Published in final edited form as:

Am J Ophthalmol. 2017 October ; 182: 8–17. doi:10.1016/j.ajo.2017.07.004.

Conjunctival autograft versus amniotic membrane transplantation for treatment of pterygium: findings from a Cochrane Systematic Review

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Abstract

Purpose—To summarize key findings from a systematic review of the effectiveness and risks of conjunctival autograft (CAG) compared with amniotic membrane transplant (AMT) for pterygium.

Design—Cochrane systematic review.

Methods—We included only randomized controlled trials (RCTs) in which CAG and AMT had been compared for primary or recurrent pterygia. The primary outcome was recurrence of pterygium 1 mm onto the cornea by 3 and 6 months post-surgery. We adhered to Cochrane methods for trial selection, data extraction, risk of bias evaluation, and data synthesis.

Results—Twenty RCTs with 1866 participants (1947 eyes) were included. Pterygium recurrence 6 months after surgery ranged from 3.3%–16.7% in the CAG group and 6.4%–42.3% in the AMT group based on data from 1021 eyes in 10 RCTs. Estimated risk ratios from meta-analysis indicated that CAG-treated eyes had a 47% lower risk of recurrence 6 months after surgery compared with the AMT group (RR, 0.53, 95% CI, 0.33 to 0.85). For 96 eyes with recurrent pterygium, the risk of recurrence 6 months after CAG was reduced by 55% compared with AMT (RR, 0.45, 95% CI, 0.21–0.99). Three-month recurrence rates were similar for CAG and AMT based on data from 538 eyes (6 RCTs).

Conclusions—CAG was more effective than AMT to prevent pterygium recurrence by 6 months post surgery, especially in recurrent pterygia. CAG-treated eyes had half the recurrence rates of AMT-treated eyes. Future RCTs should assess changes in patient-reported outcomes (symptoms, cosmesis) and visual acuity, and evaluate effects of surgical variations.

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Financial Disclosures: No other financial disclosure

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INTRODUCTION

A pterygium is a wing-shaped fibrovascular growth that extends from the conjunctiva onto the nasal, temporal, or both aspects of the cornea. It is believed that ultraviolet light is a major contributor in the formation of pterygia, though reflected, scattered light is also critical.¹ Pterygia can impair vision through altered tear film, induced astigmatism, photophobia, epiphora, and binocular diplopia due to contraction of the Tenon's capsule. A recent meta-analysis of 20 studies, mostly from Asia, estimated the prevalence of pterygium to be 10.2% (95% confidence interval (CI) 6.3% to 16.1%).²

Surgery is the only treatment currently known to be effective for pterygia. No technique, however, entirely prevents recurrence; recurrent pterygium is often more difficult to remove than the primary growth.²⁻⁹ The most common techniques can be divided into two basic types: 1) bare sclera excision and 2) tissue grafting using either conjunctival (or more commonly, combined conjunctival and limbal) autograft (CAG) or amniotic membrane transplantation (AMT). These surgeries can be combined with adjunctive radiation or chemotherapy agents such as alkylating agent mitomycin C (MMC) and may make use of tissue adhesive instead of sutures to secure the graft to the underlying tissue.¹⁰ The risk of recurrence after simple bare sclera excision is reported to be as high as 88% in certain populations. Although tissue grafting is significantly more time consuming and more difficult than leaving bare sclera, it has the benefit of reducing the recurrence risk to 5% to 15%.¹¹ Amniotic membrane graft is a newer technique than conjunctival autograft. Possible reasons for the effectiveness of amniotic membrane graft in pterygium surgery include inhibition of pathological neovascularization,¹²⁻¹⁴ scar formation,¹⁵ and inflammation.^{16, 17}

Despite many surgical options and modifications,¹⁸ no currently used technique has been documented to have the lowest risk of recurrence compared to others. The main objective of this summary of our Cochrane systematic review¹⁹ is to report the comparative safety and effectiveness of conjunctival autograft compared with amniotic membrane graft for pterygium based on the best available evidence.

METHODS

Adhering to the methods in the Cochrane Handbook for Systematic Reviews of Interventions, we included only randomized controlled trials (RCTs) in the review.²⁰ Methods are summarized below; details are given in the full Cochrane systematic review.¹⁹ Eligible trials compared CAG with AMT for treatment of pterygium, both primary and recurrent. Trials that permitted ancillary use of MMC or fibrin glue instead of sutures were eligible.

Search methods

To identify RCTs potentially eligible for this review, we searched CENTRAL (which contains the Cochrane Eyes and Vision Trials Register), Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid MEDLINE Daily, Ovid OLDMEDLINE, EMBASE, PubMed, Latin American and Caribbean Health Sciences Literature Database (LILACS), the metaRegister of Controlled Trials (mRCT) (www.controlledtrials.com),

ClinicalTrials.gov (www.clinicaltrials.gov) and the World Health Organization (WH O) International Clinical Trials Registry Platform(ICTRP) (www.who.int/ictcp/search/en). We did not impose any date or language restrictions in the electronic search for trials. We also used the Science Citation Index Expanded database to identify additional studies that had cited trials included in this review. We last searched the electronic databases on 23 November 2015. The Cochrane systematic review provides our detailed search strategies for the electronic databases.¹⁹ We also reviewed the reference lists of reviews and reports from included trials.

Trial Selection

Pairs of authors independently reviewed titles and abstracts resulting from the search to identify citations referring to trials that definitely or possibly were eligible based on our inclusion criteria. The final eligibility decision was based on independent review by two authors of the full text of articles; disagreements were resolved by discussion.

Outcomes of Interest

The primary outcome for this review was the risk of recurrence of pterygium, commonly defined as recurrence 1mm or more anterior to the limbus, at 3 months and 6 months after surgery. We used risk ratios to compare rates of recurrence after CAG versus AMT. We wished to compare at 6-month and 1-year after surgery the following secondary outcomes: the proportion of participants with clinical improvement as defined in the included studies, such as resolution of pre-operative symblepharon, binocular diplopia, hyperemia, or vascularization; the mean change in best corrected and uncorrected visual acuity from baseline during follow-up, as reported by individual studies; vision-related quality of life as assessed by a validated questionnaire (e.g., the National Eye Institute Visual Functioning Questionnaire); and direct or indirect costs of either type of surgery.

Data Collection and Assessment of Trials for Risk of Bias

Two review authors independently assessed the included studies for potential sources of bias according to Cochrane guidelines.²⁰ The same authors independently extracted data from the included studies regarding trial characteristics, methods, participants, interventions, outcomes, and funding sources and recorded data on standard forms. One author entered the data using the Review Manager software;²¹ the other author verified the data entered. We compared participant and surgery characteristics among the trials to judge clinical and methodologic heterogeneity.

Studies were evaluated for risk of selection, outcome detection, attrition, selective reporting of outcomes, and other bias based on the Cochrane Risk of Bias tool. We judged each included study to have been at “low risk,” high risk,” or “unclear risk” (insufficient information to permit judgment of low or high risk of bias) of bias of each type. We attempted to contact study investigators when there was insufficient information in publications and other sources to assess bias or when information was not reported clearly.

Data Synthesis and Analysis

Data synthesis and analysis were performed following Cochrane methods. We calculated summary risk ratios (RRs) with 95% confidence intervals (CIs) for post-surgery recurrence of pterygium, adverse outcomes, and other dichotomous outcomes for which sufficient data were available from the included trials. The unit of analysis was the eye for all outcomes analyzed.

We calculated the I^2 statistic (%) to determine the proportion of variation in outcomes due to heterogeneity; we considered a value above 50% to suggest substantial statistical heterogeneity.

We performed meta-analysis when clinical and methodological heterogeneity was minimal. We combined the results of included trials in a meta-analysis using a random-effects model, unless fewer than three studies were included, in which case we used a fixed-effect model. Whenever sufficient data were available, we conducted subgroup analyses by stratifying participants based on whether they had primary pterygia or recurrent pterygia at study entry.

RESULTS

The electronic searches yielded 1841 records, of which we screened 1236 after removing duplicates (Figure 1). We obtained and screened the full-text reports of 35 citations that were potentially relevant. We included 20 RCTs, published in 22 reports, in this review. Our searches of other sources did not identify any other potentially eligible trials. All of the studies were parallel-group RCTs, except one that was a within-person RCT. In the latter trial, both eyes of participants had pterygia; one eye was randomly assigned to CAG and the other eye was assigned to AMT.

The studies were conducted in 8 different countries: 6 trials in Turkey, 3 trials each in China and Cuba, 2 each in Iran and Thailand, and 1 each in Egypt, Brazil, and Venezuela. Report authors for one study did not report where it had been conducted. Investigators of 11 studies restricted enrollment to primary pterygium alone, 5 studies were restricted to patients with recurrent pterygium, and three studies included participants with either primary or recurrent pterygium. Two of the three studies that included participants with both types of pterygium reported outcomes separately by pterygium status, and one presented combined results only. In one study, it was unclear whether participants had primary or recurrent pterygia or both because participants were reported only as having “symptomatic pterygium.”

The studies reported data from a total of 1947 eyes of 1866 participants, of which 858 eyes had received CAG, and 887 eyes had received AMT; there was little clinical or methodological heterogeneity based on participant characteristics and descriptions of surgical technique provided in the trials (Table 1). Recurrence of pterygium was the primary outcome in 19 of 20 included studies; the primary outcome of interest in one study was graft vascularization.

No trial was judged to have low risk of bias across all criteria (Figure 2). Most trials (17 of 20) had unclear or high risk of bias in five or more of the seven risk of bias domains.

Attrition bias (outcome data not reported for all participants enrolled) was the bias domain for which the largest number of trials was at high risk.

Risk of recurrence of pterygium

Length of post-surgery follow-up in the included trials (except for two studies with no mention of follow-up) ranged from 1 to 69 months. The primary time points for this review were 3 and 6 months post-surgery; whenever outcomes were not reported at those exact time points from the included study, we chose recurrence assessments between 2 and 4 months to represent the 3-month rate, and between 5 and 7 months to represent the 6-month rates. Of the 20 studies, 13 specified the time point(s) at which recurrence was assessed after surgery; the rest reported only recurrence “during the study period.” Though all studies reported on risk of pterygium recurrence, not all included this data at the time points of interest for our review: six of the 20 included studies (30%) reported data on recurrence 3 months post-surgery and 10 (50%) reported on recurrence at 6 months post-surgery (four studies reported both 3- and 6-month outcomes) Two studies reported recurrence by 12 months and 24 months only and could not be included in meta-analyses of recurrence at shorter follow-up times. Seven other included studies did not report the post-surgery time at which the recurrence data had been collected; therefore 11 of 20 studies contributed data to our meta-analyses.

Recurrence of pterygium at 3 months ranged from 0% to 16.7% in the CAG group and 4.8% to 26.9% in the AMT group in the 6 studies that reported this outcome. These studies included participants who underwent surgery for both primary and recurrent pterygia. There were 46 recurrences among 538 eyes. In a meta-analysis of 3-month recurrence data from these six studies, the risk of recurrence by 3 months was statistically equivalent between CAG and AMT groups (RR, 0.87; 95% CI, 0.43–1.77; Figure 3). The quality of the estimate is low due to the small number of recurrences in the 3-month period, which resulted in imprecise estimates of rates, inconsistencies among the individual study results, and potential selection bias.

In a subgroup analysis, we analyzed recurrences in four studies that included only participants with primary pterygium. There was no clinically or statistically significant difference at 3 months in recurrence of pterygium between CAG and AMT groups (RR, 0.92; 95% CI, 0.37–2.30), consistent with the findings from all 6 studies.

Recurrence of pterygium 6 months after surgery ranged from 3.33% to 16.7% in the CAG group and 6.4% to 42.3% in the AMT group among the 10 studies that reported this outcome. Statistical heterogeneity was observed among the studies that included participants with primary pterygia ($I^2 = 60\%$) and was attributed to one large study,³⁴ which we discovered was not reported in a peer-review journal but was a published doctoral thesis. This study included 228 participants; the risk of recurrence of pterygium was reported to have been higher with CAG compared to AMT (RR, 2.32; 95% CI, 1.02–5.25). In our meta-analysis, we first included this large study and estimated that CAG-treated eyes had a 47% lower rate of recurrence by 6 months than AMT-treated eyes (RR 0.53, 95% CI 0.33 to 0.85; Figure 4). These estimates were based on 151 recurrences among 1021 eyes. We next performed a sensitivity analysis on the recurrence of pterygium outcomes in which we

removed the doctoral thesis data from the meta-analysis. This study met the criteria of studies we planned to exclude in a sensitivity analysis—possessing high risk of bias and not being published as a full article at the time of the review. In the analysis of pterygium recurrence at 6 months after surgery excluding this study, the risk of recurrence was lower in the CAG group compared with the AMT group (RR 0.43, 95% CI 0.30 to 0.62). Participants in the CAG group had a statistically significantly 57% lower risk of recurrence compared with the AMT group. Since the doctoral thesis had also reported data that we included in our meta-analysis of pterygium recurrence at 3 months post-surgery, we additionally performed the same sensitivity analysis of 3-month data. For this analysis, the risk of recurrence of pterygium at 3 months after surgery in the CAG group remained not statistically different from the risk in the AMT group, as found when we included the questionable study data (RR 0.62, 95% CI 0.30 to 1.27). In short, a sensitivity analysis excluding the data from the non-peer reviewed publication accounting for high statistical heterogeneity resulted in even greater statistical support of CAG having a lower risk of recurrence at 3 and 6 months after surgery compared with AMT. We graded the quality of evidence for recurrence 6 months after surgery as moderate because of concerns about possible selection and attrition bias in the studies contributing to this meta-analysis.

In our subgroup analysis of 6-month recurrence rates, among the subgroup of participants (815 eyes) with primary pterygium at baseline, there was no statistically significant difference between eyes treated with CAG and those who received AMT (RR, 0.58, 95% CI, 0.27–1.27; Figure 4); data from the doctoral thesis were included in this analysis of primary pterygium at baseline. For the 96 eyes with recurrent pterygium at baseline, there was a 55% reduction in risk of recurrence for CAG (7/46, 15%) compared with AMT (18/50, 36%) (RR, 0.45; 95% CI, 0.21–0.99; Figure 4). The authors of two studies did not specify whether the pterygia were primary or recurrent, except to say that their studies included both types; there were 19 recurrences among 110 eyes in these two studies, but these data were not included in any subgroup analysis. For these two studies, the risk of recurrence was 62% lower for CAG compared with AMT (RR, 0.38; 95% CI, 0.15–0.95; Figure 4). The overall risk ratio comparing CAG to AMT for all 10 studies reporting recurrence at 6 months post-surgery regardless of the type of pterygia that was removed was 0.53 (95% CI 0.33 to 0.85), as noted above. Thus, in all meta-analyses of recurrence of pterygia by 3 and 6 months, the estimated risk ratios favored CAG, although the confidence intervals often included unity (1.0).

Secondary outcomes

The proportion of participants with clinical improvement, the proportion requiring repeat surgery, quality of life measures and direct and indirect cost of pterygium surgeries were secondary outcomes that were either not reported in any included study or were reported inadequately or as an adverse event; thus, no meta-analyses were performed. No study reported clinical improvement in vision after surgery, an important clinical measure; however, one trial that enrolled only participants with recurrent pterygium compared baseline and postoperative logMAR visual acuity.²⁷ The mean baseline logMAR VAs in eyes in the CAG group (0.2 ± 1.4 , $n=30$) and in the AMT group (0.2 ± 1.0 , $n=25$) were similar. The mean postoperative logMAR VAs during the follow-up period also were

similar: 0.1 ± 1.3 for CAG-treated eyes and 0.1 ± 1.2 for AMT-treated eyes; mean post-surgery difference 0.00 (95% CI -0.66 to 0.66). The mean follow-up time was 27.2 ± 20.8 months (range, 12–94 months) with no difference between CAG and AMT groups. The authors of another trial noted that “no eye had a loss of uncorrected visual acuity greater than 1 line at the last visit” but did not report measures of visual acuity.³⁹

Adverse events

Thirteen trials reported adverse events associated with CAG and AMT; serious adverse events are listed in Table 2. The majority of adverse events were not pre-specified or described in detail: “conjunctival edema,” “conjunctivitis,” “conjunctival inflammation,” “corneal scar,” “graft reaction,” punctate epithelial erosions, eyelid edema, pain.

DISCUSSION

In this review of 20 randomized controlled trials in which a total of 1947 eyes of 1866 participants were analyzed, we compared the effects of CAG relative to AMT with respect to pterygium recurrence at 3 and 6 months after surgery and found no statistically significant difference in risk of recurrence for primary or recurrent pterygia 3 months after surgery; at 6 months, amongst 1021 eyes in 10 RCTs, CAG conferred a 47% lower risk of recurrence than did AMT. Although at 6 months after surgery, subgroup analysis showed no difference in recurrence between the two procedures performed for primary pterygia, for the 96 eyes with recurrent pterygia at baseline, there was a 55% reduction in risk of recurrence with CAG compared with AMT. In addition, the analysis of primary pterygia included a non-peer reviewed paper that showed the opposite result and likely contributed to the lack of statistical significance between CAG and AMT for primary pterygia. To the best of our knowledge, our systematic review and meta-analysis includes the largest group of RCTs reviewed to date from which we have quantified the reduction in risk of pterygium recurrence with CAG compared with AMT. In a meta-analysis, this reduction is statistically significant at 6 months after surgery for recurrent pterygium. This review highlights the advantage of CAG in treatment of recurrent pterygium. Adverse events were uncommon and were not well-defined or pre-specified by trial investigators. Change in visual acuity, change in vision-related quality of life, patient-reported improvement in symptoms, cosmesis, or costs of the interventions were not reported in any trial.

The findings for the primary outcome of recurrence are consistent with two other smaller systematic reviews of surgery for pterygium, which also found CAG had a lower recurrence risk compared to AMT.^{41,42} Our review included only RCTs (level 1 evidence) and made use of additional databases to identify eligible trials, allowing inclusion of studies published in non-English language journals and small studies, many performed in countries where the prevalence of pterygium is high. This feature distinguishes this review from a review by the American Academy of Ophthalmology that limited their search to PubMed and Cochrane library databases and to articles published in English. Their searches yielded four studies, which demonstrated that CAG is superior to AMT in reducing the rate of pterygium recurrence. In our study, a sensitivity analysis excluding the data from the non-peer reviewed publication that accounted for high statistical heterogeneity³⁴ resulted in even greater

statistical support for a lower risk of recurrence at 3 and 6 months after CAG compared with AMT. Moreover, our systematic review and meta-analysis estimate the magnitude of the reduction in risk of pterygium recurrence with CAG.

The quality of the estimate of relative risk of recurrence 3 months after surgery is low due to the small number of recurrences (46 of 538 eyes), inconsistencies among the individual study estimates, and potential selection bias. Despite selection and attrition bias in studies of recurrence at 6 months after surgery, there were 151 recurrences in 1021 eyes and the quality of data were higher than at 3 months. Although the significance of the benefit of CAG over AMT in patients with recurrent pterygia is arguable based on the upper bound of the confidence interval on the estimated relative risk [0.21–0.99], the chance of recurrence was 15% for CAG patients and 36% for AMT patients, a clinically significant difference. Moreover, outcomes at 6 months after pterygium surgery are more clinically relevant than 3-month outcomes; as in other corneal procedures (e.g., corneal transplantation, laser in-situ keratomileusis, photorefractive keratectomy), extensive wound healing and remodeling are likely still occurring 3 months after surgery. In fact, in their analysis of surgery and adjuvants for pterygium excision, the American Academy of Ophthalmology's Ophthalmic Technical Assessment excluded reports with follow-up period shorter than 6 months to avoid underestimation of recurrence rates.⁴² One group has depicted survival time of pterygium excision to time of recurrence in recurrent cases and has shown an asymptotic decay in incidence, describing a 57% chance of recurrence within 4 months of removal and a 97% chance of recurrence in 12 months in a survival curve analysis of pterygium recurrences.⁴³ Because the rate of recurrence decreases over time (with the majority of recurrences that occur detected within the first 3 months after surgery), follow-up beyond 6–8 months would add little information about rates.

We cannot estimate the effect of performance or detection bias on the findings of the superiority of CAG over AMT. Even if masked to the type of surgery performed, in the early postoperative period (and possibly beyond 3 months), a surgeon or other trained observer could distinguish which surgery had been performed by noting whether there were two surgical sites (CAG) or only one surgical site (AMT). Most studies did not identify who assessed eyes for pterygium recurrence, and the potential for detection bias was present in all studies.

We cannot be certain that recurrence rate is not in part related to elements of surgeon technique or technical difficulty of the procedure; differences in surgical techniques may introduce heterogeneity that we cannot control for or quantify. We classified techniques as “CAG” if thus described by authors, regardless of underlying differences, for example, in how much Tenon's layer was transplanted. No study reported whether the initial surgery in cases of recurrent pterygium had been performed with CAG or AMT. Recurrent pterygia are more fibrovascular and adherent to underlying tissue than are primary pterygia; repeat surgery is often more difficult.³ When the primary surgery was done with CAG, there may be limited tissue from which to harvest a second autograft, yet we found CAG to be superior to AMT with regard to recurrence in cases of excision of recurrent pterygia. This finding may seem counterintuitive, given that some surgeons favor AMT in settings of large

conjunctival defects, poor availability of autologous conjunctival tissue, and recurrent pterygia associated with conjunctival scarring.

Use of adjuvants, age of patient, graft fixation method, and postoperative steroid regimen represent additional variables introducing heterogeneity into our meta-analysis. Adjuvant use and fixation methods are listed in Table 1, but small sample sizes preclude a robust meta-analysis of the effect of these factors on recurrence. However, a recently published review on the use of fibrin glue versus sutures for CAG in primary pterygium found that using fibrin glue may result in lower recurrence of pterygium.⁴⁴ Advantages of CAG over AMT are the avoidance of allograft tissue and the direct or indirect cost of surgery, including the cost of the amniotic membrane. CAG is more time-consuming than is AMT because of time spent harvesting the graft. Advantages attributed to AMT include wound-healing properties and anti-inflammatory properties.

Clinical improvement implies a favorable change in patients' quality of vision or quality of life and also may imply that patients would choose surgery again if presented with the option. To our knowledge, no trial addressed this question. No study evaluated the participant-reported outcome of vision-related quality of life, which may include patient concerns about cosmesis. Future RCTs comparing CAG (or AMT) with methods such as extended removal with extended transplantation¹⁸ should include both clinical and patient-reported outcomes.

In conclusion, both CAG and AMT appear to be safe for excision of pterygium. Although this review does not answer which technique is associated with fewer adverse events or a clinically significant change in visual acuity or cosmesis, in a meta-analysis of 1021 eyes, pterygium excision accompanied by CAG conferred a lower risk of recurrence at 6 months compared to excision accompanied by AMT. We did not account for fixation technique or adjuvant use; each one is a source of heterogeneity in our included studies and may have affected recurrence risk. We suggest a systematic review comparing CAG with versus without MMC in order to elucidate the effects of this adjuvant. Future studies are also needed to compare outcomes and adverse effects of other techniques¹⁸ with CAG.

Acknowledgments

Funding/Support: Ms. Clearfield and Dr. Hawkins receive salary support from the Cochrane Eyes and Vision U.S. Project co-operative agreement with the National Eye Institute, National Institutes of Health, U.S. Department of Health and Human Services, Bethesda, Maryland. The Wilmer Eye Institute receives unrestricted institutional support from Research to Prevent Blindness, NY, NY.

We thank Dr. Vallimmai Muthappan and Xue Wang, co-authors of the Cochrane Systematic Review.

References

1. Droutsas K, Sekundo W. Epidemiology of pterygium. A review. *Ophthalmology*. 2010; 107(6):511–2. 514–516. [PubMed: 20393731]
2. Liu L, Wu J, Geng J, Yuan Z, Huang D. Geographical prevalence and risk factors for pterygium: A systematic review and meta-analysis. *BMJ Open*. 2013; 3(11):1–8.
3. Hirst LW. Recurrent pterygium surgery using pterygium extended removal followed by extended conjunctival transplant: recurrence rate and cosmesis. *Ophthalmology*. 2009; 116(7):1278–1286. [PubMed: 19576496]

4. Dusenbery KE, Alul IH, Holland EJ, Khan FM, Levitt SH. β Irradiation of recurrent pterygia: results and complications. *International Journal of Radiation Oncology* Biology* Physics*. 1992; 24(2): 315–320.
5. Al Fayed MF. Limbal versus conjunctival autograft transplantation for advanced and recurrent pterygium. *Ophthalmology*. 2002; 109(9):1752–1755. [PubMed: 12208727]
6. Küçükerdönmez C, Akova YA, Altınörs DD. Comparison of conjunctival autograft with amniotic membrane transplantation for pterygium surgery: surgical and cosmetic outcome. *Cornea*. 2007; 26(4):407–413. [PubMed: 17457187]
7. Ma DH, See LC, Hwang YS, Wang SF. Comparison of amniotic membrane graft alone or combined with intraoperative mitomycin C to prevent recurrence after excision of recurrent pterygia. *Cornea*. 2005; 24(2):141–150. [PubMed: 15725881]
8. Mutlu FM, Sobaci G, Tatar T, Yildirim E. A comparative study of recurrent pterygium surgery: Limbal conjunctival autograft transplantation versus mitomycin C with conjunctival flap. *Ophthalmology*. 1999; 106(4):817–821. [PubMed: 10201608]
9. Shimazaki J, Shinozaki N, Tsubota K. Transplantation of amniotic membrane and limbal autograft for patients with recurrent pterygium associated with symblepharon. *Br J Ophthalmol*. 1998; 82(3): 235–240. [PubMed: 9602618]
10. Kirwan JF, Constable PH, Murdoch IE, Khaw PT. Beta irradiation: new uses for an old treatment: a review. *Eye*. 2003; 17(2):207–215. [PubMed: 12640408]
11. Chen PP, Ariyasu RG, Kaza V, LaBree LD, McDonnell PJ. A randomized trial comparing mitomycin C and conjunctival autograft after excision of primary pterygium. *Am J Ophthalmol*. 1995; 120(2):151–160. [PubMed: 7639298]
12. Hao Y, Ma DH, Hwang DG, Kim WS, Zhang F. Identification of antiangiogenic and antiinflammatory proteins in human amniotic membrane. *Cornea*. 2000; 19(3):348–352. [PubMed: 10832697]
13. Kim JC, Tseng SC. Transplantation of preserved human amniotic membrane for surface reconstruction in severely damaged rabbit corneas. *Cornea*. 1995; 14(5):473–484. [PubMed: 8536460]
14. Kobayashi, A., Inana, G., Meller, D., Li, DQ., Tseng, SC. Differential gene expression by human cultured umbilical vein endothelial cells on amniotic membrane. 4th Ocular Surface and Tear Conference; 1999; p. 14
15. Tseng SC, Li DQ, Ma X. Suppression of transforming growth factor-beta isoforms, TGF-beta receptor type II, and myofibroblast differentiation in cultured human corneal and limbal fibroblasts by amniotic membrane matrix. *J Cell Physiol*. 1999; 179(3):325–335. [PubMed: 10228951]
16. Bultmann S, You L, Spandau U, Rohrschneider K, Volcker HE, Kruse FE. Amniotic membrane down-regulates chemokine expression in human keratocytes. *Invest Ophthalmol Visual Sci*. 1999; 40:S578.
17. Solomon, A., Monroy, D., Ji, Z. Suppression of epithelial expression of IL-1-beta by the amniotic membrane. 4th Ocular Surface and Tear Conference; 1999; p. 14
18. Hirst LW. Recurrence and complications after 1000 surgeries using pterygium extended removal followed by extended conjunctival transplant. *Ophthalmology*. 2012; 119(11):2205–2210. [PubMed: 22892149]
19. Clearfield E, Muthappan V, Wang X, Kuo IC. Conjunctival autograft for pterygium. *Cochrane Database Syst Rev*. 2016; 2:CD011349. [PubMed: 26867004]
20. Higgins, JPT., Green, S., editors. *Cochrane Handbook for Systematic Reviews of Interventions* version 5.1.0 (updated March 2011). The Cochrane Collaboration; 2011. Available at: www.handbook.cochrane.org
21. Review Manager (RevMan) [computer software]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration; 2014.
22. Aragonés Cruz B, Alemañy Martorell J. Comparative study of the use of mitomycin C in recurrent pterygium [Estudio comparativo del uso de mitomicina C en el pterigium recidivante]. *Revista Cubana de Oftalmología*. 2008; 21(2):1–11.
23. Besharati MR, Miratashi SA, Ahmadi AB. Pterygium surgery: amniotic membrane or conjunctival autograft transplantation. *International Journal of Ophthalmology*. 2008; 1(4):362–366.

24. Chen L, Mu L, Li MX. Clinical observation of three different operation methods for recurrent pterygium. *International Journal of Ophthalmology*. 2009; 9(11):2211–2213.
25. Chen LR, Yao JP, Zhu Y, Zhang YZ, Zhou Y, Gao B. Comparative analysis of surgical excision combined with limbal stem cell transplantation and amniotic membrane transplantation for the treatment of pterygium. *International Eye Science*. 2012; 12(10):2006–2008.
26. Fernández García K, Gómez Castillo Z, Castillo Pérez A, Pérez Parra Z, Jareño Ochoa M, Perea Ruiz CA. Use of conjunctival autograft and amniotic membrane in primary pterygium surgery [Autoinjerto conjuntival y membrana amniótica en la cirugía del pterigión primario]. *Revista Cubana de Oftalmología*. 2012; 25(2):212–217.
27. Katircioglu YA, Altıparmak U, Goktas SE, Cakir B, Singar E, Ornek F. Comparison of two techniques for the treatment of recurrent pterygium: amniotic membrane vs conjunctival autograft combined with mitomycin C. *Seminars in Ophthalmology*. 2015; 30(5–6):321–327. [PubMed: 24506693]
28. Keklikci U, Celik Y, Cakmak SS, Unlu MK, Bilek B. Conjunctival-limbal autograft, amniotic membrane transplantation, and intraoperative mitomycin C for primary pterygium. *Annals of Ophthalmology*. 2007; 39(4):296–301. [PubMed: 18025649]
29. Kheirkhah A, Nazari R, Nikdel M, Ghassemi H, Hashemi H, Behrouz MJ. Postoperative conjunctival inflammation after pterygium surgery with amniotic membrane transplantation versus conjunctival autograft. *Am J Ophthalmol*. 2011; 152(5):733–738. [PubMed: 21742306]
30. Küçükerdönmez C, Akova YA, Altınörs DD. Vascularization is more delayed in amniotic membrane graft than conjunctival autograft after pterygium excision. *Am J Ophthalmol*. 2007; 143(2):245–249. [PubMed: 17173849]
31. Liang W, Li R, Deng X. Comparison of the efficacy of pterygium resection combined with conjunctival autograft versus pterygium resection combined with amniotic membrane transplantation. *Eye Science*. 2012; 27(2):102–105. [PubMed: 22678875]
32. Luanratanakorn P, Ratanapakorn T, Suwan-Apichon O, Chuck RS. Randomised controlled study of conjunctival autograft versus amniotic membrane graft in pterygium excision. *Br J Ophthalmol*. 2006; 90(12):1476–1480. [PubMed: 16837545]
33. Ozer A, Yildirim N, Erol N, Yurdakul S. Long-term results of bare sclera, limbal-conjunctival autograft and amniotic membrane graft techniques in primary pterygium excisions. *Ophthalmologica*. 2009; 223(4):269–73. [PubMed: 19339811]
34. Pereira Paes, J. Surgical Treatment of the Primary Pterygium: Comparison Between Rotation of Conjunctival Flap and Amniotic Membrane Transplant [Tratamento Cirúrgico do Pterigio Primario: Comparação Entre as Técnicas de Rotação de Retalho Conjuntival e Transplante de Membrana Amniótica] [Doctoral dissertation]. Universidade Estadual de Campinas. Faculdade de Ciências Médicas; 2010.
35. Pérez Parra Z, Castillo Pérez ADLC, Escalona Leyva E, López Hernández S, Márquez Villalón S. Conjunctival autograft versus amniotic membrane graft in primary pterygium surgery [Autoinjerto conjuntival versus injerto de membrana amniótica en la cirugía del pterigión primario]. *Revista Cubana de Oftalmología*. 2008; 2(1)
36. Perry HD, Kanellopoulos AJ, Donnenfeld ED, Doshi SJ. Comparison of amniotic membrane transplantation (AMT) to conjunctival autograft (CAT) in the surgical management of pterygia. *American Academy of Ophthalmology*. 2000:225.
37. Salman AG, Mansour DE. The recurrence of pterygium after different modalities of surgical treatment. *Saudi Journal of Ophthalmology*. 2011; 25(4):411–5. [PubMed: 23960956]
38. Stangogiannis-Druya E, Martínez M, Paz EL, Márquez K, Stangogiannis-Druya C. Amniotic membrane graft or conjunctival autograft in recurrent nasal pterygium Hospital Universitario de Caracas January-June 2004 [Transplante de membrana amniótica o auto injerto conjuntival en pterigión nasal recidivantes Hospital universitario de Caracas enero-junio 2004]. *Revista Oftalmológica Venezolana*. 2004; 60(4):181–7.
39. Tananuvat N, Martin T. The results of amniotic membrane transplantation for primary pterygium compared with conjunctival autograft. *Cornea*. 2004; 23(5):458–63. [PubMed: 15220729]

40. Toker E, Eraslan M. Recurrence after primary pterygium excision: amniotic membrane transplantation with fibrin glue versus conjunctival autograft with fibrin glue. *Curr Eye Res.* 2016; 41(1):1–8. [PubMed: 25849961]
41. Li M, Zhu M, Yu Y, Gong L, Zhao N, Robitaille MJ. Comparison of conjunctival autograft transplantation and amniotic membrane transplantation for pterygium: A meta-analysis. *Graefes Arch Clin Exp Ophthalmol.* 2012; 250(3):375–81. [PubMed: 21935607]
42. Kaufman SC, Jacobs DS, Lee WB, Deng SX, Rosenblatt MI, Shtein RM. Options and adjuvants in surgery for pterygium: a report by the American Academy of Ophthalmology. *Ophthalmology.* 2013; 120(1):201–8. [PubMed: 23062647]
43. Hirst LW, Sebban A, Chant D. Pterygium recurrence time. *Ophthalmology.* 1994; 101(4):755–8. [PubMed: 8152771]
44. Romano V, Cruciani M, Conti L, Fontana L. Fibrin glue versus sutures for conjunctival autografting in primary pterygium surgery. *Cochrane Database Syst Rev.* 2016; 12:CD011308. [PubMed: 27911983]

Figure 1. Identification and selection of trials that compared conjunctival autograft with amniotic membrane transplantation for pterygium.

	Random sequence generation (selection bias)	Allocation concealment before randomization (selection bias)	Masking of participants and personnel (performance bias)	Masking of outcome assessment (detection bias)	Incomplete outcome data collected, reported, or analyzed (attrition bias)	Selective reporting of outcomes (reporting bias)	Other bias
Aragónes Cruz 2008	?	?	?	?	?	?	?
Besharati 2008	?	?	?	?	?	?	?
Chen 2009	?	?	?	?	+	?	?
Chen 2012	?	?	?	?	+	?	?
Fernández García 2012	?	?	?	?	?	?	?
Katircioglu 2014	?	?	?	?	?	?	?
Keklikci 2007	?	?	?	?	?	?	?
Kheirkhah 2011	?	?	?	?	?	?	?
Küçükerdönmez 2007	+	?	+	+	+	?	+
Küçükerdönmez 2007a	+	?	+	+	+	?	+
Liang 2012	?	?	?	?	+	?	?
Luanratanakorn 2006	?	?	?	+	?	?	+
Ozer 2009	?	?	?	?	+	?	?
Paes 2010	+	?	?	?	?	?	?
Pérez Parra 2008	?	?	?	?	+	?	?
Perry 2000	?	?	?	?	?	?	?
Salman 2011	?	?	?	?	+	?	?
Stangogiannis-Druya 2004	?	?	?	?	?	?	?
Tananuvat 2004	?	?	?	?	?	?	?
Toker 2016	+	?	?	?	?	?	?

Figure 2.

Risk of bias for individual trials by domain assessed. *Green*, low risk of bias; *yellow*, unclear/unknown risk of bias; *red*, high risk of bias.

Figure 3.

Forest plot showing estimated risk ratios (RRs) with their 95% confidence intervals (CIs) for recurrence of pterygium 3 months after surgery

Figure 4.

Forest plot showing estimated risk ratios (RRs) with their 95% confidence intervals (CIs) for recurrence of pterygium 6 months after surgery

Table 1

Summary of studies by characteristics of participants and of surgery.

Study	Year	Country	Number of Participants Analyzed	Primary or Recurrent Pterygia	Planned Follow-Up (months)	Mean Follow-up (months)		Adjuvant use of 0.02% MMC	Type of Sutures Used
						CAG	AMT		
<i>Aragónés Cruz</i> ²²	2008	Cuba	51	recurrent	16	NR	NR	✓	NR
<i>Besharat</i> ²³	2008	Iran	40	both	24	NR	NR		8-0 Vicryl *
<i>Cheir</i> ²⁴	2009	China	127	recurrent	12-24	NR	NR		10-0 nylon (interrupted)
<i>Cheir</i> ²⁵	2012	China	90	primary	24	Overall: 20.6 ± 2.5			10-0 nylon (interrupted)
<i>Fernández García</i> ²⁶	2012	Cuba	80	primary	6	NR	NR		8-0 silk *
<i>Katircioglu</i> ²⁷	2014	Turkey	55	recurrent	minimum 12	25.9 ± 24.4	28.8 ± 15.7	✓	7-0 Vicryl (interrupted)
<i>Kekliç</i> ²⁸	2007	Turkey	94	primary	36	24.4 ± 7.9	23.6 ± 7.3		CAG: 8-0 Vicryl (limbal side: 10-0 nylon); AMT: 10-0 nylon *
<i>Kheirkhalil</i> ²⁹	2011	Iran	39	primary	12	NR	NR	✓	10-0 nylon *
<i>Küçükdönmez</i> ³⁰	2007	Turkey	27	primary	minimum 6	13.7 ± 5.2	14.4 ± 3.3		8-0 Vicryl (interrupted)
<i>Küçükdönmez (af)</i>	2007	Turkey	78	both	minimum 6	16.6 ± 3.5	13.4 ± 2.1		8-0 Vicryl (interrupted)
<i>Liang</i> ³¹	2012	China	118	primary	12	NR	NR		CAG, AMT: 10-0 nylon *
<i>Luamatanakorn</i> ³²	2006	Thailand	287	both	6	NR	NR		10-0 nylon (interrupted)
<i>Ozer</i> ³³	2009	Turkey	163	primary	NR	69.9 ± 12.4	61.4 ± 9.8		10-0 nylon *
<i>Paes</i> ³⁴	2010	Brazil	228	primary	12	NR	NR		10-0 nylon *
<i>Pérez Parra</i> ³⁵	2008	Cuba	60	primary	12	NR	NR		NR
<i>Perry</i> ³⁶	2000	NR	8	NR	NR	overall: 12.5			NR
<i>Sulman</i> ³⁷	2011	Egypt	48	recurrent	24	NR	NR		10-0 silk *
<i>Stangogiannis-Drury</i> ³⁸	2004	Venezuela	60	recurrent	5	NR	NR		10-0 nylon *
<i>Tananuval</i> ³⁹	2004	Thailand	78	primary	12	12.4 ± 3.1	14.4 ± 5.4		8-0 Vicryl *
<i>Toker</i> ⁴⁰	2016	Turkey	65	primary	12	NR	NR		fibrin glue

NR=not reported;

* denotes authors did not specify whether running or interrupted sutures were used

Table 2

Summary of Estimated Relative Risk of Serious Ocular Adverse Events with Conjunctival Autograft Versus Amniotic Membrane Transplantation for Pterygium

Serious Adverse Event	Time Point	Number of Studies	Conjunctival Autograft n (%)	Amniotic Membrane Transplant n, (%)	Risk Ratio (95% CI)
Diplopia	3 months	1	0	1 (3.8)	0.36 (0.02 to 8.43)
	6 months	1	0	2 (7.7)	0.22 (0.01 to 4.28)
Granuloma	During study	3	4 (4.3)	6 (6.5)	0.71 (0.23 to 2.18)
Increased Intraocular Pressure	6 months	2	8 (6.7)	5 (3)	2.52 (0.91 to 7.00)
	During study	1	5 (11.9)	4 (9.1)	1.31 (0.38 to 4.55)
Pyogenic Granuloma	1 month	1	4 (16.7)	2 (7.7)	2.17 (0.44 to 10.78)
	3 months	1	4 (16.7)	2 (7.7)	2.17 (0.44 to 10.78)
	6 months	2	8 (5.6)	5 (2.6)	1.99 (0.67 to 5.90)
Restriction of Eye Movement	3 months	1	0	1 (3.8)	0.36 (0.02 to 8.43)
Symblepharon	6 months	1	0	1 (3.8)	0.36 (0.02 to 8.43)