.controlled-trials.com), ClinicalTrials.gov (www.clinicaltrials.gov), and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/search/en). We did not use any date or language restrictions in the electronic search for trials. We last searched the electronic databases on 22 December 2014.

Selection criteria

We included randomized controlled trials comparing devices used during trabeculectomy with trabeculectomy alone. We also included studies where antimetabolites were used in either or both treatment groups.

Data collection and analysis

We used standard procedures expected by Cochrane.

Main results

We found 33 studies that met our inclusion criteria, of which 30 were published as full-length journal articles and three as conference abstracts. Only five studies have been registered. The 33 studies included a total of 1542 participants with glaucoma, and compared five types of devices implanted during trabeculectomy versus trabeculectomy alone. Five studies reported the use of Ex-PRESS (386

participants), eight studies reported the use of Ologen (327 participants), 18 studies reported the use of amniotic membrane (726 participants), one study reported the use of E-PTFE (60 participants), and one study reported the use of Gelfilm (43 participants). These studies were conducted in North America, South America, Europe, Asia, and the Middle East. Planned participant follow-up periods ranged from three months to five years. The studies were reported poorly which limited our ability to judge risk of bias for many domains. Only two studies explicitly masked outcome assessment so, we rated 31 studies at high risk of detection bias.

Low-quality evidence from three studies showed that use of Ex-PRESS compared with trabeculectomy alone may be associated with a slightly lower IOP at one year (mean difference (MD) -1.58 mm Hg, 95% confidence interval (CI) -2.74 to -0.42; 165 eyes). Cataract surgery and hyphema may be less frequent in the Ex-PRESS group than in the trabeculectomy-alone group (cataract surgery: risk ratio (RR) 0.32, 95% CI 0.14 to 0.74, 3 studies, low-quality evidence; hyphema: RR 0.33, 95% CI 0.12 to 0.94, 4 studies, low-quality evidence). The effect of whether Ex-PRESS prevents hypotony was uncertain (RR 0.92, 95% CI 0.63 to 1.33, 2 studies, very low-quality evidence). All these studies received funding from the device manufacturer.

Very low-quality evidence from five studies suggests that use of Ologen compared with trabeculectomy alone is associated with slightly higher IOP at one year (MD 1.40 mm Hg, 95% CI -0.57 to 3.38; 177 eyes). The effect of Ologen on preventing hypotony was uncertain (RR 0.75, 95% CI 0.47 to 1.19, 5 studies, very low-quality evidence). Differences between the two treatment groups for other reported complications also were inconclusive.

Low-quality evidence from nine studies suggests that use of amniotic membrane with trabeculectomy may be associated with lower IOP at one year compared with trabeculectomy alone (MD -3.92 mm Hg, 95% CI -5.41 to -2.42; 356 eyes). Low-quality evidence showed that use of amniotic membrane may prevent adverse events and complications, such as hypotony (RR 0.40, 95% CI 0.17 to 0.94, 5 studies, low-quality evidence).

The report from the only E-PTFE study (60 eyes) showed no important differences for postoperative IOP at one year (MD -0.44 mm Hg, 95% CI -1.76 to 0.88) between the trabeculectomy + E-PTFE versus the trabeculectomy-alone groups. Hypotony was the only postoperative complication observed less frequently in the E-PTFE group compared to the trabeculectomy-alone group (RR 0.29, 95% CI 0.11 to 0.77).

The one Gelfilm study reported uncertainty in the difference in IOP and complication rates between the two groups at one year; no further data were provided in the study report.

Authors' conclusions

Overall, the use of devices with standard trabeculectomy may help with greater IOP reduction at one-year follow-up than trabeculectomy alone; however, due to potential biases and imprecision in effect estimates, the quality of evidence is low. When we examined outcomes within subgroups based on the type of device used, our findings suggested that the use of an Ex-PRESS device or an amniotic membrane as an adjunct to trabeculectomy may be slightly more effective in reducing IOP at one year after surgery compared with trabeculectomy alone. The evidence that these devices are as safe as trabeculectomy alone is unclear. Due to various limitations in the design and conduct of the included studies, the applicability of this evidence synthesis to other populations or settings is uncertain. Further research is needed to determine the effectiveness and safety of other devices and in subgroup populations, such as people with different types of glaucoma, of various races and ethnicity, and with different lens types (e.g. phakic, pseudophakic).

PLAIN LANGUAGE SUMMARY

Device-modified trabeculectomy for glaucoma

Review Question

We reviewed the evidence about the effectiveness and safety of the use of devices in a standard glaucoma surgery (trabeculectomy) for the treatment of glaucoma.

Background

Glaucoma is a disease of the optic nerve that leads to vision loss and blindness. It is the second leading cause of worldwide blindness, and the blindness caused by glaucoma is permanent. Treatment for glaucoma aims to reduce pressure in the eye (IOP), which helps to slow down or prevent further vision loss from glaucoma. Eye pressure can be lowered with medications, laser therapy, or surgery. Trabeculectomy, the most common standard surgical procedure for the treatment of glaucoma, can be modified by using aids or devices during the surgery. Current studies have reported using various devices such as Ex-PRESS, Ologen, amniotic membrane, expanded polytetrafluoroethylene (E-PTFE) membrane, Gelfilm, gold shunt, T-flux, etc.

Study Characteristics

We found 33 studies that met our inclusion criteria. These studies included a total of 1542 glaucoma participants and compared five types of devices implanted during trabeculectomy versus trabeculectomy alone. Five studies reported the use of Ex-PRESS (386 participants), eight studies reported the use of Ologen (327 participants), 18 studies reported the use of amniotic membrane (726 participants), one study reported the use of E-PTFE (60 participants), and one study reported the use of Gelfilm (43 participants). These studies were conducted

in North America, South America, Europe, Asia, and the Middle East. Planned participant follow-up periods ranged from three months to five years.

Key Results

Three studies found that the use of the Ex-PRESS shunt during trabeculectomy may slightly reduce eye pressure by about 1.6 mm Hg more than trabeculectomy alone. Another study did not find any difference in eye pressure at one year between trabeculectomy combined with Ex-PRESS versus trabeculectomy alone. Five studies did not find any important difference between trabeculectomy and Ologen compared to trabeculectomy alone. Nine studies found that the use of amniotic membrane during trabeculectomy may reduce IOP by about 4 mm Hg more than trabeculectomy alone at one-year follow-up. We did not find important differences for postoperative eye pressure at one year between trabeculectomy + E-PTFE and trabeculectomy alone. We did not find enough data regarding the evidence for the use of Gelfilm. It is uncertain whether these devices are as safe as trabeculectomy alone. The evidence is current to 22 December 2014.

Quality of the Evidence

The overall quality of the included studies varied by the type of device studied. Specifically, the quality was very low for Ex-PRESS studies, very low for Ologen studies, low for amniotic membrane studies, and unclear for other devices. Due to the various flaws in study design and incomplete reporting, the data need to be interpreted with caution, particularly for the amniotic membrane studies.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Summary of findings for Ex-PRESS

Ex-PRESS implanted during trabeculectomy compared with trabeculectomy alone for people with open-angle glaucoma

Patient or population: people with open-angle glaucoma

Settings: ophthalmic surgery

Intervention: Ex-PRESS implanted during trabeculectomy

Comparison: trabeculectomy alone

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Eyes (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	trabeculectomy alone	Ex-PRESS				
Postoperative mean IOP at 1 year	The mean IOP in the trabeculectomy-alone groups was **13.9 mm Hg**, ranged from 11.6 to 16.4 mm Hg	The mean IOP in the Ex-PRESS groups was **1.58 lower** (2.74 lower to 0.42 lower)	-	165 (3 studies)	⊕⊕⊖⊖ **low** [1,2]	-
Postoperative mean logMAR BCVA at 1 year	The mean logMAR BCVA in the trabeculectomy-alone groups was **0.59**, ranged from 0.43 to 0.80	The mean logMAR BCVA in the Ex-PRESS groups was **0.15 lower** (0.40 lower to 0.10 higher)	-	90 (2 studies)	⊕⊖⊖⊖ **very low** [1,2,3]	-
Complication as defined in protocol- Hypotony Follow-up: ranged from 1 to 5 years	**565 per 1000**	**520 per 1000** (356 to 751)	**RR 0.92** (0.63 to 1.33)	94 (2 studies)	⊕⊖⊖⊖ **very low** [1,2,3]	-
Other complications reported by included studies						
Shallow/flat anterior chamber Follow-up: ranged from 1 to 5 years	**150 per 1000**	**108 per 1000** (60 to 198)	**RR 0.72** (0.40 to 1.32)	294 (4 studies)	⊕⊖⊖⊖ **very low** [1,2,3]	-

Bleb leakage Follow-up: ranged from 1 to 5 years	**48 per 1000**	**60 per 1000** (24 to 154)	**RR 1.26** (0.50 to 3.20)	294 (4 studies)	⊕⊝⊝⊝ **very low** [1,2,3]	-
Hyphema Follow-up: ranged from 1 to 5 years	**82 per 1000**	**27 per 1000** (10 to 77)	**RR 0.33** (0.12 to 0.94)	294 (4 studies)	⊕⊕⊝⊝ **low** [1,2]	-
Cataract surgery Follow-up: ranged from 1 to 5 years	**152 per 1000**	**49 per 1000** (21 to 112)	**RR 0.32** (0.14 to 0.74)	264 (3 studies)	⊕⊕⊝⊝ **low** [1,2]	-

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
BCVA: best-corrected visual acuity; **CI:** confidence interval; **IOP:** intraocular pressure; **logMAR**: logarithm of the minimum angle of resolution; **RR:** risk ratio.

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

[1]Downgraded for limitations in the design and implementation of available studies suggesting high likelihood of bias (-1); high likelihood that studies did not mask outcome assessors.
[2]Downgraded for high probability of reporting bias (-1).
[3]Downgraded for imprecision (-1): wide confidence intervals.

Summary of findings 2. Summary of findings for Ologen

Ologen implanted during trabeculectomy compared with trabeculectomy alone for people with glaucoma

Patient or population: people with glaucoma, including open-angle, angle-closure, and uncontrolled IOP

Settings: ophthalmic surgery

Intervention: Ologen implanted during trabeculectomy

Comparison: trabeculectomy alone

Outcomes	Illustrative comparative risks* (95% CI)	Relative effect (95% CI)	No of Eyes (studies)	Quality of the evidence	Comments

	Assumed risk	Corresponding risk			(GRADE)	
	trabeculectomy alone	**Ologen**				
Postoperative mean IOP at 1 year	The mean IOP in the trabeculectomy-alone groups was 15.2 mm Hg, ranged from 11 to 19.3 mm Hg.	The mean IOP in the Ologen groups was **1.40 higher** (0.57 lower to 3.38 higher)	-	177 (5 studies)	⊕⊝⊝⊝ **very low** [1,2,3]	Analyzed using the generic inverse method
Postoperative mean logMAR BCVA at 1 year	See comment.	See comment.	-	-	-	Senthil 2013 reported BCVA for 32 eyes at 6 weeks post-surgery: MD -0.24 logMAR, 95% CI -0.58 to 0.10
Complication as defined in protocol-Hypotony Follow-up: ranged from 6 to 24 months	**223 per 1000**	**167 per 1000** (105 to 265)	**RR 0.75** (0.47 to 1.19)	233 (6 studies)	⊕⊝⊝⊝ **very low** [1,2,3]	-
Other complications reported by included studies						
Shallow anterior chamber Follow-up: ranged from 6 to 24 months	**90 per 1000**	**71 per 1000** (29 to 174)	**RR 0.79** (0.32 to 1.93)	213 (5 studies)	⊕⊝⊝⊝ **very low** [1,2,3]	-
Bleb leakage Follow-up: ranged from 6 to 24 months	**138 per 1000**	**117 per 1000** (46 to 304)	**RR 0.85** (0.33 to 2.20)	129 (4 studies)	⊕⊝⊝⊝ **very low** [1,2,3]	-
Hyphema Follow-up: ranged from 6 to 24 months	**78 per 1000**	**114 per 1000** (40 to 327)	**RR 1.46** (0.51 to 4.19)	229 (6 studies)	⊕⊝⊝⊝ **very low** [1,2,3]	-
Surgical revision Follow-up: ranged from 6 to 24 months	**40 per 1000**	**68 per 1000** (15 to 305)	**RR 1.70** (0.38 to 7.63)	150 (4 studies)	⊕⊝⊝⊝ **very low** [1,2,3]	-

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
BCVA: best-corrected visual acuity; **CI:** confidence interval; **IOP:** intraocular pressure; **logMAR**: logarithm of the minimum angle of resolution; **RR:** risk ratio.

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

[1]Downgraded for limitations in the design and implementation of available studies suggesting high likelihood of bias (-1); high likelihood that studies did not mask outcome assessors.
[2]Downgraded for high probability of reporting bias (-1).
[3]Downgraded for imprecision (-1): wide confidence intervals.

Summary of findings 3. Summary of findings for amniotic membrane

Amniotic membrane implanted during trabeculectomy compared with trabeculectomy alone for people with glaucoma

Patient or population: people with glaucoma, including open-angle, angle-closure, uncontrolled IOP, and refractive glaucoma

Settings: ophthalmic surgery

Intervention: Amniotic membrane implanted during trabeculectomy

Comparison: trabeculectomy alone

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Eyes (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	trabeculectomy alone	amniotic membrane				
Postoperative mean IOP at 1 year	The mean IOP in the trabeculectomy alone groups was 17.6 mm Hg, ranged from 15.1 to 19.8 mm Hg.	The mean IOP in the Ologen groups was 3.92**lower** (5.41 lower to 2.42 lower)	-	356 (9 studies)	⊕⊕⊖⊖ **low** [1,2]	
Postoperative mean logMAR BCVA at 1 year	See comment.	See comment.				Only 1 study reported this outcome; the

						amniotic membrane group had statistically significantly better BCVA than the trabeculectomy group, but no data for between-group difference were provided
Complications - Hypotony Follow-up: ranged from 3 to 24 months	**206 per 1000**	**82 per 1000** (35 to 193)	RR 0.40 (0.17 to 0.94)	205 (5 studies)	⊕⊕⊖⊖ **low** [1,3]	-
Other complications reported by included studies						
Complications - Shallow anterior chamber Follow-up: ranged from 3 to 24 months	**240 per 1000**	**113 per 1000** (72 to 175)	RR 0.47 (0.30 to 0.73)	632 (13 studies)	⊕⊕⊖⊖ **low** [1,2]	-
Complications - Bleb leakage Follow-up: ranged from 3 to 24 months	**327 per 1000**	**91 per 1000** (32 to 258)	RR 0.28 (0.10 to 0.79)	98 (2 studies)	⊕⊕⊖⊖ **low** [1,2]	-
Complications - Hyphema Follow-up: ranged from 3 to 24 months	**91 per 1000**	**39 per 1000** (12 to 122)	RR 0.43 (0.14 to 1.34)	235 (5 studies)	⊕⊖⊖⊖ **very low** [1,2,3]	-
Complications - Surgical revision Follow-up: ranged from 3 to 24 months	See comment.	See comment.	-	-		None of the studies reported this outcome.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
BCVA: best corrected visual acuity; **CI:** Confidence interval; **IOP:** intraocular pressure; **logMAR**: Logarithm of the Minimum Angle of Resolution; **RR:** Risk Ratio.

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

[1]Downgraded for limitations in the design and implementation of available studies suggesting high likelihood of bias (-1); high likelihood that studies did not mask outcome assessors.
[2]Downgraded for high probability of reporting bias (-1).
[3]Downgraded for imprecision (-1): wide confidence intervals.

BACKGROUND

Description of the condition

Glaucoma is an optic neuropathy that leads to vision loss and blindness (Foster 2002). Among the many known and unknown factors that contribute to the damage to the optic nerve, elevated intraocular pressure (IOP) is the only modifiable risk factor (Coleman 2012). Normally, the IOP is maintained in balance when the rate of aqueous production by the ciliary body is equal to the rate of its outflow from the posterior to the anterior chamber through the trabecular meshwork and the canal of Schlemm in the anterior chamber angle (Small 1986). When excess aqueous humor is produced or when part or all of the drainage system of aqueous humor is blocked, the result is an increase in IOP, which has been shown to be associated with progressive glaucomatous optic nerve damage (Pan 2011; Turkoski 2012).

There are several types of glaucoma, of which open-angle glaucoma (OAG) and angle-closure glaucoma (ACG) are two major types.

Epidemiology

The World Health Organization (WHO) has estimated that glaucoma is the second most frequent cause of blindness worldwide (Quigley 2011). It has been estimated that there were 60.5 million people with OAG and ACG in 2010, and the number will increase globally to 79.6 million by 2020. The most common type of glaucoma is OAG, accounting for 74% of glaucoma cases worldwide. ACG is less common. Women comprise 55% of OAG cases, 70% of ACG cases, and 59% of all glaucoma cases. Asians represent 47% of people who have glaucoma and 87% of those with ACG (Quigley 2006).

Symptoms and diagnosis

OAG is often asymptomatic initially. There is no pain and those affected tend not to notice the loss of visual field until central vision is affected in the later stage of the disease; by then optic nerve damage is often already severe (Boland 2008; Quigley 2011; Small 1986). The symptoms for ACG vary. It may occur suddenly without warning or gradually with progressive deterioration; patients may have signs and symptoms including severe pain and red eye, decreased or cloudy vision, nausea, vomiting, and bradycardia (Boland 2008; Douglas 1975; Small 1986). Clinical examinations for diagnosing glaucoma include, but are not limited to, tonometry, gonioscopy, optic nerve imaging, visual acuity measurement, and visual field assessment.

Description of the intervention

Trabeculectomy, first introduced by John Cairns in 1968 and then modified by Watson in 1972, remains the gold standard and is the most common incisional surgical procedure for the treatment of glaucoma (Cairns 1968; Watson 1972; Watson 1981). It includes lifting the conjunctiva and dissecting a partial thickness scleral flap and then making a perforating scleral entrance into the anterior chamber to allow aqueous humor drainage. Trabeculectomy may also include removing part of the eye's trabecular meshwork and adjacent structures. This procedure lowers IOP by allowing aqueous fluid to percolate into the subconjunctival space through the scleral hole or the cut ends of the trabecular meshwork into the subconjunctival space. Over the years trabeculectomy has been modified in various ways, including the use of 5-fluorouracil (5-FU) (Green 2014) and mitomycin C (MMC) (Wilkins 2005), and creation of a fornix-based rather than the traditional limbus-based conjunctival flap. Most recently, the modifications have included the use of adjunctive devices with standard trabeculectomy. Surgeons may use a tube without a reservoir (for example, Ex-PRESS) or a space-holder or reservoir to enhance aqueous humor outflow or to modify healing (for example, Ologen) and to promote continued drainage from the anterior chamber through a standard partial thickness scleral flap used in a standard trabeculectomy. Another technique, a device composed of both a silicone tube and an explant plate, called an aqueous shunt, is also a surgical option to treat glaucoma, but this technique is not within the scope of this review (Minckler 2006).

How the intervention might work

We consider in this review adjunctive devices used with trabeculectomy to lower IOP, with and without concomitant use of antimetabolites. The devices used with standard trabeculectomy are intended to maintain drainage of aqueous humor, and may be used with or without antimetabolites to maintain patency of the bleb (a bubble-like blister of conjunctiva to facilitate drainage).

Tube implants

1. Ex-PRESS mini glaucoma implant

The Ex-PRESS implant is a miniature stainless steel shunt developed as an adjunct to trabeculectomy to promote continued aqueous drainage. The device is implanted under a partial thickness scleral flap to allow aqueous humor to flow from the anterior chamber to the subconjunctival space; implantation leads to the formation of a thin-walled filtration bleb, similar to the bleb formed during standard trabeculectomy. Investigators who have conducted retrospective studies and randomized controlled trials have reported that the Ex-PRESS shunt provides IOP control that is similar to or better than that provided by standard trabeculectomy (Dahan 2012; De Jong 2009; Francis 2011; Gallego-Pinazo 2009; Maris 2007). They have also reported that the Ex-PRESS shunt results in fewer complications, fewer postoperative surgical interventions, and less need for glaucoma medications. The device is manufactured by Alcon (a Novartis company).

2. Silicon tube implant

Jordan 2006 reported the use of a silicon tube implant for suprachoroidal drainage during a standard trabeculectomy. The tube was inserted at a junction connecting the anterior chamber and the suprachoroidal space. These investigators concluded that the tube was an effective surgical adjunct to treat intractable glaucoma. However, Jordan 2006 was not a randomized controlled trial, and the effectiveness and safety of silicon tube implants are unclear. The device is produced by a variety of manufacturers.

Antimetabolites and biodegradable implant

Wound healing and scar formation are the main sequelae that limit IOP lowering after standard trabeculectomy. They may lead to fibrosis of the bleb and obstruction of the drainage fistula, and finally cause bleb failure (Skuta 1987). Antifibrotic agents, such as 5-FU and MMC, have been demonstrated to be effective in delaying wound healing and thus improving the success rate of trabeculectomy (Azuara-Blanco 1998; Fraser 2004). Therefore, 5-FU and MMC have become widely used as adjuncts to glaucoma-filtering surgery. Although 5-FU and MMC

improve the success of trabeculectomy, concern persists about the complications associated with antimetabolites, for example bleb-related infections, bleb leaks, and bleb dysesthesia (defined as burning, foreign body sensation, tearing, pain, or ocular discomfort in an eye with a filtering bleb) (Bell 1997; Jampel 1992; Lama 2003). Biodegradable implants have therefore been developed for use with trabeculectomy to maintain drainage while avoiding the use or reducing the amount of antimetabolite used by the surgeon.

1. Ologen implant

The Ologen implant is a plate-shaped, tissue bioengineered, biodegradable porous collagen-glycosaminoglycan matrix used during trabeculectomy. The device randomly reorganizes the regeneration of myofibroblasts, fibroblasts, and the secreted extracellular matrix, and consequently reduces postoperative scar formation (Dietlein 2008; Tseng 1999). Investigators who have conducted studies in animal models and several randomized clinical trials have reported that Ologen implanted in the subconjunctival space provides an alternative method for controlling the wound-healing process and avoids the complications associated with the use of antifibrotic agents (Chen 2006; Cillino 2011; Hsu 2008; Papaconstantinou 2010; Rosentreter 2010). The device is manufactured by PRO Top & Mediking Co. Ltd and its subsidiaries: Body organ biomedical Corps, Optous, Aeon Astron B.V., OculusGen Biomedical.

2. Amniotic membrane

Human amniotic membrane is an antifibrotic, anti-inflammatory agent. It was known for its beneficial effect in preventing subconjunctival fibrosis in glaucoma filtering surgery by suppressing transforming growth factor ß, as this signaling system is a strategy for preventing scarring during wound healing (Ricci 2013). A Cochrane review also found amniotic membrane to be useful for treating acute ocular surface burns (Clare 2012). Although recent animal and human studies on amniotic membrane have been promising, it remains unclear whether these membranes can provide a potential alternative tissue to conjunctiva in the construction of filtration blebs during trabeculectomy (Barton 2001; Eliezer 2006; Ji 2013; Khairy 2015; Sheha 2008; Stavrakas 2012). The device is produced by a variety of manufacturers.

Other implants

Other devices have been developed and studied for non-penetrating glaucoma surgeries.

1. Expanded polytetrafluoroethylene (E-PTFE) membrane implant

E-PTFE is an expanded polytetrafluoroethylene implant made up of solid nodes interconnected by a thin fibril matrix. Its use has been reported in several animal studies and human trials in the form of either a membrane patch or an implant placed beneath the partial thickness scleral flap (Bae 1988; Cillino 2008; Jacob 2001) or combined with a silicone tube shunt (Choi 2003; Kim 2003). The device is manufactured by GORE Inc., under the brand names Gore-Tex® and PRECLUDE®.

2. Gelfilm (absorbable gelatin film) implant

Gelfilm is a sterile film derived from denaturated collagen. When moistened, the film is about 0.075 mm thick and can be cut to fit the eye during surgery. The film is absorbed completely within one to six months, so that no additional surgery is required to remove the implant. Gelfilm is thought to prevent adhesion of ocular structures, which may be helpful in preventing closure of drainage passages created by trabeculectomy. The device is manufactured by Pfizer.

3. SOLX Gold Shunt

The SOLX Gold Shunt is a new biocompatible device made of pure gold (24 carat) that reduces IOP by using the eye's natural pressure difference (www.solx.com/content/solx-gold-shunt). The device is inserted into the anterior chamber through a special corneal or scleral incision, with the posterior end left in the suprachoroidal space. The device is currently approved for use in Canada and a few European countries, and is under evaluation in a multicenter clinical trial in the United States (clinicaltrials.gov; NCT01282346). The device is manufactured by SOLZ Inc.

Why it is important to do this review

The purpose of this review is to compare the effectiveness and safety of device-modified trabeculectomy procedures versus standard trabeculectomy in the surgical treatment of glaucoma with or without the use of antifibrotic agents. Device-modified trabeculectomy is a relatively new procedure; many studies have not had sample sizes sufficiently large to provide reliable evidence to assess the effectiveness and safety of the procedure. It is therefore important to examine the evidence from multiple completed studies. When meta-analysis of outcomes is appropriate, pooling across studies should increase the power and yield valuable information. Authors of a few recently published articles have addressed the effectiveness and safety of the Ex-PRESS and Ologen devices (Chen 2014; He 2014; Wang 2013a). However, a comprehensive, rigorous systematic review in this area is warranted.

OBJECTIVES

To assess the relative effectiveness, primarily with respect to IOP control and safety, of the use of different devices as adjuncts to trabeculectomy compared with standard trabeculectomy in eyes with glaucoma.

METHODS

Criteria for considering studies for this review

Types of studies

We included only randomized controlled trials in this review.

Types of participants

We include trials in which the participants were 18 or more years of age and had been diagnosed with glaucoma. We include trials in which participants had any type of glaucoma (for example, primary open-angle glaucoma, angle-closure glaucoma, pigmentary glaucoma, exfoliation glaucoma, and secondary glaucoma such as neovascular glaucoma) except pediatric and congenital glaucoma. There were no restrictions with regard to participant gender, ethnicity, comorbidity, use of adjunctive medication, lens status (phakic, aphakic, or pseudophakic), or number of participants enrolled in an individual trial. We excluded studies in which all participants were less than 18 years of age, as pediatric glaucoma and congenital glaucoma were not

the purpose of this review. Surgical interventions for primary congenital glaucoma are evaluated in another Cochrane review (Ghate 2015).

Types of interventions

We include trials that compared, with or without the use of antimetabolites, device-modified trabeculectomy versus standard trabeculectomy. The devices we intended to assess include the Ex-PRESS, silicone tube implant, Ologen, amniotic membrane, expanded polytetrafluoroethylene (E-PTFE), Gelfilm, and SOLX Gold Shunt, which are all popular devices used in glaucoma surgeries and can be deployed under a standard trabeculectomy flap. In future updates of this review, we will include other new devices used in a trabeculectomy. We planned to make the following comparisons:

1. Trabeculectomy + any of the above devices versus trabeculectomy alone;
2. Trabeculectomy + any device + antimetabolites (MMC, 5-FU, or both) versus trabeculectomy + antimetabolites (MMC, 5-FU, or both);
3. Trabeculectomy + Ologen device versus trabeculectomy + antimetabolites (MMC, 5-FU, or both).

There are two pairs of comparisons that we did not plan to include, as these are already covered in other Cochrane reviews:

1. MMC with 5-FU on the outcome of standard trabeculectomy (Clarke 2006);
2. Fornix-based (the modification) versus traditional limbus-based trabeculectomy (Al-Haddad 2015).

In addition, we excluded studies in which trabeculectomy combined with cataract surgery were performed or were permitted, as this was outside the scope of this review.

Types of outcome measures

Primary outcomes

The primary outcomes for comparison of treatments of this review included:

1. Change in IOP, measured as a mean decrease from baseline (immediate preoperative IOP) at one year after the intervention when IOP had been measured using Goldmann tonometry, TonoPen, or another standard device. When change in IOP was not available, and when baseline IOP distributions were similar in the two surgery groups, we compared postoperative IOP as a surrogate to estimate the effect of device-modified trabeculectomy.
2. We planned to report IOP fluctuation, assessed as a standard deviation or range of IOPs before or one year after the procedure, whenever such data were available.

Secondary outcomes

The secondary outcomes for comparison of treatments included:

1. Mean change in IOP from baseline, measured on day one, during weeks one to 12, at four to six months, seven to 12 months, and thereafter as available throughout follow-up. When change in IOP was not available, and when baseline IOPs were similar between treatment groups, we used postoperative IOP to estimate the relative effect of device-modified trabeculectomy in the meta-analyses.
2. Best-corrected visual acuity (BCVA), measured using a Snellen chart or Snellen equivalent and assessed at one year postintervention. We analyzed BCVA data as a continuous outcome in the meta-analyses.
3. Visual field change, measured in units of mean deviation or mean defect (the average point-wise difference between a given test result and the normal age-matched reference value) at one year postintervention.
4. Quality of life, measured by the National Eye Institute Visual Function Questionnaire (NEI VFQ) or any other validated instrument at one year postintervention.
5. Frequency of the following complications: loss of vision of more than two lines, IOP < 5 mm Hg (hypotony), surgical revision within three months and one year after surgery, endophthalmitis or blebitis, retinal detachment, corneal transplant, cataract extraction (among phakic eyes), choroidal hemorrhage, and others as reported in the included studies.

Search methods for identification of studies

Electronic searches

We searched CENTRAL (which contains the Cochrane Eyes and Vision Trials Register) (2014 Issue 12), Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid MEDLINE Daily, Ovid OLDMEDLINE (January 1946 to December 2014), EMBASE (January 1980 to December 2014), PubMed (1948 to December 2014), Latin American and Caribbean Literature on Health Sciences (LILACS) (January 1982 to December 2014), the *meta*Register of Controlled Trials (*m*RCT) (www.controlled-trials.com), ClinicalTrials.gov (www.clinicaltrials.gov), and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/search/en). We did not impose any date, language, or publication status restrictions in the electronic search for trials. All electronic databases were all searched on 22 December 2014.

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

Searching other resources

We searched the references listed in reports from included studies to identify additional relevant studies, without restriction regarding language or date of publication.

Data collection and analysis

Selection of studies

Two review authors independently reviewed the titles and abstracts of all reports identified through the electronic and manual searches. We first classified all titles and abstracts as 'definitely relevant', 'unsure', or 'definitely not relevant'. We then adjudicated discrepancies through discussion and retrieved full-text reports for those classified as 'definitely relevant' or 'unsure' by both review authors. By review of full-text reports, we independently assessed eligibility and classified each study as 'include', 'unsure', or 'exclude'. For studies labeled as 'unsure' at this stage, we requested further information from study investigators.

When they did not respond within two weeks, we used the information available. We resolved disagreements by discussion between the two review authors. When resolution was not possible, we consulted a third review author. All publications from studies that met the inclusion criteria then underwent assessment of risk of bias and data extraction. We recorded the reasons for exclusion of studies classified as 'exclude' in the 'Characteristics of excluded studies' tables. For reports not published in English or Chinese, we planned to use Google Translate to screen titles and abstracts and to ask translators to translate or assess reports for full-text screening. However, all reports relevant to this review were published in English or Chinese languages.

Data extraction and management

Two review authors independently extracted data regarding study design and methods, participant characteristics, and the primary and secondary outcomes, and recorded the information onto paper data collection forms developed in collaboration with Cochrane Eyes and Vision. Whenever there were discrepancies between review authors, we reached consensus by discussion. When we could not reach a consensus, we consulted a third review author who made the final decision. We contacted study investigators to obtain missing information and to elucidate unclear reporting. When they did not respond within two weeks, we used the information available. One review author entered data into Review Manager 5 (RevMan 2014) and a second review author verified the data entered.

Assessment of risk of bias in included studies

Two review authors independently assessed each included study for risks of bias as part of the data extraction process. We based our judgments on the tools for assessing risk of bias set forth in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

We judged each study with respect to the following risk of bias domains:

1. Selection bias (sequence generation and allocation concealment before randomization);
2. Performance bias (masking of participants and personnel);
3. Detection bias (masking of outcome assessors);
4. Attrition bias (incomplete outcome data);
5. Reporting bias (selective outcome reporting);
6. Other potential sources of bias (e.g., funding source).

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

Measures of treatment effect

Dichotomous outcomes

We analyzed dichotomous outcomes, such as complications, using summary risk ratios (RRs) with 95% confidence intervals (CIs).

Continuous outcomes

We estimated the difference between continuous outcomes, such as mean change (or mean) IOP and BCVA, as the mean difference (MD) with 95% CIs for IOP. We planned to analyze IOP fluctuations, visual field changes, and quality-of-life scores as continuous outcomes, but such data were not available.

Unit of analysis issues

The unit of analysis was the eye that had glaucoma surgery. We recorded whether studies used a parallel-group design or a paired-eye design, and whether the study used matched-analysis when a paired-eye design was used. When both eyes of all or some participants were allocated to the same intervention group, we recorded the information as available and did not estimate or impute intra-person correlations for individual outcomes.

More than half of the studies (18/33) were parallel-group designs and included only one eye per participant. Both eyes of some participants were included in another 13 parallel-group trials; an average of 22% of participants across these 13 trials contributed both eyes to the analysis. Two trials were paired-eye designs in which each participant had one eye in each intervention group. None of the 13 studies that included more than one eye per participant accounted for intra-person correlation.

Dealing with missing data

We contacted study investigators to request missing data or to clarify unclearly reported data or information, including but not limited to information about study methods, effect estimates, and standard deviations of effect estimates. When study investigators did not respond within two weeks or after three attempts to contact them, we used the available information. We did not impute data for this review.

Assessment of heterogeneity

We assessed clinical and methodological heterogeneity among included trials by examining variations in the trial designs and methods, characteristics of the trial participants, variations in interventions, and lengths of follow-up. We assessed statistical heterogeneity among the reported treatment effect estimates of included trials by examining the overlap of the 95% CIs on estimates from individual trials in forest plots and I^2 values (Higgins 2003). We considered poor overlap in the 95% CIs and an I^2 above 50% as indications of substantial statistical heterogeneity.

Assessment of reporting biases

We investigated whether our review was subject to reporting biases. For selective reporting bias, we compared outcomes specified in trial protocols or trial register records with outcomes reported in published full-text articles. When no trial protocol or trial register record was available, we examined whether outcomes specified in the Methods section were reported in the Results section of the same published report. We did not use funnel plots to examine signs of asymmetry due to the limited number of studies included in the same meta-analysis.

Data synthesis

We determined whether data synthesis in meta-analyses was appropriate based on evidence of heterogeneity. When we considered that there was substantial heterogeneity, we presented results in a narrative summary. In the absence of clinical and methodological heterogeneity across studies, and when the I^2 statistic was less than 50% (indicating no substantial statistical heterogeneity), when the I^2 statistic was greater than 50% but all

studies favored the same intervention, or when the I^2 statistic was greater than 50% but no study showed a clinical difference between groups, we combined study results using a random-effects meta-analysis model. When the number of included studies was small (three or fewer), we used a fixed-effect model.

Subgroup analysis and investigation of heterogeneity

We conducted subgroup analysis for comparisons of outcomes with use of individual devices and surgeries including adjuvant antimetabolites (e.g. MMC) in one or both the intervention groups. We were not able to carry out the following planned subgroup analyses as the included studies did not stratify participants based on 1) the status of the lens (i.e. eyes that possessed their natural lens (phakic), eyes without the crystalline lens (aphakic, cataract extraction), or eyes with an intraocular lens implanted that replaced the eye's natural lens (pseudophakic)); 2) ethnicity; 3) baseline IOP; or 4) type of glaucoma.

Sensitivity analysis

We were not able to conduct sensitivity analyses to assess the influence on effect estimates of excluding studies at a high risk of reporting bias, as studies at a high risk of reporting bias were grouped with respect to interventions compared. We had also planned to conduct a sensitivity analysis after excluding industry-funded studies; however, funding information was not always available, so we did not have enough information to conduct such analyses.

Summary of findings

We reported risk ratios and measures of effect in a 'Summary of findings' table, showing our judgment of the quality of the evidence by outcome using the GRADE system (Guyatt 2011).

Our prespecified outcome measures were:

- Change in IOP, measured as a mean decrease from baseline (immediate preoperative IOP) at one year after the intervention, when IOP had been measured using Goldmann tonometry, TonoPen, or another standard device. When change in IOP was not available, and when baseline IOP distributions were similar in the two surgery groups, we compared postoperative IOPs as a surrogate to estimate the effect of device-modified trabeculectomy.
- We planned to report IOP fluctuation, assessed as a standard deviation or range of IOPs before or one year after the procedure, whenever such data were available.
- Mean change in IOP from baseline, measured on day one, during weeks one to 12, at four to six months, seven to 12 months, and thereafter as available throughout follow-up. When change in IOP was not available, and when baseline IOPs were similar between treatment groups, we used postoperative IOP to estimate the relative effect of device-modified trabeculectomy in the meta-analyses.
- Best-corrected visual acuity (BCVA), measured using a Snellen chart or Snellen equivalent and assessed at one year postintervention. We analyzed BCVA data as a continuous outcome in the meta-analyses.
- Visual field change, measured in units of mean deviation or mean defect (the average point-wise difference between a given test result and the normal age-matched reference value) at one year postintervention.
- Quality of life, measured by the National Eye Institute Visual Function Questionnaire (NEI VFQ) or any other validated instrument at one year postintervention.
- Frequency of the following complications: loss of vision of more than two lines, IOP < 5 mm Hg (hypotony), surgical revision within three months and one year after surgery, endophthalmitis or blebitis, retinal detachment, corneal transplant, cataract extraction (among phakic eyes), choroidal hemorrhage, and others as reported in the included studies.

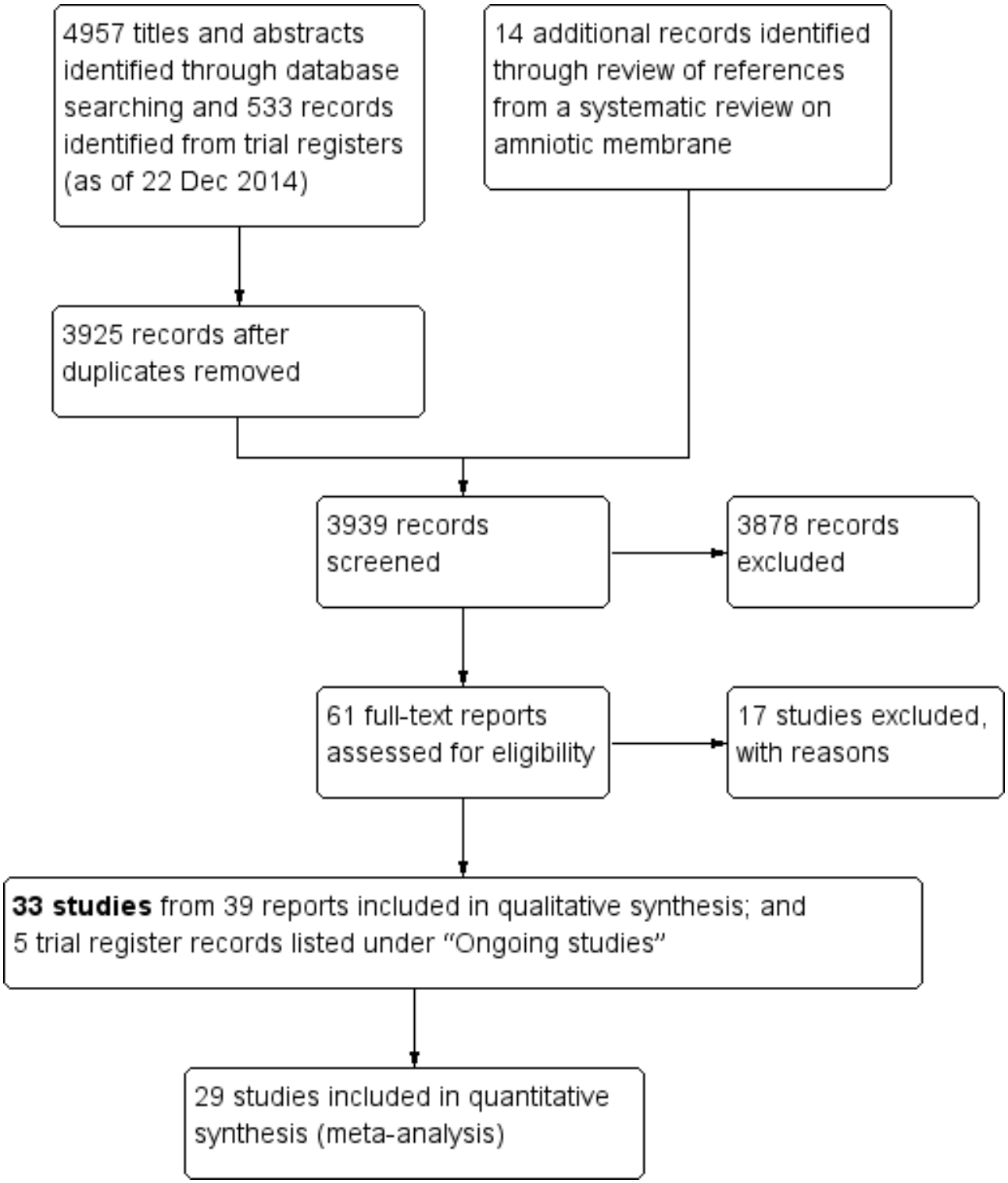
RESULTS

Description of studies

Results of the search

The electronic searches as of 22 December 2014 yielded 4957 titles and abstracts and 533 records from trial registers (Figure 1). After the Trials Search Co-ordinator removed 1565 duplicate records, there remained 3509 unique titles and abstracts and 416 unique records from trial registers. Two review authors (XW and RK) independently reviewed these 3925 records and through review of titles and abstracts identified a systematic review written in Chinese that included another 14 Chinese articles that we had not identified in our searches (Gao 2013). We therefore screened a total of 3939 records and assessed 3878 as 'not relevant', leaving 61 reports for full-text review. Two review authors (XW and RK) independently reviewed these 61 full-text reports, and found 39 reports of 33 unique studies that were eligible for this review. These included 30 studies published as full-length journal articles and three studies reported only as conference abstracts (Birt 1998; Bruno 2008; De Jong 2005). Additionally, five trials were ongoing and we recorded the study characteristics in the 'Characteristics of ongoing studies' tables. We excluded the remaining 17 reports from 17 studies.

Figure 1. Study flow diagram.



Included studies

The following is a summary of the characteristics of the 33 included studies. Twenty-one studies were published in English and 12 studies that had assessed amniotic membrane were published in Chinese. Details of each trial are presented in the 'Characteristics of included studies' tables. We also summarized the basic study characteristics in Table 1.

Types of participants

The 33 studies included 1542 participants and had follow-up periods ranging from three months to five years after surgery. The

studies represented adults of both genders. One study did not specify the participants' diagnoses (Birt 1998), but all other studies included participants with different types of glaucoma, including primary open-angle glaucoma, angle-closure glaucoma, uveitic glaucoma, pseudophakic glaucoma, pseudoexfoliation glaucoma, refractory glaucoma, and uncontrolled intraocular pressure (IOP). None of the studies stratified participants by type of glaucoma, race, or lens type. These studies were conducted in North America, South America, Europe, Asia, and the Middle East.

Types of interventions

The 33 studies, reported in 36 full-text articles and three conference abstracts, assessed five different devices used with standard trabeculectomy: Ex-PRESS, Ologen, amniotic membrane, expanded polytetrafluoroethylene (E-PTFE), and Gelfilm. No trials assessed silicon tube implant or SOLX Gold Shunt.

Five studies assessed the use of trabeculectomy with Ex-PRESS compared with trabeculectomy alone (Dahan 2012; De Jong 2005; De Jong 2009; Netland 2014; Wagschal 2013). Five studies enrolled a total of 412 eyes of 386 participants. Four of the five studies were two-arm studies that compared trabeculectomy alone versus trabulectomy and Ex-PRESS, with mitomycin C (MMC) applied to both groups. One study was a three-arm trial: (1) Ex-PRESS implanted under scleral flap with standard trabeculectomy, (2) Ex-PRESS implanted under conjunctiva with standard trabeculectomy, and (3) trabeculectomy alone (De Jong 2005).

Eight studies assessed the use of Ologen (Cillino 2011; Maheshwari 2012; Marey 2013; Mitra 2012; Papaconstantinou 2010; Rosentreter 2010; Rosentreter 2014; Senthil 2013). They enrolled a total of 333 eyes of 327 participants. While seven of the eight studies compared trabeculectomy + MMC with trabeculectomy + Ologen implant, one study compared trabeculectomy versus trabeculectomy + Ologen implant without any use of MMC or 5-fluorouracil (5-FU) (Papaconstantinou 2010).

Eighteen studies, reported in 17 full-text articles and one conference abstract, assessed the use of amniotic membrane compared with trabeculectomy, with or without the use of MMC (Bruno 2008; Cai 2012; Cho 2013; Eliezer 2006; Huang 2007; Ji 2013; Khairy 2015; Li 2010; Liu 2009; Ren 2009; Sheha 2008; Stavrakas 2012; Wang 2008; Wang 2009; Yan 2004; Yang 2004; Zhang 2009; Zheng 2005). Findings from 13 of these studies were published in Chinese and accounted for 647 eyes of 536 participants, more than 70% of all 726 participants in the 18 studies.

One study assessed the use of E-PTFE and compared four intervention groups: 1) trabeculectomy; 2) trabeculectomy + E-PTFE; 3) trabeculectomy + MMC; and 4) trabeculectomy + E-PTFE + MMC (Cillino 2008). The study included 60 eyes of 60 glaucoma participants who had primary open-angle glaucoma, pseudoexfoliation glaucoma or uncontrolled IOP; 15 eyes of 15 participants were assigned to each of the four surgery groups. The study was conducted in Italy and all participants were followed for 24 months.

One study, which was reported only in a conference abstract, evaluated Gelfilm and MMC using a two-by-two factorial design, and compared outcomes among four intervention groups (Birt 1998). The study included 43 participants (number of eyes not specified): 14 participants in the trabeculectomy group, 11 in the trabeculectomy + Gelfilm group, seven in the trabeculectomy + MMC group, and 11 in the trabeculectomy + Gelfilm + MMC group. All participants completed one year of follow-up.

Types of outcomes

All studies considered IOP control as their main outcome; however, the method in which IOP outcomes were reported differed among studies. None of the studies reported the data as change of IOP from baseline (although two studies reported individual participant data so we were able to calculate the mean change in IOP from baseline). All studies reported postoperative IOP at certain time points, and one study did not report any quantitative data but provided a descriptive summary only.

Thirteen studies reported visual acuity outcomes at different time points; one study reported visual field outcomes; and all studies reported postoperative complications. None of the studies reported IOP fluctuation or quality-of-life outcomes.

Funding sources

Of the 33 studies, the funding source of seven studies had been reported: six studies were supported by industry (Dahan 2012; De Jong 2009; Netland 2014; Rosentreter 2010; Rosentreter 2014; Wagschal 2013) and one study reported receiving no funding (Senthil 2013). Reports from the other 26 studies did not disclose information about sources of funding.

Excluded studies

We excluded 17 studies and listed the reasons for exclusion in the 'Characteristics of excluded studies' tables. We excluded nine studies due to insufficient information for confirmation of randomized controlled trial (RCT) status, three studies due to their inclusion of children under 18 years of age and failure to report outcomes for adult participants separately, two studies for not being RCTs, one study due to insufficient follow-up time, one study with no device included in the comparison group, and one study was only available as a registered trial in clinicaltrials.gov with no indication of having enrolled participants.

Risk of bias in included studies

Figure 2 shows a summary of the 'Risk of bias in included studies' assessments. All but one study had a high risk of detection bias. Most studies either had missing or inadequate information in study reports to assess the risk of selection bias. A description for each domain is summarized below.

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

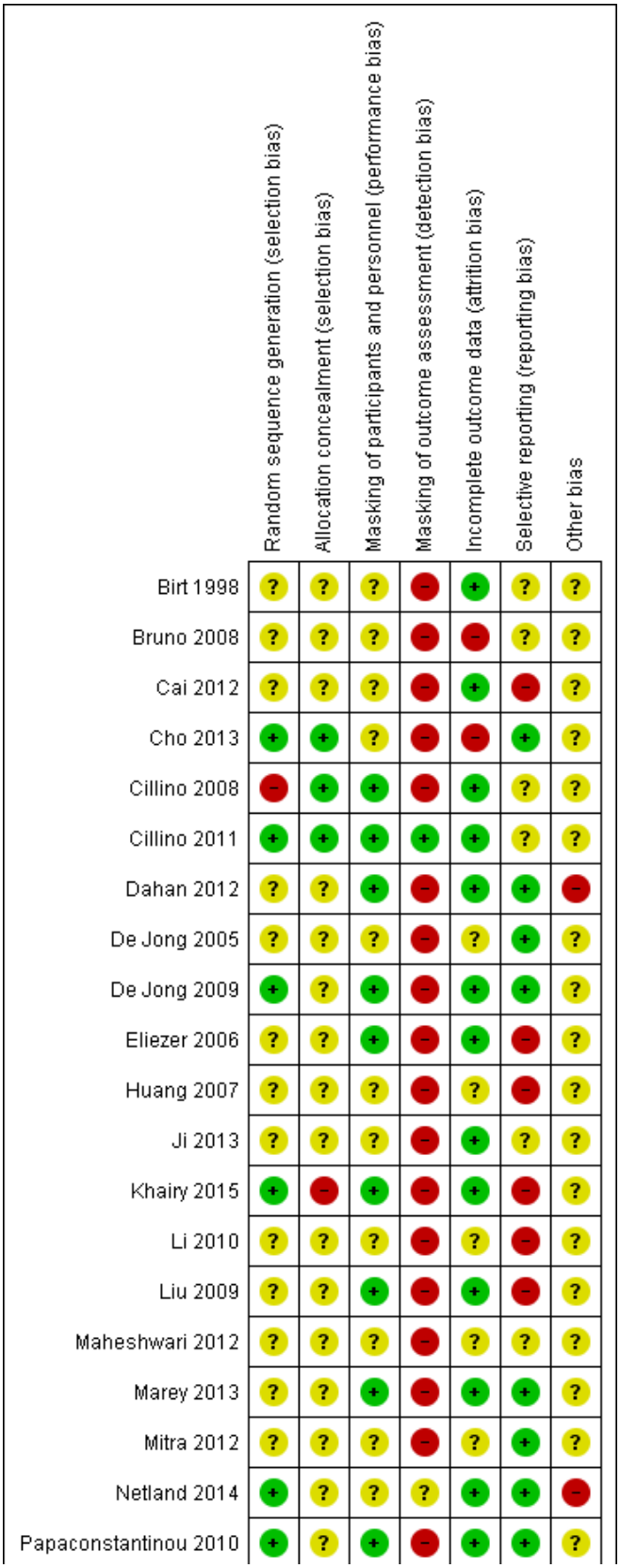


Figure 2. (Continued)

Allocation

Of the 33 studies, 10 specified adequate methods of randomization and we assessed them as being at low risk of bias: three out of five studies for Ex-PRESS (De Jong 2009; Netland 2014; Wagschal 2013), four out of eight studies for Ologen (Cillino 2011; Papaconstantinou 2010; Rosentreter 2014; Senthil 2013), three out of 18 studies for amniotic membrane (Cho 2013; Khairy 2015; Stavrakas 2012). The one study that evaluated E-PTFE did not use a completely random allocation method (medical chart number), so we judged it to be at high risk of bias (Cillino 2008). All other 22 studies did not specify methods for random sequence generation, so we judged them to be at unclear risk of bias.

Of the 33 studies, only three performed proper allocation concealment and we judged them to be at low risk of bias: one out of eight studies for Ologen, one out of 18 studies for amniotic membrane, and one study for E-PTFE (Cho 2013; Cillino 2008; Cillino 2011). We judged Khairy 2015 to be at high risk of bias as the investigators labeled the envelope used to allocate the treatment. The other 29 studies did not specify the method for allocation concealment, so we judged them to be at unclear risk of bias.

Masking (performance bias and detection bias)

Authors of reports from 14 of the 33 studies noted masking of participants: two of five studies for Ex-PRESS (Dahan 2012; De Jong 2009), six of eight studies for Ologen (Cillino 2011; Marey 2013; Papaconstantinou 2010; Rosentreter 2010; Rosentreter 2014; Senthil 2013), five of 18 studies for amniotic membrane (Eliezer 2006; Khairy 2015; Liu 2009; Sheha 2008; Stavrakas 2012), and one study for E-PTFE (Cillino 2008). The remaining 19 studies did not report whether participants were masked and we judged them to be at unclear risk of performance bias. Because masking of surgeons is logistically difficult and because trabeculectomy is a standardized procedure (all 14 studies described the surgical procedures in detail), we did not consider the lack of masking of surgeons to be an important modifiable source of bias.

Investigators of one of the 33 studies reported masking of outcome assessors (Cillino 2011) and one study used a special protocol to minimize bias (Netland 2014); we judged these two studies to be at low and unclear risk of detection bias, respectively. None of the other 31 studies specified masking of outcome assessors. Due to the easy detection of devices when examining the eye, unmasked outcome assessors could tend to anticipate and thus report favorable change in IOP among participants with the implant or alternatively, among participants who received the surgery the outcome assessor preferred; we therefore judged these studies to be at high risk of detection bias.

Incomplete outcome data

Of the 33 studies, investigators of 17 studies reported few or no losses to follow-up, resulting in our assessment of them to be at low risk of attrition bias: four of six trials of Ex-PRESS (Dahan 2012; De Jong 2009; Netland 2014; Wagschal 2013), five of eight studies for Ologen (Cillino 2011; Marey 2013; Papaconstantinou 2010; Rosentreter 2010; Rosentreter 2014), six of 18 studies for amniotic membrane (Cai 2012; Eliezer 2006; Ji 2013; Khairy 2015; Liu 2009; Stavrakas 2012), one study for E-PTFE (Cillino 2008), and one study for Gelfilm (Birt 1998). Four studies had a relatively large percentage of losses to follow-up (> 10%) and we assessed the risk of attrition bias to be high for these studies (Bruno 2008; Cho 2013; Senthil 2013; Sheha 2008). We assessed the remaining 12 studies at unclear risk of attrition bias as they did not report the number of

losses to follow-up; nine of the 12 studies were amniotic membrane studies.

Selective reporting

We judged 16 of 33 studies as being at low risk of reporting bias as they had 1) clinical trial registry records and reported all outcomes listed in the registry (Dahan 2012; Netland 2014; Rosentreter 2010; Rosentreter 2014; Wagschal 2013), or 2) reported all outcome measures defined in the Methods section of the full-text reports (Cho 2013; De Jong 2005; De Jong 2009; Marey 2013; Mitra 2012; Papaconstantinou 2010; Senthil 2013; Sheha 2008; Stavrakas 2012; Wang 2008; Zhang 2009). We judged six studies to have unclear risk of bias because some outcomes that were measured were not reported in primary result papers, but we presume they will be reported in future publications from the trials (Bruno 2008; Cillino 2008; Cillino 2011; Ji 2013; Maheshwari 2012). We rated the remaining 11 studies at high risk of bias, as the outcome measures were not defined in the Methods section of the full text and no protocol or trial registration was publicly available.

Studies judged to be at low risk of reporting bias by devices: all studies for Ex-PRESS, six of eight studies for Ologen, and five of 18 studies for amniotic membrane (Cho 2013; Sheha 2008; Stavrakas 2012; Wang 2008; Zhang 2009). Studies judged to be at unclear risk of reporting bias by devices: one of eight studies for Ologen, two of 18 studies for amniotic membrane, the only study that evaluated E-PTFE (Bruno 2008; Cillino 2008; Cillino 2011; Ji 2013; Maheshwari 2012). The study for Gelfilm was at a high risk of reporting bias (Birt 1998), as were 11 of 18 studies for amniotic membrane (Cai 2012; Eliezer 2006; Huang 2007; Khairy 2015; Li 2010; Liu 2009; Ren 2009; Wang 2009; Yan 2004; Yang 2004; Zheng 2005).

Other potential sources of bias

We judged one out of 33 included studies to be at low risk of having other potential sources of bias. We judged three studies to be at high risk because one did not recruit an adequate number of participants that met the prespecified power requirements of the study (Rosentreter 2010), and two studies received funding from the manufacturer of the device (Dahan 2012; Netland 2014). We judged the remaining studies to be at unclear risk of bias, as methodological details were reported insufficiently to render a judgment of low or high risk of bias.

Effects of interventions

See: **Summary of findings for the main comparison** Summary of findings for Ex-PRESS; **Summary of findings 2** Summary of findings for Ologen; **Summary of findings 3** Summary of findings for amniotic membrane

Trabeculectomy + Ex-PRESS versus trabeculectomy

Five studies assessed the use of Ex-PRESS (Dahan 2012; De Jong 2005; De Jong 2009; Netland 2014; Wagschal 2013). Four of five studies reported a sample size calculation: Dahan 2012 had a power of 96% to detect a 2.0 mm Hg intraocular pressure (IOP) difference between groups; De Jong 2009 had a power of 80% to detect a 32% between-group difference in IOP; and both Netland 2014 and Wagschal 2013 had power of 80% to detect a 2.0 mm Hg IOP difference between groups. De Jong 2005 did not report a power or sample size calculation. The overall risk of bias for these studies was high or unclear, especially with respect to detection bias and potential conflicts of interest. Four of five studies reported receiving some funding or resource support from the device manufacturer (Dahan 2012; De Jong 2009; Netland 2014; Wagschal 2013) and one study did not reported information on potential conflicts of interest (De Jong 2005).

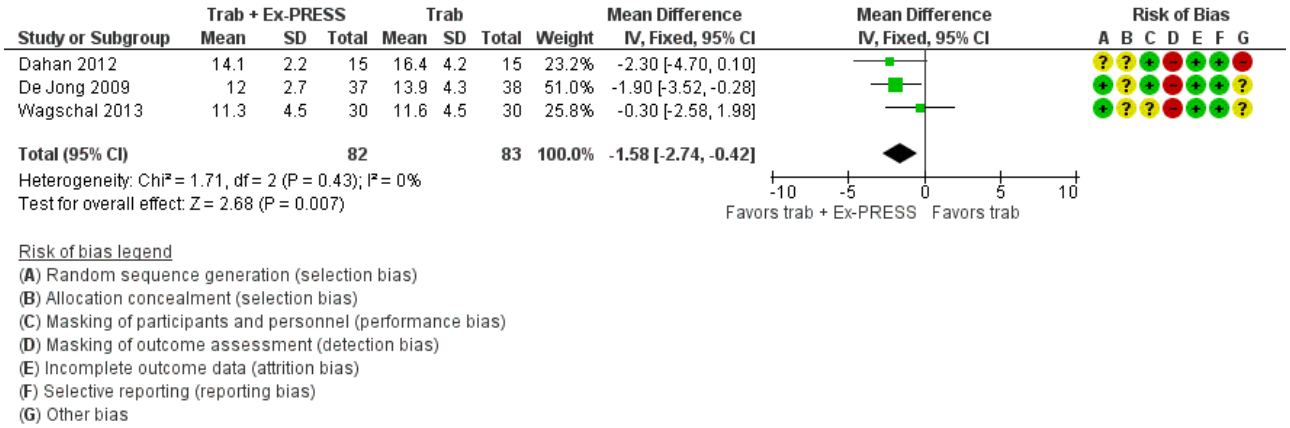
Intraocular pressure (IOP)

Four studies reported postoperative IOP at follow-up time points (Dahan 2012; De Jong 2009; Netland 2014; Wagschal 2013). Dahan 2012 reported IOP data at last follow-up time point and presented a figure with IOP reduction over time. The study encompassed 30 eyes of 15 participants at one year, 20 eyes of 10 participants at two years, and 14 eyes of seven participants at 30 months (last follow-up). Upon our request, the study investigators shared their original data, so we were able to calculate the mean change in IOP from baseline to one-year follow-up and postoperative IOP at various follow-up time points (months 6, 12, and 24).

At one year, only Dahan 2012 provided data on the mean change in mean IOP for 30 eyes of 15 participants from baseline to one-year follow-up. We calculated the mean change in IOP from baseline to one-year follow-up. It is uncertain whether use of Ex-PRESS (MD -14.07, SD 8.50) leads to IOP reduction at one year (MD -14.73, SD 12.60) because the quality of the evidence is very low (MD 0.67**,** 95**%** CI -7.52 to 8.86).

At one year, three studies comprising 165 eyes reported mean IOP by treatment group (Dahan 2012; De Jong 2009; Wagschal 2013). We rated the low-quality evidence at high risk of detection and publication bias. We found that the use of Ex-PRESS may lead to a slightly improved IOP reduction at one year (Analysis 1.1; Figure 3; MD -1.58 mm Hg, 95% CI -2.74 to -0.42; I^2 = 0%). A fourth study did not provide quantitative data, but reported that there was no between-group difference in IOP reduction at one year (Netland 2014).

Figure 3. Forest plot of comparison: 2 Trabeculectomy + Ex-PRESS versus Trabeculectomy, outcome: Postoperative IOP at one year.



At six months, three studies comprising 205 eyes reported mean IOP (Dahan 2012; Netland 2014; Wagschal 2013). It is unclear whether the use of Ex-PRESS leads to IOP reduction at six months because the quality of the evidence is very low (Analysis 1.2; MD 0.18, 95% CI -0.90 to 1.26). The I^2 was 75%, indicating inconsistency in the effect of treatments among studies.

At two years, three studies comprising 212 eyes reported IOP outcomes (Dahan 2012; De Jong 2009; Netland 2014). The low-quality evidence shows Ex-PRESS may slightly improve IOP reduction at two years (Analysis 1.3; MD -1.45 mm Hg, 95% CI -2.52 to -0.37).

Best-corrected visual acuity (BCVA) at one year postintervention

We combined Wagschal 2013 and Dahan 2012 in a meta-analysis for logMAR BCVA at one year. We judged the very low-quality evidence to be at high risk of detection and publication bias. It is unclear whether Ex-PRESS prevents loss in BCVA because the quality of the evidence is very low (Analysis 1.4; MD -0.15, 95% CI -0.40 to 0.10; 90 eyes).

Wagschal 2013 reported logMAR BCVA at one year, but Dahan 2012 did not publish quantitative data for this outcome. The authors of Dahan 2012 provided us with original data from which we calculated the postoperative mean logMAR BCVA to be 0.41 ± 0.11 (mean ± SE) for the Ex-PRESS group and 0.43 ± 1.33 (mean ± SE) for the trabeculectomy group at one year.

Although De Jong 2009 also assessed visual acuity preoperatively and at each follow-up visit, quantitative data were not reported. They reported that visual acuity remained equivalent in the majority of participants, with no significant difference between the groups at one year. Netland 2014 did not report on this outcome.

IOP fluctuation, visual field, and quality of life

No study reported these outcomes.

Complications

All four full-text studies reported complications in a total of 294 eyes during their respective follow-up visits. The four studies had different lengths of follow-up periods, ranging from one to two years. We considered the reported postoperative complications as occurring within the first year after surgery. These results should be interpreted with caution, due to possible differences in length of follow-up. We conducted a meta-analysis using the proportion of participants with each complication in each group (Analysis 1.5). De Jong 2005 did not report any complications.

Loss of vision of more than two lines

Wagschal 2013 reported loss of vision more than two lines of BCVA within and after the first six months follow-up. Within the first six months follow-up period, there were seven of 30 eyes in the trabeculectomy group and 11 of 31 eyes in the Ex-PRESS group with loss of vision more than two lines of BCVA (RR 0.66, 95% CI 0.29 to 1.47).

IOP < 5 mm Hg (hypotony)

Two studies comprising 94 eyes reported this complication (Dahan 2012; Wagschal 2013). We judged the very low-quality evidence to be at high risk of detection and publication bias. It is unclear whether Ex-PRESS prevents hypotony because the quality of the evidence is very low (Analysis 1.5.1; RR 0.92, 95% CI 0.63 to 1.33).

None of the included studies reported these complications: Surgical revision within three months and one year after surgery, endophthalmitis or blebitis, retinal detachment, corneal transplant, cataract extraction (among phakic eyes), choroidal hemorrhage.

Others as reported from the included studies

Other complications not included in the protocol were: shallow/flat anterior chamber, hyphema, and needling.

Shallow/flat anterior chamber

Four studies comprising 294 eyes reported this complication (Dahan 2012; De Jong 2009; Netland 2014; Wagschal 2013). We rated the very low-quality evidence at high risk of detection and publication bias. It is unclear whether Ex-PRESS prevents shallow/flat anterior chamber because the quality of the evidence is very low (Analysis 1.5.2; RR 0.72, 95% CI 0.40 to 1.32).

Bleb leakage

Four studies comprising 294 eyes reported this complication (Dahan 2012; De Jong 2009; Netland 2014; Wagschal 2013). It is unclear whether Ex-PRESS prevents bleb leakage because the quality of the evidence is very low (Analysis 1.5.3; RR 1.26, 95% CI 0.50 to 3.20).

Hyphema

Four studies comprising 294 eyes reported this complication (Dahan 2012; De Jong 2009; Netland 2014; Wagschal 2013). The low-quality evidence shows that Ex-PRESS may prevent hyphema (Analysis 1.5.4; RR 0.33, 95% CI 0.12 to 0.94).

Cataract surgery

Three studies comprising 264 eyes reported this complication (De Jong 2009; Netland 2014; Wagschal 2013). The low-quality evidence shows that Ex-PRESS may prevent cataract surgery (Analysis 1.5.5; RR 0.32, 95% CI 0.14 to 0.74).

Needling

Only one study covering 80 eyes reported this complication (De Jong 2009). There were nine of 40 eyes in the trabeculectomy group and three of 40 eyes in the Ex-PRESS group that required needling. The low-quality evidence shows that the use of Ex-PRESS may prevent needling (RR 0.33, 95% CI 0.10 to 1.14).

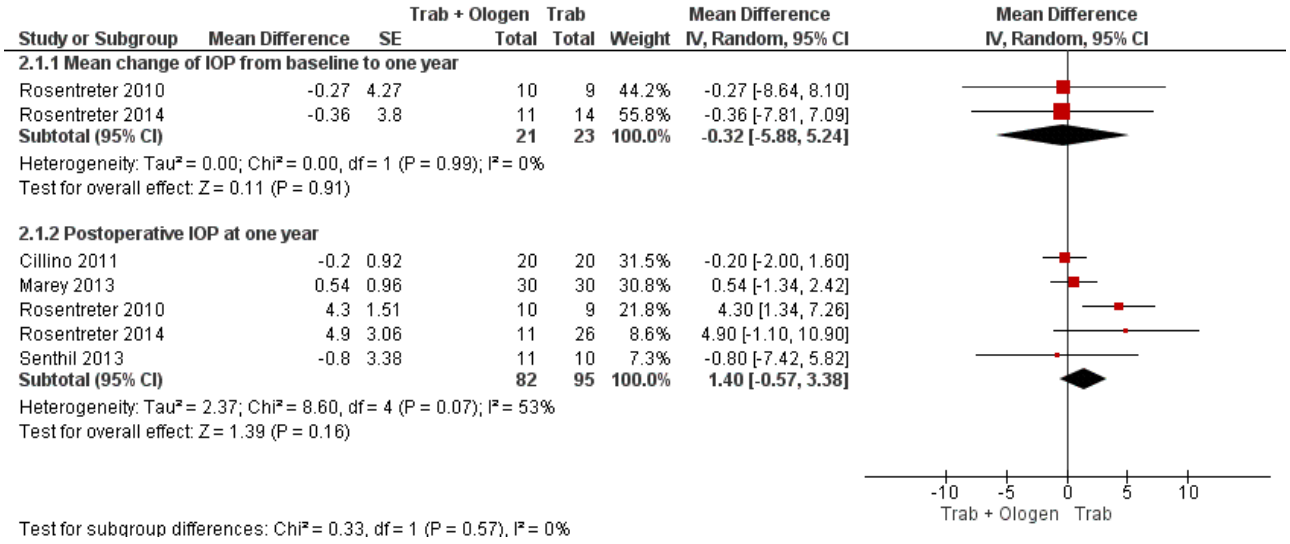
Trabeculectomy + Ologen versus trabeculectomy

Eight studies assessed the use of Ologen during trabeculectomy (Cillino 2011; Maheshwari 2012; Marey 2013; Mitra 2012; Papaconstantinou 2010; Rosentreter 2010; Rosentreter 2014; Senthil 2013). Only three studies reported sample size calculations. Cillino 2011 reported a power of 90% to detect a 3 mm Hg IOP difference between groups; Rosentreter 2014 reported a power of 50% to detect a 2.73 mm Hg IOP difference between groups and a power of 95% to detect a difference of 5.03 mm Hg in IOP. The sample size calculation originally performed for Rosentreter 2010 targeted 40 participants, but the desired power was not reported. Only 20 participants enrolled. We judged the very low-quality evidence on IOP and BCVA outcomes at all follow-up time points to be at high risk of detection and publication bias.

Intraocular pressure (IOP)

Overall, the effect of Ologen on IOP compared to trabeculectomy alone is uncertain (Analysis 2.1). None of the eight studies reported mean change in IOP from baseline. However, two of eight studies reported individual participant data, so we were able to calculate the mean change in IOP from baseline to all follow-up time points between the trabeculectomy-alone group and the Ologen group (Rosentreter 2010; Rosentreter 2014). It is uncertain whether Ologen led to IOP reduction because the quality of the evidence is very low at every follow-up time point (Figure 4; Analysis 2.1.1; MD -0.32 mm Hg, 95% CI -5.88 to 5.24). Six of eight studies reported postoperative IOP at certain time points instead, and these six studies had comparable baseline IOP values between groups, except for Maheshwari 2012. For the six studies without reporting of change of IOPs, we analyzed the postoperative IOP at certain time points between groups as a surrogate for mean difference in change of IOP from baseline between groups.

Figure 4. Forest plot of comparison: 2 Trabeculectomy (Trab) + Ologen versus Trabeculectomy (Trab), outcome: 2.1 IOP at one year.



At one year, six studies comprising 217 eyes reported IOP outcomes (Cillino 2011; Maheshwari 2012; Marey 2013; Rosentreter 2010; Rosentreter 2014; Senthil 2013). We excluded Maheshwari 2012 from the pooled analysis as the baseline IOP in Maheshwari 2012 differed between the two groups. At one year, they reported a mean IOP of 15.6 mm Hg, and a 43% reduction in IOP from baseline in the Ologen group, and a mean IOP of 10.5 mm Hg, and a 50% reduction in IOP in the trabeculectomy-alone group. However, the two groups were not comparable as the baseline IOP in the Ologen group was about 30% greater than in the trabeculectomy-alone group. It is unclear whether Ologen improves IOP reduction at one year because the quality of the evidence is very low (Analysis 2.1; MD 1.40 mm Hg, 95% CI -0.57 to 3.38; 5 studies). The I^2 was not substantial (I^2 = 0%) and no study showed a clinical difference between groups, so we combined the data.

At the first day after surgery, five studies comprising 162 eyes reported IOP outcomes (Cillino 2011; Papaconstantinou 2010; Rosentreter 2010; Rosentreter 2014; Senthil 2013). It is unclear whether Ologen improves IOP reduction because the quality of the evidence is very low (Analysis 2.2; MD 0.51, 95% CI -1.95 to 2.97). Although there was substantial statistical heterogeneity (I^2 = 55%), mostly due to Cillino 2011, we combined the data as there was a high degree of overlap among the confidence intervals of studies.

At six months, seven studies comprising 282 eyes reported on IOP outcomes (Cillino 2011; Marey 2013; Mitra 2012; Papaconstantinou 2010; Rosentreter 2010; Rosentreter 2014; Senthil 2013). It is unclear whether Ologen improves IOP reduction because the quality of the evidence is very low (Analysis 2.3.1; MD -1.24 mm Hg, 95% CI -6.23 to 3.76; I^2 = 0%; Rosentreter 2010; Rosentreter 2014). Similarly, at six months follow-up, we found that it is unclear whether Ologen improves IOP reduction because the quality of the evidence is very low (Analysis 2.3.2; MD 0.43, 95% CI -0.97 to 1.84). Although there was substantial heterogeneity (I^2 = 53%), no study showed a clinical difference between groups, so we combined the data.

At two years, the longest length of follow-up in two studies comprising 55 eyes (Cillino 2011; Senthil 2013), it is unclear whether Ologen improves IOP reduction because the quality of the evidence is very low (Analysis 2.4; MD 0.20 mm Hg, 95% CI -1.29 to 1.69).

Best-corrected visual acuity (BCVA)

Two studies comprising 51 eyes reported BCVA data at different time points. None of the studies reported BCVA at one year after surgery.

Senthil 2013 reported BCVA for 32 eyes at six weeks post-surgery. We judged the very low-quality evidence to be at high risk of detection and attrition bias. The BCVA for the Ologen group was 0.44 ± 0.66 (mean ± SD) and for the trabeculectomy-alone group was 0.20 ± 0.24 (mean ± SD), and showed it is uncertain whether use of Ologen may prevent loss in BCVA (MD -0.24 logMAR, 95% CI -0.58 to 0.10). The estimated mean difference is equivalent to more than two lines on a logMAR chart; however, the small number of participants yielded a wide confidence interval.

Rosentreter 2010 reported that in all 19 eyes observed, the visual acuity remained stable over the one-year follow-up (no data provided).

Visual field

Only one study reported on this outcome (Rosentreter 2010). It reported that the visual field remained stable over one-year follow-up among all 19 participants but did not provide any data.

IOP fluctuation and quality of life

No study reported these outcomes.

Complications

All eight studies reported complications in 333 eyes of 327 participants during their respective follow-up visits, with the exception of Maheshwari 2012, who reported no complications. Although these studies had different lengths of follow-up, ranging from six months to two years, we assumed that most postoperative complications occurred within the first six months after the surgery, so we combined the data in the meta-analyses. These results should be interpreted with caution, due to our assumption that the complications all occurred within the six-month window. Other complications not included in the protocol were: bleb leakage, hyphema, choroidal detachment, shallow anterior chamber, Tenon's cysts, anterior chamber reaction, positive Seidel test, needling, and flat anterior chamber. We judged the very low-quality evidence to be at high risk of detection and publication bias, and are therefore uncertain if there is a difference between the two groups for each complication (Analysis 2.5).

Loss of vision of more than two lines

None of the included studies reported this complication.

IOP < 5 mm Hg (hypotony)

Six studies including 233 eyes reported this complication (Cillino 2011; Mitra 2012; Papaconstantinou 2010; Rosentreter 2010; Rosentreter 2014; Senthil 2013). It is unclear whether use of Ologen prevents hypotony because the quality of the evidence is very low (Analysis 2.5.1; RR 0.75, 95% CI 0.47 to 1.19).

Surgical revision within three months and one year after surgery

Four studies including 150 eyes reported this complication (Marey 2013; Papaconstantinou 2010; Rosentreter 2010; Rosentreter 2014). It is unclear whether use of Ologen prevents surgical revision within three months and one year after surgery, because the quality of the evidence is very low (Analysis 2.5.2; RR 1.70, 95% CI 0.38 to 7.63).

Endophthalmitis or blebitis

Three studies including 164 eyes reported this complication (Marey 2013; Mitra 2012; Papaconstantinou 2010). It is unclear whether use of Ologen prevents endophthalmitis or blebitis because the quality of the evidence is very low (Analysis 2.5.3; RR 1.57, 95% CI 0.25 to 9.70).

None of the included studies reported these complications: retinal detachment, corneal transplant, cataract extraction (among phakic eyes), and choroidal hemorrhage.

Others as reported from the included studies

Bleb leakage

Four studies including 129 eyes reported this complication (Cillino 2011; Rosentreter 2010; Rosentreter 2014; Senthil 2013). It is unclear whether use of Ologen prevents bleb leakage because the quality of the evidence is very low (Analysis 2.5.4; RR 0.85, 95% CI 0.33 to 2.20).

Hyphema

Six studies including 229 eyes reported this complication (Cillino 2011; Marey 2013; Papaconstantinou 2010; Rosentreter 2010; Rosentreter 2014; Senthil 2013). It is unclear whether use of Ologen prevents hyphema because the quality of the evidence is very low (Analysis 2.5.5; RR 1.46, 95% CI 0.51 to 4.19).

Choroidal detachment

Four studies including 129 eyes reported this complication (Cillino 2011; Rosentreter 2010; Rosentreter 2014; Senthil 2013). It is unclear whether use of Ologen prevents choroidal detachment because the quality of the evidence is very low (Analysis 2.5.6; RR 0.83, 95% CI 0.33 to 2.09).

Shallow anterior chamber

Five studies including 213 eyes reported this complication (Marey 2013; Mitra 2012; Rosentreter 2010; Rosentreter 2014; Senthil 2013). It is unclear whether use of Ologen prevents shallow anterior chamber because the quality of the evidence is very low (Analysis 2.5.7; RR 0.79, 95% CI 0.32 to 1.93).

Anterior chamber reaction

Two studies including 99 eyes reported this complication (Marey 2013; Senthil 2013). It is unclear whether use of Ologen prevents anterior chamber reaction because the quality of the evidence is very low (Analysis 2.5.8; RR 1.21, 95% CI 0.56 to 2.60)

Positive Seidel test

Three studies including 164 eyes reported this complication (Marey 2013; Mitra 2012; Papaconstantinou 2010). It is unclear whether use of Ologen prevents a positive Seidel test because the quality of the evidence is very low (Analysis 2.5.9; RR 1.93, 95% CI 0.32 to 11.54)

Tenon's cysts

Three studies including 124 eyes reported this complication (Mitra 2012; Papaconstantinou 2010; Rosentreter 2010). It is unclear whether use of Ologen prevents Tenon's cysts because the quality of the evidence is very low (Analysis 2.5.10; RR 0.88, 95% CI 0.21 to 3.66)

Flat anterior chamber

Only one study covering 40 eyes reported this complication (Papaconstantinou 2010). There was one of 20 eyes in the trabeculectomy-alone group and two of 20 eyes in the Ex-PRESS group with flat anterior chamber, and it is unclear whether use of Ologen prevents flat anterior chamber because the quality of the evidence is very low (RR 2.00, 95% CI 0.20 to 20.33)

Trabeculectomy + AMT (amniotic membrane) versus trabeculectomy

We identified 18 studies that compared the use of amniotic membrane (AMT) during trabeculectomy versus standard trabeculectomy (Bruno 2008; Cai 2012; Cho 2013; Eliezer 2006; Huang 2007; Ji 2013; Khairy 2015; Li 2010; Liu 2009; Ren 2009; Sheha 2008; Stavrakas 2012; Wang 2008; Wang 2009; Yan 2004; Yang 2004; Zhang 2009; Zheng 2005). Only one study reported a sample size calculation, where a power of 80% was achieved with a sample size of 15 participants (Sheha 2008). However, the minimum detectable difference was not specified. In consideration of potential losses to follow-up, the study recruited 37 participants.

Intraocular pressure (IOP)

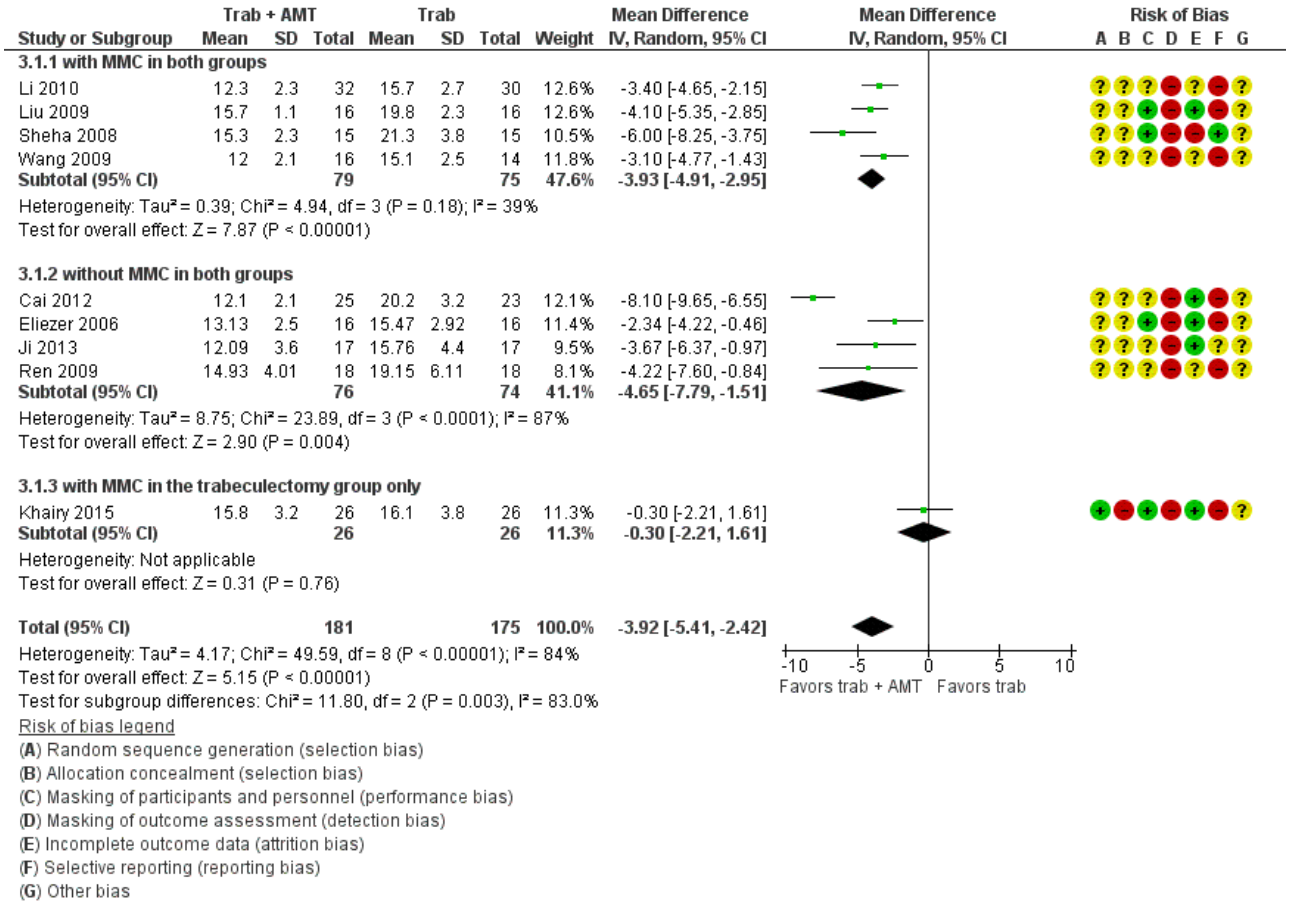
None of the 18 included studies reported change in IOP from baseline; instead, they all reported postoperative IOP at follow-up time points. Caution must be used in interpreting the evidence from each time point, as a lower mean IOP favoring the amniotic membrane group could be attributable to eyes in the amniotic membrane group having a lower baseline IOP. Futhermore, we judged most studies to be at high risk of detection and reporting bias.

Among the 18 studies, only seven accounted for participants lost to follow-up, whereby 316 of 346 eyes were assessed at their respective last follow-up visits. For the remaining 11 studies we used the eyes randomized in data analyses (see Table 1 for losses to follow-up). Numbers of eyes below refers to those randomized, when numbers of eyes analyzed were not reported. Wang 2009 had three groups, including trabeculectomy, trabeculectomy + MMC, and trabeculectomy + amniotic membrane + MMC. We only analyzed the latter two groups, as they both included MMC.

Of the 18 studies, one was a conference abstract that did not give any IOP data in the results (Bruno 2008). However, it concluded that smaller IOP changes were associated with larger avascular blebs. Another study reported median IOP values and the inter-quartile range from 52 eyes (Stavrakas 2012). The median IOP at 24 months was 15.5 mm Hg for the amniotic membrane group and 16 mm Hg for the trabeculectomy-alone group. It did not report a median difference, but reported that there was no difference between the two groups. The remaining 16 studies provided postoperative IOP findings at various time points; we summarize data from those 16 studies below.

At one year, nine studies comprising 356 eyes provided postoperative IOP data (Cai 2012; Eliezer 2006; Ji 2013; Khairy 2015; Li 2010; Liu 2009; Ren 2009; Sheha 2008; Wang 2009). The low-quality evidence showed that the use of amniotic membrane may slightly improves IOP reduction (Analysis 3.1; Figure 5; MD -3.92 mm Hg, 95% CI -5.41 to -2.42; I^2 = 84%). We stratified these studies on whether MMC was applied to both groups or to neither group or to the trabeculectomy-alone group, and found no differences from the overall results. Because Khairy 2015 is the only study that does not have comparable groups (MMC was added to one group only), we excluded that study in a sensitivity analysis, and found the pooled mean IOP in the amniotic membrane group to be about 4 mm Hg lower than in the trabeculectomy-alone group (MD -4.38, 95% CI -5.77 to -2.98).

Figure 5. Forest plot of comparison: 4 Trabeculectomy + AMT (amniotic membrane) versus Trabeculectomy, outcome: 4.1 Postoperative IOP at one year.



At one day, eight studies comprising 405 eyes provided postoperative IOP data (Huang 2007; Khairy 2015; Liu 2009; Sheha 2008; Wang 2008; Yan 2004; Yang 2004; Zheng 2005). We did not report the pooled data as the results of different studies were inconsistent in the direction of effect and there was substantial heterogeneity (I^2 = 91%). There was also substantial statistical heterogeneity for two subgroups: 'with MMC in both groups' (I^2 = 75%) and 'without MMC in both groups' (I^2 = 95%). The subgroup 'with MMC in the trabeculectomy group' had no substantial heterogeneity (I^2 = 0%) and each study showed that It remains uncertain if there is a difference in mean IOP comparing the AMT and trabeculectomy-alone groups (Analysis 3.2).

At one week, 13 studies comprising 625 eyes provided postoperative IOP data (Cai 2012; Cho 2013; Huang 2007; Ji 2013; Khairy 2015; Li 2010; Liu 2009; Sheha 2008; Wang 2008; Wang 2009; Yan 2004; Yang 2004; Zheng 2005). We did not combine the data as results of different studies were inconsistent in the direction of effect and there was substantial heterogeneous (I^2 = 89%). There was also substantial statistical heterogeneity for two subgroups: 'with MMC in both groups' (I^2 = 96%) and 'without MMC in both groups' (I^2 = 87%) . The subgroup 'with MMC in the trabeculectomy-only group' had no substantial statistical heterogeneity (I^2 = 48%) and each study showed that there was no difference in mean IOP comparing the AMT and trabeculectomy-alone groups (Analysis 3.3).

At one month, 13 studies comprising 646 eyes provided postoperative IOP data (Cai 2012;Cho 2013; Huang 2007; Ji 2013; Khairy 2015; Li 2010; Liu 2009; Sheha 2008; Wang 2008; Yan 2004; Yang 2004; Zhang 2009; Zheng 2005), and suggests that the use of amniotic membrane may lead to little or no difference in IOP-lowering effect (Analysis 3.4; MD -1.05 mm Hg, 95% CI -1.96 to -0.13). We stratified these studies on whether MMC was applied to both or neither or to the trabeculectomy-alone group and found the results to be the same as the overall results. Although there was overall substantial statistical heterogeneity (I^2 = 83%), we combined the data as the direction of effect was consistent in favoring the amniotic membrane group.

At three months, 11 studies comprising 551 eyes provided postoperative IOP data (Cho 2013; Huang 2007; Ji 2013; Khairy 2015; Li 2010; Liu 2009; Sheha 2008; Yan 2004; Yang 2004; Zhang 2009; Zheng 2005), and showed the use of amniotic membrane may slightly improve IOP reduction compared to the trabeculectomy-alone group (Analysis 3.5; MD -2.23 mm Hg, 95% CI -2.93 to -1.53) . We stratified these studies on whether MMC was applied to both or neither or to the trabeculectomy-alone group and found no differences from the overall results. As with one-year outcomes, Khairy 2015 and Zheng 2005 were the only studies that included MMC in the trabeculectomy-only group. We excluded these two studies in a sensitivity analysis, which showed that IOP in the amniotic membrane group was 2.54 mm Hg lower than in the

trabeculectomy-only group at three months (MD -2.54, 95% CI -3.27 to -1.81). Although there was substantial statistical heterogeneity (I^2 = 62%), we combined the data as the direction of effect was consistent in favoring the amniotic membrane group. It also is important to note that there was a lot of missing data for these studies due to underreporting of numbers of eyes analyzed at different time points, and the results were likely to be biased.

At six months, 13 studies comprising 613 eyes provided postoperative mean IOP data (Huang 2007; Ji 2013; Khairy 2015; Li 2010; Liu 2009; Ren 2009; Sheha 2008; Wang 2008; Wang 2009; Yan 2004; Yang 2004; Zhang 2009; Zheng 2005), and showed the use of amniotic membrane may slightly improve IOP reduction compared to the trabeculectomy-alone group (Analysis 3.6; MD -2.50 mm Hg, 95% CI -3.34 to -1.67). We stratified these studies on whether MMC was applied to both or neither or to the trabeculectomy-alone group and the results still show an IOP-lowering effect favoring the amniotic membrane group. Although there was overall substantial statistical heterogeneity (I^2 = 74%), we combined the data as the direction of effect was consistent in favoring the amniotic membrane group.

At two years, two studies comprising 86 eyes provided postoperative mean IOP data (Analysis 3.7; Ji 2013; Khairy 2015). Although Khairy 2015 showed no difference between the two groups, the study only applied MMC in the trabeculectomy-alone group and the groups were not comparable to Ji 2013 (which did not apply MMC to both groups). Ji 2013 reported that IOP in the amniotic membrane group was 2.96 mm Hg lower than the trabeculectomy-alone group (MD -2.96, 95% CI -5.52 to -0.40). Due to the substantial statistical heterogeneity (I^2 = 64%), methodological heterogeneity, and high risk of bias, we did not combine these two studies.

Best-corrected visual acuity (BCVA)

Only one study comprising 48 eyes reported BCVA at one year and reported that the amniotic membrane group had better BCVA than the trabeculectomy-alone group, but no additional data were provided (Cai 2012).

IOP fluctuation, visual field and quality of life

No study reported on these outcomes.

Complications

All 17 studies reported in full-length articles provided data on complications in 840 eyes during postoperative follow-up. We compared proportions of participants with each complication between groups in meta-analyses. Complications reported included loss of vision, hypotony, shallow anterior chamber, hyphema, bleb leakage, encapsulated blebs, choroidal detachment, anterior chamber reaction, and flat anterior chamber. Complications were less frequent in the amniotic membrane group than in the trabeculectomy-alone group (Analysis 3.8), except for anterior chamber reaction (Li 2010).

Loss of vision of more than two lines

None of the included studies reported this complication.

IOP < 5 mm Hg (hypotony)

Five studies including 205 eyes reported this complication (Khairy 2015; Liu 2009; Ren 2009; Sheha 2008; Zheng 2005). The low-quality evidence showed use of amniotic membrane may prevent hypotony (Analysis 3.8.1; RR 0.40, 95% CI 0.17 to 0.94).

None of the included studies reported these complications: surgical revision within three months and one year after surgery, endophthalmitis or blebitis, retinal detachment, corneal transplant, cataract extraction (among phakic eyes), and choroidal hemorrhage.

Others as reported from the included studies

Shallow anterior chamber

Thirteen studies including 632 eyes reported this complication (Cho 2013; Eliezer 2006; Huang 2007; Ji 2013; Khairy 2015; Li 2010; Ren 2009; Wang 2008; Wang 2009; Yan 2004; Yang 2004; Zhang 2009; Zheng 2005). The low-quality evidence showed that use of amniotic membrane may prevent shallow anterior chamber (Analysis 3.8.2; RR 0.47, 95% CI 0.30 to 0.73).

Hyphema

Five studies including 235 eyes reported this complication (Cai 2012; Cho 2013; Sheha 2008; Wang 2009; Yang 2004). It is unclear whether use of amniotic membrane prevents hyphema because the quality of the evidence is very low (Analysis 3.8.3; RR 0.43, 95% CI 0.14 to 1.34).

Bleb leakage

Two studies including 98 eyes reported this complication (Cho 2013; Zheng 2005). The low-quality evidence showed use of amniotic membrane may prevent bleb leakage (Analysis 3.8.4; RR 0.28, 95% CI 0.10 to 0.79).

Encapsulated blebs

Five studies including 175 eyes reported this complication (Eliezer 2006; Ji 2013; Liu 2009; Sheha 2008; Wang 2008). The low-quality evidence showed use of amniotic membrane may prevent encapsulated blebs (Analysis 3.8.5; RR 0.23, 95% CI 0.08 to 0.69).

Choroidal detachment

Four studies including 187 eyes reported this complication (Eliezer 2006; Ji 2013; Li 2010; Stavrakas 2012). The low-quality evidence showed use of amniotic membrane may prevent choroidal detachment (Analysis 3.8.6; RR 0.47, 95% CI 0.13 to 1.71).

Anterior chamber reaction

Only one study comprising 62 eyes reported this complication (Li 2010). There were 21 of 30 eyes in the trabeculectomy-alone group and 25 of 32 eyes in the AMT group with flat anterior chamber, but there was uncertainty if the relative risk of flat anterior chamber favored the AMT or the trabeculectomy-alone group, as the result was statistically non-significant (RR 1.12, 95% CI 0.83 to 1.50).

Flat anterior chamber

Only one study comprising 37 eyes reported this complication (Sheha 2008). There were two of 18 eyes in the trabeculectomy-alone group and none of 19 eyes in the AMT group with flat anterior chamber, but there was uncertainty if the relative risk of flat anterior chamber favored the AMT or the trabeculectomy-alone group, as the result was statistically non-significant (RR 0.19, 95% CI 0.01 to 3.71).

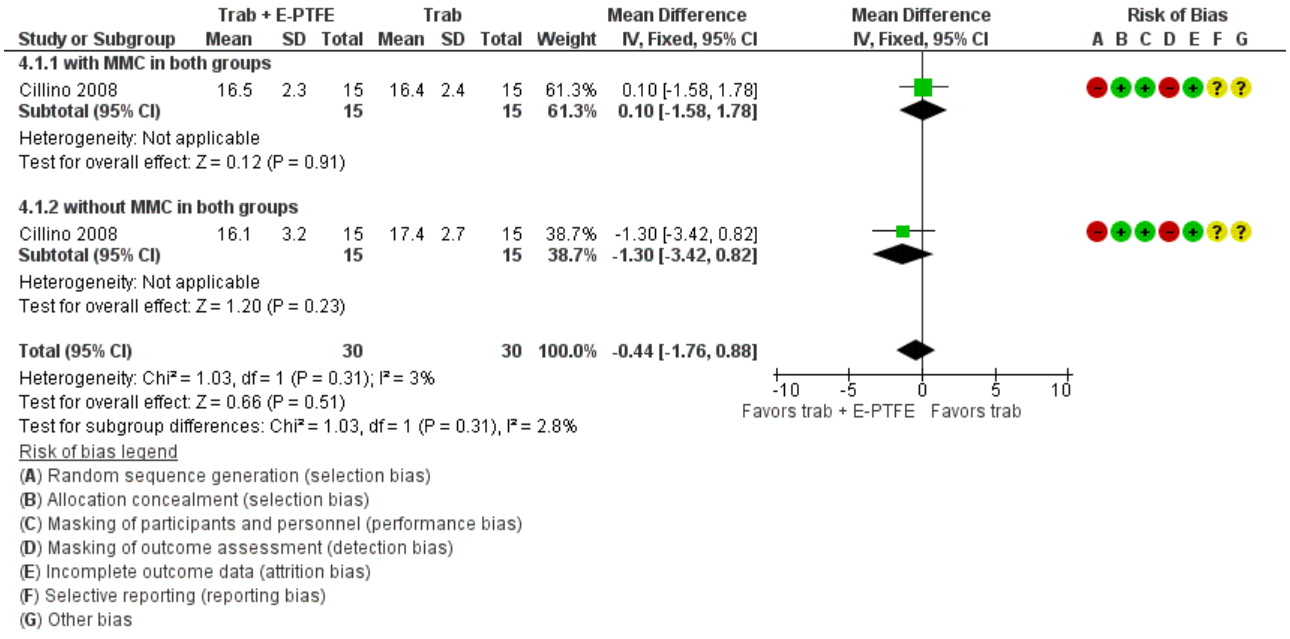
Trabeculectomy + expanded polytetrafluoroethylene (E-PTFE) versus trabeculectomy

One study assessed the use of E-PTFE (Cillino 2008). Because all participants completed 24 months of follow-up, all 60 eyes of 60 participants contributed to all of the following outcomes measured. The study performed sample size calculations, based on a power of 90% or greater to detect at least a 3 mm Hg IOP difference among groups. Cillino 2008 did not report on IOP fluctuation, BCVA, visual field, or quality of life.

Intraocular pressure (IOP)

The study did not report change in IOP from baseline; instead, it reported postoperative IOP measured at one day, one week, and 1, 3, 6, 9, 12, 18, and 24 months. It also reported that baseline IOPs among the four intervention groups did not show any statistically significant differences. We therefore compared the postoperative IOP among groups as a surrogate for change of IOP from baseline between groups. At all follow-up time points, it remains uncertain if there is a difference between the intervention groups. Specifically, at one year, the low-quality evidence showed that use of E-PTFE may lead to little or no difference in lower mean IOP compared to use of trabeculectomy alone (MD -0.44 mm Hg, 95% CI -1.76 to 0.88), and it remains uncertain if there is a between-group difference with or without the use of MMC (Analysis 4.1; Figure 6; with MMC: MD 0.10, 95% CI -1.58 to 1.78; without MMC: MD -1.30, 95% CI -3.42 to 0.82).

Figure 6. Forest plot of comparison: 1 Trabeculectomy + E-PTFE versus Trabeculectomy, outcome: 1.1 Postoperative IOP at one year.



IOP fluctuation, BCVA, visual field, and quality of life

Cillino 2008 did not report on IOP fluctuation, BCVA, visual field, or quality of life.

Complications

The study assessed complications at 24 months, including other complications: hyphema, inflammation, shallow anterior chamber, flat anterior chamber, choroidal detachment, and cystic/avascular bleb.

Loss of vision of more than two lines

The included study did not report this complication.

IOP < 5 mm Hg (hypotony)

There were 14 of 30 eyes in the trabeculectomy-alone group and four of 30 eyes in the E-PTFE group with hypotony. We judged the very low-quality evidence to be at high risk of selection and detection bias. It is unclear whether use of E-PTFE prevents hypotony because the quality of the evidence is very low (Analysis 4.2; RR 0.29, 95% CI 0.11 to 0.77). Futhermore, after stratifying by the presence or absence of MMC, the 95% CIs went from being narrow to being wide, and the results changed from possibly different to little or no difference. In the E-PTFE group with MMC, three of 15 eyes had hypotony, compared to the trabeculectomy-alone group (seven of 15 eyes), leaving it unclear whether the use of E-PTFE prevents hypotony, because the quality of the evidence is very low (Analysis 4.2.1; RR 0.43, 95% CI 0.14 to 1.35). In the E-PTFE group without MMC, one of 15 eyes had hypotony, compared to the trabeculectomy-alone group (seven of 15 eyes), leaving it unclear whether the use of E-PTFE prevents hypotony because the quality of the evidence is very low (Analysis 4.2.2; RR 0.14, 95% CI 0.02 to 1.02).

The included study did not report these complications: surgical revision within three months and one year after surgery, endophthalmitis or blebitis, retinal detachment, corneal transplant, cataract extraction (among phakic eyes), and choroidal hemorrhage.

Others as reported from the included studies

Hyphema

There were eight of 30 eyes in the E-PTFE group with hyphema and 10 of 30 eyes in the trabeculectomy-alone group, but it was uncertain whether the E-PTFE group was favored over the trabeculectomy-alone group (Analysis 4.3; RR 0.80, 95% CI 0.37 to 1.74). There was uncertainty after stratifying by the presence or absence of MMC. In the E-PTFE group with MMC, four of 15 participants had hyphema compared to the trabeculectomy-alone group (five of 15 eyes), but there was uncertainty and the result was not statistically significant (Analysis 4.3.1; RR 0.80, 95% CI 0.27 to 2.41). In the E-PTFE group without MMC, four of 15 eyes had hyphema, compared to the trabeculectomy-alone group (five of 15 eyes), but there was uncertainty and the result was not statistically significant (Analysis 4.3.2; RR 0.80, 95% CI 0.27 to 2.41).

Inflammation

There were seven of 30 eyes in the E-PTFE group with inflammation and five of 30 eyes in the trabeculectomy-alone group, but it was uncertain whether the E-PTFE group was favored over the trabeculectomy-alone group (Analysis 4.4; RR 1.40, 95% CI 0.50 to 3.91). There was uncertainty after stratifying by the presence or absence of MMC. In the E-PTFE group with MMC, three of 15 eyes had inflammation compared to the trabeculectomy-alone group (three of 15 eyes), but there was uncertainty and the result was not statistically significant (Analysis 4.4.1; RR 1.33, 95% CI 0.36 to 4.97). In the E-PTFE group without MMC, four of 15 eyes had inflammation compared to the trabeculectomy-alone group (two of 15 eyes), but there was uncertainty and the result was not statistically significant (Analysis 4.4.2; RR 1.50, 95% CI 0.29 to 7.73).

Shallow anterior chamber

There were four of 30 eyes in the E-PTFE group with shallow anterior chamber and nine of 30 eyes in the trabeculectomy-alone group, but there was uncertainty whether the E-PTFE group was favored over the trabeculectomy-alone group (Analysis 4.5; RR 0.44, 95% CI 0.15 to 1.29). There was uncertainty after stratifying by the presence or absence of MMC. In the E-PTFE group with MMC, two of 15 eyes had shallow anterior chamber, compared to the trabeculectomy-alone group (four of 15 eyes) but there was uncertainty and the result was not statistically significant (Analysis 4.5.1; RR 0.50, 95% CI 0.11 to 2.33). In the E-PTFE group without MMC, two of 15 eyes had shallow anterior chamber compared to the trabeculectomy-alone group (five of 15 eyes), but there was uncertainty and the result was not statistically significant (Analysis 4.5.2; RR 0.40, 95% CI 0.09 to 1.75).

Flat anterior chamber

There were one of 30 eyes in the E-PTFE group with flat anterior chamber and two of 30 eyes in the trabeculectomy-alone group, but there was uncertainty whether the E-PTFE group was favored over the trabeculectomy-alone group (Analysis 4.6; RR 0.60, 95% CI 0.08 to 4.28). There was uncertainty after stratifying by the presence or absence of MMC. In the E-PTFE group with MMC, one of 15 eyes had flat anterior chamber, compared to the trabeculectomy-alone group (one of 15 eyes) but there was uncertainty and the result was not statistically significant (RR 1.00, 95% CI 0.07 to 14.55). In the E-PTFE group without MMC, zero of 15 eyes had flat anterior chamber compared to the trabeculectomy-alone group (one of 15 eyes), but there was uncertainty and the result was not statistically significant (RR 0.33, 95% CI 0.01 to 7.58).

Choroidal detachment

There were three of 30 eyes in the E-PTFE group with choroidal detachment and seven of 30 eyes in the trabeculectomy-alone group, but there was uncertainty whether the E-PTFE group was favored over the trabeculectomy-alone group (Analysis 4.7; RR 0.43, 95% CI 0.12 to 1.51). There was uncertainty after stratifying by the presence or absence of MMC. In the E-PTFE group with MMC, one of 15 eyes had choroidal detachment compared to the trabeculectomy-alone group (four of 15 eyes), but there was uncertainty and the result was not statistically significant (Analysis 4.7.1; RR 0.25, 95% CI 0.03 to 1.98). In the E-PTFE group without MMC, two of 15 eyes had choroidal detachment compared to the trabeculectomy-alone group (three of 15 eyes), but there was uncertainty and the result was not statistically significant (Analysis 4.7.2; RR 0.67, 95% CI 0.13 to 3.44).

Cystic/avascular bleb

We could not compare findings with and without MMC as there were no eyes with cystic/avascular bleb in the without-MMC group. In the E-PTFE group with MMC, three of 15 eyes had cystic/avascular bleb compared to the trabeculectomy-alone group (three of 15 eyes), but there was uncertainty and the result was not statistically significant (RR 1.00, 95% CI 0.24 to 4.18).

Trabeculectomy + Gelfilm versus trabeculectomy

No quantitative data were reported from the only study of Gelfilm (43 eyes) (Birt 1998). The study investigators concluded that at one month, six months, and one year after surgery there was uncertainty about the differences among the four intervention groups for postoperative IOP or complication rates. This study was reported only in a conference abstract and we were unable to find other information.

DISCUSSION

Summary of main results

Ex-PRESS

Ex-PRESS may slightly lower IOP based on data from three trials (Dahan 2012; De Jong 2009; Wagschal 2013), which were funded by the device manufacturer and assessed at high risk of detection bias. It is uncertain if Ex-PRESS prevents loss of visual acuity or if the complication rates are similar between the two groups. For best-corrected visual acuity (BCVA), all four studies reported wide 95% confidence intervals alluding to uncertainty in the treatment effect difference between the two groups at one year (Dahan 2012; De Jong 2009; Netland 2014; Wagschal 2013). We conducted meta-analyses for complications for four studies in 294 eyes. They appeared to be similar between the two groups, except that the Ex-PRESS group may prevent postoperative interventions compared with trabeculectomy alone (for example, needling, cataract surgery, repeat trabeculectomy, etc.).

Ologen

It is uncertain whether the use of Ologen lowers IOP, prevents loss of visual acuity, or prevents complications. Very low-quality evidence from two studies in 44 eyes contributed to the primary outcome of this review, and showed that it is uncertain whether the use

of Ologen decreases the postoperative mean IOP from baseline to one year, at one day, six months, and two years compared with trabeculectomy alone (Analysis 2.1; Analysis 2.2; Analysis 2.3; Analysis 2.4). The evidence was supported by varying number of studies and eyes at each follow-up time point: five studies in 177 eyes at one year; five studies in 162 eyes at one day; seven studies in 236 eyes at six months; two studies in 55 eyes at two years (Analysis 2.2; Analysis 2.3; Analysis 2.4).

Evidence from two studies in 51 eyes contributed data to show no statistically significant difference in change in BCVA at one year and six weeks of follow-up, respectively (Rosentreter 2010; Senthil 2013). One study reported on visual field changes, but did not find any changes over time (Rosentreter 2010). We did not find any overall statistical difference between the two treatment groups for any complications, although hypotony appeared to be more frequent in the trabeculectomy-alone group.

Amniotic membrane

None of the included studies reported the primary outcome of this review of change in IOP from baseline to one year; instead, they all reported postoperative IOP at certain time points. Caution should be used in interpreting the evidence from nine studies in 356 eyes, showing that the use of amniotic membrane may slightly lower the mean IOP at one year follow-up, as eyes in the amniotic membrane group could have had lower baseline mean IOP than in the trabeculectomy-alone group (Analysis 3.1). Similar results were shown at one month, three months and six months (Analysis 3.4; Analysis 3.5; Analysis 3.6). Six studies reported BCVA (no meta-analysis) at one year or six months, but the findings were inconsistent. The amniotic membrane group appeared to have a lower frequency of complications than the trabeculectomy-alone group, although the time points assessed were inconsistent or unclear across studies.

Expanded polytetrafluoroethylene (E-PTFE)

One study (Cillino 2008) reported the use of E-PTFE during trabeculectomy, and found no statistically significant difference between the groups with E-PTFE with or without MMC and standard trabeculectomy in IOP control at all follow-up time points up to two years. In the E-PTFE group, the complication (hypotony) rates were no different in the subgroups with and without MMC at 24 months, although the pooled result favored the E-PTFE group (Analysis 4.2).

Overall completeness and applicability of evidence

Of the 33 included studies, 16 reported numbers of antiglaucoma medications used during the postoperative follow-up periods; within these, 11 reported IOP by 'complete success' (defined as IOP reached < 21 mm Hg without use of medication), 'qualified success' (defined as IOP reached < 21 mm Hg with use of medication), or 'failure' (defined at IOP > 22 mm Hg at follow-up).

Ex-PRESS

Four studies were powered to detect a between-group difference between Ex-PRESS and controls (Dahan 2012; De Jong 2009; Netland 2014; Wagschal 2013). The studies were conducted in South Africa, the Netherlands, USA, and Canada respectively. They included a mix of white, African-American, Asian, and Indian participants, and all with a mean age of around 65 years. Three studies could be meta-analyzed for efficacy of Ex-PRESS. One study reported that the Ex-PRESS device was associated with a one-year overall cost of USD 956 greater than trabeculectomy (Wagschal 2013). Patients' choices could be affected by the effectiveness, safety, and cost of the intervention.

Since all five studies included participants with open-angle glaucoma, the Ex-PRESS results are most applicable to people with open-angle glaucoma. The effectiveness and safety in people with other types of glaucoma remain uncertain.

Ologen

Only one study was adequately powered to detect a between-group difference (Cillino 2011). The other seven studies were either inconclusive or did not find any statistically significant difference for postoperative IOP reduction. The findings from the meta-analysis remain inconclusive and should be interpreted with caution.

Ologen implant is an alternative method for controlling the wound-healing process similar to antifibrotic agents. Among the eight Ologen trials, only one (Papaconstantinou 2010) did not use MMC in the standard trabeculectomy group.

All or some of the participants in all eight studies had open-angle glaucoma; two studies included some participants with angle-closure glaucoma (Marey 2013; Senthil 2013), and one study did not specify the glaucoma type (Papaconstantinou 2010). None of the studies stratified participants by type of glaucoma.

Amniotic membrane

Only one study reported power and sample size calculations (Sheha 2008). In addition, a majority of the studies did not report losses to follow-up and did not report details of study design (i.e. randomization, allocation concealment, and masking). Due to the poor quality of most of the studies, concerns still remain as to whether IOP is reduced when amniotic membrane is used compared with standard trabeculectomy, and how safe it is.

Three studies used MMC in the trabeculectomy group only and not in the amniotic membrane group (Cho 2013; Khairy 2015; Zheng 2005).

Of the 18 studies, three included only participants with open-angle glaucoma (Eliezer 2006; Khairy 2015; Stavrakas 2012), four studies included only participants with angle-closure glaucoma (Huang 2007; Ren 2009; Yan 2004; Zhang 2009), two studies included open-angle and angle-closure glaucoma (Cho 2013; Zheng 2005), seven studies included participants with refractory glaucoma (Cai 2012; Ji 2013; Li 2010; Liu 2009; Sheha 2008; Wang 2009; Yang 2004), and two studies did not specify the glaucoma type (Birt 1998; Wang 2008).

Expanded polytetrafluoroethylene (E-PTFE)

Cillino 2008 enrolled the number of participants needed to be adequately powered to detect a between-group difference. The study reported the number of antiglaucoma medications as an outcome, so the efficacy of E-PTFE to control IOP might be partially attributed to antiglaucoma medication and not to E-PTFE alone.

Quality of the evidence

Overall, the agreement in IOP measurement across the included studies was high, as the width of the 95% CI for postoperative IOP at one year ranged from 2 to 7 mm Hg for each device. Similarly,

the evidence showed a small and consistent effect size, with mean differences ranging from -4 to 2 mm Hg.

Most of the trials were at high risk of detection bias for lack of masking outcome assessors. Further, the Ex-PRESS studies had potential conflicts of interest for receiving funding support from the device manufacturer. Overall, we graded the quality of the evidence as low or very low for most outcomes due to potential risks of bias and imprecision for many adverse events.

Potential biases in the review process

We conducted comprehensive electronic searches for studies with no imposed date or language restrictions to minimize potential biases in the study selection process. We followed standard Cochrane review methodology.

Agreements and disagreements with other studies or reviews

Trabeculectomy + Ex-PRESS versus trabeculectomy

Our meta-analyses of three trials found that the use of Ex-PRESS may lead to IOP reduction compared with trabeculectomy alone at one year and two years. Our review also showed there is uncertainty whether the risk of complications differs between the Ex-PRESS and trabeculectomy-alone group.

A retrospective comparative series by Maris 2007 of 100 eyes, Good 2011 of 70 eyes, and Moisseiev 2015 of 200 eyes did not find a significant difference between Ex-PRESS and trabeculectomy in lowering IOP. A retrospective review by Marzette 2011 of 153 eyes showed a lower risk of postoperative hypotony and a greater but statistically nonsignificant decrease in IOP with Ex-PRESS.

A systematic review by Wang 2013a concluded that Ex-PRESS has the same effectiveness in IOP reduction compared to trabeculectomy alone, with significantly fewer events of hypotony and hyphema compared to trabeculectomy alone. However, these pooled results were from a mix of RCTs, prospective non-RCTs, and retrospective studies, which limits the reliability of their inference.

A recent meta-analysis by Chen 2014 found no statistically significant reduction in IOP between Ex-PRESS and trabeculectomy alone, and a significantly lower frequency of hyphema with Ex-PRESS. The other complications were not statistically significantly different between the two groups. However, this review was flawed in that it mixed the different follow-up periods from different studies for IOP control (e.g. six months and one year) in one meta-analysis. Also, one included study was a subset of another (both were references from Wagschal 2013), and its meta-analyses of complications included both studies, thereby double-counting the data.

Trabeculectomy + Ologen versus trabeculectomy

Our meta-analyses of five trials showed that there is uncertainty if there is a difference in IOP postoperatively and at one year. This is contrary to Narayanaswamy 2012, which conducted a non-randomized prospective comparative study of 33 participants and found a greater decrease in IOP and a lower incidence of bleb needling procedures in the trabeculectomy and MMC group than in the trabeculectomy and Ologen group. However, our results are in agreement with a systematic review by He 2014 of seven RCTs (227 eyes), which found no statistically significant difference between the two groups except at one and 12 months, in which the amount of IOP reduction was less in the Ologen group. However, the review is limited because it included a non-randomized trial (Nilforushan 2010), despite being restricted to RCTs only.

Our meta-analysis of complications in all studies showed that there is uncertainty whether there is a difference between the two groups. Similarly, the authors of He 2014 reported comparable rates of adverse events in the Ologen and trabeculectomy-alone groups.

Trabeculectomy + amniotic membrane versus trabeculectomy

Our meta-analysis of nine trials found a slight decrease in IOP in the amniotic membrane group compared to the trabeculectomy-alone group. This is similar to an animal model study, that also showed a greater decrease in IOP (Barton 2001).

Expanded polytetrafluoroethylene (E-PTFE)

A retrospective study enrolling 43 eyes with refractory glaucoma found that an E-PTFE membrane safely reduced IOP in 65% of the eyes (Kim 2003). The mean follow-up period was 32.9 months. However, in the remaining 35% of the eyes, surgical revisions were needed to control IOP or treat complications.

Other devices

We did not find any randomized controlled trials (RCTs) for other devices used in a standard trabeculectomy procedure, but a few case series without comparators have shown some benefit of using them. Dahan 2011 conducted a trial on the use of T-flux in trabeculectomy for neovascular glaucoma. The trial showed that modified trabeculectomy augmented by MMC and T-flux adequately controlled IOP in neovascular participants after a mean follow-up of 32 ± 12 months. However, surgical revisions may be required to maintain an IOP ≤ 21 mm Hg. Two trials reported the use of gold micro shunt (GMS). One study with 38 participants found that GMS can significantly decrease IOP, but two-thirds of participants required medications to achieve adequate IOP control (Melamed 2009). Another study with 55 participants with uncontrolled refractory glaucoma reported that GMS can achieve adequate IOP control in about 67.3% of eyes with relatively few complications (Figus 2011). The follow-up was two years in this study. Devices inserted into the suprachoroidal space are at high risk for fibrosis and failure of the procedure (Agnifili 2012).

Comparison between different devices

There was no RCT directly comparing the use of any two devices. However, we found one retrospective review that compared Ologen versus MMC in participants implanted with Ex-PRESS (Johnson 2014). The study included 99 eyes of 85 participants who had undergone trabeculectomy with implantation of an Ex-PRESS shunt, and had applied MMC in 50 eyes of 48 participants and used Ologen in 49 eyes of 37 participants. The investigators found no significant difference between the two groups in IOP reduction or rates of complications.

AUTHORS' CONCLUSIONS

Implications for practice

Our findings suggest that the use of devices with a standard trabeculectomy may help with slightly greater intraocular pressure (IOP) reduction at one-year follow-up than trabeculectomy alone;

however, conclusions for each type of device are limited due to methodological concerns for bias and poor reporting of outcomes. Currently, these devices add extra costs to insurance companies and patients compared with those incurred for a trabeculectomy alone. Whether the IOP reduction that can be achieved with these devices is sufficient to outweigh these additional costs will need to be determined for each individual patient. Since it is frequently reported that a 1 mm Hg reduction in IOP can be associated with a 10% decrease in the risk of glaucomatous progression, the additional IOP reduction that may be obtained at one-year follow-up may be valuable in selected populations (Heijl 2002).

Implications for research

Low-quality evidence warrants better quality trials to determine the comparative effectiveness of all devices included in this review. These studies are limited and the applicability of the evidence to other population or settings remains unclear. More research is therefore needed to generate evidence for or against devices such as Ex-PRESS, Ologen, amniotic membrane, Gelfilm, E-PTFE, gold micro shunt, and T-flux.

In the absence of definitive evidence, we need more trials of better quality for most comparisons and outcomes. These should account for losses to follow-up at each follow-up time point measured. They should also account for the correlation of outcomes between two eyes when applicable. They also need to consider the appropriate use of adjunctive agents, such as mitomycin C in both groups to ensure comparability. It would be helpful for future trials to specify the types of glaucomas, and also to consider stratifying participants by type of glaucoma, and perhaps by lens type, when the sample size is met. We need further research to evaluate the effectiveness and safety of each intervention on patients with different types of glaucoma. Data reporting needs to improve to include reporting of differences between groups to allow more robust inferences when applicable. Future trials should also report on the elements of trial quality identified above and ensure consistency between protocols and published studies.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Birt 1998

Methods	**Study design**: parallel-group randomized controlled trial
	Number randomized: 43 eyes of 43 participants total;
	11 participants in trabeculectomy + MMC + Gelfilm® (Pfizer) group;
	7 participants in trabeculectomy + MMC group;
	11 participants in trabeculectomy + Gelfilm® (Pfizer) group;

Birt 1998 *(Continued)*

	14 participants in trabeculectomy group **Exclusions after randomization:** none reported **Losses to follow-up:** none reported **Unit of analysis:** individual (1 eye per participant) **Number analyzed:** 43 participants total; 11 participants in trabeculectomy + MMC + Gelfilm® (Pfizer) group; 7 participants in trabeculectomy + MMC group; 11 participants in trabeculectomy + Gelfilm® (Pfizer) group; 14 participants in trabeculectomy group **How were missing data handled?:** no missing data **Power calculation:** not reported
Participants	**Country**: not reported **Mean age**: not reported **Gender**: not reported **Inclusion criteria**: not reported **Exclusion criteria**: not reported **Equivalence of baseline characteristics:** not reported
Interventions	**Intervention 1**: trabeculectomy + MMC + Gelfilm® (Pfizer) **Intervention 2**: trabeculectomy + MMC **Intervention 3**: trabeculectomy + Gelfilm® (Pfizer) **Intervention 4**: trabeculectomy **Length of follow-up:** Planned: not reported Actual: 1 year
Outcomes	Primary and secondary outcomes not distinguished **Outcomes, as reported**: postoperative IOP, use of postoperative 5-FU, and complications **Intervals at which outcomes assessed:** 1 year
Notes	**Publication type:** published abstract **Funding sources:** not reported **Disclosures of interest:** not reported **Trial registry:** not registered **Study period:** not reported **Subgroup analyses:** none reported **Publication language:** English Attempted to contact author, but unable to find contact information in abstract

Risk of bias

Bias	Authors' judgement	Support for judgement

Birt 1998 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Random sequence generation was not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported
Masking of participants and personnel (performance bias)	Unclear risk	Masking of participants and personnel was not reported
Masking of outcome assessment (detection bias)	High risk	Outcome assessors not masked as devices can be seen during eye examination
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed 1-year follow-up
Selective reporting (reporting bias)	Unclear risk	The protocol was not available and the authors did not define which outcomes and complications they were going to report
Other bias	Unclear risk	Did not report source of funding or conflict of interest The abstract did not have enough information

Bruno 2008

Methods	**Study design**: parallel-group randomized controlled trial **Number randomized**: 19 eyes of 19 participants total; not reported by intervention group **Exclusions after randomization:** 2 participants not analyzed due to death or protocol deviation **Losses to follow-up:** none reported **Unit of analysis:** individual (1 eye per participant) **Number analyzed**: 17 participants total; 9 participants in trabeculectomy + MMC + AMT group; 8 participants in trabeculectomy + MMC group **How were missing data handled?:** 2 participants excluded from analysis **Power calculation:** not reported
Participants	**Country**: not reported **Mean age**: 72 years; not reported by intervention group **Gender**: 7/19 (37%) men and 12/19 (63%) women; not reported by intervention group **Inclusion criteria**: OAG at high risk for filtration failure; previous failed surgery **Exclusion criteria**: not reported **Equivalence of baseline characteristics:** not reported
Interventions	**Intervention 1**: trabeculectomy + MMC + AMT **Intervention 2**: trabeculectomy + MMC **Length of follow-up:**

Bruno 2008 *(Continued)*

	Planned: not reported Actual: 6 months
Outcomes	Primary and secondary outcomes not distinguished **Outcomes, as reported**: target IOP, complications, association between positional IOP change (IOP supine-IOP sitting) and bleb morphology, and comparing positional IOP changes in successful versus failed trabs **Intervals at which outcomes assessed:** 2 and 6 months
Notes	**Publication type:** published abstract **Funding sources:** not reported **Disclosures of interest:** not reported **Trial registry:** not registered **Study period:** not reported **Subgroup analyses:** none reported **Publication language**: English Attempted to contact author, but unable to find contact information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random sequence generation was not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported
Masking of participants and personnel (performance bias)	Unclear risk	Masking of participants and personnel was not reported
Masking of outcome assessment (detection bias)	High risk	It is not possible to mask outcome assessors, as devices can be seen during eye examination
Incomplete outcome data (attrition bias) All outcomes	High risk	Greater than 10% of participants were excluded from the analysis
Selective reporting (reporting bias)	Unclear risk	Unclear as only published abstract was available; protocol not published. Authors did publish outcome results as defined in the abstract
Other bias	Unclear risk	Did not report source of support and conflict of interest The abstract did not have enough information

Cai 2012

Methods	**Study design**: parallel-group randomized controlled trial (8 participants both eyes included)

Cai 2012 *(Continued)*

	Number randomized: 48 eyes of 40 participants total; 25 eyes in trabeculectomy + AMT group; 23 eyes in trabeculectomy group **Exclusions after randomization:** none reported **Losses to follow-up**: none reported **Unit of analysis:** eye **Number analyzed**: 48 eyes of 40 participants total; 25 eyes in trabeculectomy + AMT group; 23 eyes in trabeculectomy group **How were missing data handled?:** no missing data **Power calculation:** not reported
Participants	**Country**: China **Mean age**: 52 years (range 22 - 75 years); not reported by intervention group **Gender**: 30/40 (75%) men and 10/40 (25%) women; not reported by intervention group **Inclusion criteria**: refractory glaucoma treatment **Exclusion criteria**: not reported **Equivalence of baseline characteristics:** yes
Interventions	**Intervention 1**: trabeculectomy + AMT **Intervention 2**: trabeculectomy **Length of follow-up:** Planned: not reported Actual: 12 months
Outcomes	Primary and secondary outcomes not distinguished **Outcome, as reported**: IOP, filtering bleb, visual acuity, complications **Intervals at which outcomes assessed:** IOP at 1 week, 1 month and 1 year; filtering bleb and visual acuity at 1 year; complications and anterior chamber condition at 1 week
Notes	**Publication type:** published article **Funding sources:** not reported **Disclosures of interest:** not reported **Trial registry:** not registered **Study period:** February 2010 to December 2011 **Subgroup analyses:** none reported **Publication language**: Chinese Attempted to contact authors to clarify methods to assess risk of bias, but no response received

Cai 2012 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random sequence generation was not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported
Masking of participants and personnel (performance bias)	Unclear risk	Masking of participants and personnel was not reported
Masking of outcome assessment (detection bias)	High risk	It is not possible to mask outcome assessors, as devices can be seen during eye examination
Incomplete outcome data (attrition bias) All outcomes	Low risk	From the published report we can see all data were analyzed
Selective reporting (reporting bias)	High risk	Protocol was not available and outcomes were not defined
Other bias	Unclear risk	Did not report source of funding or conflict of interest No other potential bias identified

Cho 2013

Methods	**Study design**: parallel-group randomized controlled trial (5 participants both eyes included) **Number randomized**: 52 eyes of 47 participants total; 26 eyes of 25 participants in trabeculectomy + AMT group; 26 eyes of 22 participants in trabeculectomy + MMC group **Exclusions after randomization:** none reported **Losses to follow-up**: 13 eyes total; 4 eyes in trabeculectomy + AMT group; 9 eyes in trabeculectomy + MMC group **Unit of analysis:** eye **Number analyzed**: 39 eyes total; 22 eyes in trabeculectomy + AMT group; 17 eyes in trabeculectomy + MMC group **How were missing data handled?:** 13 eyes with missing data excluded from analysis **Power calculation:** not reported
Participants	**Country**: China

Cho 2013 *(Continued)*

	Mean age: 64 years; 63.9 years for trabeculectomy + AMT group; 64.0 years for trabeculectomy + MMC group **Gender**: 22/52 (42%) men and 30/52 (58%) women; 8/26 (31%) men and 18/26 (69%) women in trabeculectomy + AMT group; 14/26 (54%) men and 12/26 (46%) women in trabeculectomy + MMC group **Inclusion criteria**: PACG, chronic ACG, or POAG; IOP uncontrolled after medical or laser treatment; age between 18 and 80 years; signed consent form **Exclusion criteria**: history of diabetes, leukemia, AIDS, uncontrolled blood pressure, atherosclerosis, immunological disease, Alzheimer disease, disseminated sclerosis, previous trabeculectomy, or other ongoing ocular disease **Equivalence of baseline characteristics:** yes
Interventions	**Intervention 1**: trabeculectomy + AMT **Intervention 2:** trabeculectomy + MMC **Length of follow-up:** Planned: not reported Actual: 3 months
Outcomes	Primary and secondary outcomes not distinguished **Outcomes, as reported**: IOP, anterior chamber depth, filtering bleb shape, operative efficacy, and complications (specified) **Intervals at which outcomes assessed:** non-contact IOP at 1 week, 2 weeks, 1 month, and 3 months after surgery; filtering bleb and complications at 1 week, 2 weeks, 1 month, and 3 months after surgery
Notes	**Publication type:** published article **Funding sources:** not reported **Disclosures of interest:** not reported **Trial registry:** not registered **Study period:** October 2009 to October 2011 **Subgroup analyses:** none reported **Publication language**: Chinese Authors not contacted

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The authors used “random number tables” for sequence generation
Allocation concealment (selection bias)	Low risk	The authors used “opaque envelopes” for allocation concealment

Cho 2013 *(Continued)*

Masking of participants and personnel (performance bias)	Unclear risk	Method used to mask participants and personnel was not reported
Masking of outcome assessment (detection bias)	High risk	It is not possible to mask outcome assessors, as devices can be easily seen during eye examination
Incomplete outcome data (attrition bias) All outcomes	High risk	9/26 participants (35%) in trabeculectomy + MMC and 4/22 (18%) in trabeculectomy + AMT were lost to follow-up at 3 months
Selective reporting (reporting bias)	Low risk	Protocol was not available, but defined outcomes were reported
Other bias	Unclear risk	Did not report source of funding or conflict of interest. The study used t-test for 2 independent samples, while they included both eyes of some participants but did not account for intra-person correlation. No other sources of bias identified

Cillino 2008

Methods	**Study design:** parallel-group randomized controlled trial **Number randomized:** 60 eyes of 60 participants; 15 eyes of 15 participants in each of the 4 groups **Exclusions after randomization:** none reported **Losses to follow-up**: none reported **Unit of analysis:** individual (1 eye per participant) **Number analyzed:** 60 participants total; 15 participants in each of the 4 groups **How were missing data handled?:** no missing data **Power calculation:** a power of 90% or greater to detect at least a 3 mm Hg IOP difference among groups
Participants	**Country**: Italy **Mean age:** 68 years; 65.3 years for trabeculectomy + MMC + E-PTFE group; 68.1 years for trabeculectomy + MMC group; 67.2 years for trabeculectomy + E-PTFE group; 71.1 years for trabeculectomy group; **Gender:** 24/45 (53%) men and 21/45 (47%) women; 6/15 (40%) men and 9/15 (60%) women in trabeculectomy + MMC + E-PTFE; 9/15 (60%) men and 6/15 (40%) women in trabeculectomy + MMC; 7/15 (47%) men and 8/15 (53%) women in trabeculectomy + E-PTFE; 8/15 (53%) men and 7/15 (47%) women in trabeculectomy **Inclusion criteria:** “age 18 or older, diagnosis of POAG or pseudoexfoliative glaucoma (PEXG), and inadequate IOP control (IOP > 21 mm Hg) or progressive visual field deterioration on maximum-tolerated

Cillino 2008 *(Continued)*

	medical therapy, availability, willingness and sufficient cognitive awareness to comply with examination procedures" **Exclusion criteria:** "concurrent participation during the last 30 days in any other clinical trial, use of systemic or ocular medications that may affect vision, acute or chronic disease or illness that would increase the operative risk or confound the outcomes of the study (e.g. immunodeficiency, connective tissue disease, diabetes, etc.), uncontrolled systemic or ocular disease other than glaucoma, clinically significant cataract where combined surgery was indicated, history of ocular trauma or prior ocular surgery." **Equivalence of baseline characteristics:** yes
Interventions	**Intervention 1**: trabeculectomy + MMC + E-PTFE (GORE PRECLUDE®) **Intervention 2**: trabeculectomy + MMC **Intervention 3**: trabeculectomy + E-PTFE (GORE PRECLUDE®) **Intervention 4**: trabeculectomy **Length of follow-up:** Planned: 24 months Actual: 24 months
Outcomes	Primary and secondary outcomes not distinguished **Outcomes, as reported:** IOP, complete success (with medication ≤ 21 and without medication 17 mm Hg), complications, number of antiglaucoma medications, and visual field testing by Humphrey visual field **Intervals at which outcomes assessed:** 24 hours, 7 days, 2 weeks, 3 weeks, and 1, 2, 3, 6, 12, 18, and 24 months after surgery
Notes	**Publication type:** published article **Funding sources:** not reported **Disclosures of interest:** not reported **Trial registry:** not registered **Study period:** September 2003 to August 2004 **Subgroup analyses:** none reported **Publication language**: English Authors not contacted

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	"Randomization was determined just before surgery. Sixty participants – 15 for each surgical technique – were randomly assigned based on a surgical chart number to undergo a trabeculectomy (T) (which served as surgical control group), a trabeculectomy with mitomycin-C (TMMC), a trabeculectomy with GORE PRECLUDE pericardial implant (TG) or a trabeculectomy with mitomycin-C and GORE PRECLUDE pericardial implant (TGMMC)." The method of sequence generation was not done completely randomly, thus we assessed it at high risk

Cillino 2008 *(Continued)*

Allocation concealment (selection bias)	Low risk	"Randomization was determined just before surgery by sealed-envelope technique."
Masking of participants and personnel (performance bias)	Low risk	Because trabeculectomy is a surgical procedure with informed consent, masking of the participants and personnel becomes impossible. However, given that a strict and standardized surgical protocol was followed and differences in the surgical protocol of the 2 groups were minimized, the risk of performance bias is comparably low for a surgical procedure
Masking of outcome assessment (detection bias)	High risk	It is not possible to mask outcome assessors, as devices can be easily seen during eye examination
Incomplete outcome data (attrition bias) All outcomes	Low risk	"All participants completed the 24 month follow-up period."
Selective reporting (reporting bias)	Unclear risk	Protocol was not available. In the Methods section, the study mentioned testing of visual field by Humphrey visual field, however, the Result section did not report this outcome
Other bias	Unclear risk	Did not report source of funding or conflict of interest

Cillino 2011

Methods	**Study design:** parallel-group randomized controlled trial **Number randomized:** 40 eyes of 40 participants total; 20 eyes of 20 participants in each group **Exclusions after randomization:** none reported **Losses to follow-up**: none reported **Unit of analysis:** individual (1 eye per participant) **Number analyzed:** 40 participants total; 20 participants in each group **How were missing data handled?:** no missing data **Power calculation:** a power of 90% to detect 3 mm Hg IOP difference between groups
Participants	**Country:** Italy **Mean age:** 64.5 years; 63.2 years for trabeculectomy + Ologen® group; 65.8 years for trabeculectomy + MMC group **Gender:** 23/40 (58%) men and 17/40 (42%) women; 12/20 (60%) men and 8/20 (40%) women in trabeculectomy + Ologen® group; 11/20 (55%) men and 9/20 (45%) women in trabeculectomy + MMC group **Inclusion criteria:** "age 18 or older, diagnosis of POAG or pseudoexfoliative glaucoma (PEXG), and inadequate IOP control (IOP > 21 mm Hg) or progressive visual field deterioration on maximum-tolerated medical therapy" **Exclusion criteria:** "normal-tension glaucoma, use of systemic or ocular medications that might affect vision, acute or chronic disease that could confound the outcomes of the study (e.g., immunodeficiency, connective tissue disease, and diabetes), clinically significant cataract where combined surgery was indicated, and history of ocular trauma or prior ocular surgery" **Equivalence of baseline characteristics:** yes

Cillino 2011 *(Continued)*

Interventions	**Intervention 1**: trabeculectomy + Ologen® (Aeon Astron Europe BV, Leiden, The Netherlands) **Intervention 2**: trabeculectomy + MMC **Length of follow-up:** Planned: 24 months Actual: 24 months
Outcomes	**Primary outcomes, as defined:** IOP and surgical success “IOP was the primary outcome measure” and 3 different IOP target levels were considered: ≤ 21, ≤ 17, and ≤ 15 mm Hg. "Complete success" defined as a target endpoint IOP without antiglaucomatous medications, while "qualified success" defined as a target endpoint IOP regardless of medications **Secondary outcomes, as defined:** bleb evaluation, number of glaucoma medications, frequency of postoperative adjunctive procedures, and complications **Intervals at which outcomes assessed:** 24 hours, 7 days, 2 weeks, and 1, 2, 3, 6, 12, 18, and 24 months after surgery
Notes	**Publication type:** published article **Funding sources:** not reported **Disclosures of interest:** "The authors declare no conflict of interest." **Trial registry:** not registered **Study period:** January 2008 to December 2008 **Subgroup analyses:** none reported **Publication language**: English Authors not contacted

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization was determined just before surgery by sealed-envelope technique based on their surgical chart number. The sequence of random allocation was generated by pulling 40 standard sized pieces of paper out of a hat by the trial statistician (AC). Twenty pieces of paper were marked with letter A, and 20 with letter B. Each piece of paper was sequentially placed into 40 sealed, opaque envelopes by the trial statistician. The sealed envelopes were numbered 1 to 40 and given to the surgeon (SC). Patients were numbered randomly from 1 to 40 based on a surgical chart number related to the baseline testing session and intervention period."
Allocation concealment (selection bias)	Low risk	Same support for judgment listed above
Masking of participants and personnel (performance bias)	Low risk	Given that trabeculectomy is a surgical procedure with informed consent, masking of the participants and personnel becomes impossible. However, a strict surgical protocol was followed, thus minimizing risk
Masking of outcome assessment (detection bias)	Low risk	“The clinical data collecting and measurement of outcome variables were performed by skilled personnel (ophthalmologists and optometrists) masked to randomization and who had not been directly involved in patient surgery.”

Cillino 2011 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	"All patients completed the 24-month follow-up period."
Selective reporting (reporting bias)	Unclear risk	Protocol was not available. In the Methods section, the study stated that number of glaucoma medications and frequency of postoperative adjunctive procedures was measured, but in the results, they were not reported
Other bias	Unclear risk	Information regarding funding source was not reported. No other sources of bias identified

Dahan 2012

Methods	**Study design:** paired-eye randomized controlled trial **Number randomized:** 30 eyes of 15 participants total; each participant had 1 eye in each intervention group **Exclusions after randomization:** none reported **Losses to follow-up**: none up to 1 year after surgery; 1 participant died at 13 months and 2 were subsequently lost to follow-up **Unit of analysis:** eye **Number analyzed:** 30 eyes of 15 participants total; each participant had one eye in each intervention group **How were missing data handled?:** no missing data at 1 year **Power calculation:** a power of 96% to detect a 2 mm Hg IOP difference between groups
Participants	**Country:** South Africa **Mean age:** 65 years; not reported by intervention group **Gender:** 10/15 (67%) men and 5/15 (33%) women; not reported by intervention group **Inclusion criteria:** "at least 18 years of age and presented with medically uncontrolled POAG requiring bilateral incisional surgery for IOP reduction. Patients with prior cataract operation or failed filtration surgery in either eye were eligible if surgery took place at least 3 months prior to enrolment." **Exclusion criteria:** "any form of glaucoma other than POAG; history of active uveitis; and any ocular abnormality that would preclude accurate IOP assessment." **Equivalence of baseline characteristics:** yes
Interventions	**Intervention 1:** trabeculectomy + MMC + Ex-PRESS X200 **Intervention 2:** trabeculectomy + MMC **Length of follow-up:** Planned: a minimum of 1 year Actual: all participants followed at least 1 year; the longest follow-up visit for a participant was 30 months
Outcomes	Primary and secondary outcomes not distinguished **Outcomes, as reported:** IOP, visual acuity, number of medicines for IOP control, complications **Intervals at which outcomes assessed:** 1 day, 7 days, and 1, 3, 6, 9, 12, 18, 24, and 30 months after surgery
Notes	**Publication type:** published article

Dahan 2012 *(Continued)*

Funding sources: "the study was supported by a financial grant from Alcon Laboratories"

Disclosures of interest: "E Dahan is a paid consultant in Alcon Laboratories. GJ Ben Simon and A Lafuma has no financial or proprietary interest in any of the drugs or materials mentioned in this study. A Lafuma is employed by CEMKAEVAL, a company that provides services in statistical analyses and epidemiology."

Trial registry: NCT00698438 (clinicaltrials.gov)

Study period: not reported

Subgroup analyses: none reported

Publication language: English

Study authors contacted and outcome data shared (IOP reduction, number of medications, and mean IOP at 1 day, 7 days, and 1, 3, 6, 12, 18, 24, and 30 months follow-up)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomisation of contralateral operations was achieved by opening an envelope in which the procedure (trabeculectomy or Ex-PRESS implantation) that would be applied to the first eye was stated, thereby determining the procedure in the other eye." The method of randomization is not described and thus its adequacy cannot be judged
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported
Masking of participants and personnel (performance bias)	Low risk	Because trabeculectomy is a surgical procedure with informed consent, masking of the participants and personnel becomes impossible. However, given that "After sub-tenonian local anaesthesia, surgery was performed by one experienced surgeon (ED), for consistency, using a standardized technique for both procedures", the risk of performance bias is comparably low for a surgical procedure
Masking of outcome assessment (detection bias)	High risk	The study mentioned: "It was not possible to mask the surgical technique as trabeculectomy is easily differentiated from Ex-PRESS implantation during postoperative follow-ups. However, this limitation is overcome by the fact that all patients were followed up concurrently by their referring ophthalmologists from the first month postoperatively till completion of the study." Although it is not possible to mask outcome assessors, devices can be easily seen during examination of the eye
Incomplete outcome data (attrition bias) All outcomes	Low risk	"All 15 patients were followed-up for 1 year after surgery. One patient died 13 months after surgery and two patients were subsequently lost to follow-up. All data available for these patients (i.e., up to 1 year) are included in the analyses."
Selective reporting (reporting bias)	Low risk	The study was registered in www.ClinicalTrials.gov. All defined outcomes in www.ClinicalTrials.gov were reported in full text. Complete and qualified success was reported and defined using IOP
Other bias	High risk	Received industry monetary support from device manufacturer; "ED is a paid consultant to Alcon Laboratories." "The study was supported by a financial grant from Alcon Laboratories." To consider intra-person correlation between eyes, the analysis used Wilcoxon matched-pairs *t*-test to compare pre-operative and final IOP values

Dahan 2012 *(Continued)*

	No other sources of bias identified

De Jong 2005

Methods	**Study design:** parallel-group randomized controlled trial (11 participants both eyes included) **Number randomized:** 120 eyes of 109 participants; not reported by intervention group **Exclusions after randomization:** not reported **Losses to follow-up**: not reported **Unit of analysis:** eye **Number analyzed:** not reported **How were missing data handled?:** not reported **Power calculation:** not reported
Participants	**Country**: Netherlands **Mean age:** overall not reported; 61.8 years for trabeculectomy + Ex-PRESS R50® implanted under a scleral flap group; 61.8 years for trabeculectomy + Ex-PRESS R50® implanted under the conjunctiva group; 68.7 years for trabeculectomy group; **Gender**: not reported **Inclusion criteria**: OAG; medical treatment failure, indicated for glaucoma surgery **Exclusion criteria**: not reported **Equivalence of baseline characteristics:** yes
Interventions	**Intervention 1**: trabeculectomy + Ex-PRESS R50® implanted under a scleral flap **Intervention 2**: trabeculectomy + Ex-PRESS R50® implanted under the conjunctiva **Intervention 3**: trabeculectomy **Length of follow-up:** Planned: not reported Actual: 6 months
Outcomes	Primary and secondary outcomes not distinguished **Outcomes, as reported:** success rate (defined as % IOP reduction and medication reduction), IOP, and use of IOP-lowering medications **Intervals at which outcomes assessed:** 6 months after surgery
Notes	**Publication type:** published abstract **Funding sources:** not reported **Disclosures of interest:** not reported **Trial registry:** not registered **Study period:** not reported **Subgroup analyses:** none reported

De Jong 2005 *(Continued)*

Publication language: English

Attempted to contact author, but unable to find contact information in abstract

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random sequence generation was not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported
Masking of participants and personnel (performance bias)	Unclear risk	Method use to mask participants and personnel was not reported
Masking of outcome assessment (detection bias)	High risk	It is not possible to mask outcome assessors, as devices can be easily seen during eye examination
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported
Selective reporting (reporting bias)	Low risk	Protocol was not available. All defined outcomes were reported
Other bias	Unclear risk	Did not report source of support or conflict of interest. Not enough information from the abstract

De Jong 2009

Methods	**Study design:** parallel-group randomized controlled trial (2 participants both eyes included) **Number randomized:** 80 eyes of 78 participants total; 40 eyes in each group **Exclusions after randomization:** none reported **Losses to follow-up:** 5 eyes total at 1 year; 3 eyes in trabeculectomy + Ex-PRESS group; 2 eyes in trabeculectomy group **Unit of analysis:** eye **Number analyzed:** 75 eyes total; 37 eyes in trabeculectomy + Ex-PRESS group; 38 eyes in trabeculectomy group **How were missing data handled?:** 5 eyes with missing data excluded from analysis **Power calculation:** a power of 80% to detect 32% between-group difference in IOP
Participants	**Country:** Netherlands **Mean age:** 66 years; 62.3 years for trabeculectomy + Ex-PRESS group;

De Jong 2009 *(Continued)*

	68.9 years for trabeculectomy group **Gender:** 46/80 (58%) men and 34/80 (42%) women; 19/40 (48%) men and 21/40 (52%) women in trabeculectomy + Ex-PRESS group; 27/40 (68%) men and 13/40 (32%) women in trabeculectomy group **Inclusion criteria:** "over 18 years old, and had a diagnosis of open-angle glaucoma that could not be controlled with maximal-tolerated medical therapy" **Exclusion criteria:** "any other ocular disease or previous ocular surgery other than cataract extraction" **Equivalence of baseline characteristics:** not reported
Interventions	**Intervention 1:** trabeculectomy + Ex-PRESS (Optonol Ltd., Neve Ilan, Israel) **Intervention 2:** trabeculectomy **Length of follow-up:** Planned: 5 years Actual: mean of 262 weeks for Ex-PRESS group and 266 weeks for the trabeculectomy group
Outcomes	**Primary outcome, as defined:** complete success (final IOP > 4 mm Hg and ≤ 18 mm Hg without antiglaucoma medication) and overall success (final IOP > 4 mm Hg and ≤ 18 mm Hg with or without medications) **Secondary outcomes, as defined:** IOP, postoperative medication use, surgical failure (IOP > 18 mm Hg or the requirement for further glaucoma surgery), stringent target (final IOP > 4 mm Hg and ≤ 15 mm Hg), complications, and visual acuity **Intervals at which outcomes assessed:** 1 day, 1 week, 1, 3, and 6 months, and 1, 2, 3, 4, and 5 years after surgery
Notes	**Publication type:** published article **Funding sources:** Alcon Management SA, Geneva, Switzerland **Disclosures of interest:** "L. de J. has no proprietary interest in any of the products mentioned here." **Trial registry:** not registered **Study period:** October 2003 to November 2004 **Subgroup analyses:** none reported **Publication language:** English Authors contacted to retrieve number of participants lost to follow-up at 2 to 5 years, but no response received

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The participants were assigned randomly to receive either Ex-PRESS implantation under a scleral flap (Group A), or trabeculectomy (Group B) in the study eye, according to a computer-generated randomization list." "Randomization was determined before surgery according to a block randomization sequence prepared by SAS (version 9.1; SAS Institute Inc., Cary, NC, USA)."

De Jong 2009 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported.
Masking of participants and personnel (performance bias)	Low risk	Because trabeculectomy is a surgical procedure with informed consent, masking of the participants and personnel becomes impossible. However, given that a strict and standardized surgical protocol was followed and differences in the surgical protocol of the 2 groups were minimized, the risk of performance bias is comparably low for a surgical procedure
Masking of outcome assessment (detection bias)	High risk	"Secondly, the evaluator was not blinded to the procedure used in each case; however, it is difficult to carry out truly blinded evaluation as the type of surgery used is usually visible to the assessor." But how they controlled the risk was not specified
Incomplete outcome data (attrition bias) All outcomes	Low risk	There are 2 articles related to this study, as reported in 2009, the number analyzed was 40 eyes per treatment group (no loss to follow-up); however, as reported in 2011, the number analyzed was 38 eyes per treatment group.
Selective reporting (reporting bias)	Low risk	Protocol was not available. All defined outcomes were reported
Other bias	Unclear risk	Total industry support but not other source of potential bias identified. "There were no significant differences between the two groups except for age; the Ex-PRESS group (Group A) included significantly younger patients compared with the trabeculectomy group (Group B)." Age-adjusted values are reported in de Jong 2011 and do not significantly change the results

Eliezer 2006

Methods	**Study design:** parallel-group randomized controlled trial **Number randomized:** 32 eyes of 32 participants total; 16 eyes of 16 participants in each group **Exclusions after randomization:** not reported **Losses to follow-up:** not reported **Unit of analysis:** individual (1 eye per participant) **Number analyzed:** not reported **How were missing data handled?:** not reported **Power calculation:** not reported
Participants	**Country:** Brazil **Mean age:** 68 years; 68.3 years for trabeculectomy + AMT group; 67.6 years for trabeculectomy group **Gender:** 19/32 (59%) men and 13/32 (41%) women; 8/16 (50%) men and 8/16 (50%) women in trabeculectomy + AMT group; 11/16 (69%) men and 5/16 (31%) women in trabeculectomy group **Inclusion criteria:** POAG **Exclusion criteria:** not reported

Eliezer 2006 *(Continued)*

	Equivalence of baseline characteristics: yes
Interventions	**Intervention 1:** trabeculectomy + AMT **Intervention 2:** trabeculectomy **Length of follow-up:** Planned: 12 months Actual: 12 months
Outcomes	Primary and secondary outcomes not distinguished **Outcomes, as reported:** IOP, number of glaucoma medications, visual acuity, and appearance of bleb **Intervals at which outcomes assessed:** 1 day, 1 week, and 1, 2, 3, 4, 5, 6 and 12 months after surgery
Notes	**Publication type:** published article **Funding sources:** not reported **Disclosures of interest:** not reported **Trial registry:** not registered **Study period:** August 2001 to August 2003 **Subgroup analyses:** none reported **Publication language:** English Authors contacted for the number of participants lost to follow-up at 12 months, but no response received

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Thirty-two white patients with primary open-angle glaucoma (POAG) scheduled for glaucoma filtration surgery at the Glaucoma Service of the "Santa Casa de São Paulo" from August 2001 to August 2003 were randomly assigned to two groups." The method of sequence generation is not described, thus its adequacy cannot be judged
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported
Masking of participants and personnel (performance bias)	Low risk	Because trabeculectomy is a surgical procedure with informed consent, masking of the participants and personnel becomes impossible. However, given that a strict and standardized surgical protocol was followed, differences in the surgical protocol of the 2 groups were minimized, and the same 2 surgeons performed all surgeries, the risk of performance bias is comparably low for a surgical procedure
Masking of outcome assessment (detection bias)	High risk	Not reported. Although it is not possible to mask outcome assessors, devices can be easily seen during examination of the eye
Incomplete outcome data (attrition bias) All outcomes	Low risk	"At the end of a 12-month follow-up period, in the study group two of 31 eyes (6.25%) exhibited flat, vascularized bleb, 14 eyes (45.16%) had elevated but not avascular blebs and nine eyes (56.25%) showed thin, avascular blebs." This suggests that 31 of the 32 randomized participants completed the full 12-month follow-up

Eliezer 2006 *(Continued)*

Selective reporting (reporting bias)	High risk	Protocol was not available. Complications not defined, but reported
Other bias	Unclear risk	Did not report source of funding or conflict of interest. Baseline IOP values not reported.

Huang 2007

Methods	**Study design:** parallel-group randomized controlled trial (13 participants both eyes included) **Number randomized:** 63 eyes of 50 participants total; 36 eyes of 25 participants in the trabeculectomy + AMT group; 27 eyes of 25 participants in the trabeculectomy group **Exclusions after randomization:** not reported **Losses to follow-up:** not reported **Unit of analysis:** eye **Number analyzed:** not reported **How were missing data handled?:** not reported **Power calculation:** not reported
Participants	**Country:** China **Mean age:** not reported (range 46 to 68 years) **Gender:** 23/50 (46%) men and 27/50 (54%) women; by intervention group not reported **Inclusion criteria:** not reported (included participants were diagnosed with PACG) **Exclusion criteria:** not reported **Equivalence of baseline characteristics:** yes
Interventions	**Intervention 1:** trabeculectomy + AMT **Intervention 2:** trabeculectomy **Length of follow-up:** Planned: not reported Actual: 6 months
Outcomes	Primary and secondary outcomes not distinguished **Outcomes, as reported:** depth of anterior chamber, filtering bleb, surgical success, postoperative IOP, and visual acuity **Intervals at which outcomes assessed:** 1 day, 1 week, 2 weeks, and 1, 3, and 6 months after surgery
Notes	**Publication type:** published article **Funding sources:** not reported **Disclosures of interest:** "the authors declare no conflict of interest"

Huang 2007 *(Continued)*

Trial registry: not registered

Study period: participants recruited from January 2010 and January 2011

Subgroup analyses: none reported

Publication language: Chinese

Authors contacted for the number of participants lost to follow-up, but no response received

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random sequence generation was not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported
Masking of participants and personnel (performance bias)	Unclear risk	Masking of participants and personnel was not reported
Masking of outcome assessment (detection bias)	High risk	It is not possible to mask outcome assessors, devices can be seen during eye examination
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The number of participants with missing or incomplete outcome assessment was not reported
Selective reporting (reporting bias)	High risk	Protocol was not available. Complications were not defined, but reported
Other bias	Unclear risk	Did not report source of funding. This article provided nothing on study design; we contacted the authors but did not receive a response

Ji 2013

Methods	**Study design:** paired-eye randomized controlled trial
	Number randomized: 34 eyes of 17 participants total; each participant had 1 eye in each group
	Exclusions after randomization: none reported
	Losses to follow-up: none reported
	Unit of analysis: eye
	Number analyzed: 34 eyes of 17 participants total; each participant had 1 eye in each group
	How were missing data handled?: no missing data
	Power calculation: not reported
Participants	**Country:** China
	Mean age: 61.6 years; not reported by intervention group
	Gender: 10/17 (59%) men and 7/17 (41%) women; not reported by intervention group

Ji 2013 *(Continued)*

	Inclusion criteria: at least 18 years of age; medically uncontrolled glaucoma requiring bilateral surgery for IOP reduction **Exclusion criteria:** history of active uveitis; any ocular abnormality that would influence accurate IOP assessment; refractory glaucoma and secondary glaucoma **Equivalence of baseline characteristics:** yes
Interventions	**Intervention 1:** trabeculectomy + AMT **Intervention 2:** trabeculectomy **Length of follow-up:** Planned: 24 months Actual: 24 months
Outcomes	Primary and secondary outcomes not distinguished **Outcome, as defined:** BCVA, IOP, complications, anti-glaucoma drug usage, surgical success (IOP < 21 mm Hg without glaucoma medication), and morphology of the filtering bleb **Intervals at which outcomes assessed:** 1, 3, and 7 days and 1, 3, 6, 12, 18, and 24 months
Notes	**Publication type:** published article **Funding sources:** not reported **Disclosures of interest:** not reported **Trial registry:** not registered **Study period:** not reported **Subgroup analyses:** none reported **Publication language:** English Author not contacted

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomisation of surgical procedures was achieved by opening an envelope in which the procedure (trabeculectomy or with AMT) that would be performed to the first eye was stated, thereby determining the procedure in the other eye.", but no sequence generation method was reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported
Masking of participants and personnel (performance bias)	Unclear risk	Surgeons cannot be masked. Whether participants were masked was not reported
Masking of outcome assessment (detection bias)	High risk	It is not possible to mask outcome assessors, as devices can be seen during eye examination
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were no missing data

Ji 2013 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Protocol was not available. In the Methods section, the study mentioned measuring best-corrected visual acuity; however, the Results section did not report this outcome
Other bias	Unclear risk	Did not report source of support or conflict of interest. No other sources of bias was identified

Khairy 2015

Methods	**Study design:** parallel-group randomized controlled trial **Number randomized:** 52 eyes of 52 participants total; 26 eyes of 26 participants in each group **Exclusions after randomization:** none reported **Losses to follow-up**: none reported **Unit of analysis:** individual (1 eye per participant) **Number analyzed:** 52 eyes of 52 participants total; 26 eyes of 26 participants in each group **How were missing data handled?:** no missing data **Power calculation:** not reported
Participants	**Country:** Egypt **Mean age:** 67.9 years; by intervention not reported **Gender:** 47/78 (60%) men and 31/78 (40%) women; 15/26 (58%) men and 11/26 (42%) women in trabeculectomy + AMT group; 32/52 (62%) men and 20/52 (38%) women in trabeculectomy + MMC group **Inclusion criteria:** age > 60 years; diagnosed clinically with bilateral OAG with IOP > 21; clinical evidence of glaucomatous optic disc cupping or visual field loss; BCVA of 6/36 or better in each eye; central corneal thickness measuring < 590 mm; open anterior chamber angle on gonioscopy; willing to attend the eye clinic at the timing required by the study design **Exclusion criteria:** other forms of OAG (pseudo-exfoliation syndrome, pigment dispersion syndrome, etc.); history of chronic eye diseases; previous glaucoma surgical procedure; previous ocular laser or surgical treatment; history of systemic medical condition or medications that could affect the optic nerve or visual field **Equivalence of baseline characteristics:** yes
Interventions	**Intervention 1:** trabeculectomy + AMT **Intervention 2:** trabeculectomy + MMC **Length of follow-up:** Planned: 2 years Actual: 2 years
Outcomes	**Primary outcome, as defined**: surgical success (IOP < 22 mm Hg or lowered 20% without medication) **Secondary outcomes:** bleb morphology

Khairy 2015 *(Continued)*

	Intervals at which outcomes assessed: 1 day, 7 days, 1, 3, and 6 months, 1 year, and 2 year after surgery
Notes	**Publication type:** published article **Funding sources:** not reported **Disclosures of interest:** "authors declare no conflict of interest" **Trial registry:** not registered **Study period:** January 2010 to January 2011 **Subgroup analyses:** none reported **Publication language:** English Authors not contacted

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The randomization process was carried out using 4 opaque envelops in 2 containers. One contained 2 envelops labelled AMT and MMC, and the other contained 2 envelops with the names of 2 patients listed for glaucoma surgery on that day. The 2 patients were randomized to one of the procedures by asking an independent person to choose 1 envelop from each container."
Allocation concealment (selection bias)	High risk	Allocation not concealed because envelopes marked. See above.
Masking of participants and personnel (performance bias)	Low risk	Participants were masked; surgeons cannot be masked and this was not likely to cause any bias
Masking of outcome assessment (detection bias)	High risk	It is not possible to mask outcome assessors, as devices can be seen during eye examination
Incomplete outcome data (attrition bias) All outcomes	Low risk	"There was no loss of follow-up at any point during the 2 years of follow-up for either group."
Selective reporting (reporting bias)	High risk	Protocol was not available. Complications not defined, but reported
Other bias	Unclear risk	Did not report source of funding and no conflict of interest. No other sources of bias identified

Li 2010

Methods	**Study design**: parallel-group randomized controlled trial (12 participants both eyes included) **Number randomized:** 62 eyes of 50 participants total; 32 eyes in the trabeculectomy + MMC + AMT group; 30 eyes in the trabeculectomy + MMC group

Li 2010 *(Continued)*

	Exclusions after randomization: not reported **Losses to follow-up:** not reported **Unit of analysis:** eye **Number analyzed:** not reported **How were missing data handled?:** not reported **Power calculation:** not reported
Participants	**Country:** China **Mean age:** not reported (range 24 to 72 years); not reported by intervention group **Gender:** 28/50 (56%) men and 22/50 (44%) women; not reported by intervention group **Inclusion criteria:** refractory glaucoma **Exclusion criteria:** not reported **Equivalence of baseline characteristics:** yes
Interventions	**Intervention 1:** trabeculectomy + MMC + AMT **Intervention 2:** trabeculectomy + MMC **Length of follow-up:** Planned: not reported Actual: 12 months
Outcomes	Primary and secondary outcomes not distinguished **Outcomes, as reported:** filtering bleb, surgical success, postoperative IOP, visual acuity, and complications **Intervals at which outcomes assessed:** 1 week and 1, 3, 6, and 12 months
Notes	**Publication type:** published article **Funding sources:** not reported **Disclosures of interest:** not reported **Trial registry:** not registered **Study period:** not reported **Subgroup analyses:** none reported **Publication language:** Chinese Authors contacted for the number of participants lost to follow-up at different follow-up time points, but no response received

Risk of bias

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

Li 2010 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported
Masking of participants and personnel (performance bias)	Unclear risk	Masking of participants and personnel was not reported
Masking of outcome assessment (detection bias)	High risk	It is not possible to mask outcome assessors, as devices can be seen during eye examination
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The number of participants with missing or incomplete outcome assessment was not reported
Selective reporting (reporting bias)	High risk	Protocol was not available. Visual acuity, and complications reported in the Results section were not mentioned in the Methods section
Other bias	Unclear risk	Did not report source of funding or conflict of interest This article provided nothing on study design; we contacted the authors but did not receive a response

Liu 2009

Methods	**Study design**: parallel-group randomized controlled trial **Number randomized:** 35 eyes of 35 participants total; not reported by intervention group **Exclusions after randomization:** none reported **Losses to follow-up:** 3 participants (abstract stated no losses to follow-up, but main text reported 32 participants had follow-up) **Unit of analysis:** individual (1 eye per participant) **Number analyzed:** 32 participants total; 16 participants in trabeculectomy + MMC + AMT group; 16 participants in trabeculectomy + MMC group **How were missing data handled?:** 3 participants excluded from analysis **Power calculation:** not reported
Participants	**Country:** China **Age:** not reported **Gender:** not reported **Inclusion criteria:** refractory glaucoma **Exclusion criteria:** not reported **Equivalence of baseline characteristics:** yes
Interventions	**Intervention 1:** trabeculectomy + MMC + AMT **Intervention 2:** trabeculectomy + MMC

Liu 2009 *(Continued)*

	Length of follow-up: Planned: not reported Actual: 12 months
Outcomes	Primary and secondary outcomes not distinguished **Outcomes, as reported**: postoperative IOP, number of antiglaucoma medications, bleb morphology, and complications **Intervals at which outcomes assessed:** 1 day, 1 week, and 1, 3, 6, 9, and 12 months
Notes	**Publication type:** published article **Funding sources:** not reported **Disclosures of interest:** not reported **Trial registry:** not registered **Study period:** not reported **Subgroup analyses:** none reported **Publication language:** Chinese Authors contacted for the number of participants lost to follow-up at different follow-up time points, but no response received

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random sequence generation was not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported
Masking of participants and personnel (performance bias)	Low risk	The study mentioned "double blinded". Because surgeons could not be masked, participants should have been masked
Masking of outcome assessment (detection bias)	High risk	It is not possible to mask outcome assessors, as devices can be seen during eye examination
Incomplete outcome data (attrition bias) All outcomes	Low risk	3/35 participants were lost to follow-up
Selective reporting (reporting bias)	High risk	Protocol was not available. Number of antiglaucoma medication and complications reported in the Results section were not mentioned in the Methods section
Other bias	Unclear risk	Did not report source of funding or conflict of interest. The study included 1 eye for each participant. No other potential bias identified

Maheshwari 2012

Methods	**Study design:** parallel-group randomized controlled trial **Number randomized:** 40 eyes of 40 participants total; 20 eyes of 20 participants in each group **Exclusions after randomization:** none reported **Losses to follow-up**: none reported **Unit of analysis:** individual (1 eye per participant) **Number analyzed:** 40 eyes of 40 participants total; 20 eyes of 20 participants in each group **How were missing data handled?:** no missing data **Power calculation:** not reported
Participants	**Country:** India **Age:** not reported **Gender:** not reported **Inclusion criteria:** requiring glaucoma surgery for uncontrolled IOP in POAG **Exclusion criteria:** ACG, post-traumatic,uveitic, neovascular, or dysgenetic glaucoma; allergy to collagen, preliminary conjunctival damage (trauma, vitreo–retinal surgery, previous glaucoma surgery, and other); under 18 years of age **Equivalence of baseline characteristics:** no; at 1 year, a mean IOP of 15.6 mm Hg in the Ologen group was with 43% reduction and a mean IOP of 10.5 mm Hg in the trabeculectomy group was with 50% group; based on this information, the baseline IOP in Ologen group seemed to be about 30% more than the trabeculectomy group
Interventions	**Intervention 1:** trabeculectomy + Ologen (brand not reported) **Intervention 2:** trabeculectomy + MMC **Length of follow-up:** Planned: not reported Actual: 12 months
Outcomes	Primary and secondary outcomes not distinguished **Outcome, as reported:** visual acuity, IOP measurement, filtering bleb, and complications **Intervals at which outcomes assessed:** 1 day and 1 year after the surgery
Notes	**Publication type:** published article **Funding sources:** not reported **Disclosures of interest:** not reported **Trial registry:** not registered **Study period:** not reported **Subgroup analyses:** none reported **Publication language:** English Authors not contacted

Maheshwari 2012 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random sequence generation was not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported
Masking of participants and personnel (performance bias)	Unclear risk	Masking of participants and personnel was not reported
Masking of outcome assessment (detection bias)	High risk	Not reported. Although it is not possible to mask outcome assessors, devices can be easily seen during examination of the eye
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The number of participants with missing or incomplete outcome assessment was not reported
Selective reporting (reporting bias)	Unclear risk	Protocol was not available. Visual acuity and filtering bleb were defined in the Methods section, but the results were not reported
Other bias	Unclear risk	Did not report source of funding or conflict of interest. The baseline IOP seemed not equivalent between the 2 groups. At 1 year, a mean IOP of 15.6 mm Hg in the Ologen group was with 43% reduction and a mean IOP of 10.5 mm Hg in the trabeculectomy group was with 50% group; based on this information, the baseline IOP in the Ologen group seemed to be about 30% more than the trabeculectomy group

Marey 2013

Methods	**Study design**: parallel-group randomized controlled trial **Number randomized**: 60 eyes of 60 participants total; 30 eyes of 30 participants in each group **Exclusions after randomization:** none reported **Losses to follow-up**: none reported **Unit of analysis:** individual (1 eye per participant) **Number analyzed**: 60 eyes of 60 participants total; 30 eyes of 30 participants in each group **How were missing data handled?:** no missing data **Power calculation:** not reported
Participants	**Country:** Egypt **Mean age:** 50 years; 50.2 years for trabeculectomy + Ologen® group; 49.7 years for trabeculectomy + MMC group **Gender:** 35/60 (%) men and 25/60 (%) women; 18/30 (%) men and 12/30 (%) women in trabeculectomy + Ologen® group;

Marey 2013 *(Continued)*

	17/30 (%) men and 13/30 (%) women in trabeculectomy + MMC group **Inclusion criteria:** "POAG, chronic angle-closure glaucoma (CACG), uveitic glaucoma, pseudoexfoliation glaucoma (PEXG), and pseudophakic glaucoma not controlled medically (more than 21 mm Hg despite medications)" **Exclusion criteria:** "neovascular glaucoma, age < 18, and previous ocular surgery or laser procedures" **Equivalence of baseline characteristics:** yes
Interventions	**Intervention 1:** trabeculectomy + Ologen® (Aeon Astron Group B.V. Leiden, The Netherlands) **Intervention 2:** trabeculectomy + MMC **Length of follow-up:** Planned: 12 months Actual: 12 months
Outcomes	Primary and secondary outcomes not distinguished **Outcome, as reported:** IOP, bleb status, complications, absolute success (IOP ≤ 21 mm Hg without topical medication), and qualified success (IOP ≤ 21 mm Hg with topical medication) **Intervals at which outcomes assessed:** 1, 3, 6, 9, and 12 months after surgery
Notes	**Publication type:** published article **Funding sources:** not reported **Disclosures of interest:** "no competing financial interests exist" **Trial registry:** not registered **Study period:** February 2009 to January 2011 **Subgroup analyses:** none reported **Publication language:** English Authors not contacted

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Participants were randomly enrolled in 2 groups." The method of sequence generation is not described, thus its adequacy cannot be judged
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported
Masking of participants and personnel (performance bias)	Low risk	According to the Cochrane Handbook (8.11.1): "Blinding can be impossible for at least some people (e.g. most patients receiving surgery). However, such studies can take other measures to reduce the risk of bias, such as treating patients according to a strict protocol to reduce the risk of differential behaviours by patients and healthcare providers". As masking of participants and personnel is not feasible in the case of surgical interventions, examination of the surgical protocol reveals a fairly strict surgical protocol, as the "surgical steps were the same as group I except for application of MMC"
Masking of outcome assessment (detection bias)	High risk	It is not possible to mask outcome assessors, devices can be seen during eye examination

Marey 2013 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	"This is a prospective randomized controlled study, which included 60 eyes of 60 patients who received ophthalmologic service at the Menoufia University Hospital during the period of February 2009 to January 2011." Data are available for all participants who were randomized.
Selective reporting (reporting bias)	Low risk	Protocol was not available. All defined outcomes were reported
Other bias	Unclear risk	Did not report source of funding. No other sources of bias identified

Mitra 2012

Methods	**Study design:** parallel-group randomized controlled trial **Number randomized:** 64 eyes of 64 participants total; 28 participants in trabeculectomy + Ologen® group; 36 participants in trabeculectomy + MMC group **Exclusions after randomization:** not reported **Losses to follow-up:** not reported **Unit of analysis:** individual (1 eye per participant) **Number analyzed:** not reported **How were missing data handled?:** not reported **Power calculation:** not reported
Participants	**Country:** India **Mean age:** 62 years**;** 61.2 years for trabeculectomy + Ologen® group; 62.4 years for trabeculectomy + MMC group **Gender:** 38/64 (59%) men and 26/64 (41%) women; 22/36 (%) men and 14/36 (%) women in trabeculectomy + Ologen® group; 16/28 (%) men and 12/28 (%) women in trabeculectomy + MMC group **Inclusion criteria:** age 18 years or over; uncontrolled OAG; willing to sign informed consent; able and willing to complete post-operative follow-up requirements **Exclusion criteria:** inflammatory eye diseases; ACG; single functional eye; previous conjunctival surgery; known allergic reactions to ingredients of Ologen Collagen Matrix; excessive myopia (axial length > 27 mm or more than -10 diopters); previous vitrectomy eye surgery; unconsenting **Equivalence of baseline characteristics:** yes
Interventions	**Intervention 1:** trabeculectomy + Ologen® (brand not reported) **Intervention 2:** trabeculectomy + MMC **Length of follow-up:** Planned: 6 months

Mitra 2012 *(Continued)*

	Actual: 6 months
Outcomes	**Primary outcome, as defined:** IOP **Secondary outcomes, as defined:** number of glaucoma medication and complications **Intervals at which outcomes assessed:** 1 week and 1, 3, and 6 months after surgery
Notes	**Publication type:** published article **Funding sources:** not reported **Disclosures of interest:** not reported **Trial registry:** not registered **Study period:** not reported **Subgroup analyses:** none reported **Publication language:** English Authors not contacted

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random sequence generation was not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported
Masking of participants and personnel (performance bias)	Unclear risk	Masking of participants and personnel was not reported
Masking of outcome assessment (detection bias)	High risk	It is not possible to mask outcome assessors, as devices can be seen during eye examination
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The number of participants with missing or incomplete outcome assessment was not reported
Selective reporting (reporting bias)	Low risk	Protocol was not available. Complete and qualified success was reported, but IOP cut-offs used were not reported
Other bias	Unclear risk	Did not report source of support or conflict of interest. No other sources of bias identified

Netland 2014

Methods	**Study design:** parallel-group randomized controlled trial **Number randomized:** 120 eyes of 120 participants total; 59 participants in trabeculectomy + MMC + Ex-PRESS® group; 61 participants in trabeculectomy + MMC group

Netland 2014 *(Continued)*

	Exclusions after randomization: 1 participant randomized to receive treatment but was withdrawn prior to surgery because of thin sclera **Losses to follow-up:** 6 participants total; 2 participants in trabeculectomy + MMC + Ex-PRESS® group; 4 participants in the trabeculectomy + MMC group **Unit of analysis:** individual (1 eye per participant) **Number analyzed:** 114 participants total; 57 participants in trabeculectomy + MMC + Ex-PRESS® group; 57 participants in trabeculectomy + MMC group **How were missing data handled?:** 6 participants excluded from analysis **Power calculation:** a power of 80% to detect a 2 mm Hg IOP difference between groups with a sample size of 60 participants in each group
Participants	**Country:** USA **Mean age:** 69 years; 69.4 years for trabeculectomy + MMC + Ex-PRESS® group; 67.8 years for trabeculectomy + MMC group **Gender:** 32/59 (54%) men and 27/59 (46%) women in trabeculectomy + MMC + Ex-PRESS® group; 33/61 (54%) men and 28/61 (46%) women in trabeculectomy + MMC group **Inclusion criteria:** older than 18 years of age; diagnosed with OAG (including POAG, PEXG, and pigmentary glaucoma); previously treated with ocular hypotensive medications; candidate for glaucoma surgery with intraoperative MMC; IOP ≥ 18 mm Hg **Exclusion criteria:** ACG, normal tension glaucoma, or neovascular glaucoma; history of previous incisional glaucoma surgery, penetrating keratoplasty, extracapsular cataract extraction; visually significant cataract planned for extraction at the time of filtering surgery or within 12 months thereafter; any significant ocular disease or history in the operated eye other than glaucoma and cataract; ocular pathology that could interfere with accurate IOP measurements; vitreous present in the anterior chamber for which vitrectomy is anticipated; participation in any other concurrent ophthalmic clinical trial **Equivalence of baseline characteristics:** yes
Interventions	**Intervention 1:** trabeculectomy + MMC + Ex-PRESS® (Alco Laboratories, Fort Worth, Texas, USA) **Intervention 2:** trabeculectomy + MMC **Length of follow-up:** Planned: 2 years Actual: 2 years
Outcomes	**Primary outcomes, as defined:** IOP, medication reduction, and surgical success (5 mm Hg ≤ IOP ≤ 18 mm Hg) **Secondary outcomes, as defined:** visual acuity, complications, and IOP at week 2 follow-up **Intervals at which outcomes assessed:** 1 day, 7 days, and 1, 3, 6, 12, 18, and 24 months
Notes	**Publication type:** published article

Netland 2014 *(Continued)*

Funding sources: "research support for this investigator-initiated trial was obtained from Optonol Ltd. (Neve Ilan, Israel) and Alcon Laboratories, Inc. (Fort Worth, TX)"

Disclosures of interest: several co-authors received research support, consulting fees, and speaker honoraria from industries, but no company wrote or influenced the writing of the manuscript

Trial registry: NCT00444080 (www.ClinicalTrials.gov)

Study period: not reported

Subgroup analyses: none reported

Publication language: English

Authors contacted for 1-year IOP and visual acuity data, but no response received

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization was performed separately for each study site. Each subject was assigned a 3-digit identifying number, and all subjects were randomized using a computer-based random-number generator to undergo treatment with EX-PRESS glaucoma filtration implant under scleral flap or trabeculectomy"
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported
Masking of participants and personnel (performance bias)	Unclear risk	No-one was masked in this study. We are uncertain whether this has introduced bias
Masking of outcome assessment (detection bias)	Unclear risk	The outcome assessors were not masked. However, the authors mentioned that "we did provide standardized methods for measurement of IOP and documentation of other clinical findings, which may reduce, to some degree, the potential for bias"
Incomplete outcome data (attrition bias) All outcomes	Low risk	The study had small percent of participants lost to follow-up (6/120) and with approximately even numbers of participants lost in the 2 groups
Selective reporting (reporting bias)	Low risk	The study was registered in www.ClinicalTrials.gov. All defined outcomes in www.ClinicalTrials.gov were reported in full text
Other bias	High risk	Received funding from manufacturer of device. No other sources of bias identified

Papaconstantinou 2010

Methods	**Study design:** parallel-group randomized controlled trial **Number randomized:** 40 eyes of 40 participants total; 20 eyes of 20 participants in each group **Exclusions after randomization:** none reported **Losses to follow-up**: none reported **Unit of analysis:** individual (1 eye per participant) **Number analyzed:** 40 participants total; 20 participants in each group

Papaconstantinou 2010 *(Continued)*

	How were missing data handled?: no missing data **Power calculation:** not reported
Participants	**Country:** Greece **Mean age:** 66 years; 61.3 years for trabeculectomy + Ologen® group; 70.9 years for trabeculectomy group **Gender:** 23/40 (%) men and 17/40 (%) women; 11/20 (55%) men and 9/20 (45%) women in trabeculectomy + Ologen® group; 12/20 (60%) men and 8/20 (40%) women in trabeculectomy group **Inclusion criteria:** requiring glaucoma surgery for IOP control **Exclusion criteria:** "neovascular glaucoma, age < 18 years, previous surgical interventions or laser procedures and patients unable or unwilling to be followed up for an extended period postoperatively" **Equivalence of baseline characteristics:** yes
Interventions	**Intervention 1:** trabeculectomy + Ologen® (OculusGen Biomedical Inc. Taipei, Taiwan) **Intervention 2:** trabeculectomy **Length of follow-up:** Planned: 6 months Actual: 6 months
Outcomes	**Primary outcomes, as defined:** absolute success (≤ 21 mm Hg without glaucoma medication) and qualified success (≤ 21 mm Hg with or without glaucoma medication) **Secondary outcomes, as defined:** number of postoperative medications used, complications **Intervals at which outcomes assessed:** 1, 7, and 15 days and 1, 2, 3, 4, 5, and 6 months after surgery
Notes	**Publication type:** published article **Funding sources:** not reported **Disclosures of interest:** not reported **Trial registry:** not registered **Study period:** not reported **Subgroup analyses:** none reported **Publication language:** English Authors not contacted

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Forty eyes of 40 patients were enrolled in the study and divided randomly into two groups using the random number table; 20 were assigned to receive OloGen implant on top of the scleral flap subconjunctivally (study group) and 20 were assigned to undergo trabeculectomy without any implant (control group)."

Papaconstantinou 2010 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported
Masking of participants and personnel (performance bias)	Low risk	Because trabeculectomy is a surgical procedure with informed consent, masking of the participants and personnel becomes impossible. However, given that a strict surgical protocol was followed, with the only difference in the 2 groups being that "The OloGen implant was placed on top of the scleral flap under the conjunctiva in the implant group", and that the surgeries were all performed by the same surgeon, the risk of performance bias is comparably low for a surgical procedure
Masking of outcome assessment (detection bias)	High risk	This was not reported. Although it is not possible to mask outcome assessors, devices can be easily seen during examination of the eye
Incomplete outcome data (attrition bias) All outcomes	Low risk	"None of the patients refused to enrol and none were lost to follow-up during the course of the study."
Selective reporting (reporting bias)	Low risk	Protocol was not available. All defined primary and secondary outcomes were reported
Other bias	Unclear risk	Did not report source of support or conflict of interest. Limited duration of follow-up (6 months). 5-FU was used as adjuvant therapy for encapsulated blebs (2 participants in study group (trabeculectomy with Ologen implant) and 5 participants in control group (trabeculectomy)).

Ren 2009

Methods	**Study design:** parallel-group randomized controlled trial (6 participants both eyes included) **Number randomized:** 36 eyes of 30 participants total; 18 eyes in each group **Exclusions after randomization:** not reported **Losses to follow-up:** not reported **Unit of analysis:** eye **Number analyzed:** not reported **How were missing data handled?:** not reported **Power calculation:** not reported
Participants	**Country:** China **Mean age:** 63.6 years; not reported by intervention group **Gender:** 13/30 (43%) men and 17/30 (57%) women; not reported by intervention group **Inclusion criteria**: ACG **Exclusion criteria**: not reported **Equivalence of baseline characteristics:** yes
Interventions	**Intervention 1:** trabeculectomy + AMT **Intervention 2:** trabeculectomy

Ren 2009 *(Continued)*

	Length of follow-up: Planned: not reported Actual: 12 months
Outcomes	Primary and secondary outcomes not distinguished **Outcomes, as reported:** visual acuity, anterior chamber, filtering bleb, postoperative IOP, and facility of outflow **Intervals at which outcomes assessed:** 1 week and 1, 3, 6, and 12 months after surgery
Notes	**Publication type:** published article **Funding sources:** not reported **Disclosures of interest:** not reported **Trial registry:** not registered **Study period:** not reported **Subgroup analyses:** none reported **Publication language:** Chinese Authors not contacted

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random sequence generation was not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported
Masking of participants and personnel (performance bias)	Unclear risk	Masking of participants and personnel was not reported
Masking of outcome assessment (detection bias)	High risk	It is not possible to mask outcome assessors, as devices can be seen during eye examination
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The number of participants with missing or incomplete outcome assessment was not reported
Selective reporting (reporting bias)	High risk	Protocol was not available. Complications were not defined as an outcome, but were reported
Other bias	Unclear risk	Did not report source of support or conflict of interest. This article provided nothing on study design; we contacted the authors but did not receive a response

Rosentreter 2010

Methods	**Study design:** parallel-group randomized controlled trial

Rosentreter 2010 *(Continued)*

	Number randomized: 20 eyes of 20 participants total; 10 eyes of 10 participants in each group **Exclusions after randomization:** none reported **Losses to follow-up:** 1 participant died 8 months after surgery in trabeculectomy + MMC group **Unit of analysis:** individual (1 eye per participant) **Number analyzed:** 19 participants total; 10 participants in trabeculectomy + Ologen® group; 9 participants in trabeculectomy + MMC group **How were missing data handled?:** 1 participant with missing data excluded from analysis **Power calculation:** a power calculation was originally performed for a group of 40 participants, but power of detection was not reported and the study only recruited 20 participants (required sample size not met)
Participants	**Country:** Germany **Mean age:** 62.8 years; not reported by intervention group **Gender:** 8/20 (40%) men and 12/20 (60%) women; not reported by intervention group **Inclusion criteria:** “primary or secondary open-angle glaucoma with uncontrolled IOP while receiving maximal tolerable anti-glaucomatous therapy" **Exclusion criteria:** “angle-closure glaucoma, post-traumatic, uveitic, neovascular, or dysgenetic glaucoma were not considered for this study. Participants with an allergy to collagen, preliminary conjunctival damage (trauma, vitreo–retinal surgery, previous glaucoma surgery, and other) or those < 18 years of age were excluded from the study.” **Equivalence of baseline characteristics:** yes
Interventions	**Intervention 1:** trabeculectomy + Ologen® (Aeon Astron Europe BV, Leiden, The Netherlands) **Intervention 2:** trabeculectomy + MMC **Length of follow-up:** Planned: 12 months Actual: 12 months
Outcomes	**Primary outcomes, as defined:** IOP, number of glaucoma medication, filtering bleb **Secondary outcomes, as defined:** visual acuity, visual field, and complications **Intervals at which outcomes assessed:** 1, 7, and 14 days and 1, 2, 3, 6, and 12 months (except visual field examination only done at 6 and 12 months)
Notes	**Publication type:** published article **Funding sources:** “PJ Dahlhausen & Co. GmbH (Emil-Hoffmann-Str. 53, 50996 Cologne, Germany) supported the study” **Disclosures of interest:** “the sponsor had no role in the design or conduct of this research” **Trial registry:** ClinicalTrials.gov: NCT00538590 **Study period:** not reported **Subgroup analyses:** none reported **Publication language**: English Authors not contacted

Rosentreter 2010 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"We initiated a randomised, prospective trial with two study groups undergoing penetrating anti-glaucomatous surgery (trabeculectomy)" "Randomisation was performed by an individual not involved in the study according to the Consort Guidelines description." However, the method of sequence generation is not described and thus adequacy cannot be judged
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported
Masking of participants and personnel (performance bias)	Low risk	Because trabeculectomy is a surgical procedure with informed consent, masking of the participants and personnel becomes impossible. However, given that a strict and standardized surgical protocol was followed and differences in the surgical protocol of the 2 groups were minimized, the risk of performance bias is comparably low for a surgical procedure
Masking of outcome assessment (detection bias)	High risk	It is not possible to mask outcome assessors, as devices can be seen during eye examination
Incomplete outcome data (attrition bias) All outcomes	Low risk	"Twenty (10/10) patients, 12 women and 8 men, began the study, and it was completed by 19 patients. One patient from the MMC group died 8 months after surgery."
Selective reporting (reporting bias)	Low risk	The study was registered in www.ClinicalTrials.gov. All defined outcomes in www.ClinicalTrials.gov were reported in full text.
Other bias	High risk	Total industry support and other source(s) of potential bias identified. "PJ Dahlhausen & Co. GmbH (Emil-Hoffmann-Str. 53, 50996 Cologne, Germany) supported the study." Although the authors state that "The sponsor had no role in the design or conduct of this research", the risk of bias from an industry-funded study is unclear. The authors did not specify how power of detection was affected; "the plan was to include a consecutive series of 40 patients (20 to each group)." "After the first 20 patients, an interim analysis was prearranged." "After interim analysis, the study was aborted because of the significantly lower IOP and significantly higher complete success rate in the MMC group after 1 year (P = 0.01)."

Rosentreter 2014

Methods	**Study design:** parallel-group randomized controlled trial **Number randomized:** 30 eyes of 30 participants total; 15 eyes of 15 participants in each group **Exclusions after randomization:** none reported **Losses to follow-up:** 5 participants total; 4 participants in trabeculectomy + Ologen® group; 1 participant in trabeculectomy + MMC group **Unit of analysis:** individual (1 eye per participant) **Number analyzed:** 25 participants total;

Rosentreter 2014 *(Continued)*

	14 participants in trabeculectomy + Ologen® group; 11 participants in trabeculectomy + MMC group **How were missing data handled?:** 5 participants excluded from analysis **Power calculation:** a power of 50% to detect 2.73 mm Hg IOP difference between groups and a power of 95% for a difference of 5.03 mm Hg in IOP
Participants	**Country:** Germany **Mean age:** 66.4 years; not reported by intervention group **Gender:** 13/30 (43%) men and 17/30 (57%) women; not reported by intervention group **Inclusion criteria:** “primary or secondary open-angle glaucoma with uncontrolled IOP while receiving maximal tolerable anti-glaucomatous therapy" **Exclusion criteria:** “angle-closure glaucoma, posttraumatic, uveitic, neovascular, or dysgenetic glaucoma were not considered for this study. Participants with an allergy to collagen, preliminary conjunctival damage (due to trauma, vitreoretinal surgery, previous glaucoma surgery or other causes) as well as those younger than 18 years of age were excluded from the study.” **Equivalence of baseline characteristics:** yes
Interventions	**Intervention 1:** trabeculectomy + Ologen® (Version 2; Aeon Astron Europe BV, the Netherlands) **Intervention 2:** trabeculectomy + MMC **Length of follow-up:** Planned: 12 months Actual: 12 months
Outcomes	**Primary outcomes, as defined:** IOP, number of glaucoma medications used, bleb morphology **Secondary outcomes, as defined:** visual acuity, visual field, absolute success ("IOP of 18 mm Hg or lower and an additional reduction of 20% or more in IOP compared to the preoperative IOP, without any additional glaucoma surgery, but with topical medication of a maximum medication score of 2 allowed"), and complications **Intervals at which outcomes assessed:** 1 day, 7 days, and 1, 3, 6, and 12 months (except visual field at 12 months only)
Notes	**Publication type:** published article **Funding sources:** “PJ Dahlhausen & Co. GmbH (Cologne, Germany) supported the study” **Disclosures of interest:** "no authors have any financial/conflicting interests to disclose" **Trial registry:** ClinicalTrials.gov: NCT01174420 **Study period:** not reported **Subgroup analyses:** none reported **Publication language:** English Authors not contacted

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization was performed by a person not involved in the study by drawing lots."

Rosentreter 2014 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported
Masking of participants and personnel (performance bias)	Low risk	Because trabeculectomy is a surgical procedure with informed consent, masking of the participants and personnel becomes impossible. However, given that a strict and standardized surgical protocol was followed and differences in the surgical protocol of the 2 groups were minimized, the risk of performance bias is comparably low for a surgical procedure
Masking of outcome assessment (detection bias)	High risk	It is not possible to mask outcome assessors, as devices can be seen during eye examination
Incomplete outcome data (attrition bias) All outcomes	Low risk	25/30 eyes completed 1-year follow-up of the study
Selective reporting (reporting bias)	Low risk	The study was registered in www.ClinicalTrials.gov. All defined outcomes in www.ClinicalTrials.gov were reported in full text
Other bias	Unclear risk	Total industry support but not other source of potential bias identified.

Senthil 2013

Methods	**Study design:** parallel-group randomized controlled trial (6 participants both eyes included) **Number randomized:** 39 eyes of 33 participants total; 19 eyes in trabeculectomy with Ologen® group; 20 eyes in trabeculectomy with MMC group **Exclusions after randomization:** none reported **Losses to follow-up:** 7 eyes of 5 participants had less than 6 months of follow-up **Unit of analysis:** eye **Number analyzed:** 32 eyes of 28 participants total; 16 eyes of 14 participants in each group **How were missing data handled?:** 7 eyes of 5 participants excluded from analysis **Power calculation:** not reported
Participants	**Country:** India **Mean age:** 46 years; 48 years for trabeculectomy + Ologen® group; 45 years for trabeculectomy + MMC group **Gender:** 20/39 (51%) men and 19/39 (49%) women; 9/19 (47%) men and 10/19 (53%) women in trabeculectomy + Ologen® group; 11/20 (55%) men and 9/20 (45%) women in trabeculectomy + MMC group **Inclusion criteria:** ≥ 18 years of age; medically uncontrolled POAG or PACG with no previous intraocular surgery (POAG defined as the presence of IOP > 21 mm Hg, open anterior chamber angle on gonioscopy, glaucomatous optic disc damage on clinical examination, and corresponding glaucomatous visual field defects; PACG defined as the presence of an occludable angle on gonioscopy (posterior trabecular meshwork not seen in at least 180° of the total circumference of the angle in primary position), glaucomatous optic disc damage, and corresponding glaucomatous visual field defects)

Senthil 2013 *(Continued)*

	Exclusion criteria: not reported **Equivalence of baseline characteristics:** yes
Interventions	**Intervention 1:** trabeculectomy + Ologen® (OculusGen Biomedical Inc. Taipei, Taiwan) **Intervention 2:** trabeculectomy + MMC **Length of follow-up:** Planned: 2 years Actual: 2 years
Outcomes	**Primary outcomes, as defined:** success, defined as, "complete success if an IOP was > 5 and ≤ 21 mm Hg without any glaucoma medications or re-surgery. Qualified success was defined as IOP ≤ 21 mm Hg with or without anti-glaucoma medications. Failure was defined as IOP ≥ 22 mm Hg despite medications or ≤ 5 mm Hg (on 2 or more examinations) with hypotony maculopathy or if an additional procedure like needling or repeat trabeculectomy was required to control the IOP or if there was loss of light perception", assessed at 6, 12, 18, and 24 months **Secondary outcomes, as defined:** success ("achieving IOP ≤ 18 mm Hg and ≤ 15 mm Hg in both the groups without anti-glaucoma medications"), complications, and visual acuity **Intervals at which outcomes assessed:** 1 day, 7 days, and 1, 3, 6, 12, 18, and 24 months
Notes	**Publication type:** published article **Funding sources:** "source of support: nil" **Disclosures of interest:** "none declared" **Trial registry:** not registered **Study period:** May 2007 to December 2008 **Subgroup analyses:** none reported **Publication language:** English Authors not contacted

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization was done using a permuted block randomization. Block size of 4 was determined, and 2 eyes of group 1 and 2 eyes of group 2 were randomly allocated into each block."
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported
Masking of participants and personnel (performance bias)	Low risk	Because trabeculectomy is a surgical procedure with informed consent, masking of the participants and personnel becomes impossible. However, given that a strict and standardized surgical protocol was followed and differences in the surgical protocol of the 2 groups were minimized, the risk of performance bias is comparably low for a surgical procedure
Masking of outcome assessment (detection bias)	High risk	It is not possible to mask outcome assessors, as devices can be seen during eye examination
Incomplete outcome data (attrition bias) All outcomes	High risk	Not all data were available for all participants who were randomized, given that "7 eyes of 5 participants, who had less than 6 months of follow-up, were excluded from the outcome analysis, but were included in the analysis of com-

Senthil 2013 *(Continued)*

		plications." In addition, "The number of eyes lost to follow-up at 2 years was close to 50%"
Selective reporting (reporting bias)	Low risk	Protocol was not available. All primary and secondary outcomes were reported
Other bias	Low risk	No industry support reported and no other source of potential bias identified. No other sources of bias identified

Sheha 2008

Methods	**Study design:** parallel-group randomized controlled trial **Number randomized:** 37 eyes of 37 participants total; 19 participants in trabeculectomy + MMC + AMT group; 18 participants in the trabeculectomy + MMC group **Exclusions after randomization:** none reported **Losses to follow-up:** 7 participants total at 12 months; 4 participants in trabeculectomy + MMC + AMT group; 3 participants in trabeculectomy + MMC group **Unit of analysis:** individual (1 eye per participant) **Number analyzed:** 30 participants total; 15 participants in each group **How were missing data handled?:** 7 participants excluded from analysis **Power calculation:** a power of 80% achieved with a sample size of 15 participants; the minimum detectable difference was not specified
Participants	**Country:** Saudi Arabia **Mean age:** 57 years; 57.6 years for trabeculectomy + MMC + AMT group; 56.6 years for trabeculectomy + MMC group **Gender:** 24/37 (65%) men and 13/37 (35%) women; 13/19 (68%) men and 6/19 (32%) in trabeculectomy + MMC + AMT group; 11/18 (61%) men and 7/18 (39%) women in trabeculectomy + MMC group **Inclusion criteria:** not reported (the study population was described as follows: "This prospective, randomized study included 37 eyes with refractory glaucoma at such high risks as neovascular, pseudophakic, and prior failure." "All patients had previously failed trabeculectomy with MMC once or twice. Only 1 eye of each patient was included. A number of risk factors were randomized such as race, and type of refractory glaucoma, which was subdivided into 3 subgroups including phakic open angle glaucoma, pseudophakic glaucoma, and neovascular glaucoma. All eyes with phakic open angle glaucoma had 2 previously failed trabeculectomies with MMC; all eyes with pseudophakic and neovascular glaucomas had 1 previously failed trabeculectomy with MMC.") **Exclusion criteria:** not reported **Equivalence of baseline characteristics:** yes
Interventions	**Intervention 1:** trabeculectomy + MMC + AMT **Intervention 2:** trabeculectomy + MMC

Sheha 2008 *(Continued)*

	Length of follow-up: Planned: 12 months Actual: 12 months
Outcomes	Primary and secondary outcomes not distinguished **Outcomes, as reported:** IOP, bleb characteristics, complications, and number of antiglaucoma medications, complete success ("IOP of 21mm Hg or less without antiglaucoma medications"), qualified success ("defined as having an IOP of 21mm Hg or less with or without antiglaucoma medications"), and failure ("IOP was controlled by additional surgeries such as needling, but not suture lysis, or if chronic hypotony, defined as an IOP less than 6 mm Hg after 3 months, occurred") **Intervals at which outcomes assessed:** 1 day, 1 week, and 1, 3, 6, 9, and 12 months
Notes	**Publication type:** published article **Funding sources:** not reported **Disclosures of interest:** "no author has a financial or proprietary interest in any material or method mentioned" **Trial registry:** not registered **Study period:** April 2004 to August 2005 **Subgroup analyses:** none reported **Publication language:** English Authors not contacted

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random sequence generation was not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported
Masking of participants and personnel (performance bias)	Low risk	Because trabeculectomy is a surgical procedure with informed consent, masking of the participants and personnel becomes impossible. However, given that a strict and standardized surgical protocol was followed, differences in the surgical protocol of the 2 groups were minimized, and the same surgeon performed all surgeries, the risk of performance bias is comparably low for a surgical procedure
Masking of outcome assessment (detection bias)	High risk	It is not possible to mask outcome assessors, as devices can be seen during eye examination
Incomplete outcome data (attrition bias) All outcomes	High risk	There were 4 participants lost from the trabeculectomy + MMC + AMT group and 3 from the trabeculectomy + MMC group; the reasons for loss to follow-up and how it was accounted for are not addressed
Selective reporting (reporting bias)	Low risk	Protocol was not available. All defined outcomes were reported
Other bias	Unclear risk	Did not report source of funding. No other sources of bias identified

Stavrakas 2012

Methods	**Study design:** parallel-group randomized controlled trial (9 participants both eyes included) **Number randomized:** 59 eyes of 50 participants total; 32 eyes in trabeculectomy + AMT group; 27 eyes in trabeculectomy group **Exclusions after randomization:** none reported **Losses to follow-up:** 7 eyes total at 6 months; 5 eyes in trabeculectomy + AMT group; 2 eyes in the trabeculectomy group **Unit of analysis:** eye **Number analyzed:** 52 eyes total; 30 eyes in trabeculectomy + AMT group; 22 eyes in trabeculectomy group **How were missing data handled?:** 7 eyes excluded from analysis **Power calculation:** not reported
Participants	**Country:** Greece **Mean age:** not reported; median age 70.0 (63.0, 80.0) years in trabeculectomy + AMT group; median age 71.5 (67.0, 76.0) years in trabeculectomy group **Gender:** 35/59 (59%) men and 24/59 (41%) women; 19/27 (70%) men and 8/27(30%) women in trabeculectomy + AMT group; 16/32 (50%) men and 16/32 (50%) women in trabeculectomy group **Inclusion criteria:** "presence of POAG and at least one of the following: unsatisfactory target intraocular pressure (IOP) control with topical antiglaucoma treatment; optic nerve damage progression on two consecutive visual field tests and increase of cup-to-disk ratio in a period of 24 months; allergy to topical agents; or poor compliance" **Exclusion criteria:** "any other type of glaucoma; only-eye patients; past or present anterior segment pathology coexistence (apart from cataract); and previously failed glaucoma filtration surgery" **Equivalence of baseline characteristics:** yes
Interventions	**Intervention 1:** trabeculectomy + AMT **Intervention 2:** trabeculectomy **Length of follow-up:** Planned: 24 months Actual: 24 months
Outcomes	**Primary outcomes, as defined:** IOP, and functionality and morphology of the bleb **Secondary outcomes, as defined:** visual acuity, reduction of antiglaucoma medications, and complications

Stavrakas 2012 *(Continued)*

	Intervals at which outcomes assessed: 1 day, 1 week, 2 weeks, 1 month, 2 months, and every 6 months thereafter for a minimum of 2 years after surgery
Notes	**Publication type:** published article **Funding sources:** not reported **Disclosures of interest:** "none of the authors has any financial interest in any of the materials or the methods mentioned in the study" **Trial registry:** not registered **Study period:** not reported **Subgroup analyses:** none reported **Publication language:** English Authors contacted for mean IOP and standard deviations, etc., but they were not able to provide data

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	It was not specified in the full-text. The email response from the author suggest that participants were randomized using simple randomization (flipping a coin, etc.). However, simple randomization could result in uneven number of participants in each group, thus investigators could set the ratio of participant assigned to the AMT group or trabeculectomy group to keep the groups even. "it was the method of simple randomisation with monitoring during the process in order to ensure relatively even numbers. At the end, the numbers were not even due to financial restrictions regarding the amniotic membranes."
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported
Masking of participants and personnel (performance bias)	Low risk	Because trabeculectomy is a surgical procedure with informed consent, masking of the participants and personnel becomes impossible. However, given that a strict and standardized surgical protocol was followed, differences in the surgical protocol of the 2 groups were minimized, and the same surgeon performed all surgeries, the risk of performance bias is comparably low for a surgical procedure
Masking of outcome assessment (detection bias)	High risk	It is not possible to mask outcome assessors, as devices can be seen during eye examination
Incomplete outcome data (attrition bias) All outcomes	Low risk	"Eyes lost from follow-up have been included in the analysis until they stopped attending the scheduled postoperative visit and then censored from the study (right censoring)."
Selective reporting (reporting bias)	Low risk	Protocol was not available. All defined outcomes were reported
Other bias	Unclear risk	Did not report source of funding. No other sources of bias identified

Wagschal 2013

Methods	**Study design:** parallel-group randomized controlled trial **Number randomized:** 64 eyes of 64 participants total; 33 participants in trabeculectomy + MMC + Ex-PRESS® P50 group; 31 participants in trabeculectomy + MMC group **Exclusions after randomization:** none reported **Losses to follow-up:** 4 participants total at 1 year; 3 participants in trabeculectomy + MMC + Ex-PRESS® P50 group; 1 participant in trabeculectomy + MMC group **Unit of analysis:** individual (1 eye per participant) **Number analyzed:** 60 participants total; 30 participants in each group **How were missing data handled?:** 4 participants excluded from analysis **Power calculation:** a power of 80% to detect a 2 mm Hg IOP difference with a sample size of 52 eyes
Participants	**Country:** Canada **Mean age:** overall not reported; 61.9 years for trabeculectomy + MMC + Ex-PRESS® P50 group; 65.9 years for trabeculectomy + MMC group **Gender:** 41/64 (64%) men and 23/64 (36%) women overall; not reported by intervention group **Inclusion criteria:** "participants with open-angle glaucoma between 18 and 85 years of age with uncontrolled intraocular pressure (IOP) on maximum tolerated medication and trabeculectomy as the planned surgical procedure" **Exclusion criteria:** "previous ocular incisional surgery (with the exception of clear cornea cataract surgery or 1 trabeculectomy), history of uveitis, unwilling or unable to give consent, unwilling to accept randomization, or unable to return for scheduled protocol visits" **Equivalence of baseline characteristics:** yes; baseline IOP and VA are comparable
Interventions	**Intervention 1**: trabeculectomy + MMC + Ex-PRESS® P50 (Alcon Canada Inc. Mississauga, ON, Canada) **Intervention 2**: trabeculectomy + MMC **Length of follow-up:** Planned: 1 year Actual: 1 year
Outcomes	**Primary outcome, as defined**: IOP, complete success ("IOP between 5 and 18 mm Hg and a 20% reduction from baseline without medication and qualified success was defined as above with hypotensive medications"), failure ("reoperation for glaucoma or loss of light perception") **Secondary outcomes, as defined**: visual acuity, surgery time, glaucoma medication usage, IOP, bleb morphology, Seidel test, additional procedures, complications, and potential risk factors for vision loss **Intervals at which outcomes assessed:** 1 day, 1 week, 2 weeks, and 1, 2, 3, and 6 months after surgery
Notes	**Publication type:** published article **Funding sources:** "some Ex-PRESS shunts were provided at no cost by Imed and Alcon Canada"

Wagschal 2013 *(Continued)*

Disclosures of interest: "Y.M.B. has received speaking honoraria from Alcon Canada. The remaining authors declare no conflict of interest."

Trial registry: NCT01263561 (www.ClinicalTrials.gov)

Study period: May 2009 to July 2011

Subgroup analyses: subgroup of 43 participants randomly chosen for cost-effectiveness analysis

Publication language: English

Authors contacted for randomization method, reasons for lost to follow-up, etc.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	As this was not provided in the published report, we contacted the study investigator, and received the following response: "randomization was done by drawing a piece of paper with procedure name from a bag"
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported
Masking of participants and personnel (performance bias)	Unclear risk	By contacting the study investigators, we found participants were not masked, but whether this would introduce bias is uncertain as current evidence did not show 1 procedure significantly better than the other
Masking of outcome assessment (detection bias)	High risk	By contacting the study investigators, we found the outcome assessors were not masked. Although it is not possible to mask outcome assessors, devices can be easily seen during examination of the eye
Incomplete outcome data (attrition bias) All outcomes	Low risk	The study had a low percentage of participants lost to follow-up (4 out of 64), and not much difference in numbers in the 2 groups (lost 3 versus 1). Also, exclusions were because of death (3 participants) and 1 participant not adhering to the assigned procedure
Selective reporting (reporting bias)	Low risk	The study was registered in www.ClinicalTrials.gov. All defined outcomes in www.ClinicalTrials.gov were reported in full text
Other bias	Unclear risk	Partial industry support and other source(s) of potential bias

Wang 2008

Methods

Study design: parallel-group randomized controlled trial

Number randomized: 40 eyes of 40 participants total; 20 eyes of 20 participants in each group

Exclusions after randomization: not reported

Losses to follow-up: not reported

Unit of analysis: individual (1 eye per participant)

Number analyzed: not reported

How were missing data handled?: not reported

Power calculation: not reported

Wang 2008 *(Continued)*

Participants	**Country:** China **Mean age:** overall not reported; 54 years for the trabeculectomy + AMT group; 56 years for the trabeculectomy group **Gender:** 11/40 (28%) men and 29/40 (72%) women overall; not reported by intervention group **Inclusion criteria:** glaucoma **Exclusion criteria:** not specified **Equivalence of baseline characteristics:** yes
Interventions	**Intervention 1:** trabeculectomy + AMT **Intervention 2:** trabeculectomy **Length of follow-up:** Planned: 12 months Actual: 12 months
Outcomes	Primary and secondary outcomes not distinguished **Outcomes, as reported:** filtering bleb, surgical success, postoperative IOP, adverse events, and visual acuity **Intervals at which outcomes assessed:** 1, 2, and 3 days, 1, 2, and 3 weeks, and 1, 2, and 6 months
Notes	**Publication type:** published article **Funding sources:** not reported **Disclosures of interest:** not reported **Trial registry:** not registered **Study period:** not reported **Subgroup analyses:** none reported **Publication language:** Chinese Authors contacted in regards to number with missing data at different follow-up time points, but no response received

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random sequence generation was not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported
Masking of participants and personnel (performance bias)	Unclear risk	Method use to mask participants and personnel was not reported

Wang 2008 *(Continued)*

Masking of outcome assessment (detection bias)	High risk	It is not possible to mask outcome assessors, as devices can be seen during eye examination
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The number of participants with missing or incomplete outcome assessment was not reported
Selective reporting (reporting bias)	Low risk	Protocol was not available. All defined outcomes defined were reported
Other bias	Unclear risk	Did not report source of support or conflict of interest. This article provided nothing on study design; we contacted the authors but did not receive a response

Wang 2009

Methods	**Study design:** parallel group randomized controlled trial (6 participants both eyes included) **Number randomized:** 44 eyes of 38 participants total; 16 eyes in trabeculectomy + AMT + MMC group; 14 eyes in trabeculectomy + MMC group; 14 eyes in trabeculectomy group **Exclusions after randomization:** not reported **Losses to follow-up:** not reported **Unit of analysis:** eye **Number analyzed:** not reported **How were missing data handled?:** not reported **Power calculation:** not reported
Participants	**Country:** China **Mean age:** mean age not reported; age range 19 to 75 years; not reported by intervention group **Gender:** 24 men and 14 women; not reported by intervention group **Inclusion criteria:** refractory glaucoma **Exclusion criteria:** not specified **Equivalence of baseline characteristics:** yes
Interventions	**Intervention 1:** trabeculectomy + AMT + MMC **Intervention 2:** trabeculectomy + MMC **Intervention 3:** trabeculectomy **Length of follow-up:** Planned: not reported Actual: 12 months

Wang 2009 *(Continued)*

Outcomes	Primary and secondary outcomes not distinguished **Outcomes, as reported:** filtering bleb, postoperative IOP, and adverse events **Intervals at which outcomes assessed:** 1 week, 2 weeks, and 1, 6, and 12 months after surgery
Notes	**Publication type:** published article **Funding sources:** not reported **Disclosures of interest:** not reported **Trial registry:** not registered **Study period:** not reported **Subgroup analyses:** none reported **Publication language:** Chinese Authors contacted in regards to number with missing data at different follow-up time points, but no response received

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random sequence generation was not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported
Masking of participants and personnel (performance bias)	Unclear risk	Masking of participants and personnel was not reported
Masking of outcome assessment (detection bias)	High risk	Not reported. Although it is not possible to mask outcome assessors, devices can be easily seen during examination of the eye
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The number of participants with missing or incomplete outcome assessment was not reported
Selective reporting (reporting bias)	High risk	Protocol was not available. Filtering blebs and complications reported in the Results section were not mentioned in the Methods section
Other bias	Unclear risk	Did not report source of funding or conflict of interest. This article provided nothing on study design; we contacted the authors but did not receive a response.

Yan 2004

Methods	**Study design:** parallel-group randomized controlled trial (11 participants both eyes included) **Number randomized:** 63 eyes of 52 participants total; 36 eyes of 28 participants in trabeculectomy + AMT group;

Yan 2004 *(Continued)*

	27 eyes of 24 participants in trabeculectomy group **Exclusions after randomization:** none reported **Losses to follow-up**: none reported **Unit of analysis:** eye **Number analyzed:** 63 eyes of 52 participants total; 36 eyes of 28 participants in trabeculectomy + AMT group; 27 eyes of 24 participants in trabeculectomy group **How were missing data handled?:** no missing data **Power calculation:** not reported
Participants	**Country:** China **Mean age:** mean age not reported**;** age range 45 to 76 years; not reported by intervention group **Gender:** 25/52 (48%) men and 27/52 (52%) women overall; not reported by intervention group **Inclusion criteria:** PACG **Exclusion criteria:** not specified **Equivalence of baseline characteristics:** yes
Interventions	**Intervention 1:** trabeculectomy + AMT **Intervention 2:** trabeculectomy **Length of follow-up:** Planned: not reported Actual: 6 months
Outcomes	Primary and secondary outcomes not distinguished **Outcomes, as reported:** depth of anterior chamber, IOP, visual acuity, filtering bleb, surgical success, complications **Intervals at which outcomes assessed:** 1 day, 1 week, 2 weeks, and 1, 3, and 6 months
Notes	**Publication type:** published article **Funding sources:** not reported **Disclosures of interest:** not reported **Trial registry:** not registered **Study period:** not reported **Subgroup analyses:** none reported **Publication language:** Chinese Authors not contacted

Risk of bias

Bias	Authors' judgement	Support for judgement

Yan 2004 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Random sequence generation was not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported
Masking of participants and personnel (performance bias)	Unclear risk	Masking of participants and personnel was not reported
Masking of outcome assessment (detection bias)	High risk	It is not possible to mask outcome assessors, as devices can be seen during eye examination
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The number of participants with missing or incomplete outcome assessment was not reported
Selective reporting (reporting bias)	High risk	Protocol was not available. Surgical success and visual acuity were reported in the Results section, but were not mentioned in the Methods section
Other bias	Unclear risk	Did not report source of funding or conflict of interest. This article provided nothing on study design; we contacted the authors but did not receive a response

Yang 2004

Methods	**Study design:** parallel-group randomized controlled trial **Number randomized:** 70 eyes of 70 participants total; 40 participants in trabeculectomy + AMT group; 30 participants in trabeculectomy group **Exclusions after randomization:** not reported **Losses to follow-up:** not reported **Unit of analysis:** individual (1 eye per participant) **Number analyzed:** not reported **How were missing data handled?:** not reported **Power calculation:** not reported
Participants	**Country:** China **Mean age:** mean age not reported**;** age range 20 to 72 years; not reported by intervention group **Gender:** 42/70 (60%) men and 28/70 (40%) women overall; not reported by intervention group **Inclusion criteria:** glaucoma **Exclusion criteria:** not specified **Equivalence of baseline characteristics:** yes
Interventions	**Intervention 1:** trabeculectomy + AMT

Yang 2004 *(Continued)*

	Intervention 2: trabeculectomy **Length of follow-up:** Planned: not reported Actual: 6 months
Outcomes	Primary and secondary outcomes not distinguished **Outcomes, as reported:** filtering bleb, surgical success, postoperative IOP, visual acuity, and complications **Intervals at which outcomes assessed:** 1 day, 1 week, and 1, 3, and 6 months
Notes	**Publication type:** published article **Funding sources:** not reported **Disclosures of interest:** not reported **Trial registry:** not registered **Study period:** not reported **Subgroup analyses:** none reported **Publication language:** Chinese Authors contacted in regards to number with missing data at different follow-up time points, but no response received

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random sequence generation was not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported
Masking of participants and personnel (performance bias)	Unclear risk	Masking of participants and personnel was not reported
Masking of outcome assessment (detection bias)	High risk	Not reported. Although it is not possible to mask outcome assessors, devices can be easily seen during examination of the eye
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The number of participants with missing or incomplete outcome assessment was not reported
Selective reporting (reporting bias)	High risk	Protocol was not available. Surgical success reported in the Results section were not mentioned in the Methods section
Other bias	Unclear risk	Did not report source of funding or conflict of interest. This article provided nothing on study design; we contacted the authors but did not receive a response

Zhang 2009

Methods	**Study design:** parallel-group randomized controlled trial (13 participants both eyes included) **Number randomized:** 52 eyes of 39 participants total; 26 eyes in each group **Exclusions after randomization:** not reported **Losses to follow-up:** not reported **Unit of analysis:** eye **Number analyzed:** not reported **How were missing data handled?:** not reported **Power calculation:** not reported
Participants	**Country:** China **Mean age:** mean age not reported; age range 40 to 70 years; not reported by intervention group **Gender:** 18/39 (46%) men and 21/39 (54%) women overall; not reported by intervention group **Inclusion criteria:** ACG **Exclusion criteria:** not specified **Equivalence of baseline characteristics:** yes
Interventions	**Intervention 1:** trabeculectomy + AMT **Intervention 2:** trabeculectomy **Length of follow-up:** Planned: not reported Actual: 6 months
Outcomes	Primary and secondary outcomes not distinguished **Outcomes, as reported:** filtering bleb, surgical success, postoperative IOP, visual acuity, and complications **Intervals at which outcomes assessed:** 1, 3, and 6 months after surgery
Notes	**Publication type:** published article **Funding sources:** not reported **Disclosures of interest:** not reported **Trial registry:** not registered **Study period:** not reported **Subgroup analyses:** none reported **Publication language:** Chinese Authors contacted in regards to number with missing data at different follow-up time points, but no response received

Risk of bias

Bias	Authors' judgement	Support for judgement

Zhang 2009 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Random sequence generation was not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported
Masking of participants and personnel (performance bias)	Unclear risk	Masking of participants and personnel was not reported
Masking of outcome assessment (detection bias)	High risk	It is not possible to mask outcome assessors, as devices can be seen during eye examination
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The number of participants with missing or incomplete outcome assessment was not reported
Selective reporting (reporting bias)	Low risk	Protocol was not available. All defined outcomes were reported
Other bias	Unclear risk	Did not report source of funding or conflict of interest. This article provided nothing on study design; we contacted the authors but did not receive a response

Zheng 2005

Methods	**Study design:** parallel-group randomized controlled trial (20 participants both eyes included) **Number randomized:** 48 eyes of 28 participants total; 24 eyes in each group **Exclusions after randomization:** not reported **Losses to follow-up:** not reported **Unit of analysis:** eye **Number analyzed:** not reported **How were missing data handled?:** not reported **Power calculation:** not reported
Participants	**Country:** China **Age:** not reported **Gender:** not reported **Inclusion criteria:** not reported; all participants were diagnosed primary angle-closure glaucoma or primary open-angle glaucoma **Exclusion criteria:** not specified **Equivalence of baseline characteristics:** yes
Interventions	**Intervention 1:** trabeculectomy + AMT **Intervention 2:** trabeculectomy + MMC **Length of follow-up:**

Zheng 2005 *(Continued)*

	Planned: not reported Actual: 12 months
Outcomes	Primary and secondary outcomes not distinguished **Outcomes, as reported:** filtering bleb, surgical success, IOP, visual acuity, and complications **Intervals at which outcomes assessed:** 1 day, 1 week, and 1, 3, and 6 months
Notes	**Publication type:** published article **Funding sources:** not reported **Disclosures of interest:** not reported **Trial registry:** not registered **Study period:** not reported **Subgroup analyses:** none reported **Publication language:** Chinese Authors contacted in regards to number with missing data at different follow-up time points, but no response received

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random sequence generation was not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported
Masking of participants and personnel (performance bias)	Unclear risk	Masking of participants and personnel was not reported
Masking of outcome assessment (detection bias)	High risk	Not reported. Although it is not possible to mask outcome assessors, devices can be easily seen during examination of the eye
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The number of participants with missing or incomplete outcome assessment was not reported
Selective reporting (reporting bias)	High risk	Protocol was not available. Surgical success reported in the Results section was not mentioned in the Methods section
Other bias	Unclear risk	Did not report source of funding or conflict of interest. This article provided nothing on study design; we contacted the authors but did not receive a response

5-FU: 5-fluorouracil
ACG: angle-closure glaucoma
BCVA: best-corrected visual acuity
AMT: amniotic membrane
E-PTFE: expanded polytetrafluoroethylene
IOP: intraocular pressure

MMC: mitomycin C
OAG: open-angle glaucoma
PACG: primary angle-closure glaucoma
PEXG: pseudoexfoliation glaucoma
POAG: primary open-angle glaucoma
VA: visual acuity

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

Study	Reason for exclusion
Cao 2004	This trial was published in Chinese and identified from a meta-analysis published in Chinese. The methodological quality was very low (randomization method not specified, lost to follow-up not specified, no outcome data at specific time points clearly reported). We tried to contact the study investigator, but were unsuccessful in getting a response. We excluded the study as it was unclear whether the study was a RCT
Dahan 2011	This trial evaluated augmented trabeculectomy with T-flux, but there was no comparison group
Dai 2011	This RCT compared standard trabeculectomy versus trabeculectomy + MMC; no device was included
Gao 2002	This trial was published in Chinese. The methodological quality was very low (randomization method not specified, lost to follow-up not specified, no outcome data in the scope of this review reported). We tried to contact the study investigator, but were unsuccessful in getting a response. We excluded the study as it was unclear whether the study was a RCT
Ha 2008	The study included participants from 12 to 74 years of age and did not separately report outcomes for adult participants
Jin 2006	This trial was published in Chinese and identified from a meta-analysis published in Chinese. The methodological quality was very low (randomization method not specified, lost to follow-up not specified, no outcome data at specific time points clearly reported). We tried to contact the study investigator, but were unsuccessful in getting a response. We excluded the study as it was unclear whether the study was a RCT
Lau 2008	This study was reported as an abstract only and we were unable to identify a corresponding full-text publication. The study did not specify whether it used a randomized method to allocate glaucoma patients into Ex-PRESS or standard trabeculectomy groups. We contacted the author but did not receive any response. We excluded the study as it was unclear whether the study was a RCT
Li 2003	This trial was published in Chinese and identified from a meta-analysis published in Chinese. The methodological quality was very low (randomization method not specified, lost to follow-up not specified, no outcome data at specific time points clearly reported). We tried to contact the study investigator, but were unsuccessful in getting a response. We excluded the study as it was unclear whether the study was a RCT
Li 2008	This trial was published in Chinese and identified from a meta-analysis published in Chinese. The methodological quality was very low (randomization method not specified, lost to follow-up not specified). In addition, the study authors did not report outcomes by the 2 intervention groups, but according to different types of glaucoma; thus, the results would not contribute to treatment effects even if randomization was employed correctly. We excluded the study as it was unclear whether the study was a RCT
Liu 2003	The study included participants from 12 to 75 years of age and did not separately report outcomes for adult participants

Study	Reason for exclusion
Liu 2004	This study compared amniotic membrane and trabeculectomy, but was not described as randomized. We tried to contact the study investigator, but were unsuccessful in getting a response. We excluded the study as it was unclear whether the study was a RCT
Mahdy 2010	This study included pediatric participants 1 to 13 years of age
NCT00472810	Only available as a record in clinicaltrials.gov and there is no indication that participants were enrolled into the study
NCT00597181	This trial was identified from ClinicalTrials.gov and has been terminated. We contacted the trial investigators for reasons for termination and preliminary data if applicable. The investigator responded that this study was funded by the company who developed the Ex-PRESS shunt and had introduced it to the US market. However, the study had to be terminated because soon after beginning enrolment, the company elected to stop funding the study. The study investigators provided us with preliminary data for 15 participants, but lacked data for numbers of eyes allocated to each group (Ex-PRESS and standard trabeculectomy), so we were unable to analyze the data. In addition, the study only followed participants for 2 months, which does not satisfy our primary and secondary outcomes of interest
Sugiyama 2011	This non-randomized study compared Ex-PRESS and trabeculectomy. We contacted the study investigator regarding assignment to treatment groups and found that patients themselves selected the procedures performed
Wang 2010	This trial was published in Chinese. The methodological quality was very low (randomization method not specified, lost to follow-up not specified, no outcome data in the scope of this review reported). We tried to contact the study investigator, but were unsuccessful in getting a response. We excluded the study as it was unclear whether the study was a RCT
Zhang 2008	This trial was published in Chinese. The methodological quality was very low (randomization method not specified, lost to follow-up not specified, no outcome data in the scope of this review reported). We tried to contact the study investigator, but were unsuccessful in getting a response. We excluded the study as it was unclear whether the study was a RCT

IOP: intraocular pressure
MMC: mitomycin C
RCT: randomized controlled trial

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

JPRN-UMIN000008391

Trial name or title	Comparison between Ex-PRESS shunt surgery and trabeculectomy for refractory glaucoma
Methods	**Study design:** "interventional, randomized, parallel, open label clinical trial" **Number randomized:** 40 participants total (number of eyes unknown); not reported by intervention group **Unit of analysis:** not reported **Power calculation:** not reported
Participants	**Country:** Japan **Age:** the study required participants to be 20 years and older **Gender (percent):** both genders are eligible

JPRN-UMIN000008391 *(Continued)*

	Inclusion Criteria: "Patients with exfoliation glaucoma or neovascular glaucoma who require intraocular pressure reduction by glaucoma surgery." **Exclusion criteria:** "Patients who does not agree with the informed consent."
Interventions	**Intervention 1:** Ex-PRESS **Intervention 2:** trabeculectomy **Length of follow-up:** planned: not reported
Outcomes	**Primary outcome, as defined in study reports:** IOP and adverse events **Secondary outcomes, as defined in study reports:** not reported **Adverse events reported:** not reported **Intervals at which outcomes assessed:** not reported
Starting date	1 July 2012
Contact information	Masaki Tanito: tanito-oph@umin.ac.jp Enya 89-1, Izumo Japan Shimane University Faculty of Medicine
Notes	**Funding sources:** not reported **Last updated:** 3 June 2014 This study is currently recruiting participants.

JPRN-UMIN000008981

Trial name or title	Prospective comparative study of the Ex-PRESS mini glaucoma shunt with standard trabeculectomy.
Methods	**Study design:** "interventional, randomized, parallel, open label clinical trial" **Number randomized:** 200 participants (number of eyes not reported) total; not reported by intervention group **Unit of analysis:** not reported **Power calculation:** not reported
Participants	**Country:** Japan **Inclusion criteria:** open-angle glaucoma; participants to be 20 years and older **Exclusion Criteria:** angle-closure glaucoma; uveitis
Interventions	**Intervention 1:** trabeculectomy + Ex-PRESS mini shunt implantation **Intervention 2:** trabeculectomy **Length of follow-up:** planned: not reported
Outcomes	**Primary outcome, as defined in study reports:** IOP reduction **Secondary outcomes, as defined in study reports:** not reported **Adverse events reported:** not reported

JPRN-UMIN000008981 *(Continued)*

	Intervals at which outcomes assessed: not reported
Starting date	1 October 2012
Contact information	Hideki Mochizuki: mochizuki-h@hiroshima-u.ac.jp 1-2-3 Kasumi Minamiku Hiroshima, Japan Hiroshima University Dept. of Ophthalmology
Notes	**Funding source:** self funding **Last updated:** 3 June 2014 This study is currently recruiting participants.

NCT00449098

Trial name or title	Ologen (OculusGen)-Glaucoma MMC control trial in India
Methods	**Study design:** "interventional, randomized, parallel, open label clinical trial" **Number randomized:** 40 participants (number of eyes not reported) total; not reported by intervention group **Unit of analysis:** not reported **Power calculation:** not reported
Participants	**Country:** India **Inclusion Criteria:** • Age 18 years or over. • Uncontrolled glaucoma, with failed medical and laser treatment, requiring trabeculectomy • Participant able and willing to cooperate with investigation plan • Participant able and willing to complete postoperative follow-up requirements • Participant willing to sign informed consent form **Exclusion Criteria:** • Known allergic reaction to mitomycin-C or porcine collagen • Participant is on warfarin and discontinuation is not recommended • Normal tension glaucoma • Participation in an investigational study during the 30 days preceding trabeculectomy • Ocular infection within 14 days prior to trabeculectomy • Pregnant or breast-feeding women
Interventions	**Intervention 1:** trabeculectomy + OculusGen Biodegradable Collagen Matrix Implant **Intervention 2:** trabeculectomy + MMC **Length of follow-up:** planned: 180 days
Outcomes	**Primary outcome, as defined in study reports:** reduction of IOP at 180 days **Secondary outcomes, as defined in study reports:** incidence of complications and adverse events at 180 days **Adverse events reported:** this was planned

NCT00449098 *(Continued)*

	Intervals at which outcomes assessed: "there will be 7 post-operative and follow-up visits within 6 months of surgery: postoperative days 1, 7, 14, 30, 60, 90 and 180"
Starting date	January 2007
Contact information	Rajul S Parikh, MD rajulparikh@lvpei.org L. V. Prasad Eye Institute, India
Notes	**Funding source:** not reported **Last updated:** October 6, 2011 This study is currently recruiting participants.

NCT00524758

Trial name or title	Oculusgen (Ologen) Glaucoma MMC control in Estonia
Methods	**Study design:** "interventional, randomized, parallel, open label clinical trial" **Number randomized:** 20 participants (number of eyes not reported) total; not reported by intervention group **Unit of analysis:** not reported **Power calculation:** not reported
Participants	**Country:** Estonia **Inclusion criteria:** "maximum anti glaucoma medication failed" **Exclusion Criteria:** "age less than 18, pregnant women, hemodialysis patient"
Interventions	**Intervention 1:** trabeculectomy + Ologen **Intervention 2:** trabeculectomy + MMC **Length of follow-up:** planned: 180 days
Outcomes	**Primary outcome, as defined in study reports:** IOP < 21 mm Hg without anti-glaucoma medication at 180 days **Secondary outcomes, as defined in study reports:** IOP < 21 mm Hg or IOP drops more than 30% with anti-glaucoma medication at 180 days **Adverse events reported:** not reported **Intervals at which outcomes assessed:** not reported
Starting date	July 2007
Contact information	Kuldar Kaljurand, MD +372 737 6189 kristel.mikkor@ut.ee
Notes	**Funding source:** not reported **Last updated:** October 24, 2011 This study is currently recruiting participants.

NCT01440751

Trial name or title	Comparative study of the safety and effectiveness of Ologen Collagen Matrix versus mitomycin-C in glaucoma filtering surgery
Methods	**Study design:** "interventional, randomized, parallel, open label clinical trial", multi-center trial **Number randomized:** 128 participants (number of eyes not reported) total; not reported by intervention group **Unit of analysis:** not reported **Power calculation:** not reported
Participants	**Country:** India **Inclusion Criteria:** • Age > 30 years (inclusive) • Uncontrolled treated glaucoma requiring trabeculectomy • Participant must be able and willing to cooperate with investigation plan • Participant must be able and willing to complete postoperative follow-up requirements • Participant must be willing to sign informed consent form **Exclusion Criteria:** • Known allergic reaction to MMC or porcine collagen • Neovascular, uveitic, aphakic glaucoma, previous incisional glaucoma surgery • Prior cataract, unless clear corneal incision • Previous conjunctival or strabismus surgery • Participation in an investigational study during 30 days prior to trabeculectomy • Ocular infection within 14 days prior to trabeculectomy • Pregnant or breast-feeding women
Interventions	**Intervention 1:** Ologen Collagen Matrix in trabeculectomy **Intervention 2:** MMC in trabeculectomy **Length of follow-up:** planned: 24 months
Outcomes	**Primary outcome, as defined in study reports:** "Intraocular pressure (IOP) reduction at postoperative up to 24 months; 'Complete success' is considered for IOP less than 21 mm Hg (inclusive) with no glaucoma medications and with more than 20% reduction (inclusive) from baseline IOP. Definition of success rate is calculated in percentage by the number of complete success patients over the total sample size. 'Qualified success' that meets the postoperative IOP requirements with postoperative glaucoma medications and 'Failure' of meeting the IOP requirements are the other efficacy parameters. In the specified time frame, patients will also visit for record at day 1, 7, 14, 30, 90, 180 days, 12, 18, and 24 months." **Secondary outcomes, as defined in study reports:** "Postoperative complications and appearances at postoperative up to 24 months. Inspections of hyphema, severe anterior chamber reaction, hypotony, superchoroidal hemorrhage, flat anterior chamber, endophthalmitis, choroidal detachment, wound or bleb leak. Visual acuity, bleb appearance, and anterior chamber inflammation." **Adverse events reported:** this was planned **Intervals at which outcomes assessed:** day 1, 7, 14, 30, 90, 180 days, 12, 18, and 24 months
Starting date	February 2010

NCT01440751 *(Continued)*

Contact information	Robert Ritch, MD 212-673-5140 ritchmd@earthlink.net
Notes	**Funding sources:** not reported **Last updated:** December 24, 2013 This study is ongoing, but not recruiting participants.

IOP: intraocular pressure
MMC: mitomycin C

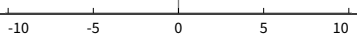
DATA AND ANALYSES

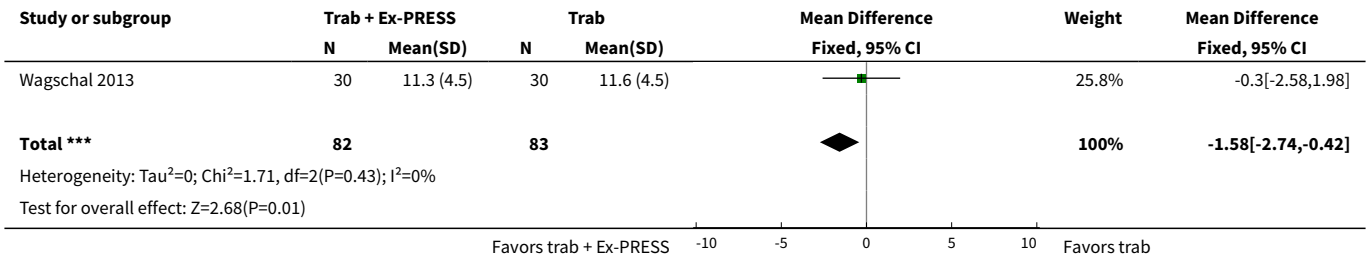
Comparison 1. Trabeculectomy (Trab) + Ex-PRESS versus Trabeculectomy (Trab)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Postoperative IOP at one year	3	165	Mean Difference (IV, Fixed, 95% CI)	-1.58 [-2.74, -0.42]
2 Postoperative IOP at six months	3	205	Mean Difference (IV, Fixed, 95% CI)	0.18 [-0.90, 1.26]
3 Postoperative IOP at two years	3	212	Mean Difference (IV, Fixed, 95% CI)	-1.45 [-2.52, -0.37]
4 Postoperative logMAR BCVA at one year	2	90	Mean Difference (IV, Fixed, 95% CI)	-0.15 [-0.40, 0.10]
5 Complications	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Hypotony	2	94	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.63, 1.33]
5.2 Shallow/flat anterior chamber	4	294	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.40, 1.32]
5.3 Bleb leakage	4	294	Risk Ratio (M-H, Fixed, 95% CI)	1.26 [0.50, 3.20]
5.4 Hyphema	4	294	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.12, 0.94]
5.5 Cataract surgery	3	264	Risk Ratio (M-H, Fixed, 95% CI)	0.32 [0.14, 0.74]

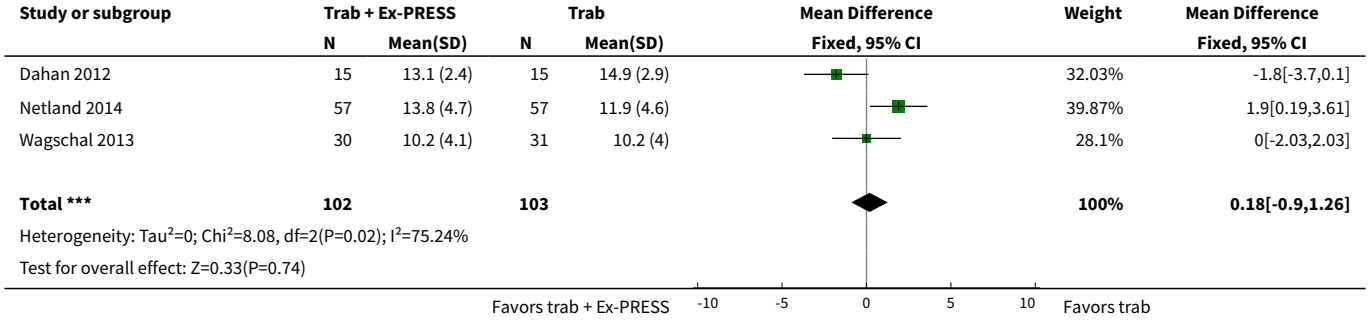
Analysis 1.1. Comparison 1 Trabeculectomy (Trab) + Ex-PRESS versus Trabeculectomy (Trab), Outcome 1 Postoperative IOP at one year.

Study or subgroup	Trab + Ex-PRESS N	Trab + Ex-PRESS Mean(SD)	Trab N	Trab Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Dahan 2012	15	14.1 (2.2)	15	16.4 (4.2)		23.24%	-2.3[-4.7,0.1]
De Jong 2009	37	12 (2.7)	38	13.9 (4.3)		50.95%	-1.9[-3.52,-0.28]

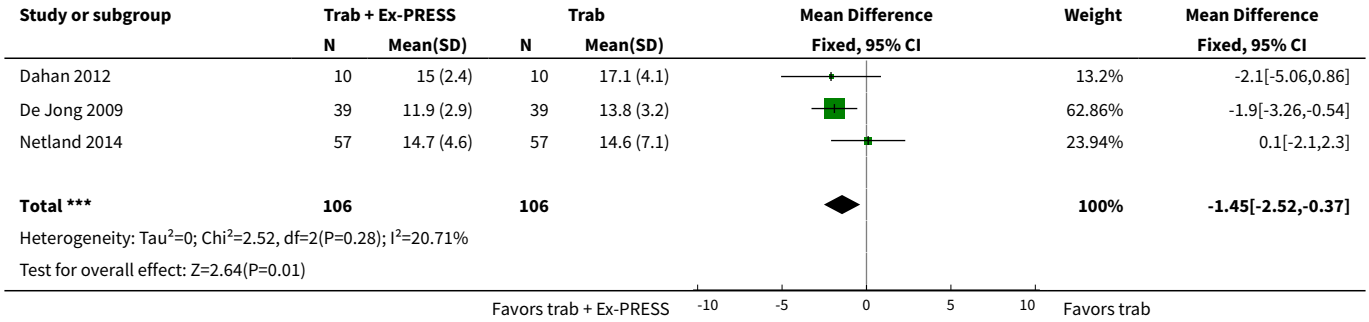




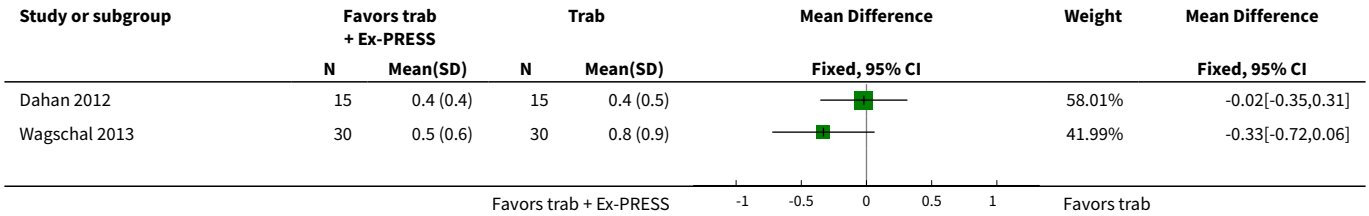
Analysis 1.2. Comparison 1 Trabeculectomy (Trab) + Ex-PRESS versus Trabeculectomy (Trab), Outcome 2 Postoperative IOP at six months.

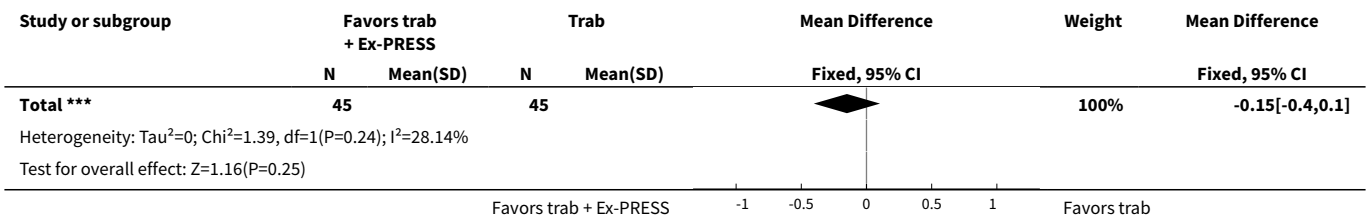


Analysis 1.3. Comparison 1 Trabeculectomy (Trab) + Ex-PRESS versus Trabeculectomy (Trab), Outcome 3 Postoperative IOP at two years.

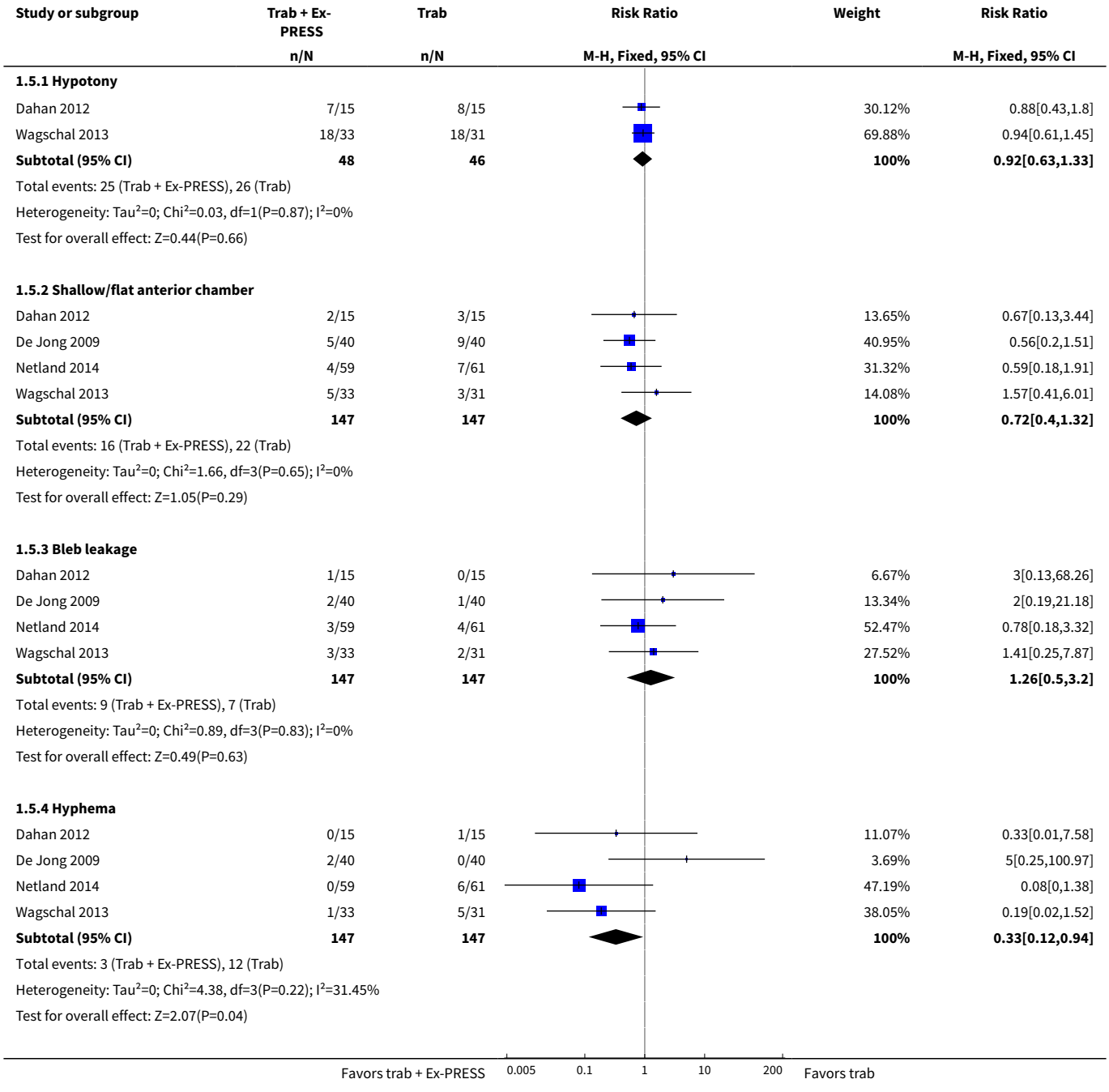


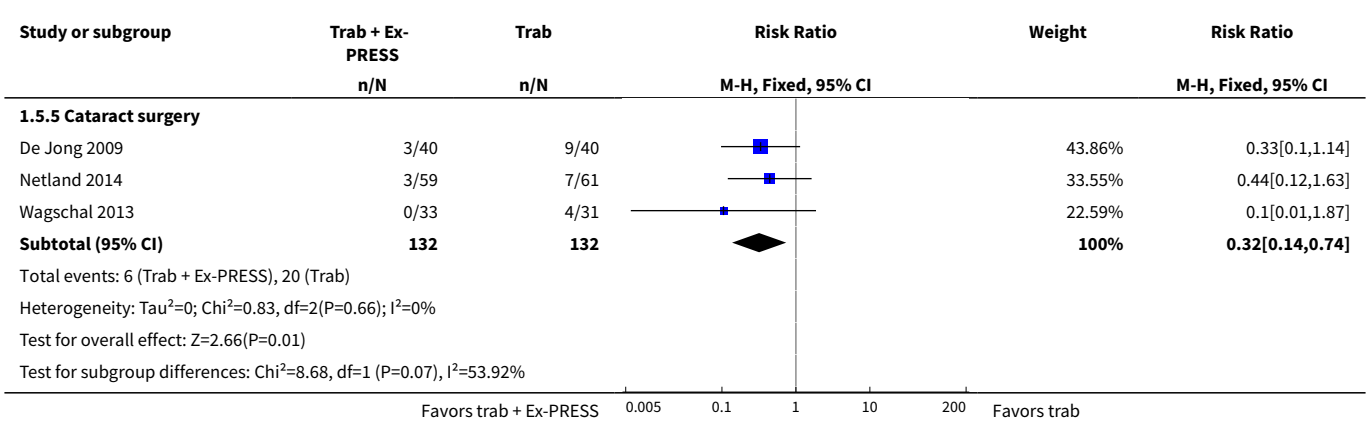
Analysis 1.4. Comparison 1 Trabeculectomy (Trab) + Ex-PRESS versus Trabeculectomy (Trab), Outcome 4 Postoperative logMAR BCVA at one year.





Analysis 1.5. Comparison 1 Trabeculectomy (Trab) + Ex-PRESS versus Trabeculectomy (Trab), Outcome 5 Complications.





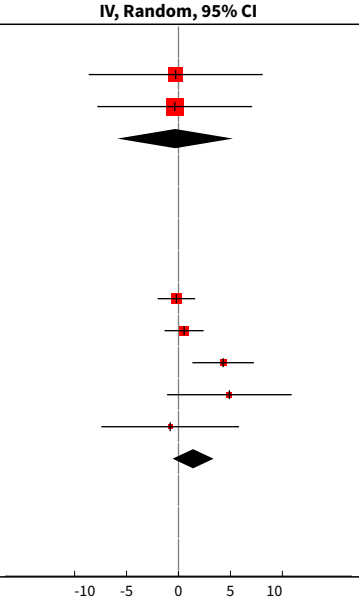
Comparison 2. Trabeculectomy (Trab) + Ologen versus Trabeculectomy (Trab)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 IOP at one year	5		Mean Difference (Random, 95% CI)	Subtotals only
1.1 Mean change of IOP from baseline to one year	2	44	Mean Difference (Random, 95% CI)	-0.32 [-5.88, 5.24]
1.2 Postoperative IOP at one year	5	177	Mean Difference (Random, 95% CI)	1.40 [-0.57, 3.38]
2 Postoperative IOP at day one	5	162	Mean Difference (IV, Random, 95% CI)	0.51 [-1.95, 2.97]
3 Postoperative IOP at six months	7		Mean Difference (IV, Random, 95% CI)	Subtotals only
3.1 Change of IOP from baseline to six months	2	46	Mean Difference (IV, Random, 95% CI)	-1.24 [-6.23, 3.76]
3.2 Postoperative IOP at six months	5	236	Mean Difference (IV, Random, 95% CI)	0.43 [-0.97, 1.84]
4 Postoperative IOP at two years	2	55	Mean Difference (IV, Fixed, 95% CI)	0.20 [-1.29, 1.69]
5 Complications	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 Hypotony	6	233	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.47, 1.19]
5.2 Surgical revision within 3 months	4	150	Risk Ratio (M-H, Random, 95% CI)	1.70 [0.38, 7.63]
5.3 Blebitis or endophthalmitis	3	164	Risk Ratio (M-H, Random, 95% CI)	1.57 [0.25, 9.70]
5.4 Bleb leakage	4	129	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.33, 2.20]
5.5 Hyphema	6	229	Risk Ratio (M-H, Random, 95% CI)	1.46 [0.51, 4.19]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.6 Choroidal detachment	4	129	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.33, 2.09]
5.7 Shallow anterior chamber	5	213	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.32, 1.93]
5.8 Anterior chamber reaction	2	99	Risk Ratio (M-H, Random, 95% CI)	1.21 [0.56, 2.60]
5.9 Positive Seidel test	3	164	Risk Ratio (M-H, Random, 95% CI)	1.93 [0.32, 11.54]
5.10 Tenon's cysts	3	124	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.21, 3.66]

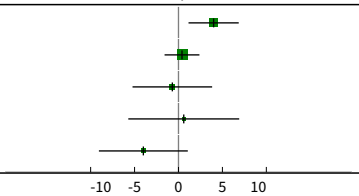
Analysis 2.1. Comparison 2 Trabeculectomy (Trab) + Ologen versus Trabeculectomy (Trab), Outcome 1 IOP at one year.

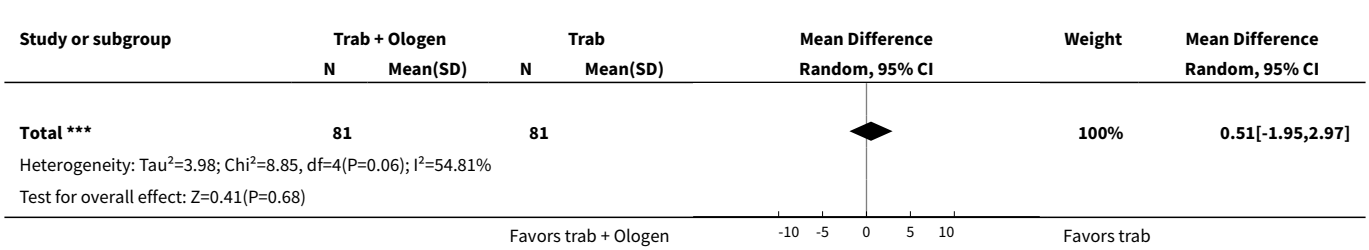
Study or subgroup	Trab + Ologen N	Trab N	Mean Difference (SE)	Mean Difference IV, Random, 95% CI	Weight	Mean Difference IV, Random, 95% CI
2.1.1 Mean change of IOP from baseline to one year						
Rosentreter 2010	10	9	-0.3 (4.27)		44.2%	-0.27[-8.64,8.1]
Rosentreter 2014	11	14	-0.4 (3.8)		55.8%	-0.36[-7.81,7.09]
Subtotal (95% CI)					**100%**	**-0.32[-5.88,5.24]**
Heterogeneity: Tau^2=0; Chi^2=0, df=1(P=0.99); I^2=0%						
Test for overall effect: Z=0.11(P=0.91)						
2.1.2 Postoperative IOP at one year						
Cillino 2011	20	20	-0.2 (0.92)		31.48%	-0.2[-2,1.6]
Marey 2013	30	30	0.5 (0.96)		30.76%	0.54[-1.34,2.42]
Rosentreter 2010	10	9	4.3 (1.51)		21.78%	4.3[1.34,7.26]
Rosentreter 2014	11	26	4.9 (3.06)		8.63%	4.9[-1.1,10.9]
Senthil 2013	11	10	-0.8 (3.38)		7.34%	-0.8[-7.42,5.82]
Subtotal (95% CI)					**100%**	**1.4[-0.57,3.38]**
Heterogeneity: Tau^2=2.37; Chi^2=8.6, df=4(P=0.07); I^2=53.49%						
Test for overall effect: Z=1.39(P=0.16)						
Test for subgroup differences: Chi^2=0.33, df=1 (P=0.57), I^2=0%						



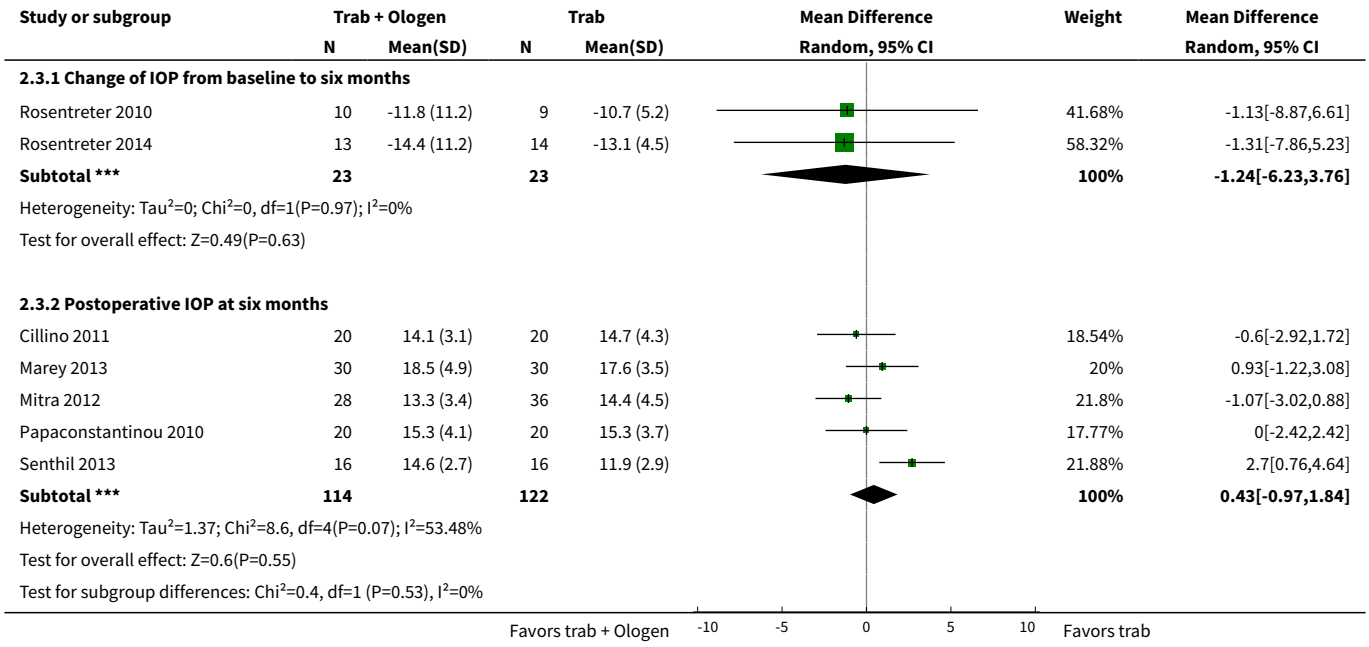
Analysis 2.2. Comparison 2 Trabeculectomy (Trab) + Ologen versus Trabeculectomy (Trab), Outcome 2 Postoperative IOP at day one.

Study or subgroup	Trab + Ologen N	Trab + Ologen Mean(SD)	Trab N	Trab Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Cillino 2011	20	9.2 (5.5)	20	5.2 (3.5)		25.82%	4[1.14,6.86]
Papaconstantinou 2010	20	8.4 (3.1)	20	8 (3.3)		31.5%	0.4[-1.58,2.38]
Rosentreter 2010	10	10.1 (5.6)	10	10.8 (4.7)		16.9%	-0.7[-5.23,3.83]
Rosentreter 2014	15	15 (8.2)	15	14.4 (9.4)		10.98%	0.6[-5.71,6.91]
Senthil 2013	16	10.1 (7.5)	16	14.1 (7.1)		14.8%	-4[-9.06,1.06]

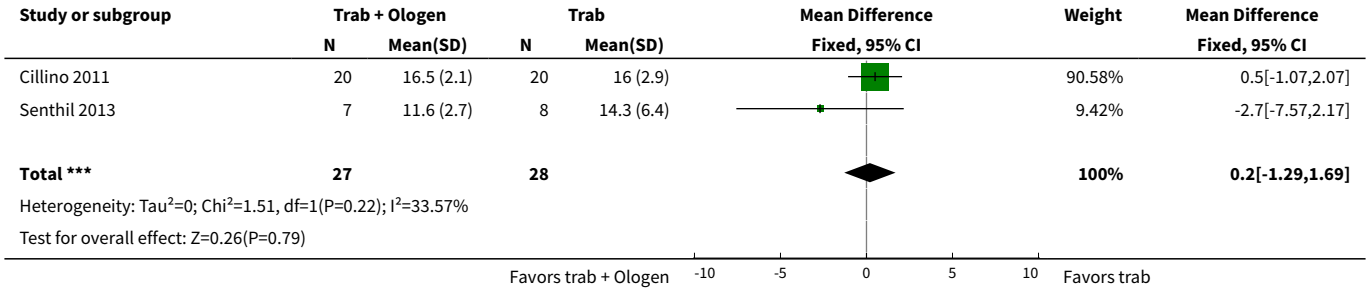




Analysis 2.3. Comparison 2 Trabeculectomy (Trab) + Ologen versus Trabeculectomy (Trab), Outcome 3 Postoperative IOP at six months.

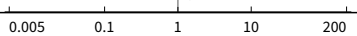


Analysis 2.4. Comparison 2 Trabeculectomy (Trab) + Ologen versus Trabeculectomy (Trab), Outcome 4 Postoperative IOP at two years.

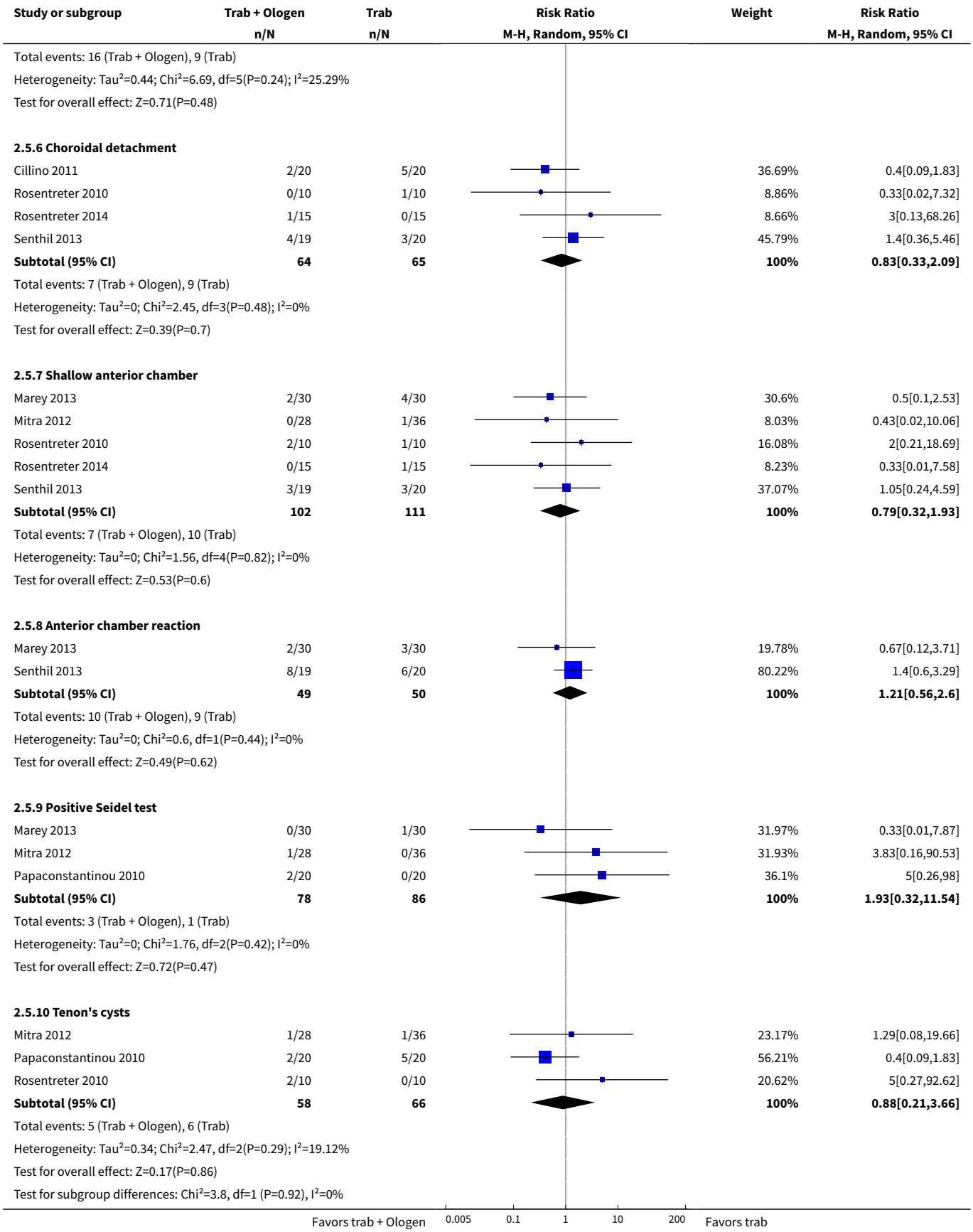


Analysis 2.5. Comparison 2 Trabeculectomy (Trab) + Ologen versus Trabeculectomy (Trab), Outcome 5 Complications.

Study or subgroup	Trab + Ologen n/N	Trab n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.5.1 Hypotony					
Cillino 2011	4/20	8/20		20.1%	0.5[0.18,1.4]
Mitra 2012	1/28	1/36		2.85%	1.29[0.08,19.66]
Papaconstantinou 2010	1/20	1/20		2.91%	1[0.07,14.9]
Rosentreter 2010	6/10	6/10		41.46%	1[0.49,2.05]
Rosentreter 2014	4/15	8/15		22.87%	0.5[0.19,1.31]
Senthil 2013	3/19	3/20		9.8%	1.05[0.24,4.59]
Subtotal (95% CI)	**112**	**121**		**100%**	**0.75[0.47,1.19]**
Total events: 19 (Trab + Ologen), 27 (Trab)					
Heterogeneity: Tau^2=0; Chi^2=2.34, df=5(P=0.8); I^2=0%					
Test for overall effect: Z=1.22(P=0.22)					
2.5.2 Surgical revision within 3 months					
Marey 2013	0/30	1/30		19.39%	0.33[0.01,7.87]
Papaconstantinou 2010	3/20	0/20		22.43%	7[0.38,127.32]
Rosentreter 2010	0/10	1/10		20.17%	0.33[0.02,7.32]
Rosentreter 2014	4/15	1/15		38.01%	4[0.5,31.74]
Subtotal (95% CI)	**75**	**75**		**100%**	**1.7[0.38,7.63]**
Total events: 7 (Trab + Ologen), 3 (Trab)					
Heterogeneity: Tau^2=0.43; Chi^2=3.65, df=3(P=0.3); I^2=17.91%					
Test for overall effect: Z=0.69(P=0.49)					
2.5.3 Blebitis or endophthalmitis					
Marey 2013	0/30	1/30		33.21%	0.33[0.01,7.87]
Mitra 2012	1/28	0/36		33.18%	3.83[0.16,90.53]
Papaconstantinou 2010	1/20	0/20		33.61%	3[0.13,69.52]
Subtotal (95% CI)	**78**	**86**		**100%**	**1.57[0.25,9.7]**
Total events: 2 (Trab + Ologen), 1 (Trab)					
Heterogeneity: Tau^2=0; Chi^2=1.39, df=2(P=0.5); I^2=0%					
Test for overall effect: Z=0.48(P=0.63)					
2.5.4 Bleb leakage					
Cillino 2011	3/20	1/20		19.21%	3[0.34,26.45]
Rosentreter 2010	3/10	3/10		50.76%	1[0.26,3.81]
Rosentreter 2014	1/15	3/15		19.74%	0.33[0.04,2.85]
Senthil 2013	0/19	2/20		10.29%	0.21[0.01,4.11]
Subtotal (95% CI)	**64**	**65**		**100%**	**0.85[0.33,2.2]**
Total events: 7 (Trab + Ologen), 9 (Trab)					
Heterogeneity: Tau^2=0; Chi^2=2.94, df=3(P=0.4); I^2=0%					
Test for overall effect: Z=0.34(P=0.73)					
2.5.5 Hyphema					
Cillino 2011	1/20	1/20		12.35%	1[0.07,14.9]
Marey 2013	1/30	1/30		12.18%	1[0.07,15.26]
Papaconstantinou 2010	1/20	3/20		17.29%	0.33[0.04,2.94]
Rosentreter 2010	1/10	2/10		16.62%	0.5[0.05,4.67]
Rosentreter 2014	2/15	0/15		10.64%	5[0.26,96.13]
Senthil 2013	10/19	2/20		30.92%	5.26[1.32,20.97]
Subtotal (95% CI)	**114**	**115**		**100%**	**1.46[0.51,4.19]**



Favors trab + Ologen Favors trab



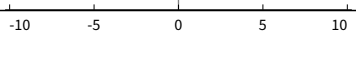
Comparison 3. Trabeculectomy (Trab) + AMT (amniotic membrane) versus Trabeculectomy (Trab)

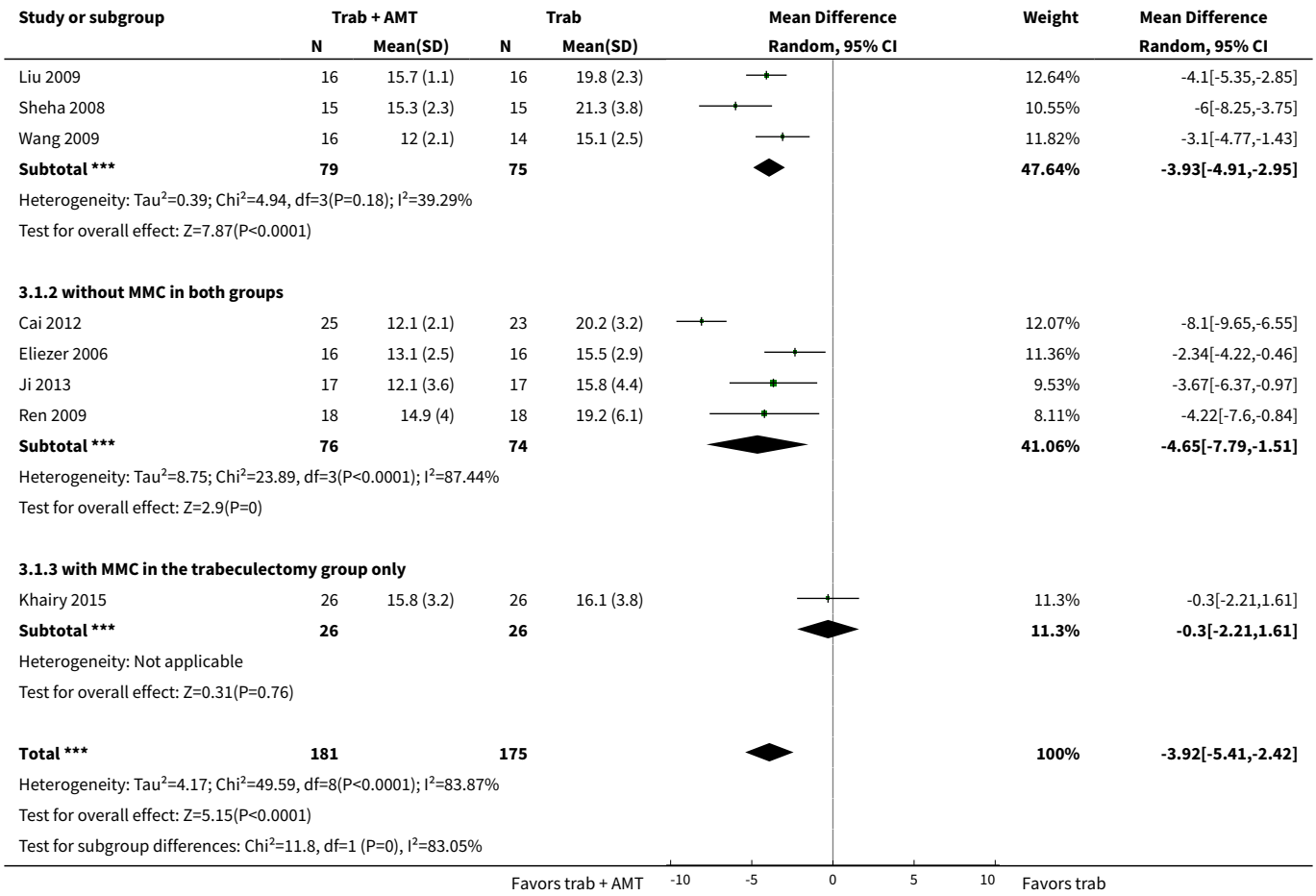
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Postoperative IOP at one year	9	356	Mean Difference (IV, Random, 95% CI)	-3.92 [-5.41, -2.42]
1.1 with MMC in both groups	4	154	Mean Difference (IV, Random, 95% CI)	-3.93 [-4.91, -2.95]
1.2 without MMC in both groups	4	150	Mean Difference (IV, Random, 95% CI)	-4.65 [-7.79, -1.51]
1.3 with MMC in the trabeculectomy group only	1	52	Mean Difference (IV, Random, 95% CI)	-0.30 [-2.21, 1.61]
2 Postoperative IOP at one day	8		Mean Difference (IV, Random, 95% CI)	Totals not selected
2.1 with MMC in both groups	2		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 without MMC in both groups	4		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2.3 with MMC in the trabeculectomy group only	2		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
3 Postoperative IOP at one week	13		Mean Difference (IV, Random, 95% CI)	Totals not selected
3.1 with MMC in both groups	4		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
3.2 without MMC in both groups	6		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
3.3 with MMC in the trabeculectomy group only	3		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
4 Postoperative IOP at one month	13	646	Mean Difference (IV, Random, 95% CI)	-1.05 [-1.96, -0.13]
4.1 with MMC in both groups	3	131	Mean Difference (IV, Random, 95% CI)	-1.06 [-1.84, -0.28]
4.2 without MMC in both groups	7	370	Mean Difference (IV, Random, 95% CI)	-1.78 [-3.65, 0.10]
4.3 with MMC in the trabeculectomy group only	3	145	Mean Difference (IV, Random, 95% CI)	0.44 [-1.21, 2.09]
5 Postoperative IOP at three months	11	551	Mean Difference (IV, Random, 95% CI)	-2.23 [-2.93, -1.53]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 with MMC in both groups	3	131	Mean Difference (IV, Random, 95% CI)	-2.64 [-3.50, -1.77]
5.2 without MMC in both groups	6	320	Mean Difference (IV, Random, 95% CI)	-2.48 [-3.89, -1.07]
5.3 with MMC in the trabeculectomy group only	2	100	Mean Difference (IV, Random, 95% CI)	-0.76 [-2.65, 1.14]
6 Postoperative IOP at six months	13	613	Mean Difference (IV, Random, 95% CI)	-2.50 [-3.34, -1.67]
6.1 with MMC in both groups	4	155	Mean Difference (IV, Random, 95% CI)	-2.91 [-3.87, -1.95]
6.2 without MMC in both groups	7	358	Mean Difference (IV, Random, 95% CI)	-3.00 [-4.52, -1.48]
6.3 with MMC in the trabeculectomy group only	2	100	Mean Difference (IV, Random, 95% CI)	0.14 [-1.27, 1.55]
7 Postoperative IOP at two years	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
7.1 with MMC in the trabeculectomy group only	1	52	Mean Difference (IV, Fixed, 95% CI)	-0.20 [-2.16, 1.76]
7.2 without MMC in both groups	1	34	Mean Difference (IV, Fixed, 95% CI)	-2.96 [-5.52, -0.40]
8 Complications	17		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
8.1 Hypotony	5	205	Risk Ratio (M-H, Random, 95% CI)	0.40 [0.17, 0.94]
8.2 Shallow anterior chamber	13	632	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.30, 0.73]
8.3 Hyphema	5	235	Risk Ratio (M-H, Random, 95% CI)	0.43 [0.14, 1.34]
8.4 Bleb leakage	2	98	Risk Ratio (M-H, Random, 95% CI)	0.28 [0.10, 0.79]
8.5 Encapsulated blebs	5	175	Risk Ratio (M-H, Random, 95% CI)	0.23 [0.08, 0.69]
8.6 Choroidal detachment	4	187	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.13, 1.71]

Analysis 3.1. Comparison 3 Trabeculectomy (Trab) + AMT (amniotic membrane) versus Trabeculectomy (Trab), Outcome 1 Postoperative IOP at one year.

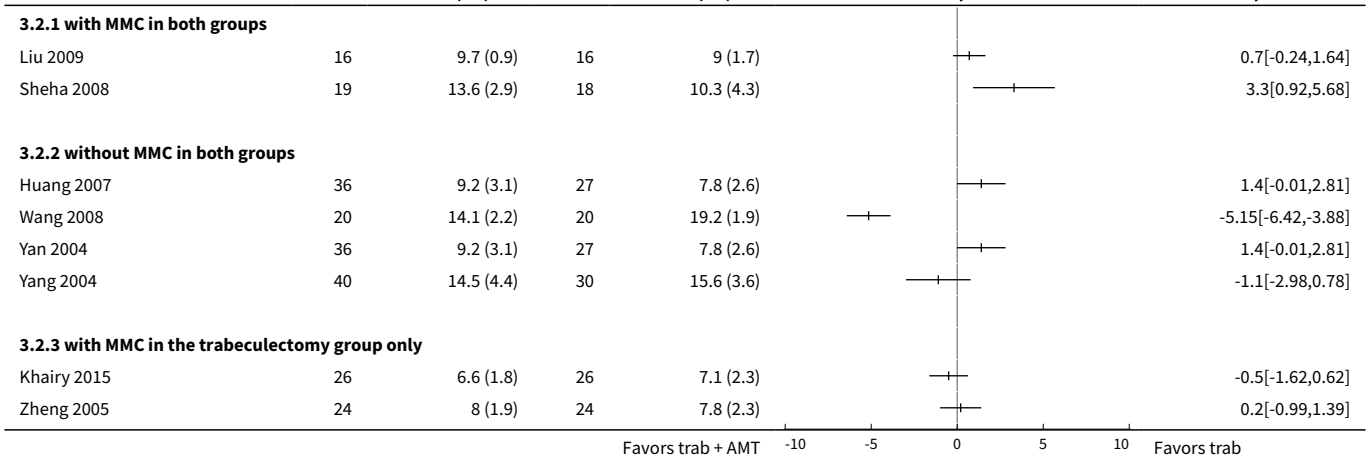
Study or subgroup	Trab + AMT N	Trab + AMT Mean(SD)	Trab N	Trab Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
3.1.1 with MMC in both groups							
Li 2010	32	12.3 (2.3)	30	15.7 (2.7)		12.63%	-3.4[-4.65,-2.15]





Study or subgroup	Trab + AMT N	Trab + AMT Mean(SD)	Trab N	Trab Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Liu 2009	16	15.7 (1.1)	16	19.8 (2.3)		12.64%	-4.1[-5.35,-2.85]
Sheha 2008	15	15.3 (2.3)	15	21.3 (3.8)		10.55%	-6[-8.25,-3.75]
Wang 2009	16	12 (2.1)	14	15.1 (2.5)		11.82%	-3.1[-4.77,-1.43]
Subtotal ***	**79**		**75**			**47.64%**	**-3.93[-4.91,-2.95]**
Heterogeneity: Tau²=0.39; Chi²=4.94, df=3(P=0.18); I²=39.29%							
Test for overall effect: Z=7.87(P<0.0001)							
3.1.2 without MMC in both groups							
Cai 2012	25	12.1 (2.1)	23	20.2 (3.2)		12.07%	-8.1[-9.65,-6.55]
Eliezer 2006	16	13.1 (2.5)	16	15.5 (2.9)		11.36%	-2.34[-4.22,-0.46]
Ji 2013	17	12.1 (3.6)	17	15.8 (4.4)		9.53%	-3.67[-6.37,-0.97]
Ren 2009	18	14.9 (4)	18	19.2 (6.1)		8.11%	-4.22[-7.6,-0.84]
Subtotal ***	**76**		**74**			**41.06%**	**-4.65[-7.79,-1.51]**
Heterogeneity: Tau²=8.75; Chi²=23.89, df=3(P<0.0001); I²=87.44%							
Test for overall effect: Z=2.9(P=0)							
3.1.3 with MMC in the trabeculectomy group only							
Khairy 2015	26	15.8 (3.2)	26	16.1 (3.8)		11.3%	-0.3[-2.21,1.61]
Subtotal ***	**26**		**26**			**11.3%**	**-0.3[-2.21,1.61]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.31(P=0.76)							
Total ***	**181**		**175**			**100%**	**-3.92[-5.41,-2.42]**
Heterogeneity: Tau²=4.17; Chi²=49.59, df=8(P<0.0001); I²=83.87%							
Test for overall effect: Z=5.15(P<0.0001)							
Test for subgroup differences: Chi²=11.8, df=1 (P=0), I²=83.05%							

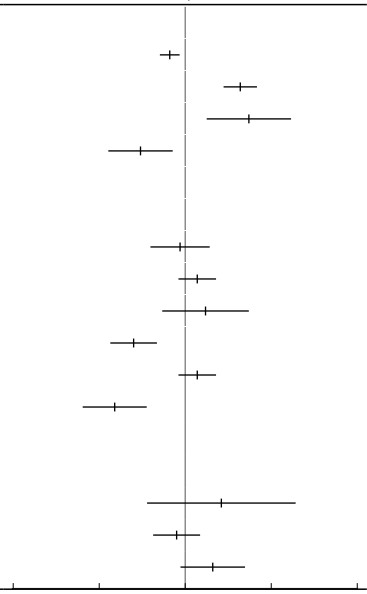
Analysis 3.2. Comparison 3 Trabeculectomy (Trab) + AMT (amniotic membrane) versus Trabeculectomy (Trab), Outcome 2 Postoperative IOP at one day.



Study or subgroup	Trab + AMT N	Trab + AMT Mean(SD)	Trab N	Trab Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
3.2.1 with MMC in both groups						
Liu 2009	16	9.7 (0.9)	16	9 (1.7)		0.7[-0.24,1.64]
Sheha 2008	19	13.6 (2.9)	18	10.3 (4.3)		3.3[0.92,5.68]
3.2.2 without MMC in both groups						
Huang 2007	36	9.2 (3.1)	27	7.8 (2.6)		1.4[-0.01,2.81]
Wang 2008	20	14.1 (2.2)	20	19.2 (1.9)		-5.15[-6.42,-3.88]
Yan 2004	36	9.2 (3.1)	27	7.8 (2.6)		1.4[-0.01,2.81]
Yang 2004	40	14.5 (4.4)	30	15.6 (3.6)		-1.1[-2.98,0.78]
3.2.3 with MMC in the trabeculectomy group only						
Khairy 2015	26	6.6 (1.8)	26	7.1 (2.3)		-0.5[-1.62,0.62]
Zheng 2005	24	8 (1.9)	24	7.8 (2.3)		0.2[-0.99,1.39]

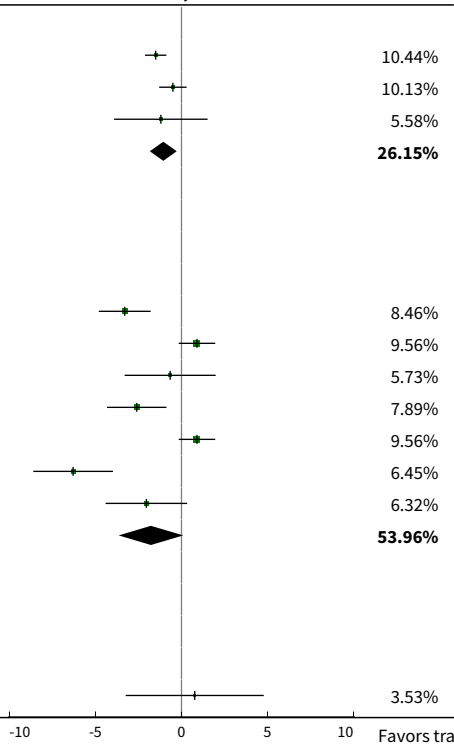
Analysis 3.3. Comparison 3 Trabeculectomy (Trab) + AMT (amniotic membrane) versus Trabeculectomy (Trab), Outcome 3 Postoperative IOP at one week.

Study or subgroup	Trab + AMT N	Trab + AMT Mean(SD)	Trab N	Trab Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
3.3.1 with MMC in both groups						
Li 2010	32	9.6 (1.1)	30	10.5 (1.2)		-0.9[-1.47,-0.33]
Liu 2009	16	16.9 (1.4)	16	13.7 (1.4)		3.2[2.23,4.17]
Sheha 2008	19	17.1 (3.7)	18	13.4 (3.9)		3.7[1.25,6.15]
Wang 2009	16	11.2 (2.5)	14	13.8 (2.7)		-2.6[-4.47,-0.73]
3.3.2 without MMC in both groups						
Cai 2012	25	8.9 (2.1)	23	9.2 (3.7)		-0.3[-2.02,1.42]
Huang 2007	36	11.2 (2.3)	27	10.5 (2.1)		0.7[-0.39,1.79]
Ji 2013	17	11.9 (4.2)	17	10.7 (3.3)		1.18[-1.34,3.7]
Wang 2008	20	12.8 (2.3)	20	15.8 (2)		-3[-4.35,-1.65]
Yan 2004	36	11.2 (2.3)	27	10.5 (2.1)		0.7[-0.39,1.79]
Yang 2004	40	12.6 (3.2)	30	16.7 (4.4)		-4.1[-5.96,-2.24]
3.3.3 with MMC in the trabeculectomy group only						
Cho 2013	24	15.4 (9.4)	23	13.3 (5.3)		2.1[-2.22,6.42]
Khairy 2015	26	10.7 (1.9)	26	11.2 (3)		-0.5[-1.86,0.86]
Zheng 2005	24	10.1 (2.6)	24	8.5 (3.9)		1.6[-0.28,3.48]

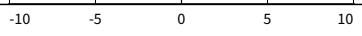


Analysis 3.4. Comparison 3 Trabeculectomy (Trab) + AMT (amniotic membrane) versus Trabeculectomy (Trab), Outcome 4 Postoperative IOP at one month.

Study or subgroup	Trab + AMT N	Trab + AMT Mean(SD)	Trab N	Trab Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
3.4.1 with MMC in both groups							
Li 2010	32	11.3 (1.3)	30	12.8 (1.2)		10.44%	-1.5[-2.12,-0.88]
Liu 2009	16	15.1 (1.2)	16	15.6 (1.1)		10.13%	-0.5[-1.3,0.3]
Sheha 2008	19	14.5 (4.7)	18	15.7 (3.7)		5.58%	-1.2[-3.92,1.52]
Subtotal ***	**67**		**64**			**26.15%**	**-1.06[-1.84,-0.28]**
Heterogeneity: Tau²=0.21; Chi²=3.76, df=2(P=0.15); I²=46.76%							
Test for overall effect: Z=2.66(P=0.01)							
3.4.2 without MMC in both groups							
Cai 2012	25	11.8 (2.5)	23	15.1 (2.8)		8.46%	-3.3[-4.81,-1.79]
Huang 2007	36	13.5 (2.4)	27	12.6 (1.9)		9.56%	0.9[-0.16,1.96]
Ji 2013	17	10.6 (4)	17	11.2 (3.9)		5.73%	-0.66[-3.31,1.99]
Wang 2008	20	15.5 (3)	20	18.1 (2.5)		7.89%	-2.6[-4.33,-0.87]
Yan 2004	36	13.5 (2.4)	27	12.6 (1.9)		9.56%	0.9[-0.16,1.96]
Yang 2004	40	11.6 (4.6)	30	17.9 (5.1)		6.45%	-6.3[-8.62,-3.98]
Zhang 2009	26	12 (4.1)	26	14.1 (4.6)		6.32%	-2.04[-4.41,0.33]
Subtotal ***	**200**		**170**			**53.96%**	**-1.78[-3.65,0.1]**
Heterogeneity: Tau²=5.52; Chi²=57.15, df=6(P<0.0001); I²=89.5%							
Test for overall effect: Z=1.85(P=0.06)							
3.4.3 with MMC in the trabeculectomy group only							
Cho 2013	23	16.6 (8.6)	22	15.9 (4.7)		3.53%	0.77[-3.24,4.78]



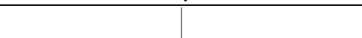
Study or subgroup	Trab + AMT N	Trab + AMT Mean(SD)	Trab N	Trab Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Khairy 2015	26	14.9 (1.4)	26	15.3 (1.7)		10.03%	-0.4[-1.25,0.45]
Zheng 2005	24	11.7 (3.6)	24	9.7 (4.7)		6.33%	2[-0.37,4.37]
Subtotal ***	**73**		**72**			**19.89%**	**0.44[-1.21,2.09]**
Heterogeneity: Tau²=1.03; Chi²=3.68, df=2(P=0.16); I²=45.69%							
Test for overall effect: Z=0.52(P=0.6)							
Total ***	**340**		**306**			**100%**	**-1.05[-1.96,-0.13]**
Heterogeneity: Tau²=1.99; Chi²=69.45, df=12(P<0.0001); I²=82.72%							
Test for overall effect: Z=2.24(P=0.03)							
Test for subgroup differences: Chi²=3.53, df=1 (P=0.17), I²=43.34%							



Favors trab + AMT — Favors trab

Analysis 3.5. Comparison 3 Trabeculectomy (Trab) + AMT (amniotic membrane) versus Trabeculectomy (Trab), Outcome 5 Postoperative IOP at three months.

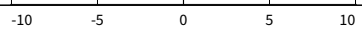
Study or subgroup	Trab + AMT N	Trab + AMT Mean(SD)	Trab N	Trab Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
3.5.1 with MMC in both groups							
Li 2010	32	11.6 (1.2)	30	13.6 (0.8)		17.02%	-2[-2.5,-1.5]
Liu 2009	16	13.3 (1.1)	16	16.3 (1.1)		15.3%	-3[-3.76,-2.24]
Sheha 2008	19	13 (2.3)	18	16.4 (2.6)		9.57%	-3.4[-4.98,-1.82]
Subtotal ***	**67**		**64**			**41.88%**	**-2.64[-3.5,-1.77]**
Heterogeneity: Tau²=0.38; Chi²=6.31, df=2(P=0.04); I²=68.3%							
Test for overall effect: Z=5.96(P<0.0001)							
3.5.2 without MMC in both groups							
Cho 2013	21	16.6 (5)	17	17 (3.7)		4.76%	-0.44[-3.22,2.34]
Huang 2007	36	14.7 (1.8)	27	16.8 (3.6)		10.2%	-2.1[-3.58,-0.62]
Ji 2013	17	11.2 (3.7)	17	12.1 (4.3)		5.01%	-0.93[-3.61,1.75]
Yan 2004	36	14.7 (1.8)	27	16.8 (3.6)		10.2%	-2.1[-3.58,-0.62]
Yang 2004	40	12.6 (7.4)	30	19.7 (6.1)		3.89%	-7.1[-10.27,-3.93]
Zhang 2009	26	14.2 (4.3)	26	17.5 (5.1)		5.36%	-3.31[-5.87,-0.75]
Subtotal ***	**176**		**144**			**39.43%**	**-2.48[-3.89,-1.07]**
Heterogeneity: Tau²=1.73; Chi²=12.29, df=5(P=0.03); I²=59.31%							
Test for overall effect: Z=3.45(P=0)							
3.5.3 with MMC in the trabeculectomy group only							
Khairy 2015	26	14.5 (2.3)	26	16 (1.9)		12.46%	-1.5[-2.65,-0.35]
Zheng 2005	24	14 (4.3)	24	13.5 (3.8)		6.23%	0.5[-1.8,2.8]
Subtotal ***	**50**		**50**			**18.69%**	**-0.76[-2.65,1.14]**
Heterogeneity: Tau²=1.14; Chi²=2.33, df=1(P=0.13); I²=57.14%							
Test for overall effect: Z=0.78(P=0.43)							
Total ***	**293**		**258**			**100%**	**-2.23[-2.93,-1.53]**
Heterogeneity: Tau²=0.69; Chi²=26.12, df=10(P=0); I²=61.72%							
Test for overall effect: Z=6.22(P<0.0001)							
Test for subgroup differences: Chi²=3.17, df=1 (P=0.21), I²=36.82%							



Favors trab + AMT — Favors trab

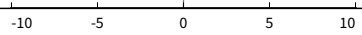
Analysis 3.6. Comparison 3 Trabeculectomy (Trab) + AMT (amniotic membrane) versus Trabeculectomy (Trab), Outcome 6 Postoperative IOP at six months.

Study or subgroup	Trab + AMT N	Trab + AMT Mean(SD)	Trab N	Trab Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
3.6.1 with MMC in both groups							
Li 2010	32	12 (1.3)	30	13.9 (1.1)		11.82%	-1.9[-2.5,-1.3]
Liu 2009	16	14.2 (1)	16	17.2 (1)		11.58%	-3[-3.69,-2.31]
Sheha 2008	16	14.4 (2.8)	15	18.7 (2.3)		7.96%	-4.3[-6.1,-2.5]
Wang 2009	16	12.2 (2.3)	14	15.6 (2.6)		8.06%	-3.4[-5.17,-1.63]
Subtotal ***	**80**		**75**			**39.43%**	**-2.91[-3.87,-1.95]**
Heterogeneity: Tau^2=0.61; Chi^2=10.68, df=3(P=0.01); I^2=71.9%							
Test for overall effect: Z=5.93(P<0.0001)							
3.6.2 without MMC in both groups							
Huang 2007	36	15.2 (1.7)	27	17.5 (3.9)		8.71%	-2.3[-3.87,-0.73]
Ji 2013	17	12.5 (3.5)	17	13.1 (3.8)		6.02%	-0.57[-3.04,1.9]
Ren 2009	18	14.1 (2.9)	18	17 (4.6)		5.91%	-2.92[-5.43,-0.41]
Wang 2008	20	17 (2.3)	20	18.9 (3.4)		8.06%	-1.95[-3.72,-0.18]
Yan 2004	36	15.2 (1.7)	27	17.5 (3.9)		8.71%	-2.3[-3.87,-0.73]
Yang 2004	40	13.6 (6.7)	30	23.5 (7.6)		4.06%	-9.9[-13.32,-6.48]
Zhang 2009	26	14.1 (4.6)	26	17.5 (5.3)		5.51%	-3.38[-6.06,-0.7]
Subtotal ***	**193**		**165**			**46.98%**	**-3[-4.52,-1.48]**
Heterogeneity: Tau^2=2.89; Chi^2=21.28, df=6(P=0); I^2=71.8%							
Test for overall effect: Z=3.86(P=0)							
3.6.3 with MMC in the trabeculectomy group only							
Khairy 2015	26	15.8 (2.6)	26	15.9 (3.3)		8.57%	-0.1[-1.71,1.51]
Zheng 2005	24	15 (5.5)	24	14.1 (4.7)		5.03%	0.9[-1.99,3.79]
Subtotal ***	**50**		**50**			**13.6%**	**0.14[-1.27,1.55]**
Heterogeneity: Tau^2=0; Chi^2=0.35, df=1(P=0.55); I^2=0%							
Test for overall effect: Z=0.19(P=0.85)							
Total ***	**323**		**290**			**100%**	**-2.5[-3.34,-1.67]**
Heterogeneity: Tau^2=1.45; Chi^2=45.38, df=12(P<0.0001); I^2=73.56%							
Test for overall effect: Z=5.86(P<0.0001)							
Test for subgroup differences: Chi^2=13.69, df=1 (P=0), I^2=85.39%							

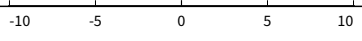


Analysis 3.7. Comparison 3 Trabeculectomy (Trab) + AMT (amniotic membrane) versus Trabeculectomy (Trab), Outcome 7 Postoperative IOP at two years.

Study or subgroup	Trab + AMT N	Trab + AMT Mean(SD)	Trab N	Trab Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
3.7.1 with MMC in the trabeculectomy group only							
Khairy 2015	26	15.7 (3.3)	26	15.9 (3.9)		100%	-0.2[-2.16,1.76]
Subtotal ***	**26**		**26**			**100%**	**-0.2[-2.16,1.76]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.2(P=0.84)							
3.7.2 without MMC in both groups							

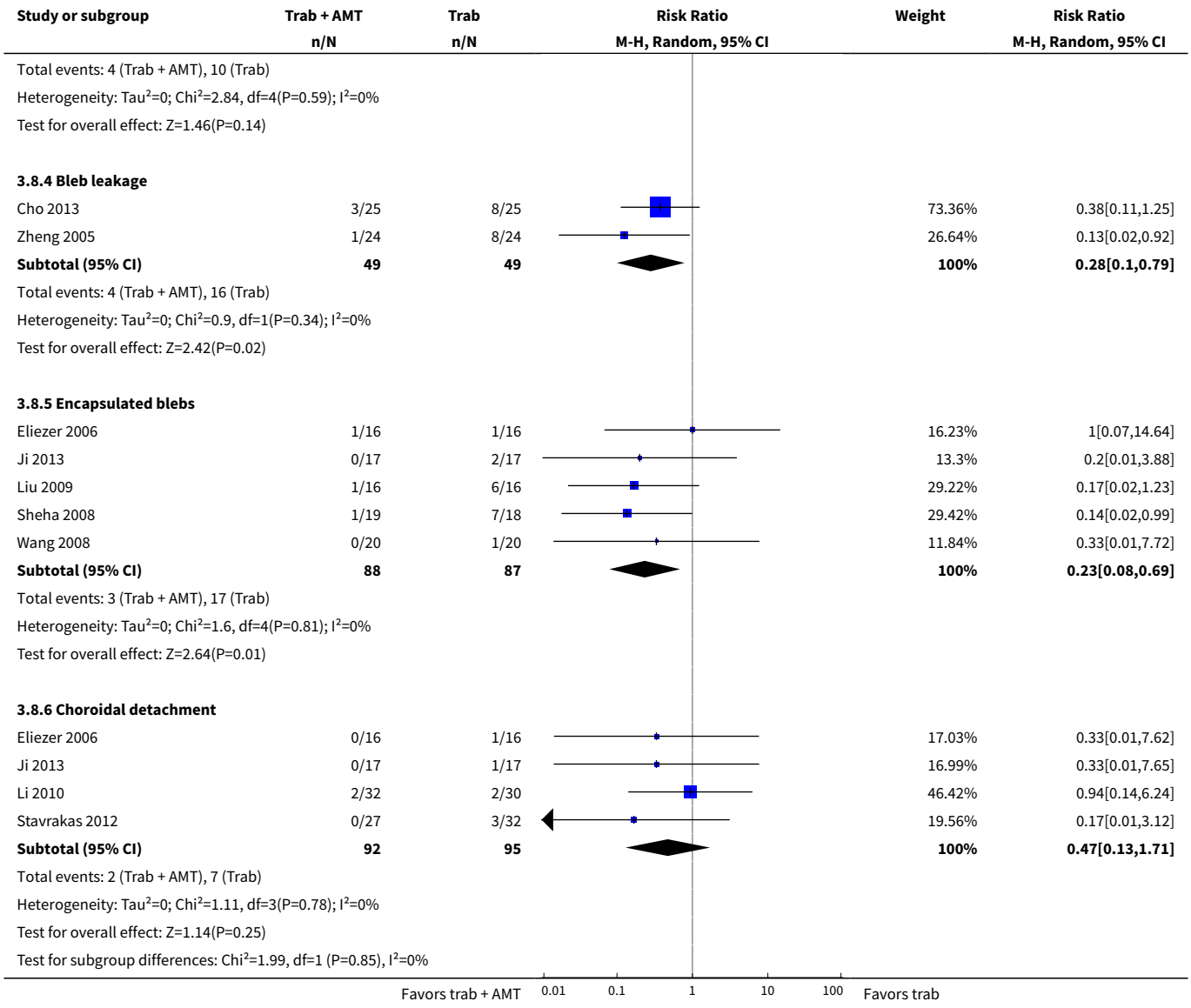


Study or subgroup	Trab + AMT N	Trab + AMT Mean(SD)	Trab N	Trab Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Ji 2013	17	11.8 (4)	17	14.7 (3.6)		100%	-2.96[-5.52,-0.4]
Subtotal ***	**17**		**17**			**100%**	**-2.96[-5.52,-0.4]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.26(P=0.02)							
Test for subgroup differences: Chi^2=2.8, df=1 (P=0.09), I^2=64.34%							



Analysis 3.8. Comparison 3 Trabeculectomy (Trab) + AMT (amniotic membrane) versus Trabeculectomy (Trab), Outcome 8 Complications.

Study or subgroup	Trab + AMT n/N	Trab n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
3.8.1 Hypotony					
Khairy 2015	1/26	2/26		13.23%	0.5[0.05,5.18]
Liu 2009	0/16	3/16		8.76%	0.14[0.01,2.56]
Ren 2009	4/18	5/18		51.39%	0.8[0.26,2.5]
Sheha 2008	0/19	3/18		8.7%	0.14[0.01,2.46]
Zheng 2005	1/24	8/24		17.91%	0.13[0.02,0.92]
Subtotal (95% CI)	**103**	**102**		**100%**	**0.4[0.17,0.94]**
Total events: 6 (Trab + AMT), 21 (Trab)					
Heterogeneity: Tau^2=0.04; Chi^2=4.13, df=4(P=0.39); I^2=3.26%					
Test for overall effect: Z=2.1(P=0.04)					
3.8.2 Shallow anterior chamber					
Cho 2013	1/25	3/25		3.67%	0.33[0.04,2.99]
Eliezer 2006	0/16	1/16		1.89%	0.33[0.01,7.62]
Huang 2007	5/36	13/27		15.26%	0.29[0.12,0.71]
Ji 2013	1/17	3/17		3.78%	0.33[0.04,2.89]
Khairy 2015	1/26	2/26		3.27%	0.5[0.05,5.18]
Li 2010	5/32	3/30		8.59%	1.56[0.41,5.98]
Ren 2009	4/18	5/18		11.03%	0.8[0.26,2.5]
Wang 2008	3/20	0/20		2.18%	7[0.38,127.32]
Wang 2009	1/16	7/14		4.47%	0.13[0.02,0.9]
Yan 2004	5/36	13/27		15.26%	0.29[0.12,0.71]
Yang 2004	7/40	5/30		12.52%	1.05[0.37,2.99]
Zhang 2009	2/26	8/26		7.56%	0.25[0.06,1.07]
Zheng 2005	3/24	9/24		10.52%	0.33[0.1,1.08]
Subtotal (95% CI)	**332**	**300**		**100%**	**0.47[0.3,0.73]**
Total events: 38 (Trab + AMT), 72 (Trab)					
Heterogeneity: Tau^2=0.12; Chi^2=14.79, df=12(P=0.25); I^2=18.86%					
Test for overall effect: Z=3.37(P=0)					
3.8.3 Hyphema					
Cai 2012	1/25	4/23		29.27%	0.23[0.03,1.91]
Cho 2013	1/25	0/25		13.19%	3[0.13,70.3]
Sheha 2008	1/19	1/18		18.05%	0.95[0.06,14.04]
Wang 2009	0/16	3/14		15.81%	0.13[0.01,2.25]
Yang 2004	1/40	2/30		23.69%	0.38[0.04,3.95]
Subtotal (95% CI)	**125**	**110**		**100%**	**0.43[0.14,1.34]**



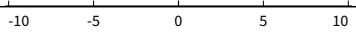
Comparison 4. Trabeculectomy (Trab) + E-PTFE versus Trabeculectomy (Trab)

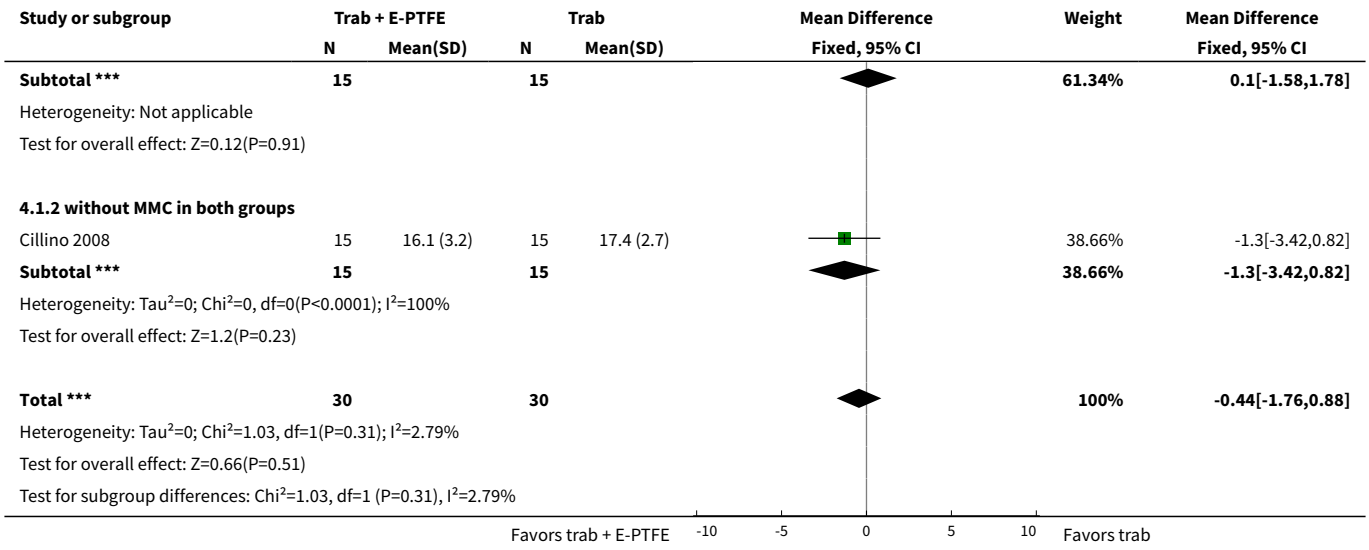
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Postoperative IOP at one year	1	60	Mean Difference (IV, Fixed, 95% CI)	-0.44 [-1.76, 0.88]
1.1 with MMC in both groups	1	30	Mean Difference (IV, Fixed, 95% CI)	0.10 [-1.58, 1.78]
1.2 without MMC in both groups	1	30	Mean Difference (IV, Fixed, 95% CI)	-1.30 [-3.42, 0.82]
2 Hypotony at 24 months	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.29 [0.11, 0.77]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 with MMC in both groups	1	30	Risk Ratio (M-H, Fixed, 95% CI)	0.43 [0.14, 1.35]
2.2 without MMC in both groups	1	30	Risk Ratio (M-H, Fixed, 95% CI)	0.14 [0.02, 1.02]
3 Hyphaema at 24 months	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.8 [0.37, 1.74]
3.1 with MMC in both groups	1	30	Risk Ratio (M-H, Fixed, 95% CI)	0.8 [0.27, 2.41]
3.2 without MMC in both groups	1	30	Risk Ratio (M-H, Fixed, 95% CI)	0.8 [0.27, 2.41]
4 Inflammation at 24 months	1	60	Risk Ratio (M-H, Fixed, 95% CI)	1.4 [0.50, 3.91]
4.1 with MMC in both groups	1	30	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [0.36, 4.97]
4.2 without MMC in both groups	1	30	Risk Ratio (M-H, Fixed, 95% CI)	1.5 [0.29, 7.73]
5 Shallow anterior chamber at 24 months	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.44 [0.15, 1.29]
5.1 with MMC in both groups	1	30	Risk Ratio (M-H, Fixed, 95% CI)	0.5 [0.11, 2.33]
5.2 without MMC in both groups	1	30	Risk Ratio (M-H, Fixed, 95% CI)	0.4 [0.09, 1.75]
6 Flat anterior chamber at 24 months	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.6 [0.08, 4.28]
6.1 with MMC in both groups	1	30	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.07, 14.55]
6.2 without MMC in both groups	1	30	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.58]
7 Choroidal detachment at 24 months	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.43 [0.12, 1.51]
7.1 with MMC in both groups	1	30	Risk Ratio (M-H, Fixed, 95% CI)	0.25 [0.03, 1.98]
7.2 without MMC in both groups	1	30	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.13, 3.44]

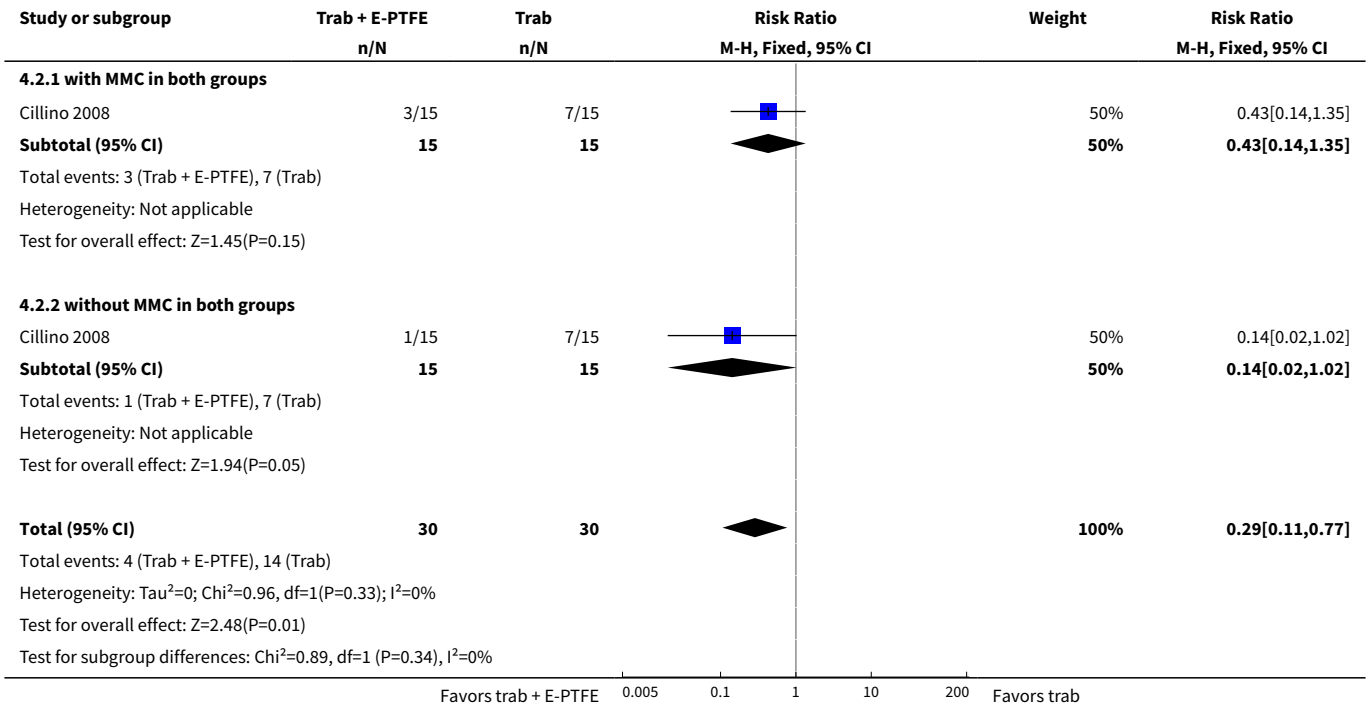
Analysis 4.1. Comparison 4 Trabeculectomy (Trab) + E-PTFE versus Trabeculectomy (Trab), Outcome 1 Postoperative IOP at one year.

Study or subgroup	Trab + E-PTFE N	Trab + E-PTFE Mean(SD)	Trab N	Trab Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
4.1.1 with MMC in both groups							
Cillino 2008	15	16.5 (2.3)	15	16.4 (2.4)		61.34%	0.1[-1.58,1.78]





Analysis 4.2. Comparison 4 Trabeculectomy (Trab) + E-PTFE versus Trabeculectomy (Trab), Outcome 2 Hypotony at 24 months.



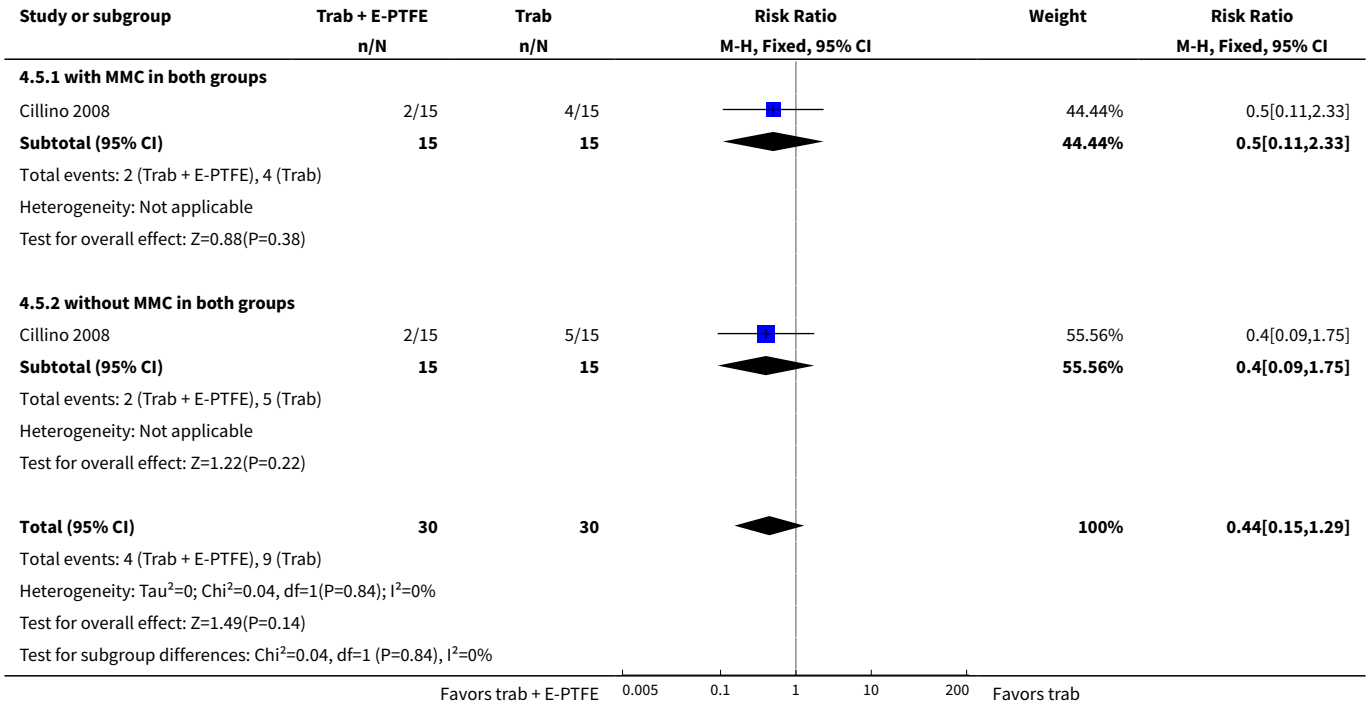
Analysis 4.3. Comparison 4 Trabeculectomy (Trab) + E-PTFE versus Trabeculectomy (Trab), Outcome 3 Hyphaema at 24 months.

Study or subgroup	Trab + E-PTFE n/N	Trab n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
4.3.1 with MMC in both groups					
Cillino 2008	4/15	5/15		50%	0.8[0.27,2.41]
Subtotal (95% CI)	**15**	**15**		**50%**	**0.8[0.27,2.41]**
Total events: 4 (Trab + E-PTFE), 5 (Trab)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.4(P=0.69)					
4.3.2 without MMC in both groups					
Cillino 2008	4/15	5/15		50%	0.8[0.27,2.41]
Subtotal (95% CI)	**15**	**15**		**50%**	**0.8[0.27,2.41]**
Total events: 4 (Trab + E-PTFE), 5 (Trab)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.4(P=0.69)					
Total (95% CI)	**30**	**30**		**100%**	**0.8[0.37,1.74]**
Total events: 8 (Trab + E-PTFE), 10 (Trab)					
Heterogeneity: Tau^2=0; Chi^2=0, df=1(P=1); I^2=0%					
Test for overall effect: Z=0.56(P=0.57)					
Test for subgroup differences: Not applicable					

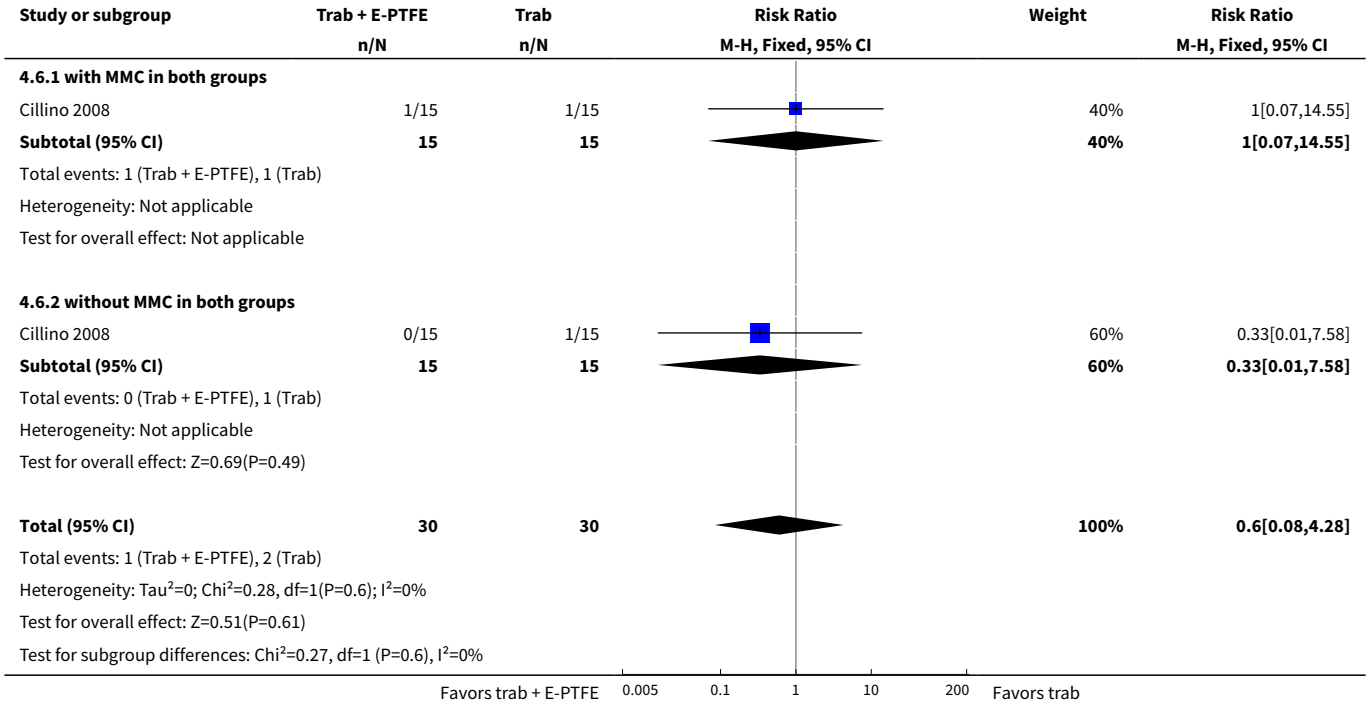
Analysis 4.4. Comparison 4 Trabeculectomy (Trab) + E-PTFE versus Trabeculectomy (Trab), Outcome 4 Inflammation at 24 months.

Study or subgroup	Trab + E-PTFE n/N	Trab n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
4.4.1 with MMC in both groups					
Cillino 2008	4/15	3/15		60%	1.33[0.36,4.97]
Subtotal (95% CI)	**15**	**15**		**60%**	**1.33[0.36,4.97]**
Total events: 4 (Trab + E-PTFE), 3 (Trab)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.43(P=0.67)					
4.4.2 without MMC in both groups					
Cillino 2008	3/15	2/15		40%	1.5[0.29,7.73]
Subtotal (95% CI)	**15**	**15**		**40%**	**1.5[0.29,7.73]**
Total events: 3 (Trab + E-PTFE), 2 (Trab)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.48(P=0.63)					
Total (95% CI)	**30**	**30**		**100%**	**1.4[0.5,3.91]**
Total events: 7 (Trab + E-PTFE), 5 (Trab)					
Heterogeneity: Tau^2=0; Chi^2=0.01, df=1(P=0.91); I^2=0%					
Test for overall effect: Z=0.64(P=0.52)					
Test for subgroup differences: Chi^2=0.01, df=1 (P=0.91), I^2=0%					

Analysis 4.5. Comparison 4 Trabeculectomy (Trab) + E-PTFE versus Trabeculectomy (Trab), Outcome 5 Shallow anterior chamber at 24 months.



Analysis 4.6. Comparison 4 Trabeculectomy (Trab) + E-PTFE versus Trabeculectomy (Trab), Outcome 6 Flat anterior chamber at 24 months.



Analysis 4.7. Comparison 4 Trabeculectomy (Trab) + E-PTFE versus Trabeculectomy (Trab), Outcome 7 Choroidal detachment at 24 months.

Study or subgroup	Trab + E-PTFE n/N	Trab n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
4.7.1 with MMC in both groups					
Cillino 2008	1/15	4/15		57.14%	0.25[0.03,1.98]
Subtotal (95% CI)	**15**	**15**		**57.14%**	**0.25[0.03,1.98]**
Total events: 1 (Trab + E-PTFE), 4 (Trab)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.31(P=0.19)					
4.7.2 without MMC in both groups					
Cillino 2008	2/15	3/15		42.86%	0.67[0.13,3.44]
Subtotal (95% CI)	**15**	**15**		**42.86%**	**0.67[0.13,3.44]**
Total events: 2 (Trab + E-PTFE), 3 (Trab)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.48(P=0.63)					
Total (95% CI)	**30**	**30**		**100%**	**0.43[0.12,1.51]**
Total events: 3 (Trab + E-PTFE), 7 (Trab)					
Heterogeneity: Tau^2=0; Chi^2=0.54, df=1(P=0.46); I^2=0%					
Test for overall effect: Z=1.32(P=0.19)					
Test for subgroup differences: Chi^2=0.53, df=1 (P=0.47), I^2=0%					

ADDITIONAL TABLES

Table 1. Summary of included studies

Device	Study ID	Study design	Country	Participant diagnosis	Interventions	Total number of participants randomized	Total number of eyes randomized	Total number of eyes analyzed	Longest follow-up period (months)
Ex-PRESS	Dahan 2012	RCT, paired-eye design	South Africa	POAG	Trab + MMC Trab + MMC + Ex-PRESS	15	30	30	12
	De Jong 2005 (abstract)	RCT, parallel-group design	The Netherlands	OAG	Trab + Ex-PRESS under a scleral flap Trab Trab + Ex-PRESS under conjunctiva	109	120	N/A	6
	De Jong 2009	RCT, parallel-group design	The Netherlands	OAG	Trab Trab + Ex-PRESS	78	78	78	60
	Netland 2014	RCT, parallel-group design	USA	OAG	Trab + MMC Trab + MMC + Ex-PRESS	120	120	114	24
	Wagschal 2013	RCT, parallel-group design	Canada	OAG, uncontrolled IOP	Trab + MMC Trab + MMC + Ex-PRESS	64	64	60	12
	Subtotal for Ex-PRESS					**386**	**412**	**N/A**	**Range 6 to 60 months**
Ologen	Cillino 2011	RCT, parallel-group design	Italy	POAG, PEXG, uncontrolled IOP	Trab + MMC Trab + Ologen	40	40	40	24
	Maheshwari 2012	RCT, parallel-group design	India	OAG	Trab + MMC Trab + Ologen	40	40	40	12
	Marey 2013	RCT, parallel-group design	Egypt	POAG, ACG, PEXG, uveitic	Trab + MMC	60	60	60	12

Table 1. Summary of included studies *(Continued)*

				glaucoma, uncontrolled pseudophakic glaucoma	Trab + Ologen				
	Mitra 2012	RCT, parallel-group design	India	Uncontrolled OAG	Trab + MMC Trab + Ologen	64	64	N/A	6
	Papaconstantinou 2010	RCT, parallel-group design	Greece	glaucoma	Trab Trab + Ologen	40	40	40	6
	Rosentreter 2010	RCT, parallel-group design	Germany	OAG, uncontrolled IOP	Trab + MMC Trab + Ologen	20	20	20	12
	Rosentreter 2014	RCT, parallel-group design	Germany	OAG, uncontrolled IOP	Trab + MMC Trab + Ologen	30	30	30	12
	Senthil 2013	RCT, parallel-group design	India	Uncontrolled POAG or PACG	Trab + MMC Trab + Ologen	33	39	32	24
	Subtotal for Ologen					**327**	**333**	**N/A**	**Range 6 to 24 month**
Amniotic membrane	Bruno 2008 (abstract)	RCT, parallel-group design	N/A	OAG and failed surgery	Trab + MMC Trab + MMC + AMT	19	N/A	N/A	6
	Cai 2012	RCT, parallel-group design	China	Refractory glaucoma	Trab Trab + AMT	40	48	48	12
	Cho 2013	RCT, parallel-group design	China	POAG, ACG, uncontrolled IOP	Trab + MMC Trab + AMT	47	52	39	3
	Eliezer 2006	RCT, parallel-group design	Brazil	POAG	Trab Trab + AMT	32	32	N/A	12

Table 1. Summary of included studies *(Continued)*

Huang 2007	RCT, parallel-group design	China	PACG	Trab Trab + AMT	50	63	N/A	6
Ji 2013	RCT, paired-eye design	China	Uncontrolled glaucoma	Trab Trab + AMT	17	34	N/A	24
Khairy 2015	RCT, parallel-group design	Egypt	OAG	Trab + MMC Trab + AMT	52	52	52	24
Li 2010	RCT, parallel-group design	China	Refractory glaucoma	Trab + MMC Trab + MMC + AMT	50	62	N/A	12
Liu 2009	RCT, parallel-group design	China	Refractory glaucoma	Trab + MMC Trab + MMC + AMT	35	35	32	12
Ren 2009	RCT	China	ACG	Trab Trab + AMT	30	36	N/A	12
Sheha 2008	RCT, parallel-group design	Saudi Arabia	Refractory glaucoma	Trab + MMC Trab + MMC + AMT	37	37	30	12
Stavrakas 2012	RCT	Greece	POAG, uncontrolled IOP	Trab Trab + AMT	50	59	52	24
Wang 2008	RCT, parallel-group design	China	glaucoma	Trab Trab + AMT	40	40	N/A	12
Wang 2009	RCT	China	Refractory glaucoma	Trab Trab + MMC Trab + MMC + AMT	38	44	N/A	12
Yan 2004	RCT	China	PACG	Trab Trab + AMT	52	63	63	6

Table 1. Summary of included studies *(Continued)*

	Yang 2004	RCT, parallel-group design	China	glaucoma	Trab Trab + AMT	70	70	N/A	6
	Zhang 2009	RCT	China	ACG	Trab Trab + AMT	39	52	N/A	6
	Zheng 2005	RCT	China	POAG, PACG	Trab + MMC Trab + AMT	28	48	N/A	12
	Subtotal for amniotic membrane					**726**	**N/A**	**N/A**	**Range 3 to 24 months**
E-PTFE	Cillino 2008	RCT, parallel-group design	Italy	POAG, PEXG, uncontrolled IOP	Trab Trab + MMC Trab + E-PTFE Trab + MMC + E-PTFE	60	60	60	24
	Subtotal for E-PTFE					**60**	**60**	**60**	**24**
Gelfilm	Birt 1998 (abstract)	RCT, parallel-group design	Not reported	Not reported	Trab Trab + Gelfilm Trab + MMC Trab + MMC + Gelfilm	43	N/A	N/A	12
	Subtotal for Gelfilm					**43**	**N/A**	**N/A**	**12**
Total for all included studies						**1542**	**N/A**	**N/A**	**Range 3 months to 5 years**

ACG: angle-closure glaucoma
AMT: amniotic membrane
E-PTFE: expanded polytetrafluoroethylene
IOP: intraocular pressure
MMC: mitomycin C

N/A: not applicable
OAG: open-angle glaucoma
PACG: primary angle-closure glaucoma
PEXG: pseudoexfoliation glaucoma
POAG: primary open-angle glaucoma
RCT: randomized controlled trial

APPENDICES

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor: [Trabeculectomy] explode all trees
#2 MeSH descriptor: [Glaucoma] explode all trees and with qualifiers: [Surgery - SU]
#3 MeSH descriptor: [Trabecular Meshwork] explode all trees and with qualifiers: [Surgery - SU]
#4 MeSH descriptor: [Filtering Surgery] explode all trees
#5 Trabeculectom* or Trabeculoplast* or Trabeculotom* or Goniotom* or Microtrabeculectom*
#6 (Glaucoma* near/5 (surg* or filter* or filtrate*))
#7 #1 or #2 or #3 or #4 or #5 or #6
#8 MeSH descriptor: [Glaucoma Drainage Implants] explode all trees
#9 (modif* near/5 (Trabeculectom* or Trabeculoplast* or Trabeculotom* or Goniotom* or Microtrabeculectom*))
#10 MeSH descriptor: [Polytetrafluoroethylene] explode all trees
#11 (Polytef or Politef or "E PTFE" or EPTFE or PTFE or TFE or FEP or SOLX or polytetrafluoroethylen* or polytetrafluorethylen* or polytetrafluoroethen* or Fluoroflex or Fluoroplast or Ftoroplast or Halon or Polyfene or Tetron or Tarflen or "GORE TEX" or Goretex or gortex or Teflon or Fluon or Ex-press or ologen or Baerveldt or Krupin or Ahmed or Molteno or ExPress or collagen matrix or collagen-GAG or collagen-glycosaminoglycan copolymer matrix)
#12 Device* or implant* or shunt* or valve* or tube*
#13 #8 or #9 or #10 or #11 or #12
#14 MeSH descriptor: [Fluorouracil] explode all trees
#15 5FU or 5-FU or Fluorouracil* or Fluoruracil* or 5-HU or Adrucil or Carac or Efudix or Fluoro Uracile or Fluoro-Uracile or Efudex or Fluoroplex or Flurodex or Fluracedyl or Haemato-fu or Neofluor or Onkofluor or Ribofluor or 5-Fluorouracil
#16 MeSH descriptor: [Mitomycin] explode all trees
#17 Mitomycin* or NSC-26980 or NSC 26980 or NSC26980 or Mutamycin or Ametycine or Mitocin-C or MitocinC or mytomycin* or mitomicin* or mytomicin* or MMC
#18 MeSH descriptor: [Mitomycins] explode all trees
#19 #18 from 1966 to 1991
#20 MeSH descriptor: [Antimetabolites] explode all trees
#21 MeSH descriptor: [Antimetabolites, Antineoplastic] explode all trees
#22 MeSH descriptor: [Nucleic Acid Synthesis Inhibitors] explode all trees
#23 Antimetabolite* or anti-metabolite*
#24 Antifibrotic* or anti-fibrotic*
#25 #14 or #15 or #16 or #17 or #19 or #20 or #21 or #22 or #23 or #24
#26 #7 and (#13 or #25)

Appendix 2. MEDLINE (OvidSP) 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 Trabeculectomy/
13. exp Glaucoma/su [Surgery]
14. exp Trabecular Meshwork/su [Surgery]
15. (Trabeculectom* or Trabeculoplast* or Trabeculotom* or Goniotom* or Microtrabeculectomy).tw.
16. (Glaucoma$ adj5 (surg$ or filter$ or filtrat$)).tw.
17. exp filtering surgery/
18. 12 or 13 or 14 or 15 or 16 or 17
19. exp Glaucoma Drainage Implants/
20. (modif* adj5 (Trabeculectom* or Trabeculoplast* or Trabeculotom* or Goniotom* or Microtrabeculectomy)).tw.
21. exp Polytetrafluoroethylene/
22. (Polytef or Politef or "E PTFE" or EPTFE or PTFE or TFE or FEP or SOLX or polytetrafluoroethylen* or polytetrafluorethylen* or polytetrafluoroethen* or Fluoroflex or Fluoroplast or Ftoroplast or Halon or Polyfene or Tetron or Tarflen or "GORE TEX" or Goretex or

gortex or Teflon or Fluon or Ex-press or ologen or Baerveldt or Krupin or Ahmed or Molteno or ExPress or collagen matrix or collagen-GAG or collagen-glycosaminoglycan copolymer matrix).tw.
23. (Device* or implant* or shunt* or valve* or tube*).tw.
24. 19 or 20 or 21 or 22 or 23
25. exp Fluorouracil/
26. (5FU or 5-FU or Fluorouracil* or Fluoruracil* or 5-HU or Adrucil or Carac or Efudix or Fluoro Uracile or Fluoro-Uracile or Efudex or Fluoroplex or Flurodex or Fluracedyl or Haemato-fu or Neofluor or Onkofluor or Ribofluor or 5-Fluorouracil).tw.
27. exp Mitomycin/
28. (Mitomycin* or NSC-26980 or NSC 26980 or NSC26980 or Mutamycin or Ametycine or Mitocin-C or MitocinC or mytomycin* or mitomicin* or mytomicin* or MMC).tw.
29. exp Mitomycins/
30. limit 29 to yr="1966 - 1991"
31. antimetabolites/
32. Antimetabolites, Antineoplastic/
33. Nucleic Acid Synthesis Inhibitors/
34. (Antimetabolite* or anti-metabolite*).tw.
35. (Antifibrotic* or anti-fibrotic*).tw.
36. 25 or 26 or 27 or 28 or 30 or 31 or 32 or 33 or 34 or 35
37. 11 and 18 and (24 or 36)

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

Appendix 3. EMBASE.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. 'trabeculectomy'/exp
34. 'trabeculoplasty'/exp
35. 'trabeculotomy'/exp
36. trabeculectom*:ab,ti OR trabeculoplast*:ab,ti OR trabeculotom*:ab,ti OR goniotom*:ab,ti OR microtrabeculectom*:ab,ti
37. 'glaucoma surgery'/de
38. 'trabecular meshwork'/exp

39. (glaucoma* NEAR/5 (surg* OR filter* OR filtrate*)):ab,ti
40. 'filtering operation'/de
41. 33 OR 34 OR 35 OR 36 OR 37 OR 38 OR 39 OR 40
42. 'glaucoma drainage implant'/exp
43. (modif* NEAR/5 (trabeculectom* OR trabeculoplast* OR trabeculotom* OR goniotom* OR microtrabeculectom*)):ab,ti
44. 'politef'/exp
45. (Polytef or Politef or 'E PTFE' or EPTFE or PTFE or TFE or FEP or SOLX or polytetrafluoroethylen* or polytetrafluorethylen* or polytetrafluoroethen* or Fluoroflex or Fluoroplast or Ftoroplast or Halon or Polyfene or Tetron or Tarflen or 'GORE TEX' or Goretex or gortex or Teflon or Fluon or Ex-press or ologen or Baerveldt or Krupin or Ahmed or Molteno or ExPress or 'collagen matrix' or 'collagen-GAG' or 'collagen-glycosaminoglycan copolymer matrix'):ab,ti
46. device*:ab,ti OR implant*:ab,ti OR shunt*:ab,ti OR valve*:ab,ti OR tube*:ab,ti
47. 42 OR 43 OR 44 OR 45
48. 'fluorouracil'/exp
49. 5fu:ab,ti OR '5 fu':ab,ti OR fluorouracil*:ab,ti OR fluoruracil*:ab,ti OR '5 hu':ab,ti OR adrucil:ab,ti OR carac:ab,ti OR efudix:ab,ti OR fluoro:ab,ti AND uracile:ab,ti OR 'fluoro uracile':ab,ti OR efudex:ab,ti OR fluoroplex:ab,ti OR flurodex:ab,ti OR fluracedyl:ab,ti OR 'haemato fu':ab,ti OR neofluor:ab,ti OR onkofluor:ab,ti OR ribofluor:ab,ti OR '5 fluorouracil':ab,ti OR '5 fluoro 2':ab,ti OR '4 pyrimidinedione':ab,ti OR '5 fu':ab,ti OR accusite:ab,ti OR 'actino hermal':ab,ti OR effluderm:ab,ti OR efurix:ab,ti OR f6627:ab,ti OR fivoflu:ab,ti OR fluoroblastin:ab,ti OR fluouracil:ab,ti OR fluoxan:ab,ti OR fluracil:ab,ti OR fluracilium:ab,ti OR fluril:ab,ti OR 'fluro uracil':ab,ti OR fluroblastin:ab,ti OR ifacil:ab,ti OR 'nsc 18913':ab,ti OR 'nsc 19893':ab,ti OR 'nsc18913':ab,ti OR nsc19893:ab,ti OR 'oncofu':ab,ti OR 'ro 2-9757':ab,ti OR 'ro 2 9757':ab,ti OR 'ro2-9757':ab,ti OR 'ro2 9757':ab,ti OR uflahex:ab,ti OR utoral:ab,ti OR verrumal:ab,ti OR '51 21 8':ab,ti
50. 'mitomycin'/exp
51. mitomycin*:ab,ti OR 'nsc 26980':ab,ti OR nsc:ab,ti AND 26980:ab,ti OR nsc26980:ab,ti OR mutamycin:ab,ti OR ametycine:ab,ti OR 'mitocin c':ab,ti OR mitocinc:ab,ti OR mytomycin*:ab,ti OR mitomicin*:ab,ti OR mytomicin*:ab,ti OR mmc:ab,ti OR datisan:ab,ti OR metomit:ab,ti OR mitocyna:ab,ti OR mitosol:ab,ti OR mixandex:ab,ti OR mytocine:ab,ti OR mytozytrex:ab,ti OR vetio:ab,ti OR '1404 00 8':ab,ti
52. 'antimetabolite'/de
53. 'antineoplastic antimetabolite'/de
54. 'nucleic acid synthesis inhibitor'/de
55. antimetabolite*:ab,ti OR (anti NEAR/1 metabolite*):ab,ti
56. antifibrotic*:ab,ti OR (anti NEAR/1 fibrotic*):ab,ti
57. 48 OR 49 OR 50 OR 51 OR 52 OR 53 OR 54 OR 55 OR 56
58. 32 AND 41 AND (47 OR 57)

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 (Trabeculectom*[tiab] OR Trabeculoplast*[tiab] OR Trabeculotom*[tiab] OR Goniotom*[tiab] OR Microtrabeculectomy[tiab]) NOT MEDLINE[sb]
#3 (Glaucoma*[tiab] AND (surge*[tiab] OR surgi*[tiab] OR filter*[tiab] OR filtrate*[tiab])) NOT MEDLINE[sb]
#4 #2 OR #3
#5 (modif*[tiab] AND (Trabeculectom*[tiab] OR Trabeculoplast*[tiab] OR Trabeculotom*[tiab] OR Goniotom*[tiab] OR Microtrabeculectomy[tiab])) NOT MEDLINE[sb]
#6 (Polytef[tiab] OR Politef[tiab] OR "E PTFE"[tiab] OR EPTFE[tiab] OR PTFE[tiab] OR TFE[tiab] OR FEP[tiab] OR SOLX[tiab] OR polytetrafluoroethylen*[tiab] OR polytetrafluorethylen*[tiab] OR polytetrafluoroethen*[tiab] OR Fluoroflex[tiab] OR Fluoroplast[tiab] OR Ftoroplast[tiab] OR Halon[tiab] OR Polyfene[tiab] OR Tetron[tiab] OR Tarflen[tiab] OR "GORE TEX"[tiab] OR Goretex[tiab] OR gortex[tiab] OR Teflon[tiab] OR Fluon[tiab] OR Ex-press[tiab] OR ologen[tiab] OR Baerveldt[tiab] OR Krupin[tiab] OR Ahmed[tiab] OR Molteno[tiab] OR ExPress[tiab] OR collagen matrix[tiab] OR collagen-GAG[tiab] OR collagen-glycosaminoglycan copolymer matrix[tiab]) NOT MEDLINE[sb]
#7 (Device*[tiab] OR implant*[tiab] OR shunt*[tiab] OR valve*[tiab] OR tube[tiab] OR tubes[tiab]) NOT MEDLINE[sb]
#8 (5FU[tiab] OR 5-FU[tiab] OR Fluorouracil*[tiab] OR Fluoruracil*[tiab] OR 5-HU[tiab] OR Adrucil[tiab] OR Carac[tiab] OR Efudix[tiab] OR Fluoro Uracile[tiab] OR Fluoro-Uracile[tiab] OR Efudex[tiab] OR Fluoroplex[tiab] OR Flurodex[tiab] OR Fluracedyl[tiab] OR Haemato-fu[tiab] OR Neofluor[tiab] OR Onkofluor[tiab] OR Ribofluor[tiab] OR 5-Fluorouracil[tiab]) NOT MEDLINE[sb]
#9 (Mitomycin*[tiab] OR NSC-26980[tiab] OR NSC 26980[tiab] OR NSC26980[tiab] OR Mutamycin[tiab] OR Ametycine[tiab] OR Mitocin-C[tiab] OR MitocinC[tiab] OR mytomycin*[tiab] OR mitomicin*[tiab] OR mytomicin*[tiab] OR MMC[tiab]) NOT MEDLINE[sb]
#10 (Antimetabolite*[tiab] OR anti-metabolite*[tiab]) NOT MEDLINE[sb]
#11 (Antifibrotic*[tiab] OR anti-fibrotic*[tiab]) NOT MEDLINE[sb]
#12 #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11
#13 #1 AND #4 AND #12

Appendix 5. LILACS Controlled Trials search strategy

(Trabeculectom$ or Trabeculoplast$ or Trabeculotom$ or Goniotom$ or Microtrabeculectom$ or **"**trabecular meshwork**"** or **"**filtering surgery**"** or glaucoma$)

AND
(Polytef or Politef or "E PTFE"or EPTFE or PTFE or TFE or FEP or SOLX or polytetrafluoroethylen$ or polytetrafluorethylen$ or polytetrafluoroethen$ or Fluoroflex or Fluoroplast or Ftoroplast or Halon or Polyfene or Tetron or Tarflen or "GORE TEX" or Goretex or gortex or Teflon or Fluon or Ex-press or ologen or Baerveldt or Krupin or Ahmed or Molteno or ExPress or "collagen matrix" or "collagen-GAG" or "collagen-glycosaminoglycan copolymer matrix" or Device$ or implant$ or shunt$ or valve$ or tube$ or (modif$ and Trabeculectom$ or Trabeculoplast$ or Trabeculotom$ or Goniotom$ or Microtrabeculectom$) or Fluorouracil$ or 5FU or 5-FU or Fluoruracil$ or 5-HU or Adrucil or Carac or Efudix or Fluoro Uracile or Fluoro-Uracile or Efudex or Fluoroplex or Flurodex or Fluracedyl or Haemato-fu or Neofluor or Onkofluor or Ribofluor or 5-Fluorouracil or Mitomycin$ or NSC-26980 or NSC 26980 or NSC26980 or Mutamycin or Ametycine or Mitocin-C or MitocinC or mytomycin$ or mitomicin$ or mytomicin$ or MMC or Antimetabolite$ or anti-metabolite$ or Antifibrotic$ or anti-fibrotic$)

Appendix 6. *meta*Register of Controlled Trials search strategy

(Trabeculectomy OR (glaucoma surgery)) AND (device OR implant OR implants OR shunt OR valve OR tube OR 5FU OR 5-FU OR Fluorouracil OR Fluoruracil OR Fluoro Uracile OR 5-Fluorouracil OR Mitomycin OR MMC OR Antimetabolite OR Antimetabolites OR Antifibrotic)

Appendix 7. ClinicalTrials.gov search strategy

(search terms) Trabeculectomy OR Trabeculoplasty OR Trabeculotomy OR Goniotomy OR Microtrabeculectomy OR glaucoma

(intervention) Device OR implant OR implants OR shunt OR valve OR tube OR Fluorouracil OR 5- Fluorouracil OR 5-FU OR Fluoruracil OR Mitomycin OR mytomycin OR mitomicin OR mytomicin OR MMC OR Antimetabolite OR Antifibrotic

Appendix 8. ICTRP search strategy

(condition) Trabeculectomy OR Trabeculoplasty OR Trabeculotomy OR Goniotomy OR Microtrabeculectomy OR Goniotomy OR Microtrabeculectomy OR glaucoma

(intervention) Device OR implant OR implants OR shunt OR valve OR tube OR Fluorouracil OR 5- Fluorouracil OR 5-FU OR Fluoruracil OR Mitomycin OR mytomycin OR mitomicin OR mytomicin OR MMC OR Antimetabolite OR Antifibrotic

CONTRIBUTIONS OF AUTHORS

XW conceived and designed the review, screened the search results, assessed trial quality, extracted and entered data, analyzed data and wrote the main text of the review.

RK assessed trial quality, extracted data, participated in the adjudication process, co-authored the Agreements and disagreements with other studies or reviews section, and helped edit and revise the main text of the review.

AC conceived and designed the review, advised on data interpretations and provided substantial comments on the content of the review.

DECLARATIONS OF INTEREST

AC reports grants unrelated to this work from the National Eye Institute, National Institutes of Health, US and the Agency for Healthcare Research and Quality (AHRQ), US. The AHRQ Comparativeness Effectiveness of glaucoma treatment trial is an observational study on the management of glaucoma patients with additional medications, laser trabeculoplasty, or incisional surgery. Modified trabeculectomies are one of the types of incisional surgeries allowed in the trial if the treating physician and patient choose that method to lower eye pressures. Since the study is observational, AC has no role in which treatment modality is chosen.

XW: None known.

RK: None known.

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

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

1. We planned to assess mean change of IOP from baseline between the two groups. However, as in most cases mean change of IOP was not reported in individual studies, we used postoperative IOP as a surrogate. This may result in some bias because of the differences in baseline IOPs in participants in a few studies.

2. For amniotic membrane studies, losses to follow-up were not reported in a majority of studies (11/18), and we used the number randomized in the analyses. This may bias the analyses as those participants lost to follow-up did not contribute to the outcome measurements.

3. For the Ologen studies, one study compared trabeculectomy without MMC versus trabeculectomy and Ologen (Papaconstantinou 2010). The other seven studies were included in the meta-analysis to give a broader view, but the lack of the use of MMC in one study may have reduced the success rate of the trabeculectomy-alone group in comparison to the trabeculectomy-with-Ologen group. This may have made the trabeculectomy-with-Ologen group appear better at IOP reduction than it is.

4. For amniotic membrane studies, three studies only used MMC in the trabeculectomy group but not in the amniotic membrane group (Cho 2013; Khairy 2015; Zheng 2005). Although both MMC and amniotic membrane affect wound healing, whether amniotic membrane can substitute for MMC is unknown. To ensure comparability, MMC should either have been used in both groups, or should not have been used at all. The impact of this on the outcome is unknown.

5. For complications reported for each study, the time of measurement may be different. We combined them in the analyses, based on the assumption that most complications occur within a short time after the surgery. These data should be interpreted with caution.

INDEX TERMS

Medical Subject Headings (MeSH)

*Glaucoma Drainage Implants; Amnion [transplantation]; Biocompatible Materials; Collagen [therapeutic use]; Gelatin [therapeutic use]; Glaucoma [*surgery]; Glycosaminoglycans [therapeutic use]; Intraocular Pressure; Polytetrafluoroethylene [therapeutic use]; Randomized Controlled Trials as Topic; Trabeculectomy [*instrumentation] [methods]; Visual Acuity

MeSH check words

Humans