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# Fornix-based versus limbal-based conjunctival trabeculectomy flaps for glaucoma

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**DECLARATIONS OF INTEREST**

Authors have no interests to declare.

**DIFFERENCES BETWEEN PROTOCOL AND REVIEW**

We planned to use the $Tau^2$ statistic to assess for statistical heterogeneity in meta-analysis; however, because we used only fixed-effect models for meta-analysis, we did not use the $Tau^2$ statistic.

We intended to perform further subgroup analyses, but due to insufficient data and the small number of trials included in this review, we could not perform subgroup analysis. Also, we intended to report outcomes for quality of life and late cases of endophthalmitis, but none of the included studies had reported these variables. We planned to conduct sensitivity analyses to determine the effect of using fixed-effect versus random-effects models; however, because each meta-analysis had a small number of trials (less than three) or low $I^2$ statistic (0%), we did not perform these sensitivity analyses.

We planned to search the Web of Science CPCI-S database, which is a database of conference proceedings. After using the resource we found that the database contained mostly journal articles which had already been identified by searching other electronic sources thus creating additional duplicate records in the searching process. Therefore we decided not to use this resource for the review.

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## Abstract

**Background—**Glaucoma is one of the leading largely preventable causes of blindness in the world. It usually is addressed first medically with topical intraocular pressure-lowering drops or by laser trabeculoplasty. In cases where such treatment fails, glaucoma-filtering surgery is considered, most commonly trabeculectomy surgery with variations in technique, for example, the type of conjunctival flap (fornix-or limbal-based). In a fornix-based flap, the surgical wound is performed at the corneal limbus; while in a limbal-based flap, the incision is further away. Many studies in the literature compare fornix- and limbal-based trabeculectomy with respect to outcomes and complications.

**Objectives—**To assess the comparative effectiveness of fornix- versus limbal-based conjunctival flaps in trabeculectomy for adult glaucoma, with a specific focus on intraocular pressure (IOP) control and complications (adverse effects).

**Search methods—**We searched CENTRAL (which contains the Cochrane Eyes and Vision Trials Register) (2015, Issue 9), Ovid MEDLINE, Ovid MED-LINE In-Process and Other Non-Indexed Citations, Ovid MEDLINE Daily, Ovid OLDMEDLINE (January 1946 to October 2015), EMBASE (January 1980 to October 2015), Latin American and Caribbean Health Sciences Literature Database (LILACS) (January 1982 to October 2015), the ISRCTN registry (www.isrctn.com/editAdvancedSearch), ClinicalTrials.gov (www.clinicaltrials.gov) and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/search/en). We did not use any date or language restrictions in the electronic searches for trials. We last searched the electronic databases on 23 October 2015.

We reviewed the bibliographic references of identified randomised controlled trials (RCTs) in order to find trials not identified by the electronic searches. We contacted researchers and practitioners active in the field of glaucoma to identify other published and unpublished trials.

**Selection criteria—**We included RCTs comparing the benefits and complications of fornix- versus limbal-based trabeculectomy for glaucoma, irrespective of glaucoma type, publication status, and language. We excluded studies on children less than 18 years of age, since wound healing is different in this age group and the rate of bleb scarring postoperatively is high.

**Data collection and analysis—**Two review authors independently extracted data and assessed trial quality. We contacted study authors for additional information.

The primary outcome was the proportion of failed trabeculectomies at 24 months. Failure was defined as the need for repeat surgery or uncontrolled IOP (more than 22 mmHg), despite additional topical/systemic medications. Needling and 5-fluorouracil (5-FU) injections were allowed only during the first six months postoperatively; additional needling or 5-FU injections were considered as failure. Mean post-operative IOP at 12 and 24 months also was recorded.

**Main results—**The review included six trials with a total of 361 participants. Two studies were conducted in America and one each in Germany, Greece, India, and Saudi Arabia. The participants of four trials had open-angle glaucoma; one study included participants with primary open-angle or primary closed-angle glaucoma, and one study did not specify the type of glaucoma. Three studies used a combined procedure (phacotrabeculectomy). Trabeculectomy with mitomycin C (MMC) was performed in four studies, and trabeculectomy with 5-fluorouracil (5-FU) was performed in only one study.

None of the included trials reported trabeculectomy failure at 24 months. Only one trial reported the failure rate of trabeculectomy as a late complication. Failure was higher among participants randomised to the limbal-based surgery: 1/50 eyes failed trabeculectomy in the fornix group compared with 3/50 in the limbal group (risk ratio (RR) 0.33, 95% confidence interval (95% CI) 0.04 to 3.10); therefore we are very uncertain as to the relative effect of the two procedures on failure rate.

Four studies including 252 participants provided measures of mean IOP at 12 months. In the fornix-based surgeries, mean IOP ranged from 12.5 to 15.5 mmHg and similar results were noted in limbal-based surgeries with mean IOP ranging from 11.7 to 15.1 mmHg without significant difference. Mean difference was 0.44 mmHg (95% CI −0.45 to 1.33) and 0.86 mmHg, (95% CI −0.52 to 2.24) at 12 and 24 months of follow-up, respectively. Neither of these pooled analyses showed a statistically significant difference in IOP between groups (moderate quality of evidence).

One trial reported number of anti-glaucoma medications at 24 months of follow-up with no difference noted between surgical groups. However, three trials reported the mean number of anti-glaucoma medications at 12 months of follow-up without significant difference in the mean number of postoperative IOP-lowering medications between the two surgical techniques. Mean difference was 0.02, (95% CI −0.15 to 0.19) at 12 months of follow-up (high quality of evidence).

Because of the small numbers of events and total participants, the risk of many reported adverse events were uncertain and those that were found to be statistically significant may have been due to chance.

For risk of bias assessment: although all six trials were randomised selection bias was mostly unclear, with unclear random sequence generation in four of the six studies and unclear allocation concealment in five of the six studies. Attrition bias was encountered in only one trial which also suffered from reporting bias. All other trials had an unclear risk of reporting bias as there was no access to study protocols. All included trials were judged to have high risk of detection bias due to lack of masking of the outcomes. Trabeculectomy is quite a standard procedure and unlikely to induce bias due to surgeon 'performance', hence performance bias was not evaluated.

**Authors' conclusions—**The main result of this review was that there was uncertainty as to the difference between fornix- and limbal-based trabeculectomy surgeries due to the small number of events and confidence intervals that cross the null. This also applied to postoperative complications, but without any impact on long-term failure rate between the two surgical techniques.

## PLAIN LANGUAGE SUMMARY

### Fornix-based versus limbal-based conjunctival trabeculectomy flaps for glaucoma

**Review question—**We reviewed the evidence for the effectiveness and complications of different approaches (fornix-based versus limbal-based incisions) of drainage surgery (trabeculectomy) in adults with glaucoma.

**Background—**Glaucoma is one of the leading largely-preventable causes of blindness in the world. Surgical treatment aims at opening the drainage system and lowering the pressure in the eye when other medical treatments with eyedrops fail. Trabeculectomy is one surgical technique that creates a fistula, allowing drainage of fluid from inside the eye to lower the eye pressure. There are two incision types in this surgery: fornix-based (between the cornea and conjunctiva) and limbal-based (further away under the eyelid). This review aims to look at whether there are any differences in the surgical outcomes (eye pressure control and complications) between these two different surgical approaches (fornix- and limbal-based techniques).

**Study characteristics—**Six randomised controlled trials (RCTs) were reviewed with a total of 361 participants consisting of adults with any type of glaucoma and follow-up of at least 24 months. We last searched the databases on 23 October 2015.

**Key results—**Failure rate at 24 months was not reported in any included studies, and one study reported “late complications” but did not specify a time period, which favoured the fornix-based treatment. No difference was noted with respect to lowering eye pressure after 24 months (two trials) and after 12 months (four trials). The number of medications needed to control eye pressure after surgery was also similar. Moreover, most of the studies reported that the complication rates after the operation were similar except in one complication which was narrowing in the anterior part of the eye after the procedure (more common in the limbal surgery group), but this did not affect the final outcome of the surgery.

**Quality of evidence—**Although all six trials were reported to be randomised, the procedures followed for randomisation were mostly unclear (four of the six studies). Masking of the outcomes was not clear or not addressed in all six trials. Missing information was encountered in only one trial which also suffered from bias in reporting its outcomes. All other trials had an unclear risk of reporting bias as there was no access to original data.

# SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

**Table 4**

| **Fornix versus limbal-based conjunctival trabeculectomy flaps for glaucoma** | | | | | | |
|---|---|---|---|---|---|---|
| **Patient or population: patients with glaucoma**<br>**Intervention: fornix-based trabeculectomy**<br>**Comparison: limbal-based trabeculectomy** | | | | | | |
| **Outcomes** | **Illustrative comparative risks*** **(95% CI)** | | **Relative effect (95% CI)** | **No of Participants (studies)** | **Quality of the evidence (GRADE)** | **Comments** |
| | **Assumed risk** | **Corresponding risk** | | | | |
| | **Limbal-based trabeculectomy** | **Fornix-based trabeculectomy** | | | | |
| **Failed trabeculectomy**<br>Follow-up: 24 months | N/A | N/A | N/A | N/A | N/A | No study reported this outcome |
| **Failed trabeculectomy**<br>Follow-up: 12 months | 60 per 1000 | 22 per 1000 (3 to 157) | **Peto OR** 0.36 (0.05 to 2. 61) | 100 (1) | ⊕⊕◯◯ **low**[1,2] | Two additional trials reported no trabeculectomy failures among 118 eyes |
| **Mean intraocular pressure**<br>Follow-up: 24 months | Mean intraocular pressure ranged across control groups from 11.3 to 13.1 mmHg | Mean intraocular pressure in the intervention groups was **0.86 mmHg higher** (0.52 mmHg lower to 2. 24 mmHg higher) | **MD** 0.86 (−0.52 to 2.24) | 139 (2) | ⊕⊕⊕◯ **moderate**[2] | One additional trial did not report measures of precision but found that the fornix-based group had a mean IOP of 17 mmHg and the limbal-based group had a mean IOP of 16 mmHg |
| **Mean intraocular pressure**<br>Follow-up: 12 months | Mean intraocular pressure ranged across control groups from 11.7 to 15.1 mmHg | Mean intraocular pressure in the intervention groups was **0.44 mmHg higher** (0.45 mmHg lower to 1. 33 mmHg higher) | **MD** 0.44 (−0.45 to 1.33) | 247 (4) | ⊕⊕⊕◯ **moderate**[2] | |
| **Visual acuity loss:** *defined as: loss of visual acuity equal to or greater than 0.3 LogMAR*<br>Follow-up: 12 months | N/A | N/A | N/A | N/A | N/A | No study reported this outcome |
| **Mean number of medications needed after surgery**<br>Follow-up: 12 months | The mean number of anti-glaucoma medications ranged across control groups from 0.22 to 1.09 | The mean number of anti-glaucoma medications in the intervention groups was **0.02 higher** (0.15 lower to 0.19 higher) | **MD** 0.02 (−0.15 to 0.19) | 194 (3 studies) | ⊕⊕⊕⊕ **high** | One additional trial reported the mean number of anti-glaucoma medications need at 24 months. The mean difference between the fornix- and limbal-based groups was −0.09 mmHg (95% CI −0.43 to 0.25; 86 eyes) |
| **Quality of life,** assessed by vision-specific questionnaires | N/A | N/A | N/A | N/A | N/A | No study reported this outcome |

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**CI:** confidence interval; **RR:** risk ratio; **OR:** odds 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 imprecision (large confidence interval)

[2] Downgraded for risk of bias (unclear randomisation and sequence generation; lack of masking)

# BACKGROUND

## Description of the condition

Glaucoma is one of the leading largely preventable causes of blindness in the world (Thylefors 1995). It is an optic neuropathy with characteristic acquired loss of optic nerve fibres due to an increase in intraocular pressure (IOP). It manifests by cupping and atrophy

of the optic disc in the absence of other known causes of optic nerve disease (Albert 2008). Glaucoma can be classified into congenital, developmental, or acquired. Further subclassification into open-angle or angle-closure glaucoma depends on the mechanism of outflow obstruction. Glaucoma can be also divided into primary or secondary (associated with other ocular or systemic disorders). Adults with glaucoma present usually with visual field loss, high IOP (> 21 mmHg) and abnormal optic discs (AAO 2002; Kanski 1999).

Prevalence of glaucoma varies by the type of glaucoma, age, race and region. Seven to 8% of the general population have IOP greater than 21 mmHg but approximately only 1% show glaucomatous visual field loss. Risk factors for primary open-angle glaucoma are older age (> 65 years), black race, myopia and family history (Kanski 1999). Normal-tension glaucoma is more common in the elderly, in females and in Japan. Primary angle-closure glaucoma presents usually at around 60 years of age and is more common in females and in Caucasians. Secondary glaucomas include pseudoexfoliative glaucoma (15% of eyes with pseudoexfoliation develop increased IOP at 10 years), pigmentary glaucoma (50% of individuals with pigment dispersion syndrome) and neo-vascular glaucoma (mostly secondary to central retinal vein occlusion and diabetes) in addition to the less common inflammatory glaucoma, post-traumatic glaucoma, phacolytic glaucoma and the iridocorneal endothelial syndrome (ICE) (Kanski 1999). Glaucoma is usually first addressed medically with topical IOP-lowering drops or by laser trabeculoplasty. In cases where such treatment fails, surgical management is considered. Surgery for glaucoma involves creating a new path for the outflow of aqueous humour, bypassing the trabecular meshwork, otherwise termed trabeculectomy (Albert 2008).

## Description of the intervention

Glaucoma-filtering surgery was first introduced by Cairns in 1968 and Watson in 1970 for the treatment of glaucoma unresponsive to medical or laser therapy (Cairns 1968; Watson 1970). Variations in technique exist as to whether the conjunctival flap is limbal- or fornix-based. The dissection in fornix-based conjunctival trabeculectomy is believed to be faster and technically easier (Traverso 1987).

A fornix-based conjunctival flap is typically prepared by starting with a conjunctival peritomy incision at the corneoscleral limbus (Murchison 1990). The conjunctiva is then dissected backwards through conjunctiva and Tenon’s capsule about 8 mm to 10 mm from the limbus. A limbal-based scleral flap is dissected 1 mm into the clear cornea. A paracentesis is then made at the corneoscleral limbus through the cornea. A block of corneoscleral or corneal tissue is excised from under the scleral flap. A peripheral iridectomy is usually done. The scleral flap is replaced in its original position and closure is adjusted to allow full inflation of the anterior chamber and to permit a small egress of fluid at the same time (Traverso 1987). The fornix-based flap is finally advanced over the clear cornea to remain taut and the borders are sutured at each end to the episclera. One or more sutures are usually required at each border (Shuster 1984; Traverso 1987). As for the limbal-based conjunctival flap, an incision is made into the conjunctiva and Tenon’s capsule approximately 8 mm from the limbus. The conjunctiva and Tenon’s capsule are then dissected from the underlying episclera towards the limbus. A scleral flap is then performed

in the same manner as for a fornix-based flap. The trabeculectomy opening and flap closure also follow as previously described (Murchison 1990; Shuster 1984; Traverso 1987).

Intraoperative mitomycin C (MMC) reduces the risk of trabeculectomy failure in eyes that have undergone previous surgery and in eyes at high risk of failure (Wilkins 2005). In addition, postoperative use of 5-fluorouracil (5-FU) injections is of benefit to eyes at high risk of failure (Green 2014). The procedure can also be performed concomitantly with cataract extraction, whether extracapsular or by phacoemulsification (Berestka 1997; Murchison 1990; Shingleton 1999).

Early complications encountered in trabeculectomy surgery include: wound leaks, hypotony, expulsive haemorrhage (a rare complication) and shallow anterior chamber (Wilkins 2005). Less commonly seen are corneal dellen, iris prolapse, fibrin reaction and ciliary body detachment (Jonescu-Cuypers 2009). Late complications include bleb-related infection, bleb-related discomfort/pain and late leaks (Yamamoto 2014).

### How the intervention might work

Since IOP is the single modifiable risk factor for glaucoma, surgical interventions for glaucoma aim at lowering IOP. Trabeculectomy, by creating a new pathway for aqueous outflow, significantly lowers IOP and prevents glaucoma progression. It is estimated that each 1 mmHg reduction in IOP produces a 14% reduction in the relative risk of conversion from ocular hypertension to glaucoma (Peeters 2009). Success rates of trabeculectomy surgery range between 36% and 89% at three years follow-up, varying by the different IOP-related definitions used for success in the various trials (Rotchford 2009). The approach to trabeculectomy surgery varies by the type of incision used, namely fornix or limbus (Murchison 1990; Shuster 1984). The main differences between the two incisions are believed to be less postoperative wound leakage with the fornix approach and easier and improved intraoperative exposure with the limbal approach. Outcomes are also affected by the use of antimetabolites, most commonly MMC and 5-FU (Green 2014; Wilkins 2005).

Adults with glaucoma often have concomitant cataracts; trabeculectomy has been safely combined with cataract surgery in the same setting in those individuals (Kozobolis 2002; Lemon 1998; Shingleton 1999).

### Why it is important to do this review

Many studies in the literature compare fornix- versus limbal-based trabeculectomy with respect to outcome and complications; however, criteria for success differ among studies; some use only IOP measurement, others also look into visual field progression, optic disc cupping and loss of visual acuity (Alwitry 2005; Grehn 1989; Murchison 1990; Shuster 1984). Although most studies show similar postoperative IOP control between the two groups, complications vary and the populations studied differ. Some studies combine trabeculectomy with antimetabolite therapy (Alwitry 2005; el Sayyad 1999); others with cataract extraction (Murchison 1990; Tezel 1997); and yet others with both (Kozobolis 2002; Lemon 1998). Many of the above studies are retrospective in nature but there are randomised controlled trials (RCTs) to address the questions of interest. The question of which of these two approaches (fornix versus limbal incision) for trabeculectomy is more

efficacious and safe has not been addressed to date by a systematic review. The aim of this systematic review is to summarise the evidence from RCTs to assess the effectiveness of either treatment approach as well as provide a more robust summary of the complications of the surgeries. During analysis, we planned to segregate subgroups according to any additional treatment performed concomitantly.

## OBJECTIVES

To assess the comparative effectiveness of fornix- versus limbal-based conjunctival flaps in trabeculectomy surgery for adult glaucoma, with a specific focus on intraocular pressure (IOP) control and complications (adverse effects).

## METHODS

### Criteria for considering studies for this review

**Types of studies—**We included all randomised controlled trials (RCTs) assessing the beneficial and harmful effects of fornix- versus limbal-based trabeculectomy for glaucoma, irrespective of publication status and language.

**Types of participants—**We included trials that enrolled the following participants:

- Adults (at least 18 years old) with glaucoma, of either sex with uncontrolled disease, defined as IOP above 21 mmHg with or without progressive visual field loss or optic disc cupping despite maximal medical therapy, without limitations as to region of residence.
- People with glaucoma irrespective of the type of glaucoma or evidence of cataract, refractive errors, retinal problems, diabetes mellitus or hypertension.
- People who underwent trabeculectomy using either the limbal or fornix approach, with or without the use of antimetabolites, with or without concurrent cataract surgery.
- People who were trabeculectomy treatment-naive with at least 12 months of follow-up.

Although trabeculectomy is also performed in children less than 18 years of age, we decided to exclude these individuals since wound healing is different in this age group and the rate of bleb scarring postoperatively is high (Parc 2001).

**Types of interventions—**Fornix-based trabeculectomy versus limbal-based trabeculectomy with or without:

1. Adjunctive use of MMC or 5-FU intra- or post-operatively;
2. Concomitant performance of cataract extraction, whether extracapsular or by phacoemulsification.

## Types of outcome measures

### Primary outcomes

1. The proportion of failed trabeculectomies at 24 months. Failure was defined as the need for repeat surgery or uncontrolled IOP (more than 22 mmHg) despite additional topical/systemic medications. Needling and 5-FU injections were allowed only during the first six months postoperatively. Additional needling or 5-FU injections were considered as failure.
2. Mean post-operative IOP at 24 months.

### Secondary outcomes

1. The proportion of failed trabeculectomies at 12 months. We defined failure as the need for repeat surgery or uncontrolled IOP (more than 22 mmHg) despite additional topical/systemic medications. Needling and 5-FU injections were allowed only during the first six months postoperatively. We considered additional needling or 5-FU injections as failure.
2. Mean IOP at 12 months.
3. The proportion of people with a loss of visual acuity equal to or greater than 0.3 LogMAR at 12 months. This approximates a Snellen visual acuity loss of 2 lines or more.
4. Number of medications required after surgery at 12 and 24 months of follow-up.
5. Quality of life (QOL) assessed by vision-specific QOL questionnaires or other surveys as reported in the included studies in the last follow-up.

**Adverse events:** The proportion of people experiencing the following adverse events at any time of the study:

- Wound leaks: the presence of a positive Seidel test (visible aqueous flow with the tear film stained with fluorescein);
- Hypotony: an IOP below 5 mmHg or associated with complications such as macular oedema and sight loss or choroidal detachments;
- Expulsive haemorrhage: choroidal haemorrhage. This is a rare complication. It usually occurs during the early postoperative period while the eye is still soft, leading to a marked rise in IOP;
- Shallow anterior chamber: prolonged shallowing of the anterior chamber giving rise to concern over possible contact of the lens with the cornea and occurring as a result of excessive drainage or choroidal effusions or both, leading to anterior displacement of the ciliary body, iris and lens;
- Early endophthalmitis (within 3 months post-operatively): an infection of the globe contents that even with prompt aggressive treatment often results in substantial loss of visual function.

- Late endophthalmitis: 'late' here implies infection arising from organisms gaining access to the globe through thin-walled drainage blebs or frank breaks in the conjunctival epithelium after the immediate postoperative period when infectious agents may have entered the eye during the surgical procedure;
- Bleb-related infection (blebitis): an infection of the bleb that prompts rapid treatment; this complication may cause progression of the infection to involve other globe contents.
- Bleb-related discomfort or pain.
- Other complications reported in included studies.

## Search methods for identification of studies

**Electronic searches—**We searched CENTRAL (which contains the Cochrane Eyes and Vision Trials Register) (2015, Issue 9), Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid MEDLINE Daily, Ovid OLDMEDLINE (January 1946 to October 2015), EMBASE (January 1980 to October 2015), Latin American and Caribbean Health Sciences Literature Database (LILACS) (January 1982 to October 2015), the ISRCTN registry (www.isrctn.com/editAdvancedSearch), ClinicalTrials.gov (www.clinicaltrials.gov) and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/search/en). We did not use any date or language restrictions in the electronic searches for trials. We last searched the electronic databases on 23 October 2015.

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

**Searching other resources—**We reviewed the bibliographic references of identified RCTs in order to find RCTs not identified by the electronic searches. We contacted researchers and practitioners active in the field of glaucoma to identify other published and unpublished trials.

## Data collection and analysis

**Selection of studies—**Two authors (MA and AM) independently assessed the titles and abstracts of all records identified by the electronic search using the 'Criteria for considering studies for this review' and classified the abstracts as (a) definitely relevant, (b) possibly relevant or (c) definitely not relevant. We retrieved full-text reports for records classified as 'definitely relevant' or 'possibly relevant' by both review authors after adjudication of discrepancies. We examined the full-text reports and then classified them as 'include', 'unsure', or 'exclude'. We contacted the investigators of studies classified as 'unsure' for further clarification. If no response was received within six weeks, we used the information as available. Any disagreements were resolved through discussion with a third review author (CH). We excluded studies labelled as 'exclude' by both review authors from the review and documented the reasons for exclusion. We assessed studies labelled 'include' for risk of bias.

**Data extraction and management—**Two authors independently extracted data using a form developed by Cochrane Eyes and Vision. If we could not reach agreement, we listed the study in the 'Studies awaiting classification' table until further clarification was available from the authors. In case of more than one publication of the same RCT, we reviewed data from all articles and extracted data as appropriate.

One author entered data into Review Manager 5 (RevMan 2014) and a second review author reviewed the accuracy of all entries. The two authors resolved disagreements by discussion.

**Assessment of risk of bias in included studies—**Two authors independently assessed the included studies for sources of bias according to the guidelines in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We evaluated the studies for the following criteria: sequence generation and allocation concealment (selection bias), masking of outcome assessors (detection bias), incomplete outcome data (attrition bias), and selective outcome reporting (reporting bias). We reported the judgement for each criterion as low risk of bias, high risk of bias or unclear (information insufficient to assess bias). We judged studies at high risk of bias when outcome assessors were not masked for postoperative outcomes like trabeculectomy failure and IOP level.

We resolved disagreements through discussion. We contacted the investigators of the studies for additional information on issues that were unclear from the information available in the original report. If no response was received within six weeks, we assessed the risk of bias based on the available information.

### Measures of treatment effect

**Dichotomous data—**We calculated a summary odds ratio (OR) with 95% confidence intervals (CI) for the outcomes: suture lysis procedure postoperatively, wound leak postoperatively, shallow anterior chamber, hypotony, choroidal detachment, choroidal effusion, hyphaema, number of eyes requiring needling by 5-FU. We had initially planned to calculate a summary risk ratio (RR) with 95% confidence intervals (CI) for the outcome of failed trabeculectomy. As a post-hoc decision, due to the low number of events reported, we used Peto OR (fixed-effect model) rather than RR (random-effects model).

**Continuous data—**We calculated mean differences with 95% CIs for mean IOP and number of medications. We had planned to analyse quality-of-life outcomes as continuous data when reported.

We intended to report the number needed to treat for an additional beneficial outcome (NNTB) when the absolute risk difference between the two groups was statistically significant.

**Unit of analysis issues—**The unit of analysis was one eye for each participant for two studies (Khan 1992; Lemon 1998). Two studies enrolled a few bilateral cases (14 participants in Cotran 2008 and 9 participants in Grehn 1989), randomising and analysing each eye separately and independently of the other eye. Two studies enrolled bilateral cases exclusively in a within-person (i.e., paired eye) design (el Sayyad 1999; Kozobolis 2002).

They randomised the first eye only, then they assigned the other technique for the second eye.

When both eyes from one participant were included in a trial, we planned to extract and analyse the data to properly account for the non-independence of eyes, following Chapter 9 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2011). Although we encountered bilateral enrolment in four studies (Cotran 2008; el Sayyad 1999; Grehn 1989; Kozobolis 2002), we could not obtain adequate information to account for the inclusion of more than one eye per participant.

**Dealing with missing data—**We contacted the study investigators for more information when data were missing or were difficult to interpret from the paper. We could not obtain complete data from all studies to perform intention-to-treat and worst-case scenario analyses. As a result we conducted 'available case analysis', analysing data as provided in the individual studies, as the primary analysis.

**Assessment of heterogeneity—**We assessed clinical and methodological heterogeneity of included studies by examining variations in the study design and methods, characteristics of the participants, variation in interventions, and length of follow-up. We also assessed statistical heterogeneity in each meta-analysis using the $I^2$ and $Chi^2$ statistics. We regarded statistical heterogeneity as substantial when either the $I^2$ statistic was greater than 50% or there was a low P value ($< 0.10$) in the $Chi^2$ test for heterogeneity.

**Assessment of reporting biases—**We could not investigate reporting biases (such as publication bias) using funnel plots as there were only six included trials. For selective outcome reporting bias, we planned to compare proto-cols with published full-text reports when available, and examine whether outcomes specified in the Methods section were reported in the Results section.

**Data synthesis—**We carried out statistical analysis using the Review Manager 5 software (RevMan 2014). We used a fixed-effect model for meta-analysis when it was reasonable to assume that studies were estimating the same underlying treatment effect, i.e., when trials were examining the same intervention and we judged the trials' populations and methods to be sufficiently similar. We did not detect sufficient clinical heterogeneity or substantial heterogeneity to use a randomeffects models for any primary meta-analysis.

**Subgroup analysis and investigation of heterogeneity—**We intended to perform the following subgroup analyses when sufficient data were available as follows.

Fornix- versus limbal-based approach when:

1. Trabeculectomy was performed without additional procedures (i.e., cataract surgery or use of antimetabolites).
2. Trabeculectomy was accompanied by use of antimetabolites (MMC or 5-FU).
3. Trabeculectomy was accompanied by cataract surgery.

4. Trabeculectomy was accompanied by cataract surgery and use of antimetabolites.

Since we did not have sufficient data and the number of trials was small, we could not perform subgroup analysis.

**Sensitivity analysis—**We planned to perform sensitivity analyses to determine the impact of excluding studies with high risk of bias. Because all included RCTs were assessed to be at high risk of detection bias for lack of masking outcome assessment, we did not conduct sensitivity analyses for this domain. We performed sensitivity analyses for all other risk of bias domains for which at least one study was assessed at high risk of bias. We considered a study influential if its exclusion changed the estimation of the effect estimate by at least 20% among included trials.

**'Summary of findings' table—**We present a 'Summary of findings' table with the main outcomes results using the GRADE approach (Langendam 2013). In order to complete the GRADE assessment, we took into account five factors that affected our confidence in the study results: study limitations, consistency of effect, imprecision, indirectness, and publication bias.

The protocol for this review was originally published in 2011 (Al-Haddad 2011). See Differences between protocol and review for changes to the methods since the publication of this protocol.

## RESULTS

### Description of studies

**Results of the search—**The electronic searches retrieved 526 records (Figure 1). After duplicate records were removed, we screened 336 records and obtained 19 full-text reports for further assessment. We excluded 13 studies: see Characteristics of excluded studies for details. Six trials met the criteria for inclusion (Cotran 2008; el Sayyad 1999; Grehn 1989; Khan 1992; Kozobolis 2002; Lemon 1998).

**Included studies—**Details of the included studies are presented in the Characteristics of included studies tables.

**Types of participants:** The six included trials randomised a total of 361 participants. These trials were conducted in America (Cotran 2008; Lemon 1998), Germany (Grehn 1989), Greece (Kozobolis 2002), India (Khan 1992), and Saudi Arabia (el Sayyad 1999). No corresponding clinical trial registrations were identified for any of the included trials. Four trials used a parallel-group design (Cotran 2008; Grehn 1989; Khan 1992; Lemon 1998); and two trials were within-person designs (el Sayyad 1999; Kozobolis 2002). We did not run a separate analysis on trials including bilateral cases since there was no significant difference when analysing outcomes between the two surgical approaches in those trials.

All of the participants had newly diagnosed glaucoma with no prior intraocular surgery (excluding laser) for glaucoma. The participants of four trials had only open-angle glaucoma (Cotran 2008; el Sayyad 1999; Kozobolis 2002; Lemon 1998); one trial included

participants with primary open-angle or primary closed-angle glaucoma (Khan 1992); and one trial did not specify the type of glaucoma (Grehn 1989). Three trials included participants that had both cataract and glaucoma (Cotran 2008; Kozobolis 2002; Lemon 1998). One study allowed enrolment of participants treated with argon laser trabeculoplasty (ALT) before surgical treatment (Cotran 2008).

**Type of interventions:** All included trials compared fornix-based versus limbal-based surgery for glaucoma. Three studies used a combined procedure (trabeculectomy plus phacoemulsification) for all participants (Cotran 2008; Kozobolis 2002; Lemon 1998). Cotran 2008 used a 1-site phacotrabeculectomy in the fornix-based conjunctival flap group and a 2-site phacotrabeculectomy in the limbal-based conjunctival flap group. Trabeculectomy with mitomycin C (MMC) was performed for all participants in three studies (Cotran 2008; Kozobolis 2002; Lemon 1998). Trabeculectomy with 5-FU was used in one study (el Sayyad 1999). Khan 1992 and Grehn 1989 did not report using either MMC or 5-FU.

**Types of outcomes:** All trials had at least 12 months of follow-up; three trials had at least 24 months of follow-up (Cotran 2008; el Sayyad 1999; Grehn 1989).

***(1) Failed trabeculectomy:*** None of the trials reported the proportion of participants who had a failed trabeculectomy at 24 months, a primary outcome measure in our review. Three trials evaluated the failure rate of trabeculectomy at 12 months (el Sayyad 1999; Khan 1992; Kozobolis 2002).

***(2) Mean post-operative IOP:*** Three trials reported mean IOP at 24 months, a primary outcome measure in our review (Cotran 2008; el Sayyad 1999; Grehn 1989). All included studies with the exception of Khan 1992 reported mean IOP at 12 months post-operatively.

***(3) Visual acuity:*** Four trials reported visual acuity outcomes (Cotran 2008; Khan 1992; Kozobolis 2002; Lemon 1998); however, none reported outcomes assessed as the proportion with a loss of visual acuity equal to or greater than 0.3 LogMAR (Snellen visual acuity loss of 2 lines or more). One trial assessed visual deterioration at one month (Khan 1992); two studies reported visual acuity improvement at 12 months (Kozobolis 2002); or 18 months (Lemon 1998).

***(4) Mean number of anti-glaucoma medications:*** Four trials reported the mean number of medications needed to control IOP after surgery: Grehn 1989 at 4 months, Kozobolis 2002 and Lemon 1998 at 12 months, and Cotran 2008 at 12 and 24 months. One trial assessed the proportion with post-operative increase in IOP requiring medical treatment, which was not an outcome specified for this review (Khan 1992).

***(5) Quality of life:*** None of the included studies assessed quality-of-life outcomes.

***(6) Adverse events:*** All trials reported post-operative adverse events. Many post-operative complications specified in Al-Haddad 2011, the protocol for this review, were assessed by at least one trial: wound leak (el Sayyad 1999; Kozobolis 2002; Lemon 1998), hypotony

(Cotran 2008; el Sayyad 1999; Lemon 1998), shallow anterior chamber (el Sayyad 1999; Grehn 1989; Khan 1992; Kozobolis 2002), and bleb infection (Cotran 2008).

Additional complications reported by included trials were choroidal detachment (el Sayyad 1999; Lemon 1998), choroidal effusion (Cotran 2008; Kozobolis 2002), hyphaema (Cotran 2008; Khan 1992; Lemon 1998), corneal toxicity (el Sayyad 1999), early and late conjunctival bleb leak (Cotran 2008), bleb vascularisation (Grehn 1989), hypertrophy of bleb (Khan 1992), iridocyclitis (Khan 1992), intra-operative trauma to lens (Khan 1992), cataract (Khan 1992), capsule opacification (Kozobolis 2002), cystic bleb or bleb fibrosis (Kozobolis 2002), fibrin exudation (Kozobolis 2002), pupillary membrane (Kozobolis 2002), cystoid macular oedema (Lemon 1998), and hemiretinal vein occlusion (Lemon 1998).

Additional post-operative procedures also were reported in the following trials:

- needling with 5-FU (Cotran 2008; Lemon 1998),
- suture lysis (Cotran 2008; el Sayyad 1999; Lemon 1998),
- digital massage (Cotran 2008),
- releasable suture removal (Lemon 1998).

No trial reported number of expulsive haemorrhage (choroidal haemorrhage), early or late endophthalmitis, or bleb-related discomfort or pain.

**Excluded studies—**See Characteristics of excluded studies for details.

We excluded 13 studies. Ten studies were not randomised (Berestka 1997; Fukuchi 2006; Henderson 2004; Lin 2007; Mandiæ 2004; Murchison 1990; Reichert 1987; Shingleton 1999; Stewart 1994; Traverso 1987); two trials had follow-up less than 12 months, the minimum follow-up time eligible for our review (Brincker 1992; Cheng 2012); and one trial had no available data at 12 or 24 months of follow-up (Auw-Haedrich 1998).

## Risk of bias in included studies

Overall, the trials included in this review had unclear or high risk of bias for most domains assessed. Details of the risk of bias assessments are shown in the Characteristics of included studies tables. Here we summarise the risk of bias assessments for trials included in this review. See also Figure 2 and Figure 3.

**Allocation—**Randomisation in two trials was adequately generated (el Sayyad 1999; Grehn 1989). The methods of allocation concealment before randomisation were reported in only one trial (Cotran 2008); and were unclear for the remaining five included trials (el Sayyad 1999; Grehn 1989; Khan 1992; Kozobolis 2002; Lemon 1998). Primary investigators whom we were able to contact could not provide further information.

**Masking of outcome assessors (detection bias)—**It was not practical to mask the assessment of the outcomes for all trials. Since trabeculectomy is a surgical intervention, the physicians knew the treatment they administered and examined postoperatively. The

examining physician (who apparently was the surgeon) also was not masked to the type of conjunctival incision performed as that would be evident during the exam. We think that the lack of masking could influence the clinical outcome interpretation (surgical failure) and the IOP measurement. For this reason we assessed all trials in this review at high risk of detection bias.

**Incomplete outcome data—**The majority of the included trials had similar rates of follow-up in the comparison groups and intention-to-treat analysis was performed for almost all of them. Most of the trials reported the outcomes with no missing data (el Sayyad 1999; Khan 1992; Kozobolis 2002; Lemon 1998); or small amounts of missing data (< 5%) (Cotran 2008). We assessed these studies at low risk of attrition bias. One study did not specify the reasons for some missing data and follow-up (Grehn 1989). The author was contacted but no further information could be obtained.

**Selective reporting—**The majority of the studies had unclear reporting bias, since we did not have access to the original protocols or additional information. We assessed one trial at high risk of reporting bias because results for only two out of five specified outcomes were reported (Grehn 1989).

## Effects of interventions

See: **Summary of findings for the main comparison** Fornix versus limbal-based conjunctival trabeculectomy flaps for glaucoma

**(1) Failed trabeculectomy—**None of the included trials reported trabeculectomy failure at 24 months. One trial noted that 2 (4.6%) of 43 eyes in each group required reoperation during 3 years of follow-up (Cotran 2008). Three trials evaluated the failure rate of trabeculectomy at 12 months (el Sayyad 1999; Khan 1992; Kozobolis 2002). No failures were observed in two of these trials (118 eyes), precluding an estimation of Peto odds ratio (OR) and inclusion in meta-analysis (el Sayyad 1999; Kozobolis 2002). In Khan 1992, 1/50 eyes failed trabeculectomy in the fornix group compared with 3/50 in the limbal group (Peto OR 0.36, 95% CI 0.05 to 2.61).

Two trials did not report trabeculectomy failure at any time-point (Grehn 1989; Lemon 1998).

**(2) Mean post-operative IOP—**Three trials reported mean IOP at 24-month follow-up (Cotran 2008; el Sayyad 1999; Grehn 1989). Grehn 1989 did not report precision measures for effect estimates, but found the mean IOP was 17 mmHg in both groups 24 months post-operatively. Analysis of the available data from two trials suggested uncertainty in the effect between groups with respect to IOP at 24-month follow-up (MD 0.86 mmHg, 95% CI −0.52 to 2.24; 139 eyes) (Analysis 1.1; Figure 4).

Five trials reported mean IOP at 12-month follow-up (Cotran 2008; el Sayyad 1999; Grehn 1989; Kozobolis 2002; Lemon 1998). No precision measures were reported by Grehn 1989, but the mean IOP was 16 mmHg among 47 eyes in the fornix-based group and 17 mmHg among 43 eyes in the limbal-based group. Analysis of the available data from four trials

demonstrated a mean difference in postoperative IOP of less than 1 mmHg between the two surgical groups at 12-month follow-up (MD 0.44 mmHg, 95% CI −0.45 to 1.33; 247 eyes) (Analysis 1.2; Figure 5). Clinically, the interval of difference in postoperative IOP between the two types of surgery also is not significant.

One trial did not report mean post-operative IOP outcomes (Khan 1992).

**(3) Visual acuity—**No trial reported visual acuity outcomes at 24 months and no trial reported the proportion with a loss of visual acuity equal to or greater than 0.3 LogMAR. One trial studied visual acuity deterioration at one month (Khan 1992): 10 of 50 eyes (20%) in the fornix-based surgery group and 15 of 50 eyes (30%) in the limbal-based surgery had visual acuity deterioration. Two trials looked into improvement in vision: Kozobolis 2002 noted no difference between the two types of incisions at 12 months and Lemon 1998 reported vision improvement was more favourable but not significantly better in the fornix-based compared with limbal-based surgery group after 18 months. The latter two trials studied phacotrabeculectomy outcomes and thus improvement in visual acuity could be more related to the cataract extraction than to glaucoma surgery or IOP control.

Cotran 2008 reported that “corrected visual acuity improved markedly in both groups after surgery”, but there was minimal clinical difference in Snellen decimal acuity between groups at three months after surgery (MD −0.09, 95% CI −0.18 to 0.00; 86 eyes).

Two trials did not report visual acuity outcomes at any time point (el Sayyad 1999; Grehn 1989).

**(4) Mean number of anti-glaucoma medications—**One trial reported the number of anti-glaucoma medications at 24 months (Cotran 2008), with no difference noted between surgical groups (MD −0.09 mmHg, 95% CI −0.43 to 0.25; 86 eyes).

Three trials reported the mean number of anti-glaucoma medications at 12 months of follow-up (Cotran 2008; Kozobolis 2002; Lemon 1998). Analysis of the available data in the three trials showed no difference between surgical groups in the mean number of post-operative IOP-lowering medications at 12 months (MD 0.02, 95% CI −0.15 to 0.19; 194 eyes) (Analysis 1.3; Figure 6).

In one trial, no difference in the number of anti-glaucoma medications between groups was noticed at 4 months of follow-up (Grehn 1989); no data at 12 or 24 months of follow-up were reported.

Two trials did not report the mean number of anti-glaucoma medications needed (el Sayyad 1999; Khan 1992).

**(5) Quality of life—**Quality-of-life data were not reported in any of the included studies.

**(6) Adverse events—**All trials reported post-operative adverse events (Table 1). Follow-up was 12 months in Khan 1992 and Kozobolis 2002, 18 months in Lemon 1998, 30 months in Grehn 1989, 3 years in Cotran 2008, and 4 years in el Sayyad 1999. No trial reported

number of expulsive haemorrhage (choroidal haemorrhage), early or late endophthalmitis, or bleb-related discomfort or pain.

**Wound leak:** Wound leak was reported by three included trials (el Sayyad 1999; Kozobolis 2002; Lemon 1998). Fornix-based surgery was associated with more cases of wound leak (OR 1.20, 95% CI 0.37 to 3.87; 185 eyes); however, the effect was uncertain with confidence intervals for all three trials crossing the line of no effect (Analysis 1.4).

**Hypotony:** Post-operative hypotony was reported in three trials (Cotran 2008; el Sayyad 1999; Lemon 1998). Participants receiving the fornix-based trabeculectomy technique had twice the odds of post-operative hypotony compared with the limbal-based technique (OR 1.97, 95% CI 0.68 to 5.74; 198 eyes). Although the direction of effect for all three trials favoured the limbal-based technique, the effect is uncertain and could favour either technique (Analysis 1.4).

**Shallow anterior chamber:** Four trials evaluated post-operative incidence of shallow anterior chamber (el Sayyad 1999; Grehn 1989; Khan 1992; Kozobolis 2002). Fewer cases in the fornix-based group had post-operative shallow anterior chamber compared with the limbal-based group (OR 0.44, 95% CI 0.22 to 0.92; 302 eyes) (Analysis 1.4).

**Bleb infection:** In one trial reporting bleb infection as an adverse event (Cotran 2008), no eyes in the fornix-based group compared with one eye in the limbal-based group had this event (OR 0.33, 95% CI 0.01 to 8.22; 86 eyes).

### Other post-operative complications

***Choroidal detachment:*** Two trials assessed this complication (el Sayyad 1999; Lemon 1998). The number of events was low and similar in the fornix-based group compared with the limbal-based group (OR 0.60, 95% CI 0.13 to 2.85; 125 eyes) (Analysis 1.4).

***Choroidal effusion:*** This complication was reported in two trials (Cotran 2008; Kozobolis 2002). There were fewer cases in the fornix-based group compared with the limbal-based group (OR 0.55, 95% CI 0.15 to 1.97; 146 eyes); however, the effect was uncertain with confidence interval crossing the line of no effect (Analysis 1.4).

***Hyphaema:*** Post-operative hyphaema was evaluated in three studies (Cotran 2008; Khan 1992; Lemon 1998). Fornix-based surgery led to fewer cases of hyphaema compared with the limbal-based surgery (OR 0.66, 95% CI 0.20 to 2.17; 215 eyes); however, due to the small number of events the effect of incision type on this complication was very uncertain.

***Corneal toxicity:*** Corneal toxicity was reported by two trials (el Sayyad 1999; Khan 1992). There were more cases in the fornix-based group compared with the limbal-based group (OR 1.39, 95% CI 0.45 to 4.30); however, the confidence interval was wide suggesting uncertainty in the estimate of this effect.

Results for additional post-operative complications reported by only one study are listed in Table 1 and include:

- Cotran 2008 (86 eyes): early and late conjunctival bleb leak
- Grehn 1989 (62 eyes): bleb vascularisation
- Khan 1992 (100 eyes): hypertrophy of bleb, iridocyclitis, intra-operative trauma to lens, and cataract
- Kozobolis 2002 (60 eyes): capsule opacification, cystic bleb or bleb fibrosis, fibrin exudation, and pupillary membrane
- Lemon 1998 (69 eyes): cystoid macular oedema and hemiretinal vein occlusion.

### Additional post-operative procedures

***Needling with 5-FU:*** Two trials compared the need for post-operative needling with 5-FU between fornix-based and limbal-based surgery (Cotran 2008; Lemon 1998). Analysis showed uncertainty as to the effect of the two types of surgery on the need for needling with 5-FU (OR 0.63, 95% CI 0.22 to 1.81; 155 eyes) (Analysis 1.4).

***Suture lysis procedure:*** Post-operative suture lysis procedure was described in three trials (Cotran 2008; el Sayyad 1999; Lemon 1998). Data analysis of these studies showed similar odds between the two types of surgical flaps with uncertainty in the effect estimate (OR 1.07, 95% CI 0.50 to 2.29; 211 eyes) (Analysis 1.4).

Results for additional post-operative procedures reported by only one study are listed in Table 1 and include:

- Cotran 2008 (86 eyes): digital massage
- Lemon 1998 (69 eyes): releasable suture removal and repair of wound.

**Sensitivity analysis results—**All included RCTs were assigned high risk of bias for masking of outcome assessment (detection bias); only one trial was additionally assigned high risk for attrition bias and reporting bias (Grehn 1989). Hence, sensitivity analysis was performed while eliminating this trial from the analysis (Grehn 1989). Conclusions regarding primary outcomes remained essentially unchanged; mean IOP at 24 months did not show a significant difference between groups (MD 1.13, 95% CI −0.63 to 2.89 with Grehn 1989, while MD 0.86, 95% CI −0.52 to 2.24 when eliminating Grehn 1989 from analysis). With regards to mean IOP at 12 months, no change in the results was seen as this outcome could not be estimated for this study. With respect to adverse events, the significant difference noted in the incidence of shallow anterior chamber became insignificant when removing Grehn 1989 from the analysis (OR = 0.44, CI 0.17 to 1.17, P = 0.10 without Grehn 1989; while OR = 0.44, CI 0.22 to 0.92, P = 0.03 with Grehn 1989 in the analysis). Grehn 1989 was the only trial reporting avascularised bleb as an outcome with no difference noted between groups.

# DISCUSSION

## Summary of main results

The main finding of this review was that there was a high level of uncertainty when comparing surgical outcomes of fornix- versus limbal- based trabeculectomy surgeries due mostly to low event rates and wide confidence intervals. This also applied to postoperative complications except in one outcome: the incidence of post-operative shallow anterior chamber which was twice as common in limbal-based trabeculectomy as compared to fornix-based trabeculectomy. As far as other complications, although limbal-based surgeries were reportedly better in regards to wound leakage, hypotony, bleb leak and bleb fibrosis, we were very uncertain as to a definite effect of incision type on those complications due to the small number of cases reported. When analysing data from a clinical perspective, there was really no clinically significant difference between groups with regards to postoperative IOP measurements or number of glaucoma medications needed after surgery. As such, surgeons would default to one surgical approach versus another based on personal preference, personal experience, or level of complexity of the case, or a combination of these factors. In eyes that have had multiple surgeries or have significant scarring, fornix-based flaps tend to provide better surgical exposure for dissection of the scleral flap and better access to the trabeculectomy performed at the iris root. Also in combined procedures where trabeculectomy is performed with cataract surgery, fornix-based surgery provides easier access to the surgical wound.

This review analysed six eligible trials: three on phacotrabeculectomy with mitomycin C (MMC) (Cotran 2008; Kozobolis 2002; Lemon 1998); one on trabeculectomy with 5-fluorouracil (5-FU) (el Sayyad 1999); and two on isolated trabeculectomy (Grehn 1989; Khan 1992). Although we did plan to include combined procedures (phacotrabeculectomy and use of antimetabolites), results should be viewed with that consideration in mind. The number of eligible trials was too small to allow sub-analysis by the specific type of procedure performed or antimetabolite used. Phacotrabeculectomy entails performing two surgeries (cataract and glaucoma surgery), thus the operating time is longer and the risk of potential complications is higher than a simple trabeculectomy. Surgical outcomes would also be expected to differ between 1-site and 2-site phacotrabeculectomy and that requires subgroup comparison separately. This could not be practically performed in this review due to the small numbers of eligible trials.

Lens extraction per se may have an effect on IOP (Friedman 2006; Shrivastava 2010); the use of antimetabolites similarly has an additional effect on glaucoma control (Wilkins 2005).

Main outcome measures were trabeculectomy failure and mean IOP at 24 and 12 months postoperatively. However, glaucoma is a chronic disease and long-term follow-up is needed to assess surgical success. Most trials looked at IOP value as the main measure of glaucoma control; visual field loss and cup-to-disc ratio have not been well reported. Trials where visual acuity was measured were those studying phacotrabeculectomy outcomes and thus improvement in visual acuity would be more related to the cataract extraction than to glaucoma surgery or IOP control (Kozobolis 2002; Lemon 1998).

Prognosis and approach to management also vary by type of glaucoma. Although most participants in the included trials had primary open-angle glaucoma, one trial also enrolled people with pseudoexfoliative glaucoma (Kozobolis 2002); and another included eyes with narrow-angle glaucoma (Khan 1992). Postoperative course and complications are expected to be different among these types of glaucoma; for example eyes with pseudoexfoliative glaucoma had higher rates of fibrin exudation and pupillary membrane formation (Kozobolis 2002).

As for risk of bias, most studies had unclear risk for random sequence generation, allocation concealment and selective outcome reporting due to insufficient information; otherwise they had low risk for attrition bias (except Grehn 1989). All trials were assessed as high risk for detection bias as outcome assessors were not masked in any of the six trials. In one trial, it was noted that two out of five outcomes were reported in the results section (Grehn 1989). We attempted to contact authors but could not obtain further information. This particular trial was assigned high risk for detection, attrition and reporting bias. However, sensitivity analysis showed no difference in primary outcome measures after eliminating this trial.

### Overall completeness and applicability of evidence

With only six trials in this review, the evidence of the difference in efficacy and complications between fornix versus limbal trabeculectomy was incomplete. It was uncertain in this review whether there was a difference between the two surgical techniques in lowering IOP at 12 and 24 months of follow-up. We found three trials that assessed the failure rate between fornix and limbal trabeculectomy at 12 months of follow-up, and none reported the failure rate at 24 months. Throughout our search we found other studies that compared fornix to limbal trabeculectomy, but most were not randomised and some of them had only short-term follow-up, so they were excluded.

Furthermore, one trial included both primary closed-angle and open-angle glaucoma cases without differentiation in the analysis (Khan 1992), while others included only open-angle glaucoma (Cotran 2008; el Sayyad 1999; Kozobolis 2002; Lemon 1998). The remaining study did not specify the glaucoma type in its methodology (Grehn 1989). On the other hand, some studies excluded individuals with certain conditions: neovascular glaucoma and phacolytic glaucoma (Cotran 2008), previous ocular surgery (el Sayyad 1999), previous laser trabeculoplasty and diabetes (Kozobolis 2002), or previous ocular surgery and secondary glaucoma (Lemon 1998). Two trials did not specify any exclusion criteria (Grehn 1989; Khan 1992). Differences in eligibility across studies and lack of the specific inclusion criteria could affect the final outcome estimate and rate of complications.

Several studies had different follow-up duration: two studies reported follow-up for one year (Khan 1992; Kozobolis 2002), and others for more than two years (Cotran 2008; el Sayyad 1999; Grehn 1989).

Most of the studies considered their main outcome as mean IOP at a specific follow-up time and did not specify a definition for trabeculectomy failure. The definition of trabeculectomy failure was variable across studies with different cutoffs for acceptable IOP. Similarly there were discrepancies in definitions for vision deterioration and the time point in the

postoperative period that these outcomes were measured. IOP measurements are subjective and thus are prone to bias by the examiner especially when the examiner is not masked. Central corneal thickness does affect IOP measurement and this confounding factor has not been considered in the included studies. Combined procedures (like trabeculectomy and cataract surgery) introduce additional sources of bias when deriving conclusions from these studies.

### Quality of the evidence

All the trials included in this review used randomised controlled methodology; all the included trials did not report masking of the outcomes. Most of the outcomes studied in the six trials included in this review were uniformly reported in all the trials. Only one study reported missing numbers of participants at 12 and 24 months of follow-up (final analysis included 43 out of 46 and 43 out of 44 eyes in limbal- and fornix-based groups respectively) (Cotran 2008). However, authors reported that a review of the data from these cases showed that the main results and conclusions were not affected. Lemon 1998 reported data for 23 out of 30 and 25 out of 39 included eyes in limbal-based and fornix-based groups respectively, and no explanation was provided for the missing eyes at 12 months of follow-up.

No study reported outcomes for failed trabeculectomy at 24 months after surgery. At 12 months, we graded the quality of evidence as low, due to methodological issues with the one study that reported this outcome and high degree of imprecision in the effect estimate. The quality of the evidence was moderate for our estimates of IOP at 24 and 12 months. For this outcome, the measurements at 12 and 24 months both had confidence intervals that crossed the null and were within 3 mmHg. The addition of other studies could change the point estimate of the effect, but is unlikely to change the clinical meaning. We graded the quality of evidence for the mean number of medications needed after surgery at 12 months as high, as the addition of other studies would be unlikely to change the clinical interpretation of no difference between groups. Because of the small numbers of events and total participants, the risk of many reported adverse events was uncertain and those that were found to be statistically significant may have been due to chance.

### Potential biases in the review process

It is likely that all relevant studies have been included in this review. The decision to exclude one RCT was based on the difficulty in obtaining all the necessary data (Auw-Haedrich 1998). It is possible that there are unpublished trials we did not identify. If trials with negative findings are more likely to remain unpublished (publication bias), the difference between the limbal and fornix approach in trabeculectomy surgery may not be fully estimated in this review. Some risk of bias criteria were not clear in a number of studies, and efforts to contact the authors have failed; these were thus labelled as ’unclear’. Also, we intended to perform further subgroup analyses, but due to insufficient data and the small number of trials included in this review, we could not practically perform such an analysis.

### Agreements and disagreements with other studies or reviews

The results of this systematic review agreed with most of the previous reviews and studies. One review article concluded that there was no statistically significant difference in IOP control between the two techniques (Kohl 2005). A fornix-based trabeculectomy had an increased incidence of early bleb leaks without serious sequelae. Similar results were reported in other studies (Shuster 1984).

## AUTHORS' CONCLUSIONS

### Implications for practice

It is unclear whether the efficacy of trabeculectomy surgery with respect to IOP control or bleb failure is related to the type of conjunctival flap incision (fornix- versus limbal-based). Only one possibly significant difference was detected in the rates of shallow anterior chamber postoperatively: this was more commonly reported in limbal-based flaps. In people with pre-existing shallow chambers or those at risk of this complication, fornix-based conjunctival flaps may be a safer option when performing trabeculectomy surgery. However the reported results in this review apply to a follow-up time of 24 months: longer follow-up may uncover different findings.

### Implications for research

Glaucoma is a chronic disease and longer follow-up is needed to assess long-term surgical failure and glaucoma control. Our review reported results at 12 and 24 months; future trials with longer follow-up may better detect differences in surgical outcomes that were not identified at this time. Additionally, cohort studies may serve as potential sources of evidence as they are better suited for longer follow-up and amenable to use of large datasets (e.g., electronic medical records). This review also included trials studying combined cataract and glaucoma surgery as well as participants who received intra-operative and peri-operative antimetabolites. Those may pose confounding effects on the comparison of surgical conjunctival incision types. Future research comparing surgical flaps in isolated trabeculectomy surgery without the use of antimetabolites would give a more definitive answer. Glaucoma progression also entails visual field losses and not only increase in IOP. Visual field changes need to be incorporated as an outcome in future studies.

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* Indicates the major publication for the study

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## APPENDICES

## Appendix 1. CENTRAL search strategy

| | |
|---|---|
| **#1** | MeSH descriptor Glaucoma |
| **#2** | glaucoma* |
| **#3** | MeSH descriptor Trabeculectomy |
| **#4** | trabeculectom* |
| **#5** | MeSH descriptor Filtering Surgery |

| | |
|---|---|
| **#6** | MeSH descriptor Trabecular Meshwork |
| **#7** | (#1 OR #2 OR #3 OR #4 OR #5 OR #6) |
| **#8** | MeSH descriptor Surgical Flaps |
| **#9** | limbal* |
| **#10** | fornix* |
| **#11** | (#8 OR #9 OR #10) |
| **#12** | (#7 AND #11) |

## Appendix 2. MEDLINE(Ovid) search strategy

1. randomized controlled trial.pt.
2. (randomized or randomised).ab,ti.
3. placebo.ab,ti.
4. dt.fs.
5. randomly.ab,ti.
6. trial.ab,ti.
7. group0.ab,ti.
8. or/1–7
9. exp animals/
10. exp humans/
11. 9 not (9 and 10)
12. 8 not 11
13. exp glaucoma/
14. glaucoma$.tw.
15. Trabeculectomy/
16. trabeculectom$.tw.
17. filtering surgery/
18. trabecular meshwork/
19. or/13–18
20. surgical flaps/
21. limbal$.tw.
22. fornix$.tw.
23. or/20–22

24. 19 and 23
25. 12 and 24

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

## Appendix 3. EMBASE (Ovid) search strategy

1. exp randomized controlled trial/
2. exp randomization/
3. exp double blind procedure/
4. exp single blind procedure/
5. random$.tw.
6. or/1–5
7. (animal or animal experiment).sh.
8. human.sh.
9. 7 and 8
10. 7 not 9
11. 6 not 10
12. exp clinical trial/
13. (clin$ adj3 trial$).tw.
14. ((singl$ or doubl$ or trebl$ or tripl$) adj3 (blind$ or mask$)).tw.
15. exp placebo/
16. placebo$.tw.
17. random$.tw.
18. exp experimental design/
19. exp crossover procedure/
20. exp control group/
21. exp latin square design/
22. or/12–21
23. 22 not 10
24. 23 not 11
25. exp comparative study/
26. exp evaluation/

27. exp prospective study/
28. (control$ or prospectiv$ or volunteer$).tw.
29. or/25–28
30. 29 not 10
31. 30 not (11 or 23)
32. 11 or 24 or 31
33. exp glaucoma/
34. glaucoma$.tw.
35. Trabeculectomy/
36. trabeculectom$.tw.
37. filtering operation/
38. trabecular meshwork/
39. or/33–38
40. limbal$.tw.
41. fornix$.tw.
42. or/40–41
43. 39 and 42
44. 32 and 43

## Appendix 4. LILACS search strategy

glaucoma$ and limbal$ and fornix$

## Appendix 5. ISRCTN search strategy

Glaucoma AND Limbal AND Fornix

## Appendix 6. ClinicalTrials.gov search strategy

Glaucoma AND Limbal AND Fornix

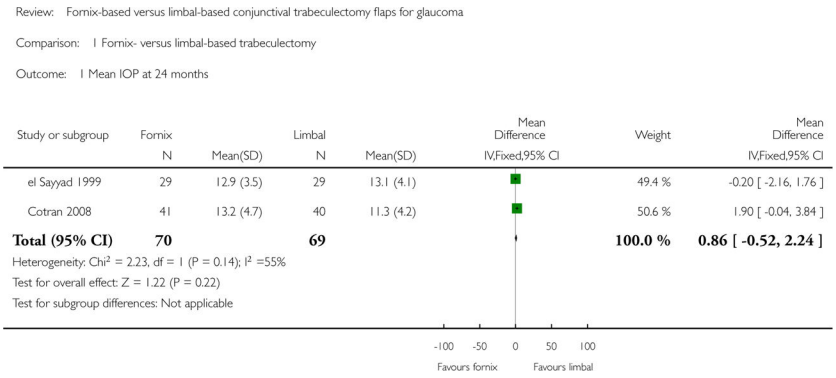
## Appendix 7. ICTRP search strategy

Glaucoma AND Limbal AND Fornix

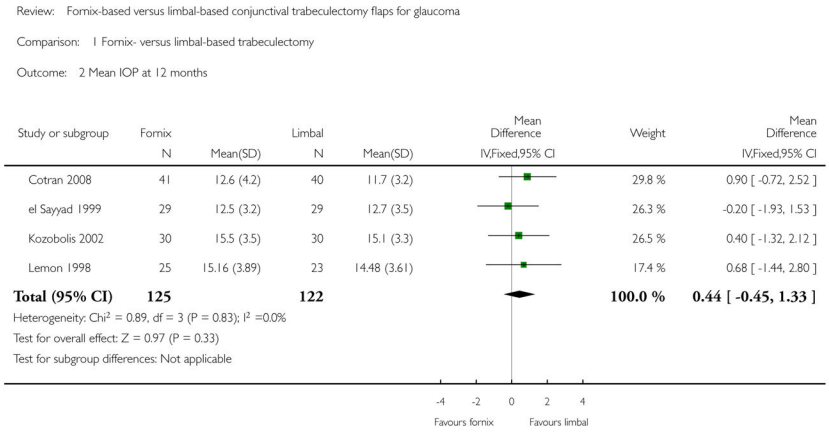
# DATA AND ANALYSES

## Comparison 1. Fornix- versus limbal-based trabeculectomy

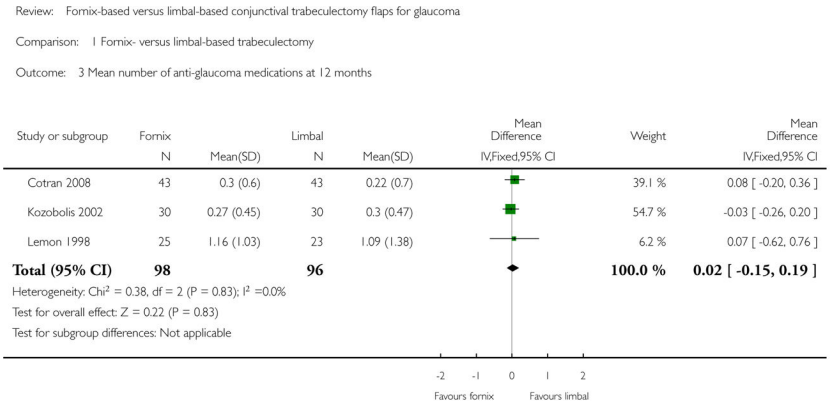
| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Mean IOP at 24 months | 2 | 139 | Mean Difference (IV, Fixed, 95% CI) | 0.86 [−0.52, 2.24] |
| 2 Mean IOP at 12 months | 4 | 247 | Mean Difference (IV, Fixed, 95% CI) | 0.44 [−0.45, 1.33] |
| 3 Mean number of anti-glaucoma medications at 12 months | 3 | 194 | Mean Difference (IV, Fixed, 95% CI) | 0.02 [−0.15, 0.19] |
| 4 Adverse events | 6 | | Odds Ratio (IV, Fixed, 95% CI) | Subtotals only |
| 4.1 Wound leak | 3 | 185 | Odds Ratio (IV, Fixed, 95% CI) | 1.20 [0.37, 3.87] |
| 4.2 Hypotony | 3 | 198 | Odds Ratio (IV, Fixed, 95% CI) | 1.97 [0.68, 5.74] |
| 4.3 Shallow anterior chamber | 4 | 302 | Odds Ratio (IV, Fixed, 95% CI) | 0.44 [0.22, 0.92] |
| 4.4 Choroidal detachment | 2 | 125 | Odds Ratio (IV, Fixed, 95% CI) | 0.60 [0.13, 2.85] |
| 4.5 Choroidal effusion | 2 | 146 | Odds Ratio (IV, Fixed, 95% CI) | 0.55 [0.15, 1.97] |
| 4.6 Hyphaema | 3 | 215 | Odds Ratio (IV, Fixed, 95% CI) | 0.66 [0.20, 2.17] |
| 4.7 Corneal toxicity | 2 | 112 | Odds Ratio (IV, Fixed, 95% CI) | 1.39 [0.45, 4.30] |
| 4.8 Needing needling with 5-FU | 2 | 155 | Odds Ratio (IV, Fixed, 95% CI) | 0.63 [0.22, 1.81] |
| 4.9 Suture lysis procedure | 3 | 211 | Odds Ratio (IV, Fixed, 95% CI) | 1.07 [0.50, 2.29] |



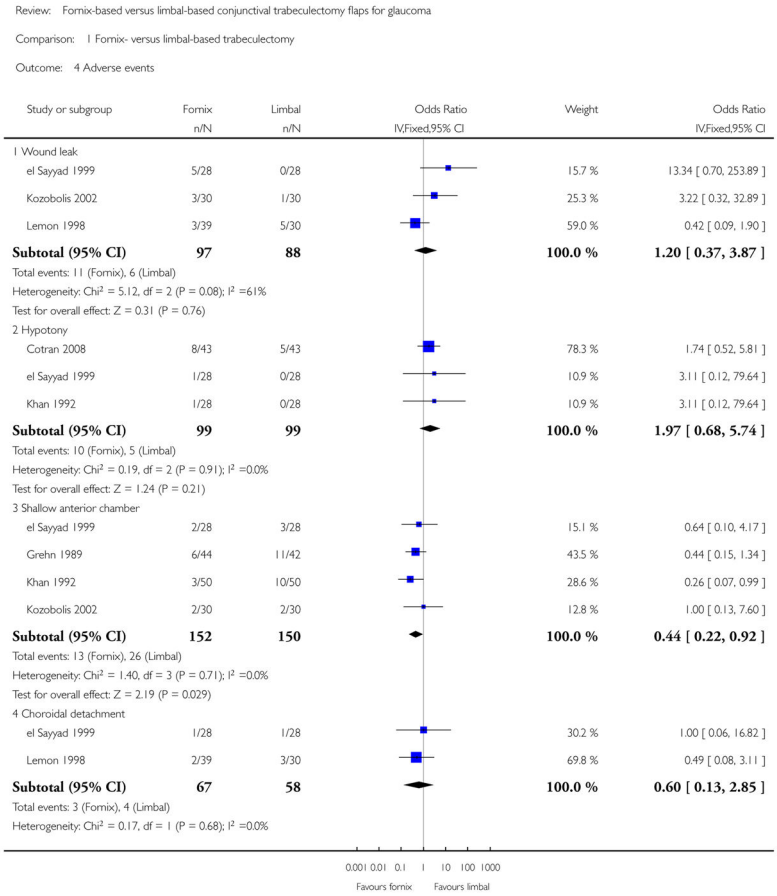

**Analysis 1.1.**
Comparison 1 Fornix- versus limbal-based trabeculectomy, Outcome 1 Mean IOP at 24 months.

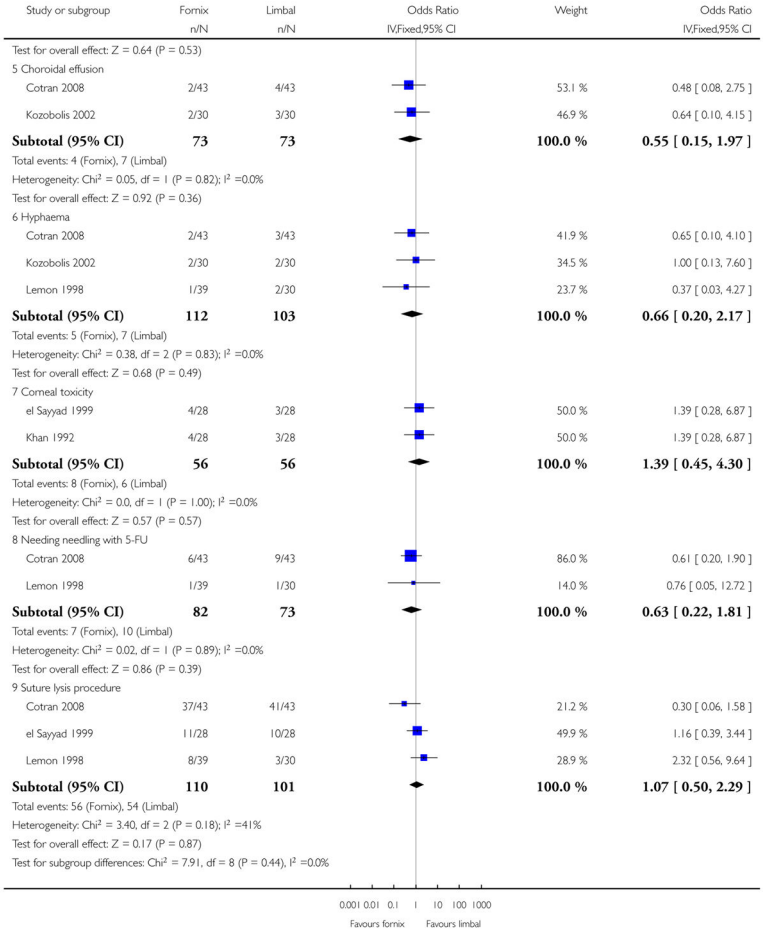



**Analysis 1.2.**
Comparison 1 Fornix- versus limbal-based trabeculectomy, Outcome 2 Mean IOP at 12 months.




**Analysis 1.3.**
Comparison 1 Fornix- versus limbal-based trabeculectomy, Outcome 3 Mean number of anti-glaucoma medications at 12 months.






**Analysis 1.4.**
Comparison 1 Fornix- versus limbal-based trabeculectomy, Outcome 4 Adverse events.

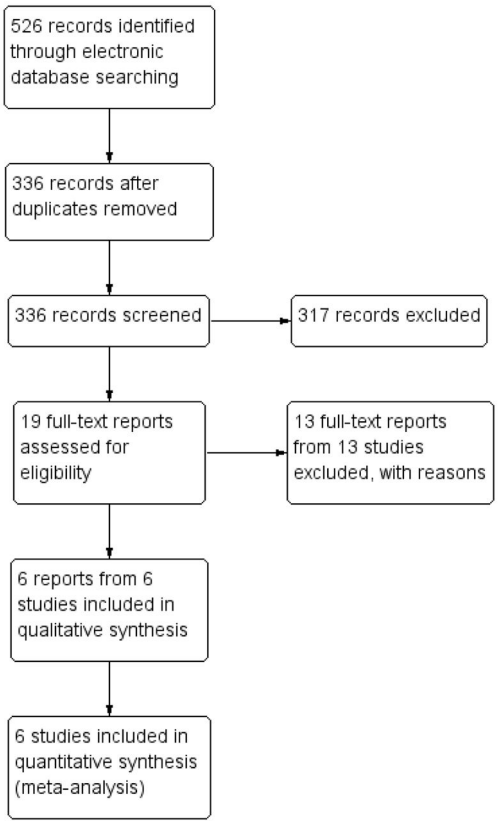



**Figure 1.**
Study flow diagram.

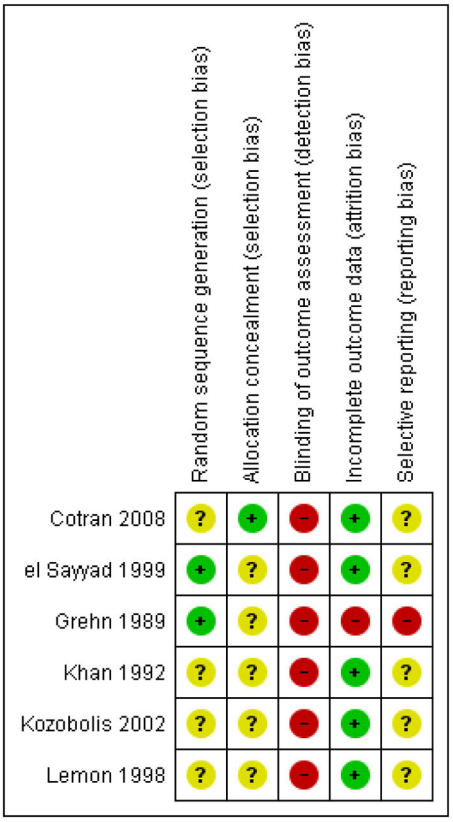



**Figure 2.**

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

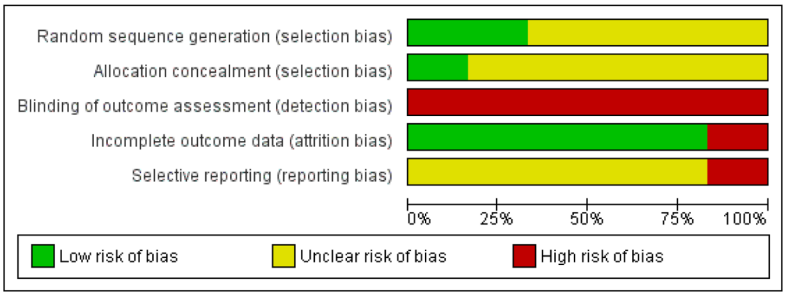



**Figure 3.**

Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

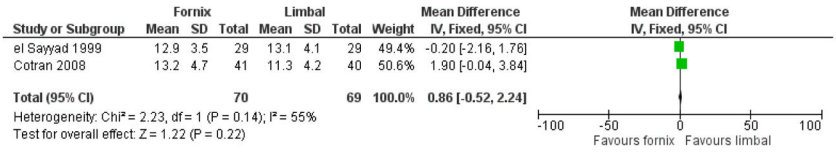



**Figure 4.**

Forest plot of comparison: 1 Fornix- versus limbal-based trabeculectomy, outcome: 1.1 Mean IOP at 24 months.

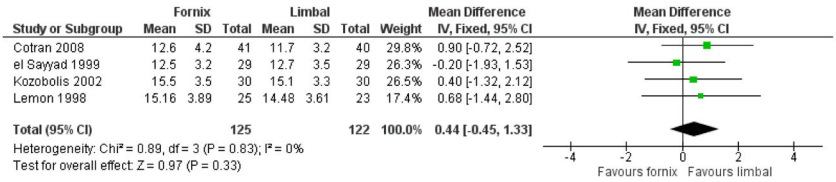



**Figure 5.**

Forest plot of comparison: 1 Fornix- versus limbal-based trabeculectomy, outcome: 1.2 Mean IOP at 12 months.

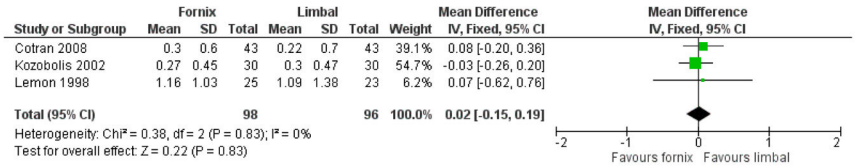



**Figure 6.**

Forest plot of comparison: 1 Fornix- versus limbal-based trabeculectomy, outcome: 1.3 Mean number of anti-glaucoma medications at 12 months.

## Table 1

Adverse events for fornix-based versus limbal-based trabeculectomy

| Adverse event | Number of trials | Number of participants | Odds ratio [95% confidence interval] |
|---|---|---|---|
| **Complications** | | | |
| Wound leak | 3 | 185 | 1.20 [0.37 to 3.87] |
| Hypotony | 3 | 198 | 1.97 [0.68 to 5.74] |
| Shallow anterior chamber | 4 | 302 | **0.44 [0.22 to 0.92]** |
| Bleb infection | 1 | 86 | 0.33 [0.01 to 8.22] |
| Choroidal detachment | 2 | 125 | 0.60 [0.13 to 2.85] |
| Choroidal effusion | 2 | 146 | 0.55 [0.15 to 1.97] |
| Hyphaema | 3 | 215 | 0.66 [0.20 to 2.17] |
| Corneal toxicity | 2 | 112 | 1.39 [0.45 to 4.30] |
| Conjunctival bleb leak within 3 months | 1 | 86 | 15.08 [0.82 to 276.66] |
| Conjunctival bleb leak after 3 months | 1 | 86 | 0.19 [0.01 to 4.09] |
| Avasculrised bleb | 1 | 62 | 2.74 [0.88 to 8.55] |
| Hypertrophy of bleb | 1 | 100 | 0.13 [0.01 to 2.60] |
| Iridocyclitis | 1 | 100 | 0.64 [0.17 to 2.41] |
| Intra-operative trauma to lens | 1 | 100 | 0.65 [0.10 to 4.09] |
| Cataract requiring surgery | 1 | 100 | **0.14 [0.03 to 0.71]** |
| Capsule opacification | 1 | 60 | 1.00 [0.28 to 3.54] |
| Cystic bleb/bleb fibrosis | 1 | 60 | 1.56 [0.24 to 10.05] |
| Fibrin exudation | 1 | 60 | 0.69 [0.21 to 2.30] |
| Pupillary membrane | 1 | 60 | 0.46 [0.08 to 2.75] |
| Cystoid macular oedema | 1 | 69 | 2.38 [0.09 to 60.42] |
| Hemiretinal vein occlusion | 1 | 69 | 0.25 [0.01 to 6.33] |
| **Post-operative procedures** | | | |
| Needling with 5-fluorouracil | 2 | 155 | 0.63 [0.22, 1.81] |
| Suture lysis procedure | 3 | 211 | 1.07 [0.50, 2.29] |
| Digital massage | 1 | 86 | 1.63 [0.53 to 5.07] |
| Releasable suture removal | 1 | 60 | 0.85 [0.27 to 2.67] |
| Repair of wound | 1 | 69 | 0.49 [0.08 to 3.11] |

Odds ratio < 1 favours fornix-based incisions (i.e., fewer adverse events in fornix-based group than limbal-based group)

Odds ratio > 1 favours limbal-based incisions (i.e., fewer adverse events in limbal-based group than fornix-based group)

## Table 2

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

| Cotran 2008 | | |
|---|---|---|
| Methods | Parallel-group randomised controlled trial<br>Assignment was performed by simple randomisation. Fourteen participants had both eyes enrolled which were independently randomised and analysed<br>**Number randomised**: 90 eyes of 76 participants (44 eyes fornix-based and 46 eyes limbal-based)<br>**Study duration:** 3 years | |
| Participants | **Primary diagnosis:** open-angle glaucoma<br>**Inclusion criteria:** glaucoma with cataract; IOP more than 21 mmHg after 2 medications<br>**Exclusion criteria:** neovascularisation, age > 89 years, phacolytic glaucoma, steroid-induced glaucoma, traumatic glaucoma, known condition causing decrease in VA (e.g., age-related macular degeneration)<br>**Demographic characteristics:** both groups were similar in age, gender, ethnicity, glaucoma diagnosis, history of laser treatment, and VA | |
| Interventions | Fornix- versus limbal-based phacotrabeculectomy with MMC | |
| Outcomes | **Primary outcome**<br>• Mean IOP up to 36 months of follow-up: 3, 6, 12, 18, 24, 30 and 36 months (reported 43/44 and 43/46 eyes in fornix- and limbal-based phacotrabeculectomy, respectively)<br>• Mean number of antiglaucoma medications up to 36 months of follow-up: 3, 6, 12, 18, 24, 30 and 36 months (reported 43/44 and 43/46 eyes in fornix- and limbal-based phacotrabeculectomy, respectively)<br>**Secondary outcomes:**<br>• Mean operative time: fornix-based at 60 minutes versus limbal-based at 83 minutes<br>• Mean postoperative visual acuity (3 months)<br>• Adverse events:<br>– Early hypotony (first 3 months)<br>– Late hypotony (after 3 months after surgery)<br>– Bleb infection<br>– Choroidal effusion<br>– Hyphaema<br>– Early conjunctival bleb leak (within the first 3 months)<br>– Late conjunctival bleb leak (after the first 3 months)<br>– Number of eyes needing needling with 5-FU<br>– Number of eyes needing suture lysis by laser<br>– Number of eyes needing digital massage | |
| Notes | The primary outcome originally was mean IOP and mean number of medications at 3-year follow-up<br>All participants underwent phacotrabeculectomy<br>**Clinical trial registration:** none reported<br>**Study dates:** not reported<br>**Funding sources:** not reported<br>**Disclosures of interest:** not reported | |
| ***Risk of bias*** | | |
| **Bias** | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | Unclear risk | The assignment was performed based on simple randomisation |
| Allocation concealment (selection bias) | Low risk | Allocation concealment was carried out using numbered opaque envelopes prepared by an independent research monitor |
| Blinding of outcome | High risk | Masking was not performed |

| | | |
|---|---|---|
| assessment (detection bias) All outcomes | | |
| Incomplete outcome data (attrition bias) All outcomes | Low risk | Data were missing for 4 eyes (4%): 1/44 and 3/46 eyes in fornix- and limbal-based phacotrabeculectomy groups, respectively |
| Selective reporting (reporting bias) | Unclear risk | No access to study protocol |
| el Sayyad 1999 | | |
| Methods | Within-person randomised controlled trial<br>Enrolled bilateral cases. The first eye was randomised, then the fellow eye was assigned to the other technique<br>**Number randomised**: 58 eyes of 29 participants (29 eyes in each group)<br>**Study duration:** 4 years | |
| Participants | **Primary diagnosis**: bilateral primary open-angle glaucoma<br>**Inclusion criteria:**<br>• Bilateral uncontrolled (IOP more than 21 mmHg) primary open-angle glaucoma with maximum medications<br>• Age between 35 and 90 years old<br>**Exclusion criteria:**<br>• Previous ocular surgery<br>• Inflammatory eye disease<br>• Significant posterior segment disease | |
| Interventions | Fornix- versus limbal-based trabeculectomy with post-operative 5-FU injection | |
| Outcomes | **Primary outcomes:**<br>• Failed trabeculectomy at 4-year follow-up (no missing data were reported)<br>• Mean IOP at 24-month follow-up (no missing data were reported)<br>**Secondary outcomes**:<br>• Failed trabeculectomy at 12-month follow-up (no missing data were reported)<br>• Mean IOP at 12 months of follow-up (no missing data were reported)<br>• Adverse events:<br>– Wound leak<br>– Hypotony<br>– Shallow anterior chamber<br>– Choridal detachment<br>– Corneal toxicity<br>– Suture lysis procedure | |
| Notes | **Clinical trial registration:** none reported<br>**Study dates:** recruitment began February 1990 and follow-up continued through November 1997<br>**Funding sources:** not reported<br>**Disclosures of interest:** not reported | |
| ***Risk of bias*** | | |
| **Bias** | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | Low risk | Eyes were randomised by use of a computer-generated table |
| Allocation concealment (selection bias) | Unclear risk | Insufficient information to permit judgment |

| | | |
|---|---|---|
| Blinding of outcome assessment (detection bias) All outcomes | High risk | Masking was not performed |
| Incomplete outcome data (attrition bias) All outcomes | Low risk | All participants that were randomised were included in the analyses |
| Selective reporting (reporting bias) | Unclear risk | No access to study protocol |
| Grehn 1989 | | |
| Methods | Parallel-group randomised controlled trial<br>One eye was enrolled in the study and randomised except for nine participants who had both eyes enrolled and analysed<br>**Number randomised:** 90 eyes of 81 participants (47 eyes fornix-based and 43 eyes limbal-based)<br>**Study duration:** 30 months | |
| Participants | **Primary diagnosis:** glaucoma (no limitation was mentioned)<br>**Inclusion criteria:** glaucoma (no limitation was mentioned)<br>**Exclusion criteria:** none reported | |
| Interventions | Fornix- versus limbal-based trabeculectomy (continuous suture) | |
| Outcomes | • Mean IOP at 24 months after trabeculectomy (no missing data were reported)<br>• Mean IOP at 12 months after trabeculectomy (no missing data were reported)<br>• Mean IOP medications post-operatively (4 months)<br>• Adverse events:<br>– Shallow anterior chamber post-operation<br>– Bleb vascularisation | |
| Notes | The authors did not report some important study details and outcomes such as: total follow-up time, demographic characteristics, the need for further surgery, proportion with failed trabeculectomy, and number of IOP medications in each group<br>The authors used a different definition of success or failure compared with our protocol<br>**Clinical trial registration:** none reported<br>**Study dates:** not reported<br>**Funding sources:** not reported<br>**Disclosures of interest:** not reported | |
| ***Risk of bias*** | | |
| **Bias** | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | Low risk | The investigators used a random list |
| Allocation concealment (selection bias) | Unclear risk | Insufficient information to permit judgment |
| Blinding of outcome assessment (detection bias) All outcomes | High risk | Masking was not performed |
| Incomplete outcome data (attrition bias) All outcomes | High risk | Not all the randomised participants were included in the study |
| Selective reporting (reporting bias) | High risk | Only 2 out of 5 outcomes were mentioned in the results |
| Khan 1992 | | |

| | |
|---|---|
| Methods | Parallel-group randomised controlled trial<br>One eye per participant was enrolled in the study and randomised<br>**Number randomised:** 100 eyes diagnosed with primary glaucomas (50 eyes in each group)<br>**Study duration:** 12 months |
| Participants | **Primary diagnosis:** primary glaucoma (65 eyes with primary open-angle and 35 eyes with narrow-angle glaucoma)<br>**Inclusion criteria:**<br>• Primary glaucoma (open- or closed-angle)<br>• Age 30 to 90 years old<br>**Exclusion:** none reported<br>**Demographic characteristics:** age and gender distributions were similar between groups |
| Interventions | Fornix- versus limbal-based trabeculectomy |
| Outcomes | • Failed trabeculectomy at 12 months (no missing data were reported)<br>• Visual deterioration at one month<br>• Post-operative increase in IOP requiring medical treatment<br>• Adverse events:<br>– Shallow anterior chamber<br>– Post-operative hyphaema<br>– Hypertrophy of bleb<br>– Post-operative iridocyclitis<br>– Intra-operative trauma to lens<br>– Cases requiring cataract extraction within 3-month duration |
| Notes | **Clinical trial registration:** none reported<br>**Study dates:** not reported<br>**Funding sources:** not reported<br>**Disclosures of interest:** not reported |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Insufficient information about the sequence generation |
| Allocation concealment (selection bias) | Unclear risk | Insufficient information to permit judgment |
| Blinding of outcome assessment (detection bias) All outcomes | High risk | Masking was not performed |
| Incomplete outcome data (attrition bias) All outcomes | Low risk | All participants that were randomised were included in the analyses |
| Selective reporting (reporting bias) | Unclear risk | No access to study protocol |

| | |
|---|---|
| Kozobolis 2002 | |
| Methods | Within-person randomised controlled trial<br>Enrolled bilateral cases. The first eye was randomised, then the fellow eye was assigned to the other technique<br>**Number randomised**: 60 eyes of 30 participants (30 eyes in each group)<br>**Study duration:** 12 months |
| Participants | **Primary diagnosis:** open-angle glaucoma<br>**Inclusion criteria:** |

| | |
|---|---|
| | • Open-angle glaucoma based on IOP on the maximum-tolerated medical therapy<br>• Glaucomatous optic nerve damage or visual field defect<br>• Cataract bilaterally without previous incisional surgery<br>**Exclusion criteria:**<br>• Previous argon laser trabeculoplasty<br>• Diabetes<br>**Demographic characteristics:** age, gender, number of IOP medications, and VA were similar between groups |
| Interventions | Fornix- versus limbal-based phacotrabeculectomy with intraoperative MMC |
| Outcomes | • Failed trabeculectomy at 12 months (no missing data were reported)<br>• Mean IOP at 12 months (no missing data were reported)<br>• Visual acuity improvement at 12 months<br>• Mean IOP medication post-operatively<br>• Adverse events:<br>– Wound leak<br>– Shallow anterior chamber<br>– Choroidal effusion<br>– Capsule opacification<br>– Cystic bleb or bleb fibrosis<br>– Fibrin exudation<br>– Pupillary membrane |
| Notes | **Clinical trial registration:** none reported<br>**Study dates:** October 1997 to May 2000<br>**Funding sources:** not reported<br>**Disclosures of interest:** "None of the authors has a financial or proprietary interest in any material or method mentioned." |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Insufficient information about the sequence generation |
| Allocation concealment (selection bias) | Unclear risk | Insufficient information to permit judgment |
| Blinding of outcome assessment (detection bias) All outcomes | High risk | Masking was not performed |
| Incomplete outcome data (attrition bias) All outcomes | Low risk | All participants that were randomised were included in the analyses |
| Selective reporting (reporting bias) | Unclear risk | No access to study protocol |

| | |
|---|---|
| Lemon 1998 | |
| Methods | Parallel-group randomised controlled trial<br>One eye was enrolled in the study and randomised<br>**Number randomised**: 69 eyes (39 eyes fornix-based and 30 eyes limbal-based)<br>**Study duration:** 18 months |

| | |
|---|---|
| Participants | **Primary diagnosis**: primary open-angle glaucoma<br>**Inclusion criteria:**<br>• Primary open-angle glaucoma<br>• Age 30 to 90 years old<br>• Cataract<br>**Exclusion criteria:**<br>• Previous ocular surgery<br>• Secondary glaucoma<br>**Demographic characteristics:** age, gender, race, presence of diabetes and hypertension, severity of glaucoma (cup:disk ratio), and mean duration of follow-up were similar between groups |
| Interventions | Fornix- versus limbal-based phacotrabeculectomy with intraoperative MMC |
| Outcomes | • Mean IOP at last follow-up (no missing data were reported)<br>• Mean IOP at 12 months (reported 25/39 and 23/30 in fornix- and limbal-based phacotrabeculectomy, respectively)<br>• Vision acuity improvement Snellen lines (last follow-up)<br>• Mean number of IOP medications at 12 months (reported 25/39 and 23/30 in fornix- and limbal-based phacotrabeculectomy, respectively)<br>• Mean number of IOP medications at last follow-up (no missing data were reported)<br>• Adverse events:<br>– Wound leak<br>– Hypotony<br>– Choroidal detachment<br>– Hyphaema<br>– Cystoid macular oedema<br>– Hemiretinal vein occlusion<br>– 5-FU revision<br>– Suture lysis by laser<br>– Releasable suture removal<br>– Repair of wound |
| Notes | **Clinical trial registration:** none reported<br>**Study dates:** not reported<br>**Funding sources:** "This study was supported in part by a grant from Research to Prevent Blindness, Inc, New York, New York"<br>**Disclosures of interest:** not reported |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Insufficient information about the sequence generation |
| Allocation concealment (selection bias) | Unclear risk | Insufficient information to permit judgment |
| Blinding of outcome assessment (detection bias) All outcomes | High risk | Masking was not performed |
| Incomplete outcome data (attrition bias) | Low risk | All participants that were randomised were included in the analyses |

| | | |
|---|---|---|
| All outcomes | | |
| Selective reporting (reporting bias) | Unclear risk | No access to study protocol |

5-FU: 5-fluorouracil

IOP: intraocular pressure

MMC: mitomycin C

mmHg: millimetre of mercury

VA: visual acuity

## Table 3

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

| Study | Reason for exclusion |
|---|---|
| Auw-Haedrich 1998 | Only abstract available: lack of specific outcome data and methodology details |
| Berestka 1997 | Non-randomised study |
| Brincker 1992 | Follow-up reported at 6 months only |
| Cheng 2012 | Follow-up reported between 6 months and 1 year |
| Fukuchi 2006 | Non-randomised study |
| Henderson 2004 | Non-randomised study |
| Lin 2007 | Non-randomised study |
| Mandiæ 2004 | Non-randomised study |
| Murchison 1990 | Non-randomised study |
| Reichert 1987 | Non-randomised study |
| Shingleton 1999 | Non-randomised study |
| Stewart 1994 | Non-randomised study |
| Traverso 1987 | Non-randomised study |