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Fibrin glue versus sutures for conjunctival autografting in primary pterygium surgery (Review)

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[Intervention Review]

Fibrin glue versus sutures for conjunctival autografting in primary pterygium surgery

Vito Romano[1], Mario Cruciani[2], Luigi Conti[3], Luigi Fontana[4]

[1]Ophthalmology, Royal Liverpool University Hospital, Liverpool, UK. [2]Center of Community Medicine and Infectious Diseases Service, ULSS 20 Verona, Verona, Italy. [3]Clinica Stabia, private practice, Castellammare di Stabia, Italy. [4]Ophthalmology, Hospital of Arcispedale Santa Maria Nuova, Reggio-Emilia, Italy

Contact address: Vito Romano, Ophthalmology, Royal Liverpool University Hospital, Prescot Street, Liverpool, L7 8XP, UK. vito.romano@gmail.com.

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ABSTRACT

Background

Pterygium, a growth of the conjunctiva over the cornea, is a progressive disease leading in advanced stages to visual impairment, restriction of ocular motility, chronic inflammation and cosmetic concerns. Surgical removal is the treatment of choice, but recurrence can be a problem. Currently the best surgical option in terms of recurrence is conjunctival autograft. To date the most common surgical methods of attaching conjunctival autografts to the sclera are through suturing or fibrin glue. Each method presents its own advantages and disadvantages. Sutures require considerable skill from the surgeon and can be associated with a prolonged operation time, postoperative discomfort and suture-related complications, whereas fibrin glue may give a decreased operation time, improve postoperative comfort and avoid suture-related problems.

Objectives

To assess the effectiveness of fibrin glue compared to sutures in conjunctival autografting for the surgical treatment of pterygium.

Search methods

We searched CENTRAL (which contains the Cochrane Eyes and Vision Trials Register) (2016, Issue 9), Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid MEDLINE Daily, Ovid OLDMEDLINE (January 1946 to October 2016), Embase (January 1980 to October 2016), 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 14 October 2016.

Selection criteria

We included randomised controlled trials (RCTs) in any setting where fibrin glue was compared with sutures to treat people with pterygium.

Data collection and analysis

Two review authors independently screened the search results, assessed trial quality, and extracted data using standard methodological procedures expected by Cochrane. Our primary outcome was recurrence of pterygium defined as any re-growth of tissue from the area of excision across the limbus onto the cornea. The secondary outcomes were surgical time and complication rate. We graded the certainty of the evidence using GRADE.

Main results

We included 14 RCTs conducted in Brazil, China, Egypt, India, Malaysia, New Zealand, Philippines, Saudi Arabia, Sweden and Turkey. The trials were published between 2004 and 2016, and were assessed as a mixture of unclear and low risk of bias with three studies at high risk of attrition bias. Only adults were enrolled in these studies.

Using fibrin glue for the conjunctival autograft may result in less recurrence of pterygium compared with using sutures (risk ratio (RR) 0.47, 95% CI 0.27 to 0.82, 762 eyes, 12 RCTs; low-certainty evidence). If pterygium recurs after approximately 10 in every 100 surgeries with sutures, then using fibrin glue may result in approximately 5 fewer cases of recurrence in every 100 surgeries (95% CI 2 fewer to 7 fewer cases). Using fibrin glue may lead to more complications compared with sutures (RR 1.92; 95% CI 1.22 to 3.02, 11 RCTs, 673 eyes, low-certainty evidence). The most common complications reported were: graft dehiscence, graft retraction and granuloma. On average using fibrin glue may mean that surgery is quicker compared with suturing (mean difference (MD) -17.01 minutes 95% CI -20.56 to -13.46), 9 RCTs, 614 eyes, low-certainty evidence).

Authors' conclusions

The meta-analyses, conducted on people with pterygium in a hospital or outpatient setting, show fibrin glue may result in less recurrence and may take less time than sutures for fixing the conjunctival graft in place during pterygium surgery. There was low-certainty evidence to suggest a higher proportion of complications in the fibrin glue group.

PLAIN LANGUAGE SUMMARY

Fibrin glue versus sutures for conjunctival autografting in primary pterygium surgery

What is the aim of this review?
The aim of this Cochrane Review was to find out if it is better to use fibrin glue or sutures (stitches) when operating on a pterygium (unwanted growth of tissue on the front of the eye). The operation involves replacing the pterygium with a piece of tissue from another part of the eye (autograft). Cochrane researchers collected and analysed all relevant studies to answer this question and found 14 studies.

Key messages
Using fibrin glue when doing the graft may result in a lower chance of recurrence of the pterygium. The operation may take less time as well. Fibrin glue may be associated with more complications such as a rupture of the graft, the graft shrinking and the development of an area of inflammation (granuloma).

What was studied in the review?
Sometimes a piece of tissue can grow on the front of the eye, and if it grows large enough it can affect vision. This tissue is known as a pterygium. People who live in hot, dusty places with high sunlight are more likely to get a pterygium. A pterygium can be uncomfortable and itchy, and may affect the appearance of the eye.

Doctors can remove this tissue and replace it with tissue from another part of the body, usually from another part of the conjunctiva (which covers the white part of the eye). This is known as a graft or autograft.

Cochrane researchers looked at two different methods of attaching this graft during pterygium surgery, either with fibrin glue or with stitches.

What are the main results of the review?
The review authors found 14 relevant studies. The studies were from Brazil, China, Egypt, India, Malaysia, New Zealand, Philippines, Saudi Arabia, Sweden and Turkey. These studies compared fibrin glue to stitches in people having their pterygium removed and a graft of tissue from the conjunctiva.

Using fibrin glue during pterygium surgery may result in fewer cases of recurrence of pterygium compared with using stitches (low-certainty evidence). It may take less time to do a pterygium operation and graft with fibrin glue (low-certainty evidence). There may be a higher chance of some complications with fibrin glue, such as a rupture of the graft, the graft shrinking or development of an area of inflammation (granuloma).

How up-to-date is this review?
The Cochrane researchers searched for studies that had been published up to 14 October 2016.

SUMMARY OF FINDINGS

Summary of findings for the main comparison.

Fibrin glue compared with sutures for primary pterygium

Patient or population: individuals with pterygium

Settings: hospital or outpatients

Intervention: fibrin glue

Comparison: sutures

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of eyes (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Sutures	Fibrin glue				
Recurrence of pterygium (follow-up 2 to 24 months)	**100 per 1000**	**47 per 1000** (27 to 82)	**RR 0.47 (**0.27 to 0.82)	762 (12 RCTs)	⊕⊕⊖⊖ **low** [1,2]	Large variability in duration of follow-up
Occurrence of complication	**70 per 1000**	**134 per 1000** (85 to 211)	**RR 1.92** (1.22 to 3.02)	673 (11 RCTs)	⊕⊕⊖⊖ **low** [1,2]	
Operating time	The mean operating time ranged across control groups from 27 to 67 minutes	The mean operating time in the intervention groups was17.0 minutes less (from 20.6 minutes less to 13.5 minutes less)		614 (9 RCTs)	⊕⊕⊖⊖ **low** [1,3]	

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

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

[1]Downgraded 1 level for risk of bias due to study limitations, in particular generation of allocation sequence, allocation concealment, and incomplete outcome data.
[2].Downgraded 1 level for imprecision as there were relatively few events.
[3] Downgraded 1 level for inconsistency (I^2 = 96%) although all studies favoured fibrin glue.

BACKGROUND

Primary pterygium is one of the most common eye diseases, affecting a large percentage of the population, especially those living between the Tropics of Cancer and Capricorn. Effectively the incidence is high in geographic areas with high ultraviolet radiation (Moran 1984) or hot, dry, windy, dusty and smoky environments (Nakaishi 1997; Norn 1991), however hereditary factors also play a role (Anguria 2014; Romano 2016). The estimated prevalence of pterygium is variable, ranging from 0.7% to 31%.

Surgical removal is the treatment of choice. For many years, the surgical management of pterygium involved a simple excision of the excessive tissue mass overlying the cornea and the adjacent sclera, leaving a wide area of bare sclera. However, recurrence of the pterygium was unacceptably high, in as many as 89% of cases (Cameron 1965; Youngson 1972). To improve surgical results, two strategies have been adopted: the destructive approach, which enhances the effect of excision by radiation and chemotherapy (mitomycin C (MMC), thiotepa, 5-fluorouracil, beta-irradiation) and the reconstructive approach, namely transplantation of various tissue grafts (conjunctival autograft, amniotic membrane transplantation, mucous membrane graft, conjunctival limbal transplantation). Recurrences after conjunctival autograft vary from 0% to 39% (Cano-Parra 1995; Chen 1995; Hirst 2009; Jaros 1988; Kenyon 1985; Lewallen 1989; Sebban 1991a; Sebban 1991b) and from 0% to 70% after adjunctive chemotherapy. Most studies have demonstrated that conjunctival autograft and MMC application are highly successful and equally effective (0% to 38% recurrence rate) (Cano-Parra 1995; Chen 1995; Hayasaka 1988; Mahar 1993; Singh 1988). However, severe complications may occur following MMC therapy, such as melting of the conjunctiva and sclera, and even perforation (Dunn 1991; Mackenzie 1991; Rubinfeld 1992). Currently several studies have demonstrated that conjunctival autograft is the best method to avoid recurrence (Al Fayez 2002; Chen 1995; Kenyon 1985; Prabhasawat 1997). To date the most common surgical methods of attaching conjunctival autografts to the sclera are through suturing or fibrin glue. Each one presents its own advantages and disadvantages. Sutures require major ability of the surgeon and can be associated with a prolonged operation time, postoperative discomfort and suture-related complications, whereas fibrin glue gives a decreased operation time, improves postoperative comfort and avoids suture-related problems. However currently the results of efficacy of fibrin glue and sutures in pterygium surgery are not completely consistent.

The aim of this review is to summarise and compare outcomes of tissue glue and sutures that are currently used to attach conjunctival autografts in pterygium surgery.

Description of the condition

Primary pterygium is a fibrovascular wing of tissue extending onto the cornea, generally situated on the nasal side. Before it enters the optical zone, an advancing pterygium can cause localised flattening of the horizontal meridian of the cornea to the leading apex (Bedrossian 1960; Fong 1998; Gasser 2016; Hansen 1980; Holladay 1985; Lin 1998; Oldenburg 1990; Starck 1991; Stern 1998; Tomidokoro 1999; Walland 1994), often resulting in with-the-rule astigmatism (Lin 1997). The pterygium is conventionally divided into three parts of a triangle: a 'head', a 'neck' and a 'body'. The former is the apex of the triangle that points towards the cornea and it is connected to the 'body' by the 'neck'. The pathogenesis of pterygium is still not fully understood. Recent studies have shown alterations of limbal stem cells along the affected pterygial area. UV-B causes mutations at the limbal edge, resulting in apoptosis and altering the production of various growth factors. Indications for surgery include visual impairment (Bedrossian 1960; Oldenburg 1990; Starck 1991), restriction of ocular motility, chronic inflammation and cosmetic concerns. Many procedures have been suggested, with or without adjunctive techniques that aim to lower the recurrence rate (Akarsu 2003; Avisar 2003; Chapman-Smith 1992; Dadeya 2002; Mackenzie 1991).

Description of the intervention

The goal of surgical treatment is the excision of the lesion, the prevention of its recurrence and the restoration of the integrity of the ocular surface. Several different techniques have been described (Haik 1962; Kenyon 1985; King 1950; Prabhasawat 1997; Singh 1988; Vastine 1982). Briefly, the operation is performed under peribulbar anaesthesia. The eye is prepped and draped in the standard fashion and a lid speculum is inserted. When removing the pterygium, the first step involves dissection and excision of the head off the cornea. This allows for exposure of the underlying fibrovascular tissue that can then be accurately removed by dissection up to the insertion of the medial rectus muscle (if the pterygium is situated on nasal side, as usually happens). It is important in this phase to preserve as much surrounding conjunctival tissue as possible. Abnormal scar tissue on the corneal and scleral surface is also removed. The scleral bed is then measured and a very thin piece of autologous conjunctiva, 1 mm larger than this area, is excised from the superior bulbar conjunctiva. Care is taken not to include Tenon's tissue when dissecting the graft, in order to avoid postoperative oedema and graft retraction. The conjunctival graft is secured to the sclera, taking care to maintain the polarity of the tissue, with interrupted 7.0 to 8.0 Vicryl or 10.0 nylon sutures, or episclerally with fibrin glue added either sequentially or simultaneously with a double-barrel syringe. This review will consider all types of sutures and glues currently used for conjunctival autograft.

How the intervention might work

The use of natural substances such as fibrin may have significant advantages over traditional suturing techniques (Calson 1987). Fibrin glue is a blood-derived product that consists of two biologic components: fibrinogen and thrombin. When the components are mixed and fibrinogen is activated by thrombin, an adhesive fibrin network is formed in 30 seconds. Within days, the two components of the fibrin glue are digested, but in the meantime a strong network has been formed between the transplant and the underlying sclera. In the last 10 years, fibrin adhesives have been used to close cataract incisions (Henrick 1987), to attach soft tissue in oculoplastic surgery (Gosain 2002), to attach conjunctiva in strabismus (Dadeya 2001; Mohan 2003; Spierer 1997), to treat leaking blebs (Wright 1998) in glaucoma surgery (O'Sullivan 1996), and to close macular holes in retinal surgeries (Tilanus 1995). Recent studies have demonstrated that the use of fibrin glue in pterygium surgery might be an ideal alternative to suturing because it shortens the time of the surgical procedure, is easy to use and is associated with less postoperative inflammation, discomfort and recurrence.

Why it is important to do this review

The use of sutures in pterygium surgery is associated with postoperative inflammation, discomfort and complications related to the sutures themselves, such as granuloma formation, suture abscesses, buttonholes, tissue necrosis, and giant papillary conjunctivitis (Sridhar 2002; Tan 1997; Ti 2000). This systematic review will compare the results obtained with sutures to those with fibrin glue in conjunctival autografting procedures for the treatment of pterygium, which present advantages related to surgical skills, postoperative complications and patient's discomfort. This information is of interest not only to ophthalmic surgeons and ophthalmologists, but also to other healthcare professionals and patients.

OBJECTIVES

To assess the effectiveness of fibrin glue compared to sutures in conjunctival autografting for the surgical treatment of pterygium.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) in any setting (hospital or outpatient basis), as planned in the protocol (Romano 2014).

Types of participants

Participants in the trials were people with advancing pterygium, especially people with visual impairment, restriction of ocular motility, chronic inflammation and cosmetic concerns. We excluded trials which recruited participants with connective tissue disease, previous ocular surgery and with other ocular disease.

Types of interventions

We included trials that compared fibrin glue (Tisseel or Full Link or Beriplast P or Quixil) to sutures (Vicryl 8/0 or Vicryl 7/0 or nylon 10-0).

Types of outcome measures

Primary outcomes

- Recurrence of pterygium: any re-growth of tissue from the area of excision across the limbus onto the cornea, calculated by the frequency of recurrences at six months after surgery. If the study's follow-up was longer, we considered the last follow-up.

Secondary outcomes

- Surgical time: the time spent to complete the surgery. We considered the mean and standard deviation.
- Complication rate: the occurrence of at least one of the following major complications such as dehiscence, displacement or loss of the autograft, infection, haemorrhage, oedema, fibrosis, retraction and other indications that required special treatment.

Search methods for identification of studies

Electronic searches

We searched CENTRAL (which contains the Cochrane Eyes and Vision Trials Register) (2016, Issue 9), Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid MEDLINE Daily, Ovid OLDMEDLINE (January 1946 to October 2016), Embase (January 1980 to October 2016), 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 14 October 2016.

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

Searching other resources

We also searched the reference lists of all potentially relevant trials to identify further reports of studies.

Data collection and analysis

Selection of studies

Two review authors (VR and LC) independently assessed the search results to see if they met the inclusion criteria. We specified reasons for exclusion of studies.

The process for selecting studies for inclusion in a review was in accordance with the following procedures, as described in Chapter 7 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a).

- Merge search results using reference management software (ProCite) and remove duplicate records of the same report.
- Examine titles and abstracts to remove obviously irrelevant reports.
- Retrieve the full text of potentially relevant reports.
- Link together multiple reports of the same study.
- Examine full-text reports for compliance of the studies with the eligibility criteria.
- Correspond with investigators, where appropriate, to clarify study eligibility.
- Make final decisions on study inclusion and proceed to data collection.

We planned to resolve any disagreements that arose through discussion.

Data extraction and management

Two review authors (VR and LC) independently extracted data from the selected trials using a standardised data extraction form, as suggested in Chapter 7 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). We considered items related to source, eligibility, methods, participants, interventions, outcomes and results. Further information can be found in Appendix 7.

Assessment of risk of bias in included studies

Each review author independently assessed the risk of bias of each trial using a simple form and followed the domain-based evaluation as described in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b). We compared

the assessment results and discussed any discrepancies between ourselves. We aimed to achieve agreement on the final assessment for each criteria by discussion.

We assessed each domain as 'low risk of bias', 'unclear risk of bias' or 'high risk of bias'. We evaluated the following domains.

- Randomisation sequence generation
- Allocation concealment
- Blinding (masking) of outcome assessors
- Incomplete outcome data
- Selective outcome reporting
- Free of other bias (e.g. baseline imbalance, early stopping)

A detailed list of items considered and measures of assessment is provided in Appendix 8.

Measures of treatment effect

We used Review Manager 5.3 (RevMan) (RevMan 2014) to analyse the data.

- We have treated the recurrence of pterygium and complication rate as dichotomous variables and have calculated them using the risk ratio (RR) with 95% confidence intervals (CI).
- We have treated the surgical time as a continuous variable and calculated it using the mean difference (MD) with 95% CI.

In accordance with Chapter 9 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2011) we checked for skewed data by calculating the observed mean minus the lowest possible value and dividing this by the standard deviation. A ratio of less than 2 suggested skewness; if the ratio was less than 1 there was strong evidence of a skewed distribution. When the data were skewed, we presented results on a log scale as geometric means and ratios.

Unit of analysis issues

Trials may be parallel group (people randomised to treatment) or within-person (eyes randomly allocated to treatment). The following table summarises the possible designs and issues in the analysis.

	Type of study	Number of eyes enrolled	Number of eyes reported	Analysis
1	Parallel group	One	One	No unit of analysis issue. Criteria for selection of study eye should be specified
2	Parallel group	Two	One	No unit of analysis issue. Criteria for choice of eye should be specified in the trial protocol and could include worst, best, average of two eyes, right eye, left eye
3	Parallel group	Two	Two	Ideally effect estimates should be adjusted for within-person correlation
4	Within-person	Two	Two	Ideally study should do a pair-matched analysis

We documented the type of study design and approach to the analysis of people and eyes. In the case of categories 3 and 4, which may represent unit of analysis issues, we contacted study investigators for further clarification or data, as needed.

Dealing with missing data

We assessed the percentages of dropouts overall for each included trial and per each randomisation arm and we evaluated whether an intention-to-treat (ITT) analysis was performed or could be performed, from the available published information.

In order to allow us to undertake an ITT analysis, we sought data from the trial authors on the number of participants by treatment group, irrespective of compliance and whether or not the participant was later thought to be ineligible or otherwise excluded from treatment or follow-up.

When additional data were needed, we contacted the corresponding author of each study by email in order to access further information. When missing data were not available, we limited our analysis to the available data.

Assessment of heterogeneity

We used the I^2 statistic to measure statistical heterogeneity among the trials in each analysis. The I^2 statistic describes the percentage of total variation across trials that is due to heterogeneity rather than sampling error (Higgins 2003). We considered there to be substantial statistical heterogeneity if the I^2 statistic was greater than 50% (Deeks 2011; Higgins 2003; Higgins 2011b). However, we considered the importance of the I^2 value by taking into consideration the magnitude and direction of effects and the strength of evidence for heterogeneity (e.g. P values from the Chi^2 test, or confidence intervals for I^2). Where possible, we explored clinical heterogeneity according to study setting and characteristics of participants).

Assessment of reporting biases

Where we suspected reporting bias (see 'Selective reporting bias' in Appendix 8), we attempted to contact study authors and asked them to provide missing outcome data. Where this was not possible, and the missing data were thought to introduce serious bias, we explored the impact of including such studies in the overall

assessment of results by a sensitivity analysis. The assessment focused on the primary outcome and, among secondary outcomes, on complication rate.

We also assessed publication bias (the publication or non-publication of research findings, depending on the nature and direction of the results) by using a funnel plot to graphically illustrate variability between trials. If asymmetry was detected, we explored causes other than publication bias. We produced a funnel plot if 10 or more RCTs were included.

Data synthesis

We used the random-effects model and used the fixed-effect model as a sensitivity analysis for evaluating the possible bias effects of smaller studies, or when there were fewer than three studies.

Subgroup analysis and investigation of heterogeneity

We did not plan to conduct subgroup analysis.

Sensitivity analysis

If a sufficient number of trials was identified, we planned to conduct a sensitivity analysis excluding low-quality studies (Higgins 2011b). Because the possibility of masking in these trials was unlikely, we used only items in the domain of randomisation (selection bias), incomplete outcome data (attrition bias), selective outcome reporting, and other bias.

'Summary of findings' table

We have included a 'Summary of findings' table (GRADEpro 2014) to give a concise overview and synthesis of the volume and certainty of the evidence for these comparisons.

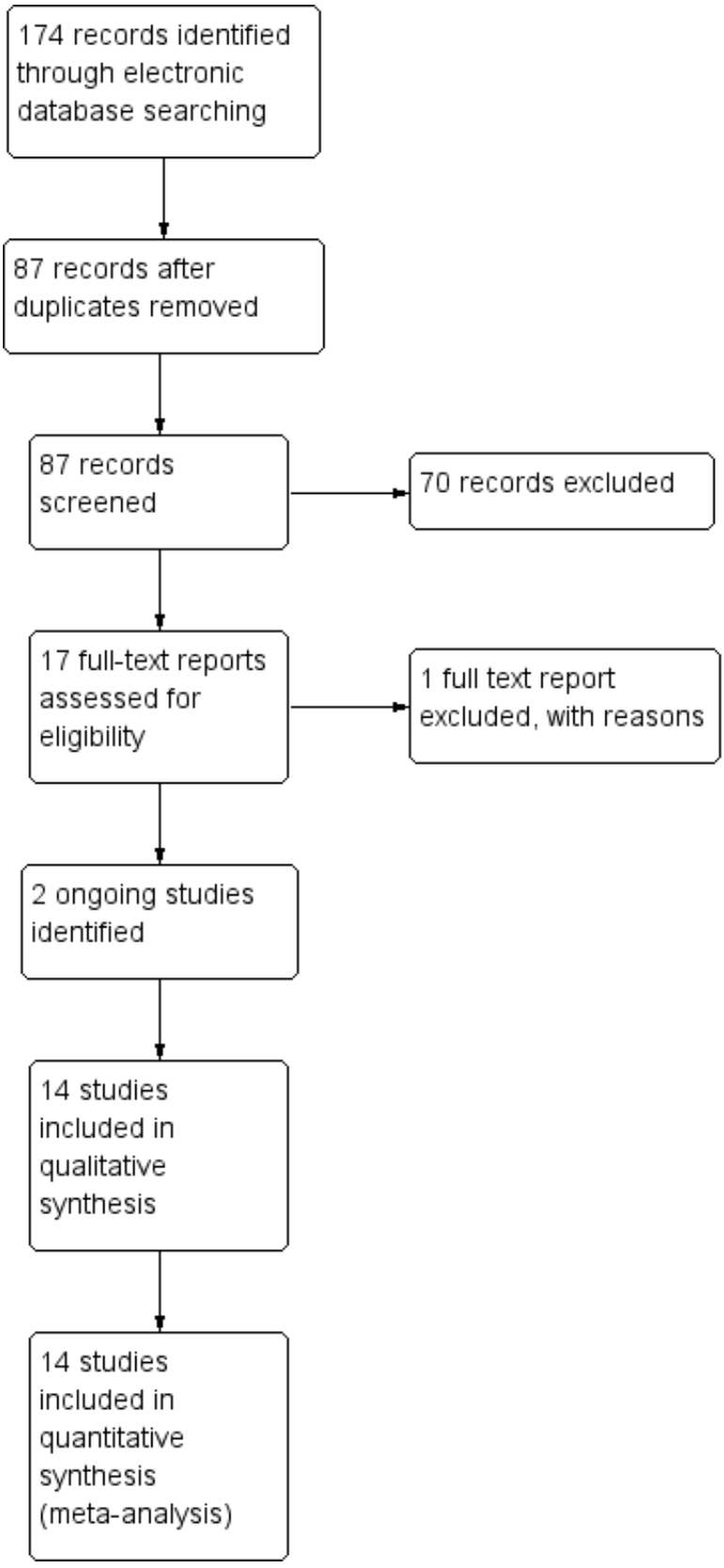
RESULTS

Description of studies

Results of the search

The electronic searches yielded a total of 174 references (Figure 1). The Cochrane Information Specialist removed 87 duplicate records and we screened the remaining 87 reports. We rejected 70 records after reading the abstracts and obtained the full-text reports of 17 references for further assessment. We identified 14 studies which met the inclusion criteria, see Characteristics of included studies and excluded one study (CTRI/2013/06/00376). There are two ongoing studies for which results are not currently available, see Characteristics of ongoing studies, If we are able to access the results for these studies, we will include them in further updates of this review.

Figure 1. Study flow diagram



Included studies

We included clinical trials which used randomisation. The sample size achieved and analysed was 811 eyes for the recurrence rate, 722 eyes for complication rate and 614 eyes for operating time. The RCTs were conducted in Brazil, China, Egypt, India, Malaysia, New Zealand, Philippines, Saudi Arabia, Sweden and Turkey. The clinical trials were conducted in academic or hospital settings. All the trials included adult participants where there was evidence of visual impairment, restriction of ocular motility, chronic inflammation and cosmetic concerns. All the RCTs compared fibrin glue to suture using the same technique for pterygium excision. The follow-up range was between 6 months and 24 months. In particular, two studies reported results at 24 months, nine at 12 months, five at 6 months, and one between 9 and 13 months. Not all included studies reported all outcomes evaluated in this meta-analysis; Al-Fayez 2008 and Ozdamar 2008 did not report operating time (see Characteristics of included studies for further details).

Excluded studies

We excluded CTRI/2013/06/00376 as this study was a randomised trial that compared autologous blood versus fibrin glue but there was no comparison with sutures.

Risk of bias in included studies

See Figure 2; Figure 3.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies

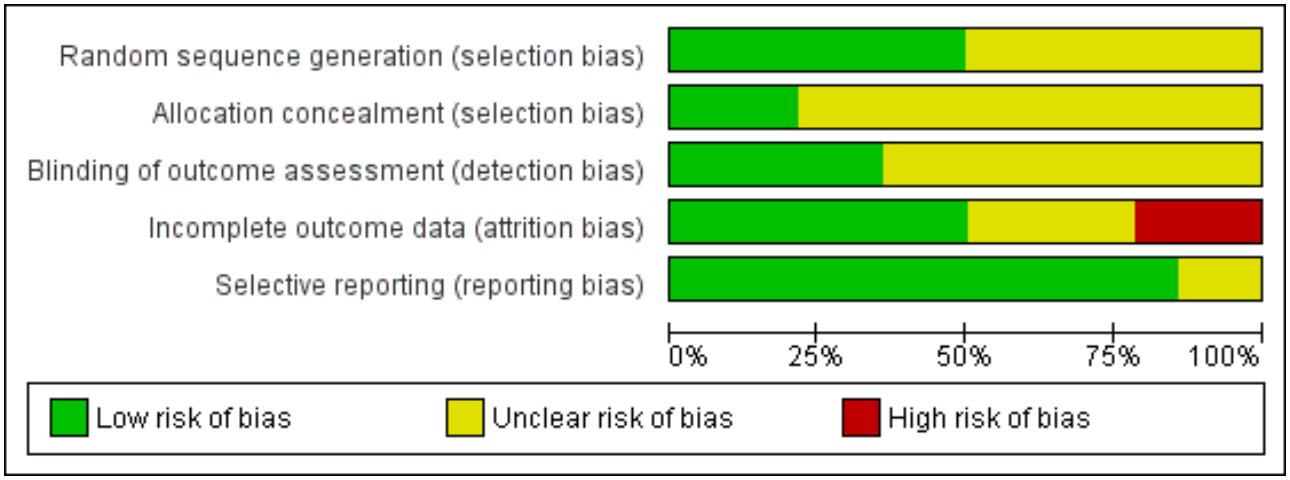
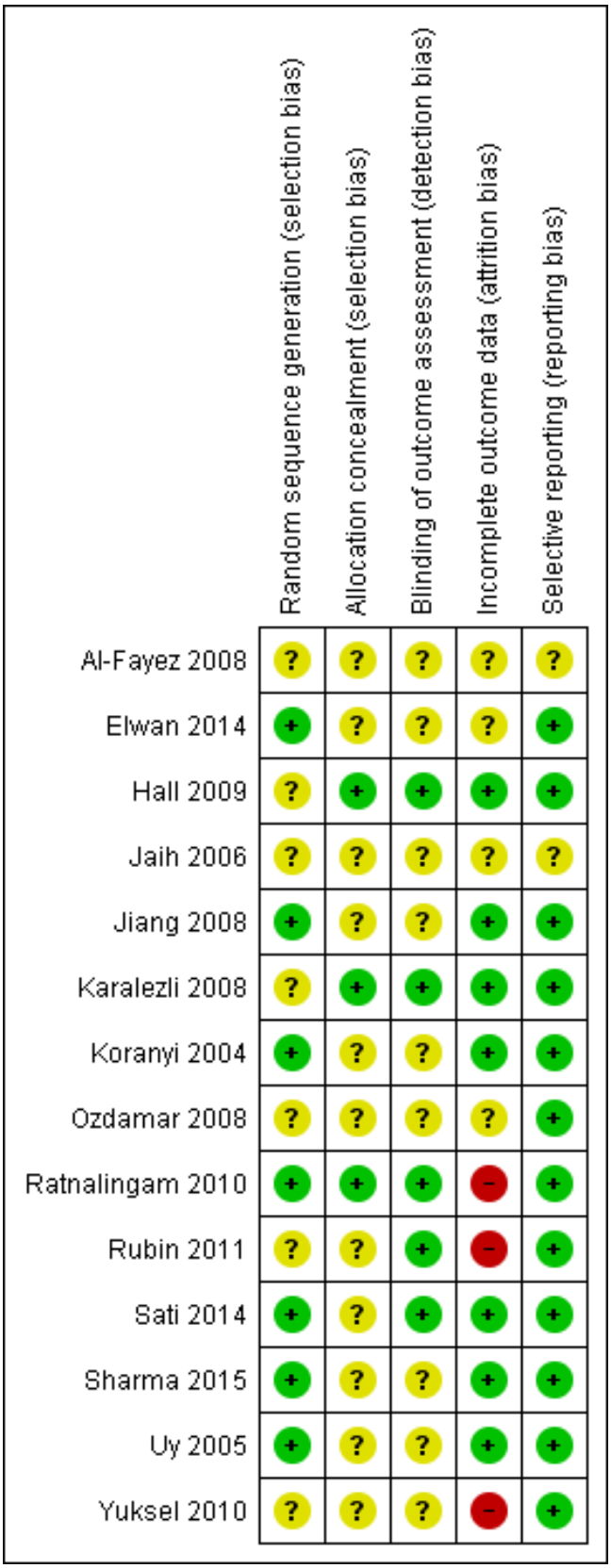


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study



Allocation

Generation of allocation sequence

In seven studies (Al-Fayez 2008; Hall 2009; Jaih 2006; Karalezli 2008; Ozdamar 2008; Rubin 2011; Yuksel 2010) investigators stated that the participants were randomly assigned to interventions and control, but the method used to achieve randomisation was not explicit; thus we judged this domain as 'unclear risk of bias'. The others studies reported how they generated the allocation sequence (e.g. computer-generated, centrally-randomised, tossing a coin) and we have judged this domain as 'low risk of bias'.

Allocation concealment

We made a judgement of 'low risk of bias' for this domain in three studies with central randomisation or with measures aimed to reduce intraobserver bias and minimise the influence of the known surgical technique (Hall 2009; Karalezli 2008; Ratnalingam 2010). In the remaining studies it was unclear if adequate measures were taken to ensure that investigators were unaware of the upcoming assignment. Therefore we judged this domain as 'unclear risk of bias' for these studies.

Blinding

We did not assess masking of participants or personnel to the intervention, as it is difficult to mask participants or personnel (clinicians for example) to the intervention. We evaluated the masking of outcome assessor to treatment allocation. However, as trials used two different types of intervention (sutures or glue), masking of outcome assessors could have been problematic, unless assessment was performed by someone not involved in the study.

All the included trials were reported as open-label studies; however, masking probably had limited importance for more objective outcomes (such as some of the primary outcomes), because the risk of ascertainment bias was limited, but not for all outcomes. We made a judgement of 'unclear risk of bias' for nine studies (Al-Fayez 2008; Elwan 2014; Jaih 2006; Jiang 2008; Koranyi 2004; Ozdamar 2008; Sharma 2015; Uy 2005; Yuksel 2010), and of 'low risk of bias' for the remaining studies that stated that particular attention was paid to limiting potential judgement biases.

Incomplete outcome data

Seven trials clarified the number of and reasons for dropouts (Hall 2009; Jiang 2008; Karalezli 2008; Koranyi 2004; Sati 2014; Sharma 2015; Uy 2005), and we made a judgement of 'low risk of bias' for this domain. Four trials did not provide sufficient information to permit a judgement (Al-Fayez 2008; Elwan 2014; Jaih 2006; Ozdamar 2008). Three trials (Ratnalingam 2010; Rubin 2011; Yuksel 2010), judged at 'high risk of bias', were not on ITT basis and did not provide information on reasons and distribution of withdrawal.

Selective reporting

There was no evidence of selective outcome reporting in the large majority of included trials and it appeared that the outcomes reported were comparable to those specified in the methods section of the reports. Two studies, however, did not provide sufficient information to provide a judgement.

Publication bias was assessed by visual inspection of funnel plots (Figure 4; Figure 5. Funnel plots had a symmetric appearance for all the outcomes analysed

Figure 4. Funnel plot of comparison: 1 Fibrin glue versus suture, outcome: 1.1 Recurrence of pterygium.

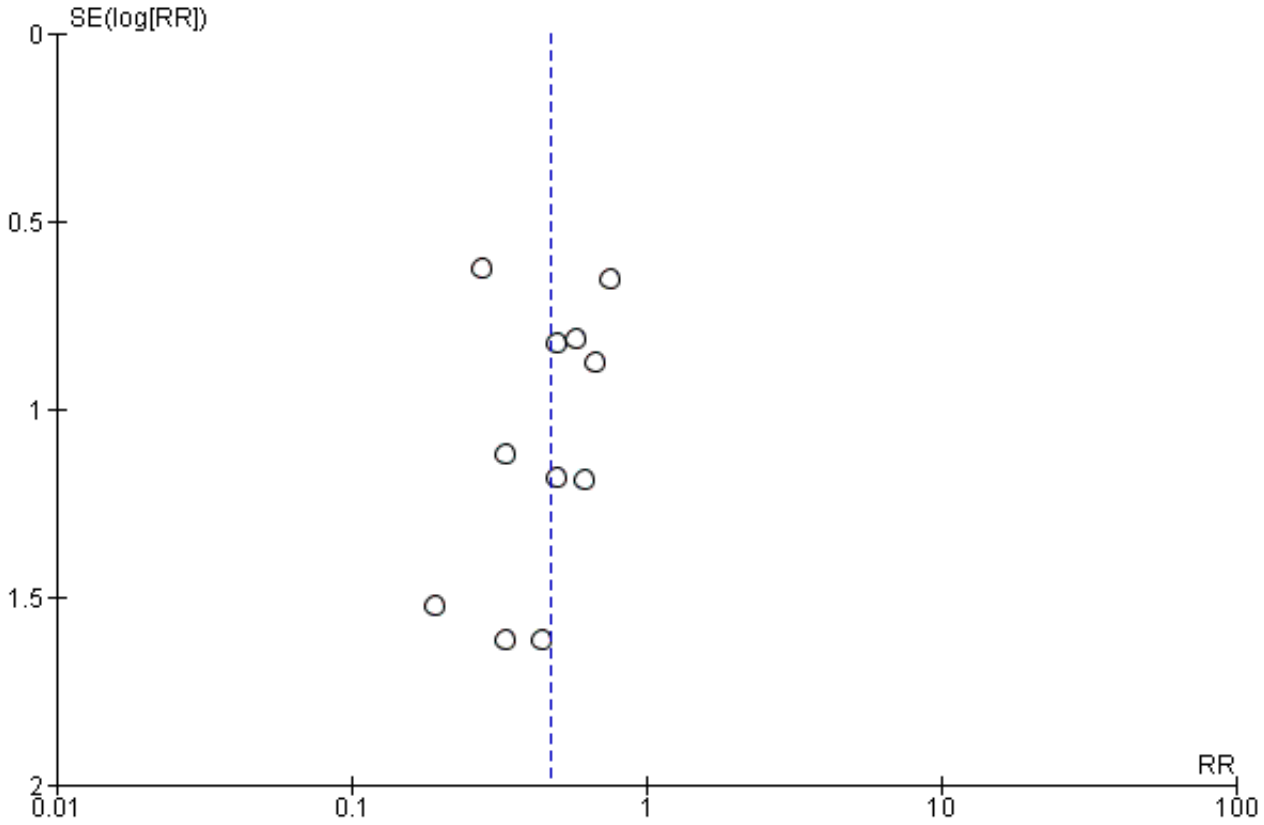
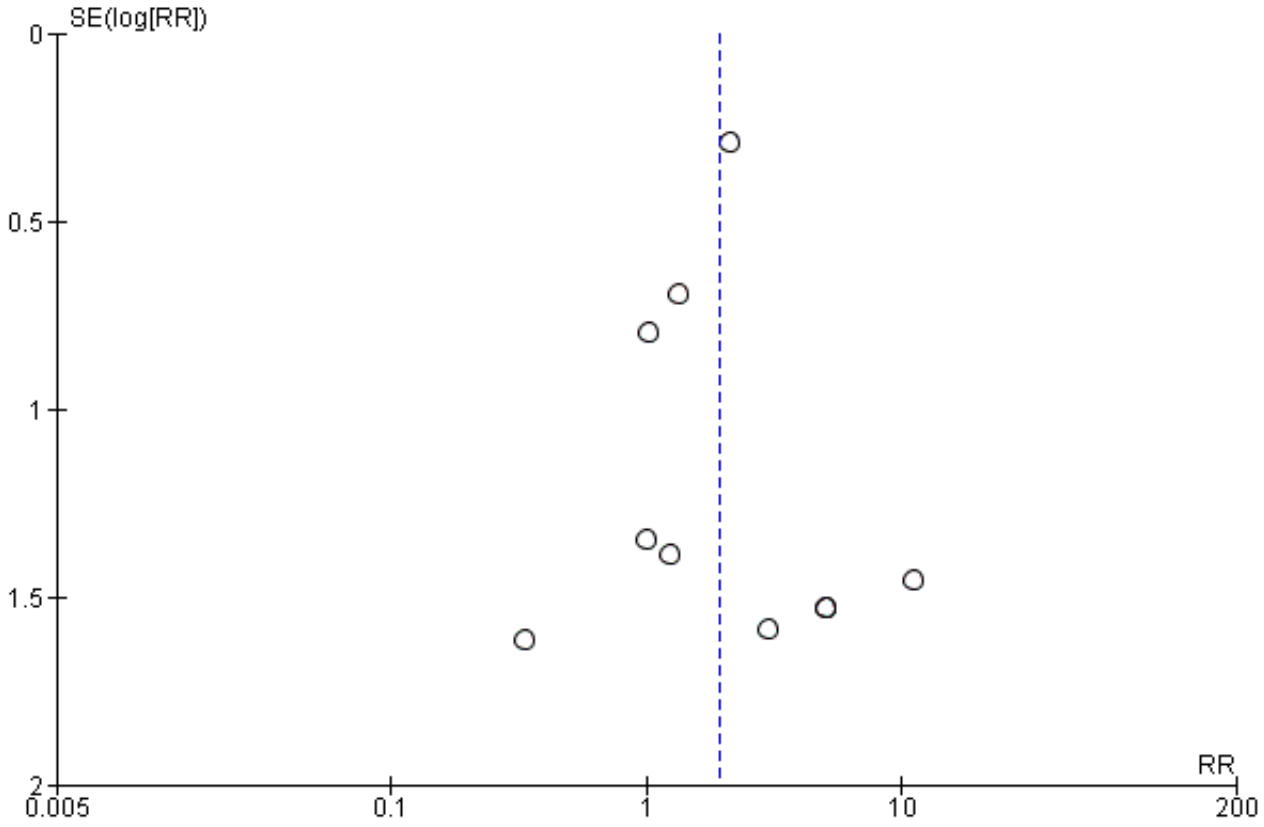


Figure 5. Funnel plot of comparison: 1 Fibrin glue versus suture, outcome: 1.2 Occurrence of 1 or more complications.



Effects of interventions

See: **Summary of findings for the main comparison**

See Summary of findings for the main comparison.

We conducted three meta-analyses for recurrence of pterygium (primary outcome), surgical time and complication rate (secondary outcomes). The meta-analyses for recurrence of pterygium shows that the recurrence of pterygium is less in the fibrin glue group (Analysis 1.1) (low-certainty evidence). Analysing 762 procedures, there were 15 recurrences in the fibrin glue group and 41 in the suture group with a risk ratio of 0.47. Instead, taking into account 673 procedures and looking at the complication rate there was evidence of a higher rate of complications in the fibrin glue group (Analysis 1.2) (low-certainty evidence), while our analysis reports a significant reduction in surgical time using a fibrin glue (Analysis 1.3) (low-certainty evidence). The main results of the meta-analyses (effect estimate and 95% confidence intervals (CIs)) are respectively: risk ratio (RR) 0.47; 95% CI 0.27 to 0.82 for recurrence of pterygium; RR 1.92; 95% CI 1.22 to 3.02 for complication rate, and mean difference -17.01; 95% CI -20.56 to -13.46 for operating time.

In sensitivity analysis, the exclusion of three studies at high risk of bias (Ratnalingam 2010; Rubin 2011; Yuksel 2010) had marginal impact on effect estimates: RR 0.54; 95% CI 0.27 to 1.08 for recurrence of pterygium (10 studies, 542 eyes; Analysis 2.1); RR 2.16; 95% CI 1.32 to 3.51 for complication rate (9 studies, 489 eyes; Analysis 2.2); and mean difference -15.59; 95% CI -19.90 to -11.28 for operating time (6 studies, 372 eyes; Analysis 2.3). For all the comparisons, we used a random-effects model.

Sensitivity analysis using a fixed-effect model showed similar estimates.

There were no reports on any adverse event due to fibrin glue or suture use in the studies analysed.

DISCUSSION

Conjunctival autograft transplantation is the most effective surgical procedure to prevent recurrence of pterygium and ensure a white cosmetic conjunctiva, with no persistent symptoms. However there is still no clear evidence to suggest whether the preferred option to fix the conjunctival autograft is fibrin glue or sutures. We conducted three meta-analyses to answer this question in terms of recurrence of pterygium, complication rate and surgical time.

Summary of main results

Pterygium recurrence is the most common complication after its removal; its etiopathogenesis is multifactorial. Our meta-analysis points out the benefits of using fibrin glues in terms of recurrence rate (RR 0.47; 95% CI 0.27 to 0.82). Exclusion of studies at high risk of bias led to a reduction of the effect size for the outcome recurrence of pterygium, though a trend towards a reduction of recurrences was still evident (RR 0.54; 95% CI 0.27 to 1.08). The

reasons could be attributed to reduced postoperative inflammation (Kheirkhah 2008) and an immediate adherence of the graft, which plays a crucial role inhibiting fibroblast ingrowth, encouraging earlier vascularisation of the graft and reducing the recurrence (Zauberman 1988). Instead this adherence is not achieved by sutures, because they can only fix the edges of the graft, having no direct apposition of the graft in proximity to the underlying episclera. Also the different tensile strength between sutures and fibrin glue could have a determinant role.

The success rate also depends on surgical time, and its increment is directly associated with an increase in postoperative inflammation. The operating time is also correlated to the surgeon's skills. In fact Ti 2000 attributed the variability of success rate of sutured conjunctival autograft to learning curves and different skill levels. The results highlight the benefits of fibrin glue in terms of operating time. Using fibrin glue with conjunctival autograft transplantation shortens the surgical time, and makes the procedure easier with minimal manipulation of the graft and therefore less inflammation. Consequently, better results may be more consistently achieved despite differences in surgical expertise.

Our results report a higher complication rate in the fibrin glue group compared to the suture group (Table 1). It must be noted that the complication rates especially depend on graft preparation, graft manipulation, surgical experience and participant selection. In the fibrin group graft dehiscence is the most common complication (Srinivasan 2007), however it is usually associated with eye trauma or a person rubbing their eyes. A meticulous graft preparation (thin donor conjunctival autograft and free of Tenon's capsule) improves the success rate of graft uptake. Foroutan 2011 reported 13.33% cases of graft dehiscence and attributed this to a low concentration of thrombin and fibrinogen in autologous glue compared to a commercial preparation. Also the graft loss in the case of fibrin glue is a common complication or consequence of dehiscence. The precautions suggested by experts to avoid it are to ensure that the conjunctival autograft and conjunctiva are properly adhered; that fibrin glue is cleared from the ocular surface; and that no Tenon's capsule remains between the graft and the conjunctiva. Graft retraction is the most common complication in the suture group. Tan 1999 attributed it to sub-conjunctival fibrosis and suggested a meticulous dissection of sub-epithelial graft tissue. Different authors (Malik 2012; de Wit 2010) postulated that no direct tension on the free edges, which occurs using fibrin glue, results in reduced stimulus for sub-conjunctival scar formation; apposition of the eyelids to the bulbar conjunctiva provides a natural biological dressing, and confers a unique wound-healing environment and a smooth, frictionless surface. The eyelids are able to provide compression and a vascular bed with immune capability in close proximity to the injury site. It must also be noted that intraoperative complications are not very common. However, there are some intraoperative advantages using fibrin glue such as the possibility of still using grafts with buttonholes, and the ability to be more efficient with unco-operative patients who persistently move their eyes. In these people, the suturing process can be very difficult. We believe that complications, such as graft dehiscence, should be expected but they can be minimised: maintaining a dry scleral bed prior to applying the tissue glue and graft; educating the patient; avoiding eye rubbing postoperatively; and patient selection may reduce this risk.

Overall completeness and applicability of evidence

There was variability across studies related to different race of participants, the use of different kinds of sutures and fibrin glue, and different length of follow-up and in particular some follow-up time was short.

Certainty of the evidence

We judged the evidence for all three outcomes to be low-certainty. We downgraded for risk of bias as we judged many studies at unclear risk of selection and detection bias and some at high risk of attrition bias. We downgraded recurrence and complications outcomes for imprecision as there were few events. We downgraded the operating time outcome for inconsistency as there was high statistical heterogeneity.

Potential biases in the review process

As far as we are aware we have minimised potential biases in the review process. We have followed the methods set out in the published protocol (Romano 2014). The only amendment was to add in a summary of findings table and GRADE assessment as required by new Cochrane standards.

Agreements and disagreements with other studies or reviews

Other retrospective studies, such as the large cohort reported by Koranyi 2005 where they studied 461 procedures with follow-up ranging from 6 to 12 months reported a recurrence rate of 5.3% for the fibrin glue group and 13.5% in the suture group. They also found all the recurrences occurred within six months after surgery. Marticorena 2006 and Uy 2002 suggested that the use of fibrin glue reduced postoperative discomfort. A previous meta-analysis of pterygium recurrence after surgery concluded that simple bare sclera resection alone is associated with six times higher odds of pterygium recurrence if a conjunctival autograft was not used and 25 times higher odds of recurrence if mitomycin C was not used. The authors recommended avoiding simple bare sclera excision (Sanchez-Thorin 1998). However, the use of MMC can be associated with sight-threatening complications such as corneoscleral melt, cataract, uveitis, secondary glaucoma, and symblepharon (Amano 2000; Hayasaka 1988; Rubinfeld 1992).

There are some drawbacks to using the fibrin glue technique, mainly the cost. Most surgeons recommend dividing one vial of fibrin glue between six to 10 patients, reducing the costs, but that means that all the patients must be operated on the same day. However, as the use of fibrin glue reduces the risk of recurrence, the cost of a second surgery will probably be avoided. In addition, reducing the surgical time provides, according to previous published data from the USA, a saving of USD 67.50/min (Montgomery 2007) in terms of surgical operating room expense. Therefore, just a reduction in surgical time would make it cost-effective compared with sutures and without the need to split the use of the glue over a number of cases. Another theoretical drawback is the risk of transmission of infectious agents, such as parvovirus B19 (Morita 2000) and prions (Hino 2000), as fibrin glue is made from blood products. Other concerns include the risk of transmission of blood-borne diseases and anaphylaxis. However, careful selection of donors and improved viral inactivation techniques has largely minimised this problem. Autologous fibrin could be the solution, however it is yet to be used

widely because of the time taken to procure the fibrin and lack of laboratory facilities at all centres.

AUTHORS' CONCLUSIONS

Implications for practice

The meta-analyses, conducted on people with pterygium in a hospital or outpatient setting, show fibrin glue may result in less recurrence and may take less time than sutures for fixing the conjunctival graft in place during pterygium surgery. There was low-certainty evidence to suggest a higher proportion of complications in the fibrin glue group. Surgery performed with fibrin glue is technically less demanding than surgery with sutures. However, there were higher rates of complications in the fibrin glue groups, even if some precautions, as suggested by experts, could reduce the number of complications.

Implications for research

The results of this review suggest that grafts attached with fibrin glue may be better than grafts attached with suture, although it must be taken into consideration limitations to the recurrence outcome. However this should encourage the research on using autologous, in-situ blood coagulum that shows different advantages: ease of use, almost zero cost, shorter surgical times, and less postoperative discomfort.

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CHARACTERISTICS OF STUDIES

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

Al-Fayez 2008

Methods	RCT investigating safety and efficacy of fibrin glue versus suture fixation of conjunctival autograft in treating pterygia. 1 eye enrolled
Participants	Country: Saudi Arabia Number of participants randomised: 56 Number of eyes randomised: 56 Number (%) of participants followed up: 100% Average age: not reported % female: not reported Inclusion criteria: participants with advanced pterygia treated by limbal-conjunctival autograft Exclusion criteria: not reported
Interventions	Intervention: fibrin glue fixation of conjunctival autograft (n = 24) Comparator: suture fixation of conjunctival autograft (n = 32)
Outcomes	List outcomes: recurrence of pterygium, complication of interventions Follow-up: 24 months
Notes	Funding source: not reported Conflict of interest: not reported Date study conducted: not reported Trial registration number: not reported

Al-Fayez 2008 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: participants were prospectively randomised. Comment: methods for the generation of sequence not described
Allocation concealment (selection bias)	Unclear risk	Quote: participants were prospectively randomised. Comment: methods used for allocation sequence generation not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Report gives the impression that there were no dropouts or withdrawals, but this was not specifically stated
Selective reporting (reporting bias)	Unclear risk	Protocol not obtained; all outcomes stated in methods reported

Elwan 2014

Methods	RCT. 1 eye enrolled
Participants	Country: Egypt Number of participants randomised: 150 Number of eyes randomised: 150 Number (%) of participants followed up: 100% Average age: 50 % female: 60% Inclusion criteria: participants with pterygium Exclusion criteria: inability to complete the 2-year follow-up period, atrophic pterygium, pseudopterygium, ocular surface pathology, infection, previous limbal surgery or double head pterygium
Interventions	Intervention: fibrin glue fixation of conjunctival autograft (n = 50) Comparator: suture fixation of conjunctival autograft (n = 100)
Outcomes	List outcomes: recurrence of pterygium, complication of interventions, gain in uncorrected visual acuity, duration of surgery, postoperative pain, foreign body sensation, photophobia, hyperemia, chemosis, overall satisfaction Follow-up: 24 months
Notes	Funding source: not reported Conflict of interest: no Date study conducted: not reported

Elwan 2014 *(Continued)*

	Trial registration number: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomly assigned by coin toss
Allocation concealment (selection bias)	Unclear risk	The trial was described as randomised, but methods used for allocation sequence generation not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Masking probably of limited importance for more objective outcomes (as some of the primary outcomes), because the risk of ascertainment bias was limited, but could have affected other outcomes
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The trial was described as randomised, but methods used for allocation sequence generation not described
Selective reporting (reporting bias)	Low risk	Protocol not obtained; all outcomes stated in methods reported

Hall 2009

Methods	RCT. Only 1 eye in each participant had surgery and was studied
Participants	Country: New Zealand Number of participants randomised: 50 Number of eyes randomised: 50 Number (%) of participants followed up: 94% Average age: 49.8 years (range 34–76 years) % female: 46% female Inclusion criteria: participants with pterygium > 4 mm in size Exclusion criteria: other ocular disease, or participant aged younger than 25 years
Interventions	Intervention: fibrin glue fixation of conjunctival autograft (n = 25) Comparator: suture fixation of conjunctival autograft (n = 25)
Outcomes	List outcomes: recurrence of pterygium, complication of interventions, surgical time, participant discomfort Follow-up: 12 months
Notes	Funding source: not reported Conflict of interest: not reported Date study conducted: May 2006-November 2006 Trial registration number: NCT00326560

Hall 2009 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Eyes randomly allocated to treatment using pre-allocated codes
Allocation concealment (selection bias)	Low risk	Eyes were independently randomised by independent nursing staff, and the surgeon was unaware which technique (sutures or glue) was to be performed until after the conjunctival graft was excised and the circulating nurse entered the room with either glue or sutures.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	For some of the outcomes, study authors tried to avoid observer influence (e.g. participants filled in the VAS questionnaire prior to follow-up visits to avoid observer influence).
Incomplete outcome data (attrition bias) All outcomes	Low risk	At 3-month follow-up, 22/25 participants for the fibrin glue attended their appointment and 22/25 participants for the suture group. At 6-month follow-up, 48/50 participants could be contacted, with 2 from the suture group lost to emigration. At 12 months, 47/50 participants could be contacted, with 2 from the suture group and one from the glue group lost due to emigration
Selective reporting (reporting bias)	Low risk	Protocol not obtained; all outcomes stated in methods reported

Jaih 2006

Methods	RCT
Participants	Country: India Number of participants randomised: 27 Number of eyes randomised: 27 Number (%) of participants followed up: not reported Average age: not reported % female: not reported Inclusion criteria: participants with pterygium Exclusion criteria: not reported
Interventions	Intervention: fibrin glue fixation of conjunctival autograft (n = 12) Comparator: suture fixation of conjunctival autograft (n = 15)
Outcomes	List outcomes: surgery time and postoperative pain Follow-up: not reported
Notes	Funding source: not reported Conflict of interest: not reported Date study conducted: not reported

Jaih 2006 *(Continued)*

	Trial registration number: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: prospective randomised trial. Comment: methods for the generation of sequence not described
Allocation concealment (selection bias)	Unclear risk	The trial was described as randomised, but methods used for allocation sequence generation not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	Unclear risk	Protocol not obtained; insufficient information to permit judgement

Jiang 2008

Methods	RCT, only 1 eye was enrolled
Participants	Country: China Number of participants randomised: 40 Number of eyes randomised: 40 Number (%) of participants followed up: 100% Average age: 57 % female: 40% Inclusion criteria: participants with nasal primary pterygium Exclusion criteria: ocular pathology, history of previous ocular surgery or trauma, suspect glaucoma, or known hypersensitivity to the glue
Interventions	Intervention: fibrin glue fixation of conjunctival autograft (n = 20) Comparator: suture fixation of conjunctival autograft (n = 20) Tobramycin-dexamethasone mixed solution was subconjunctivally injected and a pressure patch was applied for 24 h to restrict the eyeball from movement or blinking. Surgery time was recorded from the placement of the lid speculum to its removal.
Outcomes	List outcomes: operating time, postoperative symptoms, graft success, recurrence rate and complications. Follow-up: 12 months
Notes	Funding source: not reported

Jiang 2008 *(Continued)*

	Conflict of interest: not reported
	Date study conducted: June 1-June 15, 2005
	Trial registration number: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	By tossing a coin
Allocation concealment (selection bias)	Unclear risk	The trial was described as randomised, but methods used for allocation sequence generation not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Masking probably of limited importance for more objective outcomes (e.g. visual acuity, intraocular pressure), because the risk of ascertainment bias was limited, but could have affected other outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	All the participants completed the 1-year follow-up period
Selective reporting (reporting bias)	Low risk	Protocol not obtained; all outcomes stated in methods reported

Karalezli 2008

Methods	RCT. 1 eye of each participant was included in the study. If the participant had bilateral pterygium, 1 eye was selected randomly and included in the study
Participants	Country: Turkey Number of participants randomised: 50 Number of eyes randomised: 50 Number (%) of participants followed up: 100% Average age: 53-58 years % female: 56%-52% Inclusion criteria: participants with primary pterygium Exclusion criteria: participants with immune system, eyelid or ocular surface diseases, with a history of previous ocular surgery or trauma or known hypersensitivity to any component of fibrin glue
Interventions	Intervention: fibrin glue fixation of conjunctival autograft (n = 25) Comparator: suture fixation of conjunctival autograft (n = 25)
Outcomes	List outcomes: operating time, postoperative symptoms, recurrence rate and complications Follow-up: 12 months
Notes	Funding source: not reported

Karalezli 2008 *(Continued)*

	Conflict of interest: not reported
	Date study conducted: not reported
	Trial registration number: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants were randomised to 2 groups
Allocation concealment (selection bias)	Low risk	To reduce intraobserver bias and minimise the influence of the known surgical technique on the extent of removal and size of the graft, the randomisation was done after the surgeon had harvested the graft.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Masking probably of limited importance for the specified outcomes, because the risk of ascertainment bias was limited. Recurrence was defined as any fibrovascular growth that passed the corneal limbus by more than 1 mm. Reoperation was done if further growth of the recurrent pterygium was observed on any follow-up examination. To avoid observer influence, participants were asked to fill out a questionnaire on postoperative day 1 and during every follow-up examination until the 1st month, grading their symptoms using a 5-point scale
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed the 12-month follow-up. None was excluded from the study
Selective reporting (reporting bias)	Low risk	Protocol not obtained; all outcomes stated in methods reported

Koranyi 2004

Methods	RCT; 1 eye of each participant was included in the study
Participants	Country: Sweden Number of participants randomised: 43 Number of eyes randomised: 43 Number (%) of participants followed up: 100% Average age: 44-48 years % female: 35% Inclusion criteria: participants with primary pterygium Exclusion criteria: not reported
Interventions	Intervention: fibrin glue fixation of conjunctival autograft (n = 20) Comparator: suture fixation of conjunctival autograft (n = 23)
Outcomes	List outcomes: operating time, postoperative pain, recurrence rate and complications

Koranyi 2004 *(Continued)*

	Follow-up: 6 months
Notes	Funding source: not reported Conflict of interest: not reported Date study conducted: February-April 2000 Trial registration number: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomised by a computer random function into 2 groups
Allocation concealment (selection bias)	Unclear risk	The trial was described as randomised, but methods used for allocation sequence generation not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Masking probably of limited importance for the specified outcomes, because the risk of ascertainment bias was limited, but could have affected other outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	One participant in the suture group was withdrawn because of inability to fill out the VAS questionnaire
Selective reporting (reporting bias)	Low risk	Protocol not obtained; all outcomes stated in methods reported

Ozdamar 2008

Methods	RCT; 1 eye of each participant was included in the study
Participants	Country: Turkey Number of participants randomised: 24 Number of eyes randomised: 24 Number (%) of participants followed up: 100% Average age: 42 years % female: 58.3% Inclusion criteria: participants with primary pterygium Exclusion criteria: no reported
Interventions	Intervention: fibrin glue fixation of conjunctival autograft (n = 12) Comparator: suture fixation of conjunctival autograft (n = 12)
Outcomes	List outcomes: recurrence rate, complications, participant comfort, and histopathologic evaluation Follow-up: 6 months

Ozdamar 2008 *(Continued)*

Notes	Funding source: not reported Conflict of interest: not reported Date study conducted: not reported Trial registration number: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: a randomised study. Comment: methods used for random sequence generation not described
Allocation concealment (selection bias)	Unclear risk	The trial was described as randomised, but methods used for allocation sequence generation not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Masking probably of limited importance for the specified outcomes, because the risk of ascertainment bias was limited, but could have affected other outcomes
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	Low risk	Protocol not obtained; all outcomes stated in methods reported

Ratnalingam 2010

Methods	RCT; 1 eye of each participant was included in the study. In case of bilateral pterygium, each eye was randomised separately.
Participants	Country: Malaysia Number of participants randomised: 113 Number of eyes randomised: 137 Number (%) of participants followed up: 100% Average age: 60 years % female: 32% Inclusion criteria: participants with primary pterygium Exclusion criteria: not reported
Interventions	Intervention: Fibrin glue fixation of conjunctival autograft (n = 68) Comparator: suture fixation of conjunctival autograft (n = 69)
Outcomes	List outcomes: recurrence rate, surgical time, complications, participant comfort Follow-up: 12 months
Notes	Funding source: not reported

Ratnalingam 2010 *(Continued)*

	Conflict of interest: not reported
	Date study conducted: 1 June 2006-30 January 2007
	Trial registration number: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants in each subgroup were randomised into the fibrin adhesive or suture group via block permuted randomised sampling with varying block sizes of 4 and 6.
Allocation concealment (selection bias)	Low risk	Randomisation was done by an independent party who drew a sealed envelope at a different site from the study location. The results of this envelope were then informed to the surgeon via telephone
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The results were not informed to the independent observer, who was grading recurrence.
Incomplete outcome data (attrition bias) All outcomes	High risk	Only 137 out of 175 randomised eyes evaluated. No information on reasons and distribution of withdrawal provided
Selective reporting (reporting bias)	Low risk	Protocol not obtained; all outcomes stated in methods reported

Rubin 2011

Methods	RCT; 1 eye of each participant was included in the study.
Participants	Country: Brazil Number of participants randomised: 47 Number of eyes randomised: 47 Number (%) of participants followed up: 100% Average age: 18-70 years % female: not reported Inclusion criteria: participants with primary pterygium Exclusion criteria: not reported
Interventions	Intervention: fibrin glue fixation of conjunctival autograft (n = 21) Comparator: suture fixation of conjunctival autograft (n = 26)
Outcomes	List outcomes: recurrence rate, surgical time, and postoperative pain Follow-up: 12 months
Notes	Funding source: not reported

Rubin 2011 *(Continued)*

	Conflict of interest: not reported
	Date study conducted: not reported
	Trial registration number: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: a randomised study. Comment: methods used for random sequence generation not described
Allocation concealment (selection bias)	Unclear risk	The trial was described as randomised, but methods used for allocation sequence generation not described
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Evaluation by an independent observer
Incomplete outcome data (attrition bias) All outcomes	High risk	Substantial number of withdrawal at 6 months, and reasons not reported
Selective reporting (reporting bias)	Low risk	Protocol not obtained; all outcomes stated in methods reported

Sati 2014

Methods	RCT; 1 eye of each participant was included in the study.
Participants	Country: India Number of participants randomised: 60 Number of eyes randomised: 60 Number (%) of participants followed up: 100% Average age: 40 years % female: 40% Inclusion criteria: participants with primary pterygium Exclusion criteria: participants with ocular surface disorders, pseudopterygium, hypersensitivity to any blood components and positive serology for human immunodeficiency virus and hepatitis B
Interventions	Intervention: fibrin glue fixation of conjunctival autograft (n = 30) Comparator: suture fixation of conjunctival autograft (n = 30)
Outcomes	List outcomes: recurrence rate, surgical time, complications rate and postoperative participant discomfort Follow-up: 12 months
Notes	Funding source: not reported

Sati 2014 *(Continued)*

	Conflict of interest: not reported
	Date study conducted: not reported
	Trial registration number: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised using linear systematic sampling
Allocation concealment (selection bias)	Unclear risk	The trial was described as randomised, but methods used for allocation sequence generation not described
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Masking probably of limited importance for the specified outcomes, because the risk of ascertainment bias was limited
Incomplete outcome data (attrition bias) All outcomes	Low risk	No drop out because of excellent communications with participants
Selective reporting (reporting bias)	Low risk	Protocol not obtained; all outcomes stated in methods reported

Sharma 2015

Methods	RCT; 1 eye of each participant was included in the study
Participants	Country: India Number of participants randomised: 50 Number of eyes randomised: 50 Number (%) of participants followed up: 100% Average age: 43 years % female: 50% Inclusion criteria: participants of all ages and of either sex presenting with primary nasal pterygium Exclusion criteria: recurrent pterygium, glaucoma, retinal pathology requiring surgical intervention, history of previous ocular surgery or trauma
Interventions	Intervention: fibrin glue fixation of conjunctival autograft (n = 25) Comparator: suture fixation of conjunctival autograft (n = 25)
Outcomes	List outcomes: recurrence rate, surgical time, complications rate and postoperative participant discomfort Follow-up: 6 months
Notes	Funding source: not reported

Sharma 2015 *(Continued)*

	Conflict of interest: not reported
	Date study conducted: not reported
	Trial registration number: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised into 2 groups using a computer-generated random number table
Allocation concealment (selection bias)	Unclear risk	The trial was described as randomised, but methods used for allocation sequence generation not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Masking probably of limited importance for the specified outcomes, because the risk of ascertainment bias was limited, but could have affected other outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	None noted
Selective reporting (reporting bias)	Low risk	Protocol not obtained; all outcomes stated in methods reported

Uy 2005

Methods	RCT. Only 1 eye per participant was entered in the study.
Participants	Country: the Philippines Number of participants randomised: 22 Number of eyes randomised: 22 Number (%) of participants followed up: 100% Average age: 45 years % female: 41% Inclusion criteria: participants with primary pterygium Exclusion criteria: participants with ocular pathology other than error of refraction, with a history of previous ocular surgery or trauma, narrow occludable angles, ocular hypertension, physiologic or glaucomatous optic disc cupping, a family history of glaucoma, or known hypersensitivity to any component of fibrin glue
Interventions	Intervention: fibrin glue fixation of conjunctival autograft (n = 11) Comparator: suture fixation of conjunctival autograft (n = 11)
Outcomes	Graft success, recurrence rate, operating time, participant comfort List outcomes: recurrence rate, surgical time, complications rate and postoperative participant discomfort

Uy 2005 *(Continued)*

	Follow-up: 2 months. Due to the short follow-up we did not take the recurrence outcome into account, we considered just operating time and complication rate.
Notes	Funding source: not reported Conflict of interest: not reported Date study conducted: June-August 2001 Trial registration number: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The participant was then randomly assigned by coin toss
Allocation concealment (selection bias)	Unclear risk	The trial was described as randomised, but methods used for allocation sequence generation not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Masking probably of limited importance for the specified outcomes, because the risk of ascertainment bias was limited, but could have affected other outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed the 2-month follow-up period
Selective reporting (reporting bias)	Low risk	Protocol not obtained; all outcomes stated in methods reported

Yuksel 2010

Methods	RCT
Participants	Country: Turkey Number of participants randomised: 58 Number of eyes randomised: 58 Number (%) of participants followed-up: 100% Average age: 48-52 years % female: 50% Inclusion criteria: participants with primary pterygium Exclusion criteria: participants with ocular surface disorders, pseudopterygium, hypersensitivity to any blood components and positive serology for human immunodeficiency virus and hepatitis B
Interventions	Intervention: fibrin glue fixation of conjunctival autograft (n = 29) Comparator: suture fixation of conjunctival autograft (n = 29)
Outcomes	List outcomes: recurrence rate, surgical time, complications rate and cost

Yuksel 2010 *(Continued)*

	Follow-up: 6 months
Notes	Funding source: not reported Conflict of interest: not reported Date study conducted: January and April 2009 Trial registration number: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: a randomised study. Comment: methods used for random sequence generation not described
Allocation concealment (selection bias)	Unclear risk	The trial was described as randomised, but methods used for allocation sequence generation not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Masking probably of limited importance for the specified outcomes, because the risk of ascertainment bias was limited, but could have affected other outcomes
Incomplete outcome data (attrition bias) All outcomes	High risk	A total of 61 eyes of 61 participants were operated. Three participants from group 1 were excluded from the study since their conjunctival grafts were not in place at the third postoperative day. Total 58 eyes of 58 participants were included in study.
Selective reporting (reporting bias)	Low risk	Protocol not obtained; all outcomes stated in methods reported

RCT: randomised controlled trial
VAS: visual analogue scale

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

Study	Reason for exclusion
CTRI/2013/06/00376	Randomised trial comparing autologous blood versus fibrin glue, no comparison with sutures

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

ACTRN12613000986774

Trial name or title	Prospective evaluation of pterygium excision and conjunctival autograft with autologous blood, fibrin glue, or Vicryl sutures
Methods	Inclusion criteria: age of participant should be more than 18 years. Primary nasal pterygium. Participant willing to be enrolled in the study and available for all subsequent follow-ups. Exclusion criteria: age of participant less than 18 years. Recurrent pterygium (history of previous pterygium excision). Temporal pterygium. Pterygium > 4 mm. Double-headed primary pterygium (arising from both medial and lateral side of cornea). Any previous ocular surface surgery. Participant unwilling to participate in the study and all required follow-ups Age minimum: 18 Years Age maximum: 90 Years

ACTRN12613000986774 *(Continued)*

	Gender: both male and female
Participants	90
Interventions	Excision with conjunctival autograft involves removal of the pterygium leaving an area of bare sclera, which is closed by the movement of a free conjunctival transplant from another part of the ocular surface. The conjunctival autograft will be attached with autologous blood acting as a bioadhesive. The surgical intervention takes approximately 30 minutes and participants will be followed at 1 day, 1 week, 1 month, 3 months, 6 months, and 1 year.
Outcomes	Graft stability will be assessed on a slit lamp exam, grading stability based on the number of adherent edges Postoperative pain will be assessed based on a 0 (no pain) to 10 (worst pain in life) scale Pterygium recurrence will be assessed on a slit lamp exam
Starting date	1/11/2013
Contact information	Dr Ross MacIntyre, Royal Victorian Eye and Ear Hospital 32 Gisborne Street East Melbourne, VIC 3002, Australia, ross.macintyre@eyeandear.org.au
Notes	Not yet recruiting. Trial number: ACTRN12613000986774

NCT00326560

Trial name or title	Comparison of cut and paste with sutured autograft pterygium excision
Methods	Allocation: randomised Endpoint classification: efficacy study Intervention model: parallel assignment Masking: single masked Primary purpose: treatment Ages eligible for study: 20 years and older (adult, senior) Genders eligible for study: both Accepts healthy volunteers: yes Inclusion criteria: primary pterygium Exclusion criteria: ocular surface disease. Previous pterygium surgery
Participants	40
Interventions	Comparison of cut and paste with sutured autograft pterygium excision
Outcomes	Not applicable
Starting date	May 2006
Contact information	Reece C Hall, reece.hall@ccdhb.org.nz
Notes	Trial number: NCT00326560

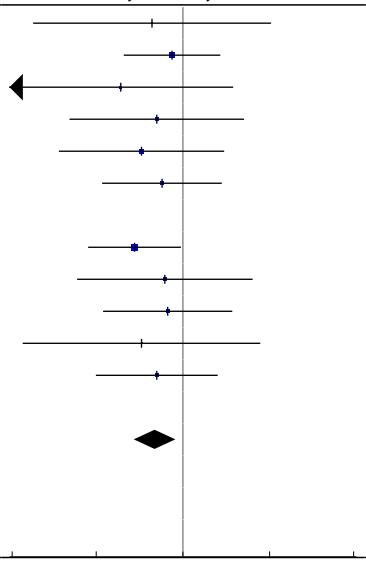
DATA AND ANALYSES

Comparison 1. Fibrin glue versus suture

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Recurrence of pterygium	12	762	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.27, 0.82]
2 Occurrence of 1 or more complications	11	673	Risk Ratio (M-H, Random, 95% CI)	1.92 [1.22, 3.02]
3 Operating time (minutes)	9	614	Mean Difference (IV, Random, 95% CI)	-17.01 [-20.56, -13.46]

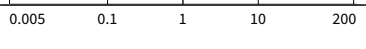
Analysis 1.1. Comparison 1 Fibrin glue versus suture, Outcome 1 Recurrence of pterygium.

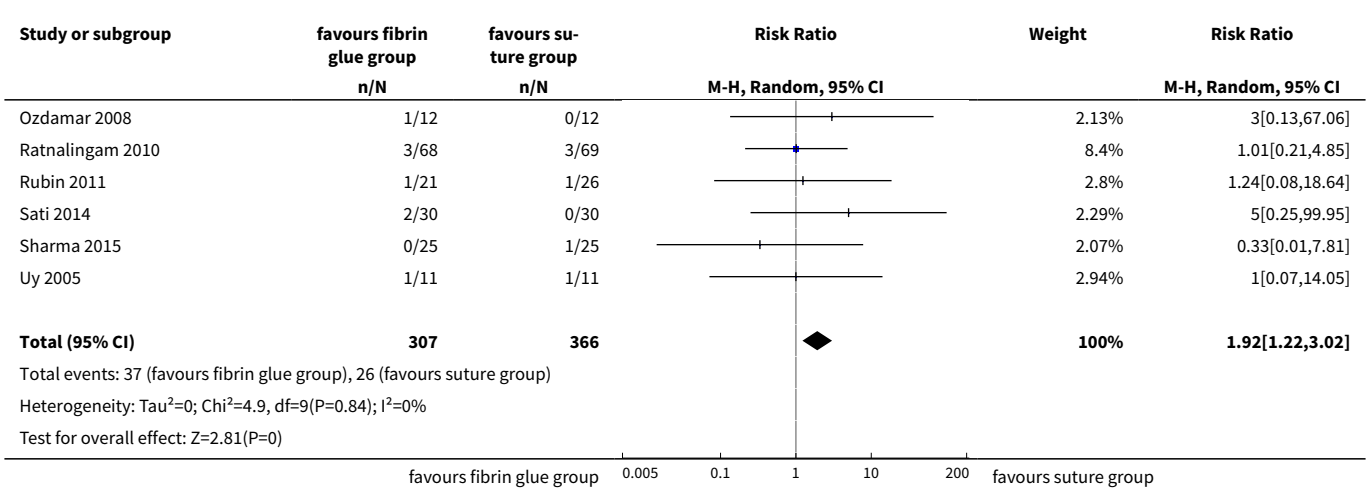
Study or subgroup	Fribrin glue group n/N	Suture group n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Al-Fayez 2008	0/24	1/32		3.06%	0.44[0.02,10.35]
Elwan 2014	3/50	8/100		18.55%	0.75[0.21,2.7]
Hall 2009	0/24	2/23		3.43%	0.19[0.01,3.8]
Jiang 2008	1/20	2/20		5.68%	0.5[0.05,5.08]
Karalezli 2008	1/25	3/25		6.34%	0.33[0.04,2.99]
Koranyi 2004	2/20	4/23		12.1%	0.57[0.12,2.81]
Ozdamar 2008	0/12	0/12			Not estimable
Ratnalingam 2010	3/68	11/69		20.12%	0.28[0.08,0.95]
Rubin 2011	1/21	2/26		5.62%	0.62[0.06,6.37]
Sati 2014	2/30	3/30		10.37%	0.67[0.12,3.71]
Sharma 2015	0/25	1/25		3.07%	0.33[0.01,7.81]
Yuksel 2010	2/29	4/29		11.67%	0.5[0.1,2.52]
Total (95% CI)	**348**	**414**		**100%**	**0.47[0.27,0.82]**
Total events: 15 (Fribrin glue group), 41 (Suture group)					
Heterogeneity: Tau^2=0; Chi^2=2, df=10(P=1); I^2=0%					
Test for overall effect: Z=2.67(P=0.01)					



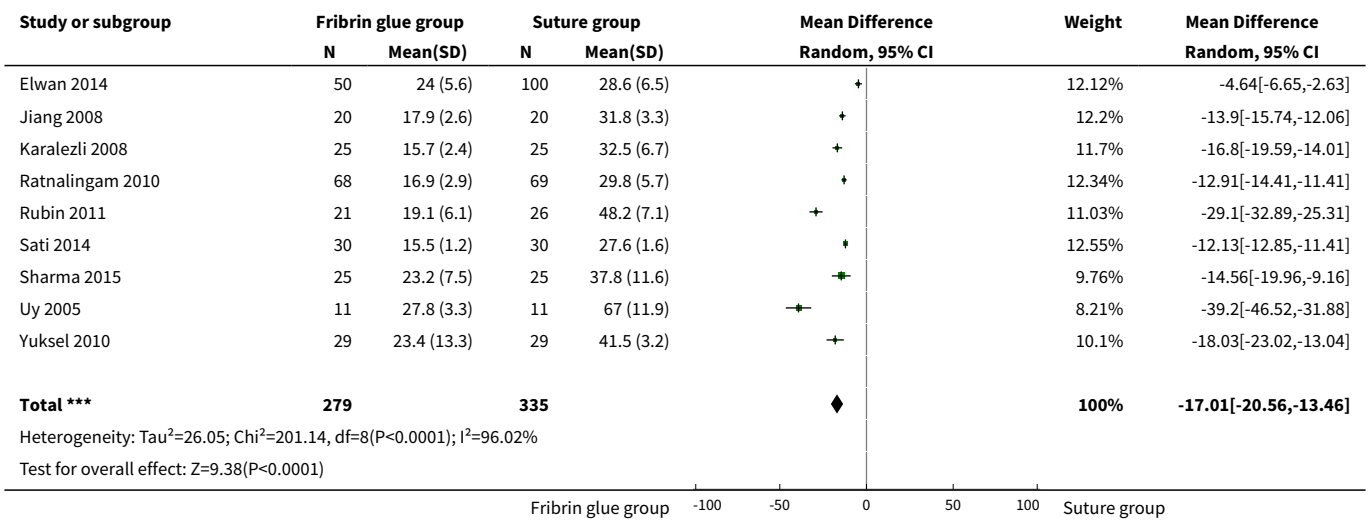
Analysis 1.2. Comparison 1 Fibrin glue versus suture, Outcome 2 Occurrence of 1 or more complications.

Study or subgroup	favours fibrin glue group n/N	favours suture group n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Elwan 2014	18/50	17/100		63.45%	2.12[1.2,3.74]
Hall 2009	5/25	0/25		2.54%	11[0.64,188.95]
Jiang 2008	4/20	3/20		11.08%	1.33[0.34,5.21]
Karalezli 2008	2/25	0/25		2.3%	5[0.25,99.16]
Koranyi 2004	0/20	0/23			Not estimable





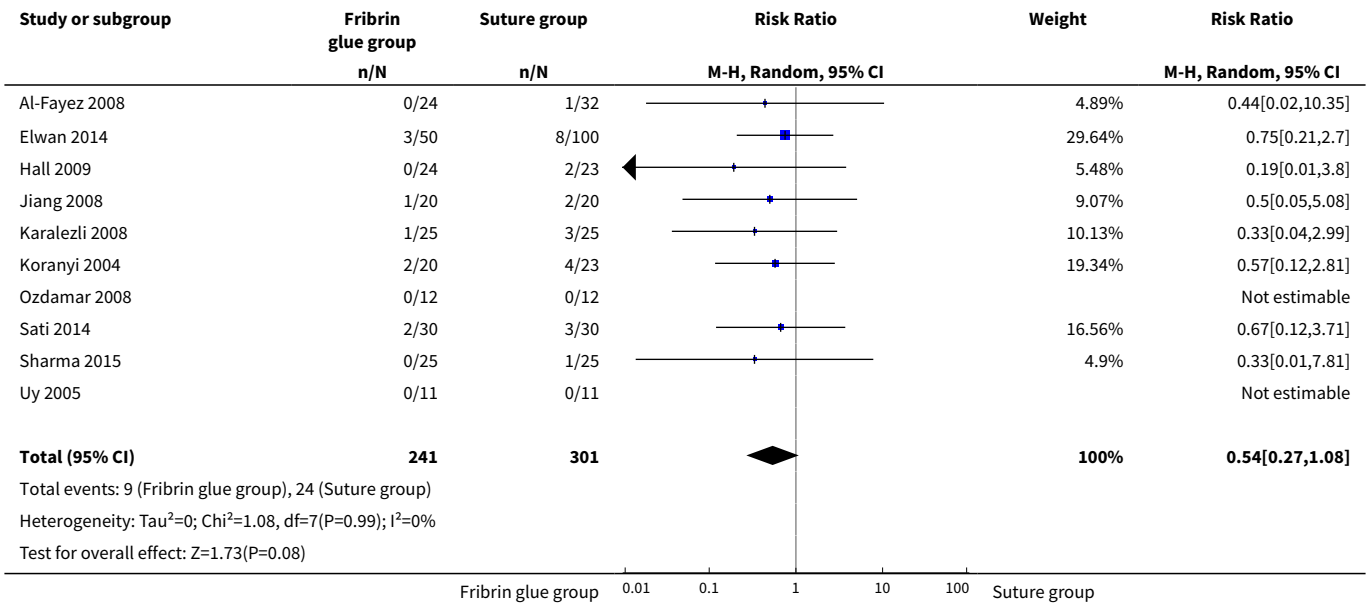
Analysis 1.3. Comparison 1 Fibrin glue versus suture, Outcome 3 Operating time (minutes).



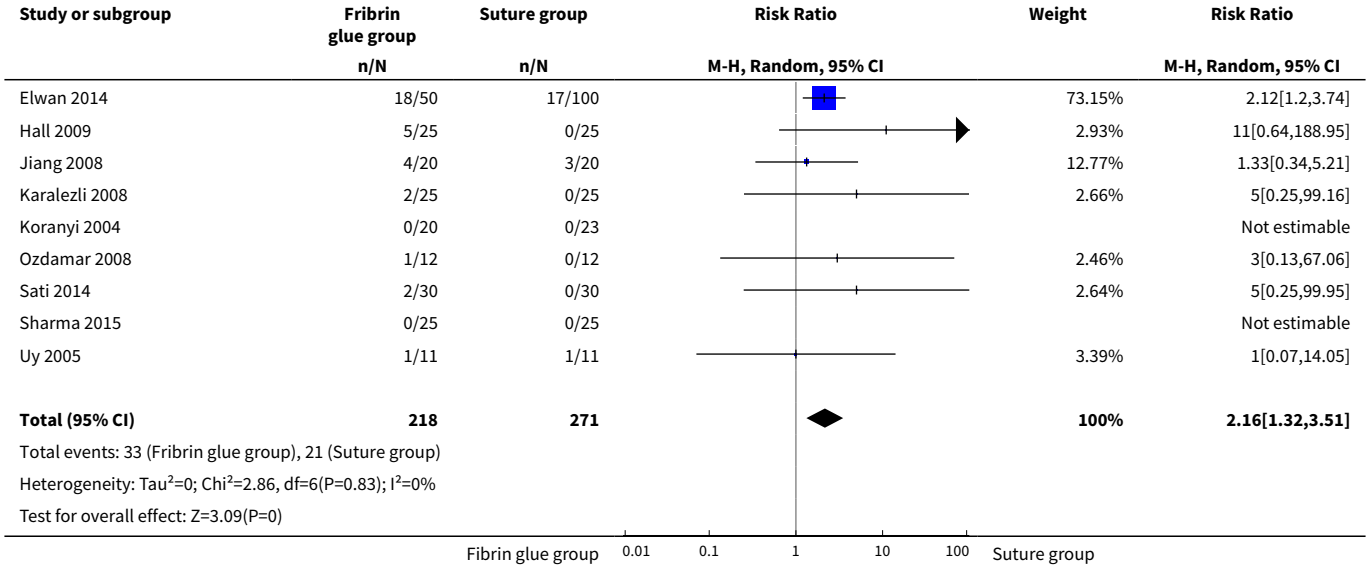
Comparison 2. Fibrin glue versus suture: excluding trials at high risk of bias

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Recurrence of pterygium	10	542	Risk Ratio (M-H, Random, 95% CI)	0.54 [0.27, 1.08]
2 Occurrence of 1 or more complications	9	489	Risk Ratio (M-H, Random, 95% CI)	2.16 [1.32, 3.51]
3 Operating time (minutes)	6	372	Mean Difference (IV, Random, 95% CI)	-15.59 [-19.90, -11.28]

Analysis 2.1. Comparison 2 Fibrin glue versus suture: excluding trials at high risk of bias, Outcome 1 Recurrence of pterygium.



Analysis 2.2. Comparison 2 Fibrin glue versus suture: excluding trials at high risk of bias, Outcome 2 Occurrence of 1 or more complications.

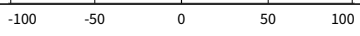


Analysis 2.3. Comparison 2 Fibrin glue versus suture: excluding trials at high risk of bias, Outcome 3 Operating time (minutes).

Study or subgroup	Fribrin glue group N	Mean(SD)	Suture group N	Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Elwan 2014	50	24 (5.6)	100	28.6 (6.5)		18.24%	-4.64[-6.65,-2.63]
Jiang 2008	20	17.9 (2.6)	20	31.8 (3.3)		18.36%	-13.9[-15.74,-12.06]
Karalezli 2008	25	15.7 (2.4)	25	32.5 (6.7)		17.6%	-16.8[-19.59,-14.01]
Sati 2014	30	15.5 (1.2)	30	27.6 (1.6)		18.9%	-12.13[-12.85,-11.41]
Sharma 2015	25	23.2 (7.5)	25	37.8 (11.6)		14.63%	-14.56[-19.96,-9.16]
Uy 2005	11	27.8 (3.3)	11	67 (11.9)		12.27%	-39.2[-46.52,-31.88]
Total ***	**161**		**211**			**100%**	**-15.59[-19.9,-11.28]**

Heterogeneity: Tau^2=25.45; Chi^2=120.86, df=5(P<0.0001); I^2=95.86%

Test for overall effect: Z=7.09(P<0.0001)



Fribrin glue group — Suture group

ADDITIONAL TABLES

Table 1. Complications of interventions

Complications	Fibrin glue	Suture
Conjunctival cyst	2/372	0/439
Dellen	1/372	3/439
Graft dehiscence	7/372	2/439
Graft loss	3/372	0/439
Graft overlying the limbus	0/372	1/439
Graft retraction	7/372	6/439
Granuloma	4/372	11/439
Subconjunctival haemorrhage	3/372	0/439

APPENDICES

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor Pterygium
#2 pterygium*
#3 (#1 OR #2)
#4 MeSH descriptor Tissue Adhesives
#5 MeSH descriptor Biological Dressings
#6 (fibrin) near/2 (glue or adhesive or seal* or tissue*)
#7 tissucol* or tisseel* or beriplast* or crosseal* or Quixil* or full link
#8 (#4 OR #5 OR #6 OR #7)
#9 MeSH descriptor Sutures

#10 MeSH descriptor Suture Techniques
#11 MeSH descriptor Polyglactin 910
#12 sutur*
#13 vicryl or nylon or mononylon
#14 (#9 OR #10 OR #11 OR #12 OR #13)
#15 (#3 AND #8 AND #14)

Appendix 2. MEDLINE (Ovid) search strategy

1. randomised controlled trial.pt.
2. (randomised or randomised).ab,ti.
3. placebo.ab,ti.
4. dt.fs.
5. randomly.ab,ti.
6. trial.ab,ti.
7. groups.ab,ti.
8. or/1-7
9. exp animals/
10. exp humans/
11. 9 not (9 and 10)
12. 8 not 11
13. pterygium/
14. pterygium$.tw.
15. 13 or 14
16. exp tissue adhesives/
17. biological dressings/
18. (fibrin adj2 (glue or adhesive or seal$ or tissue$)).tw.
19. (tissucol$ or tisseel$ or beriplast$ or crosseal$ or Quixil$ or full link).tw.
20. or/16-19
21. exp sutures/
22. Suture Techniques/
23. sutur$.tw.
24. (vicryl or nylon or mononylon).tw.
25. Polyglactin 910/
26. or/21-25
27. 15 and 20 and 26
28. 12 and 27

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

Appendix 3. Embase (Ovid) search strategy

1. exp randomised 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$).tw.
29. or/25-28
30. 29 not 10
31. 30 not (11 or 23)
32. 11 or 24 or 31
33. pterygium/
34. pterygium$.tw.
35. 33 or 34
36. exp tissue adhesive/
37. exp bandages/
38. (fibrin adj2 (glue or adhesive or seal$ or tissue$)).tw.
39. (tissucol$ or tisseel$ or beriplast$ or crosseal$ or Quixil$ or full link).tw.
40. or/36-39
41. exp sutures/
42. suturing method/
43. sutur$.tw.
44. (vicryl or nylon or mononylon).tw.
45. Polyglactin/
46. or/41-45
47. 35 and 40 and 46
48. 32 and 47

Appendix 4. ISRCTN search strategy

pterygium and fibrin

Appendix 5. ClinicalTrials.gov search strategy

Pterygium AND Fibrin

Appendix 6. ICTRP search strategy

pterygium AND fibrin

Appendix 7. Data on study characteristics

Heading in table in RevMan	Proposed subheadings	
Methods	Study design	•Parallel group RCT i.e. people randomised to treatment •Paired eye or intra-individual RCT i.e. eyes randomised to treatment •Cluster RCT i.e. communities randomised to treatment •Cross-over RCT •Other
	Eyes	•One eye included in study • Indicating how the eye was selected •Two eyes included in study, both eyes received same treatment • Indicating how data were analysed (best/worst/average/both and adjusted for within-person correlation/both and not adjusted for within-person correlation

(Continued)

		• Indicating if a mixture of one eye and two eyes were used •Two eyes included in study, eyes received different treatments (pair matched) • Indicating if a correct pair-matched analysis was done
Participants	Country	Brasil, China, Egypt, India, Malaysia, New Zealand, Philippines, Saudi Arabia, Sweden, and Turkey
	Setting	
	Number of participants	
	Number of men	
	Number of women	
	Average age	
	Age range	
	Ethnic group	
	Inclusion criteria	
	Exclusion criteria	
Interventions	Intervention Comparator	
Outcomes	List	
Notes	Date conducted	Indicating specific dates of recruitment of participants mm/yr to mm/yr
	Sources of funding	
	Declaration of interest	
	Other	

Appendix 8. Assessment of risk of bias

Randomisation sequence generation

We will assess this domain as:

- 'low risk of bias', if the allocation sequence was generated by a computer or random number table. (Drawing of lots, tossing of a coin, shuffling of cards or throwing dice will be considered as adequate if a person who was not otherwise involved in the recruitment of participants performed the procedure);
- 'unclear risk of bias', if the trial was described as randomised, but the method used for the allocation sequence generation was not described;
- 'high risk of bias', if a system involving dates, names or admittance numbers was used for the allocation of participants.

Allocation concealment

We will assess this domain as:

- 'low risk of bias', if the allocation of participants involved a central independent unit, on-site locked computer, identically appearing numbered drug bottles or containers prepared by an independent pharmacist or investigator, or sealed envelopes;
- 'unclear risk of bias', if the trial was described as randomised, but the method used to conceal the allocation was not described;
- 'high risk of bias', if the allocation sequence was known to the investigators who assigned participants or if the study was quasi-randomised.

Blinding (masking) of participants and personnel

This outcome will not be assessed as it is difficult to mask participants or personnel (clinicians for example) to the intervention.

Blinding (masking) of outcome assessors

- masking of outcome assessor to treatment allocation. However, as trials use two different types of intervention (sutures or glue), masking of outcome assessors will be problematic, unless assessment is performed by someone not involved in the study.

Incomplete outcome data

We will assess this domain as:

- 'low risk of bias', if the numbers and reasons for dropouts and withdrawals in all intervention groups were described or if it was specified that there were no dropouts or withdrawals;
- 'unclear risk of bias', if the report gives the impression that there were no dropouts or withdrawals, but this was not specifically stated;
- 'high risk of bias', if the number or reasons for dropouts and withdrawals were not described.

We will further examine the percentages of dropouts overall in each trial and per randomisation arm and we will evaluate whether intention-to-treat (ITT) analysis has been performed or could be performed, from the published information.

Were all randomised participants analysed in the group to which they were allocated? (ITT analysis).

- 'Low risk of bias': if it is specifically reported by the authors that ITT was undertaken and this is confirmed on study assessment, or not stated but evident from study assessment that all randomised participants are reported/analysed in the group they were allocated to for the most important time point of outcome measurement (minus missing values) irrespective of non-compliance and co-interventions.
- Unclear risk of bias': if it is described as ITT analysis, but we are unable to confirm on study assessment, or it is not reported and we are unable to confirm by study assessment.
- 'High risk of bias': if lack of ITT analysis is confirmed on study assessment (participants who were randomised were not included in the analysis because they did not receive the study intervention, they withdrew from the study or were not included because of protocol violation) regardless of whether ITT is reported or not; 'as treated' analysis was done with substantial departure from allocation; 'complete case' (or 'available case') analysis was done.

Selective outcome reporting

We will assess this domain as:

- 'low risk of bias': if adequate, pre-defined or clinically relevant and reasonably expected outcomes are reported on;
- 'unclear risk of bias': if not all pre-defined or clinically relevant and reasonably expected outcomes are reported on or are not reported fully, or it is unclear whether data on these outcomes were recorded or not;
- 'high risk of bias': if one or more clinically relevant and reasonably expected outcomes were not reported on; data on these outcomes were likely to have been recorded (inadequate).

Free of other bias (e.g., baseline imbalance, early stopping)

We will assess this domain as:

- 'low risk of bias': if the trial appears to be free of other components that could put it at risk of bias;
- 'unclear risk of bias': if the trial may or may not be free of other components that could put it at risk of bias;
- 'high risk of bias': if there are other factors in the trial that could put it at risk of bias, e.g., no sample size calculation made, early stopping, industry involvement or an extreme baseline imbalance; moreover, since the Unit of analysis is the person, not the eye, when it was impossible to extract data according to the unit of analysis, the study could receive a High risk of bias score in the Other Bias item.

CONTRIBUTIONS OF AUTHORS

Conception and design of study, analysis and interpretation (VR, MC, LC, LF). Drafting the review or commenting on it critically for intellectual content (VR, MC, LC, LF).

DECLARATIONS OF INTEREST

VR has no financial or commercial interest in the topic area discussed in this review.
LC has no financial or commercial interest in the topic area discussed in this review.
LF has no financial or commercial interest in the topic area discussed in this review.

MC has been an advisor/consultant for Bayer, Cephalon and ViiV Healthcare, and has received honoraria for educational lectures from Abbott, ViiV Healthcare and Novartis. These activities were not related to his work with this review.

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  * The NIHR also funds the CEV Editorial Base in London.

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

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We amended the protocol to include a Summary of findings table and GRADE assessment as required by updated Cochrane standards.

INDEX TERMS

Medical Subject Headings (MeSH)

*Autografts; *Sutures; Conjunctiva [*transplantation]; Fibrin Tissue Adhesive [adverse effects] [*therapeutic use]; Pterygium [prevention & control] [*surgery]; Randomized Controlled Trials as Topic; Recurrence; Secondary Prevention [*methods]; Tissue Adhesives [adverse effects] [*therapeutic use]; Transplantation, Autologous

MeSH check words

Humans