

The use of fibrin glue in pterygium surgery with amniotic membrane transplantation: Systematic review and meta-analysis

Mohammad Karam¹, Abdulmalik Alsaif², Ahmed Aldubaikhi^{3,4}, Meshaal Aljebreen⁵, Rand Alazaz⁵, Tariq Almudhaiyan^{6,7}, Abdullah AlBaghli¹

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¹AlBahar Ophthalmology Center, Ibn Sina Hospital, Ministry of Health, ²Department of Surgery, Walsall Healthcare NHS Trust, West Midlands, UK, ³Department of Radiology, King Faisal Specialist Hospital and Research Center, ⁴Department of Radiology, Prince Mohammed Bin Abdulaziz Hospital, ⁵Department of Ophthalmology, King Khaled Eye Specialist Hospital, ⁶Department of Ophthalmology, King Abdullah International Medical Research Center, ⁷Division of Ophthalmology, National Guard Hospital, Riyadh, Saudi Arabia

Address for correspondence:
Dr. Mohammad Karam,
AlBahar Ophthalmology Center,
Ibn Sina Hospital, Al-Sabah
Medical Area, Shuwaikh,
Kuwait.
E-mail: mhk130@outlook.com
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Abstract:

PURPOSE: To compare the outcomes of fibrin glue versus sutures in pterygium surgery with amniotic membrane transplantation.

METHODS: A systematic review and meta-analysis were performed as per the Preferred Reporting Items for Systematic Reviews and Meta-analyses Guidelines. An electronic search identified all studies comparing the outcomes of using fibrin glue versus sutures in pterygium surgery with amniotic membrane transplantation. Conjunctival inflammation, postoperative pain and discomfort, pterygium recurrence, pyogenic granuloma, and surgical time were primary outcome measures. Secondary outcome measures included amniotic membrane transplant outcomes, time to recurrence, graft loss, and subconjunctival hemorrhage. Fixed and random-effects models were used for the analysis.

RESULTS: Four studies enrolling 180 patients were identified. Conjunctival inflammation (odds ratio [OR] 0.21, $P = 0.0005$) demonstrated a significant difference favoring the fibrin glue group. Despite the trend favoring the use of fibrin glue, there were no significant differences in terms of postoperative pain and discomfort (OR = 0.46, $P = 0.25$), pterygium recurrence (OR = 0.74, $P = 0.48$), pyogenic granuloma (OR = 0.47, $P = 0.38$), and surgical time (mean difference = -17.52, $P = 0.13$). For secondary outcomes, fibrin glue had significantly fewer cases of graft loss compared with sutures. No statistically significant difference was found in amniotic membrane graft outcomes, time to recurrence, and subconjunctival hemorrhage.

CONCLUSION: Fibrin glue is comparable to the sutures used in pterygium surgery with amniotic membrane transplantation as it significantly improves conjunctival inflammation and does not increase postoperative pain and discomfort, pterygium recurrence, pyogenic granuloma, and surgical time.

Keywords:

Amniotic membrane transplant, fibrin glue, Pterygium, sutures

INTRODUCTION

Pterygium is a noncancerous development of fibrovascular tissue from the conjunctiva extending to the corneal epithelium. It is initially asymptomatic, but it could gradually disturb the visual axis and cause astigmatism when inflamed. The risk factors are not fully understood, but pterygium has been associated with excessive exposure to ultraviolet light (UV). Therefore, the prevalence increases in geographical places that are closer to the equator as they are subjected to higher sunlight.^[1]

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Treatment of pterygium ranges from conservative lubrication and protective eyewear to surgical removal and grafting based on the presence of symptoms and the cosmetic appearance.^[2] Surgical removal of the pterygium is conventionally, followed by conjunctival autografting (CA), but it has some limitations as it may not provide sufficient coverage for large pterygia, and conservation of conjunctival tissue can be more useful in case of a future glaucoma surgery.^[3] The main concern of surgical treatment was the high recurrence risk due to the traumatic impact of the surgery, which may trigger more fibrovascular growth. Surgical techniques such

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as amniotic membrane transplantation (AMT) have been used instead of (CA) to reduce the rate of recurrence as these techniques result in normal epithelial growth.^[4] The amniotic membrane is attached to the sclera after excising the pterygium by either using sutures or fibrin glue.^[4] Using sutures is usually safe but has been found to have increased postsurgical inflammation compared to fibrin glue.^[5] The use of fibrin glue instead of traditional surgical suturing has resulted in shorter surgical time, consequentially leading to faster recovery and less postsurgical pain and infections.^[6]

Although several studies have compared the effectiveness of fibrin glue and sutures when used in pterygium surgery with amniotic membrane transplantation,^[7-10] there is currently no meta-analysis on the topic. This study aims to amalgamate the data of these comparative studies to assess which technique provides superior outcomes.

METHODS

A systematic review and meta-analysis were conducted as per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.^[11]

Eligibility criteria

All randomized control trials (RCTs) and observational studies comparing fibrin glue with sutures for patients undergoing pterygium surgery with amniotic membrane transplantation were included. Fibrin glue was the intervention group of interest, and sutures were the comparator. All patients were included irrespective of age, gender, or comorbidity status. Case reports and cohort studies where no comparison was conducted were excluded from the review process as well as studies not reported in English.

Outcome measures

Primary outcomes were conjunctival inflammation, postoperative pain and discomfort, pterygium recurrence, pyogenic granuloma, and surgical time. Secondary outcomes included amniotic membrane transplant outcomes, time to recurrence, graft loss, and subconjunctival hemorrhage.

Literature search strategy

Two authors independently searched the electronic databases of MEDLINE, EMBASE, EMCARE, CINAHL, and the Cochrane Central Register of Controlled Trials. The last search was conducted on August 10, 2022. The search terms consisted of “sutures,” “fibrin glue,” “pterygium,” and “amniotic membrane.” All terms were combined with adjuncts of “and” as well as “or.” To extend the screening for eligible articles, the bibliographic lists were reviewed of the relevant studies.

Selection of studies

The title and abstract of articles identified from the literature searches were assessed. The full texts of relevant reports were retrieved and those articles that met the eligibility criteria were selected. Any discrepancies in study selection were resolved by discussion between the authors.

Data extraction and management

A data extraction spreadsheet was amalgamated that abided with Cochrane’s data collection form for intervention reviews. A pilot test was conducted with the spreadsheet extracting data from random articles and adapting it as needed.

Data synthesis

The authors aimed to perform a meta-analysis for outcomes reported by at least two studies. The odds ratio (OR) was reserved for dichotomous variables, whereas the mean difference (MD) was aimed to assess continuous variables for the study and control groups. Review Manager 5.3 and Microsoft Excel were used for data analysis. The analysis involved used was based on the fixed and random effect models. Reported outcomes were given in forest plots at 95% confidence intervals (CIs). Heterogeneity was assessed using the Cochran Q test (χ^2) and it was aimed to quantify inconsistency by calculating I^2 also, which was interpreted per the following: 0% to 25% (low heterogeneity); 25% to 75% (moderate heterogeneity); and 75% to 100% (high heterogeneity).

Methodological quality and risk of bias assessment

Articles matching the inclusion criteria were assessed for quality and risk of bias by two authors independently. Cochrane’s tool was used to evaluate the risk of bias in randomized studies. Domains assessed included selection bias, performance bias, detection bias, attrition bias, reporting bias, and other sources. RCT studies are classified into low, unclear, and high risk of bias. The Newcastle–Ottawa Scale was utilized for nonrandomized studies.^[12] It uses a star grading system to assess the selection, comparability, and outcome of studies. The total maximum score for each study is nine stars. The Agency for Healthcare Research and Quality (AHRQ) standards were used to provide an overall rating of either good, fair, or poor quality.^[12]

RESULTS

Literature search results

A literature search retrieved 13 articles in total, which were reviewed by two independent authors to filter out duplicates, abstracts, review articles, studies without the intervention of interest, as well as those without comparative control groups, and reports involving nonhuman subjects. Four studies were selected which met the eligibility criteria [Figure 1].

Description of studies

Baseline characteristics of the included studies are summarized in Table 1.

Kheirkhah *et al.*^[7] conducted a single-center retrospective cohort study that included 23 (27 eyes) patients with primary or recurrent pterygium who were operated on with bare sclera excision, followed by intraoperative application of mitomycin C and amniotic membrane transplantation. The first 13 consecutive eyes, operated on from 2002 to 2004, received

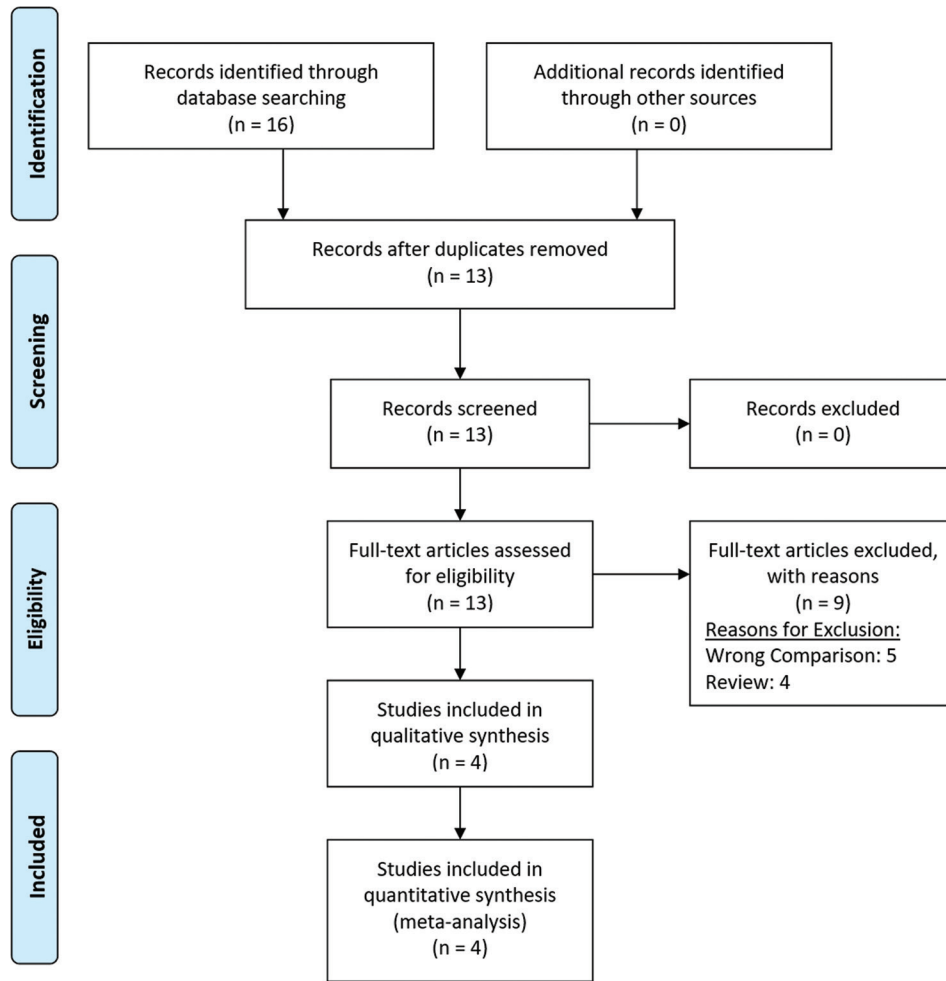


Figure 1: Prisma Flow Diagram. The PRISMA diagram details the search and selection processes applied during the overview. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses

Table 1: Baseline characteristics of the included studies

Study (year)	Journal, Country	Study design	Age (years), mean ± SD	Sex (male:female)	Total sample (fibrin glue:sutures)	Fibrin glue preparation
Kheirkhah <i>et al.</i> (2008) ^[7]	Journal of Cornea and External Disease, USA	Retrospective cohort	53.7±16.2	11:12	27 eyes (14:13) of 23 patients	NR
Kucukerdonmez <i>et al.</i> (2010) ^[8]	Eye Nature Journal, Turkey	RCT	Fibrin glue: 52.7±9.8 Sutures: 54.2±11.3	37:33	70 eyes of 70 patients (32:38)	Two-component fibrin glue was prepared according to the manufacturers' directions. A dual injection system was used to apply the glue, in which the fibrinogen and thrombin solution was attached by separate syringes, and were only mixed during application on the ocular surface
Mahdy and Wagieh (2012) ^[9]	Ophthalmic Research Journal, Egypt	RCT	51	28:12	40 eyes (20:20) of 40 patients	Fibrin glue was prepared using autologous blood from the same patient. Samples of 10 mL venous blood were collected in heparin-coated glass tubes and were sent to the pathology laboratory
Nguyen <i>et al.</i> (2012) ^[10]	Eye Science, USA	RCT	NR (range 20–90)	NR	43 eyes (24:19) of 43 patients	Fibrin glue was prepared according to the following steps Prewarming the fibrin glue kit with fibrinotherm Preparation for sealer protein solution with fibrinotherm Preparation of thrombin solution with fibrinotherm

RCT: Randomized control trials, SD: Standard deviation, NR: Not reported

sutures to attach the amniotic membrane, whereas the next 14 eyes, operated on from 2005 to 2006, received fibrin glue.

Kucukerdonmez *et al.*^[8] performed a single-center prospective RCT that included 70 (70 eyes) patients with primary nasal pterygium who underwent pterygium excision with amniotic membrane transplantation consecutively between February 2006 and March 2007 were enrolled. Patients were randomized using a list created by a random number generator into either of the two treatment groups in a masked manner, with patients not being informed of the surgical procedure they received. Thirty-two patients were treated with Fibrin glue and 38 with sutures.

Mahdy and Wagieh^[9] conducted a single-center prospective RCT that included 40 (40 eyes) patients diagnosed with recurrent pterygium who had been operated on only once. Twenty eyes underwent amniotic membrane transplantation using fibrin glue and 20 with sutures.

Nguyen *et al.*^[10] performed a single-center prospective RCT that included 43 patients (43 eyes) with primary or recurrent pterygium who underwent pterygium excision with amniotic membrane transplantation. Twenty-four eyes underwent amniotic membrane transplantation using fibrin glue and 19 with sutures.

Primary outcomes

Conjunctival inflammation

In Figure 2, conjunctival inflammation was reported in three studies enrolling 110 patients. There was a statistically significant difference seen in the OR analysis showing less conjunctival inflammation for the fibrin glue group (OR = 0.21, CI = 0.080.50, $P = 0.0005$). A low level of heterogeneity was found among the studies ($I^2 = 0\%$, $P = 0.82$).

Postoperative pain and discomfort

In Figure 3, postoperative pain and discomfort were reported in two studies enrolling 89 patients. There was no statistically significant difference seen in the OR analyses showing a trend of less pain and discomfort postoperatively in the fibrin glue group (OR = 0.46, CI = 0.121.73, $P = 0.25$). A low level of heterogeneity was found among the studies ($I^2 = 0\%$, $P = 0.95$).

Pterygium recurrence

In Figure 4, pterygium recurrence was reported in four studies enrolling 180 patients. There was no statistically significant difference seen in the OR analyses with a trend of a lower rate of pterygium recurrence in the fibrin glue group (OR = 0.74, CI = 0.331.70, $P = 0.48$). A low level of heterogeneity was found among the studies ($I^2 = 0\%$, $P = 0.64$).

Pyogenic granuloma

In Figure 5, pyogenic granuloma was reported in two studies

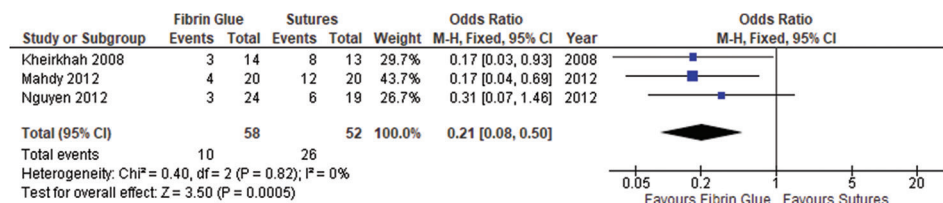


Figure 2: Forest Plot for Odds Ratio of Fibrin Glue versus Sutures– Conjunctival inflammation. Quantitative analysis showing a statistically significant lower conjunctival inflammation in the fibrin glue group compared with the sutures group

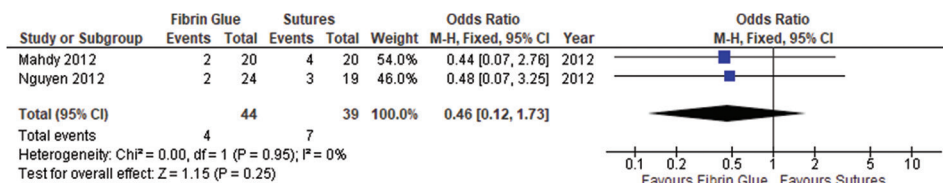


Figure 3: Forest Plot for Odds Ratio of Fibrin Glue versus Sutures – Postoperative Pain and Discomfort. Quantitative analysis showing no significant difference in postoperative pain and discomfort between the fibrin glue group and the sutures group

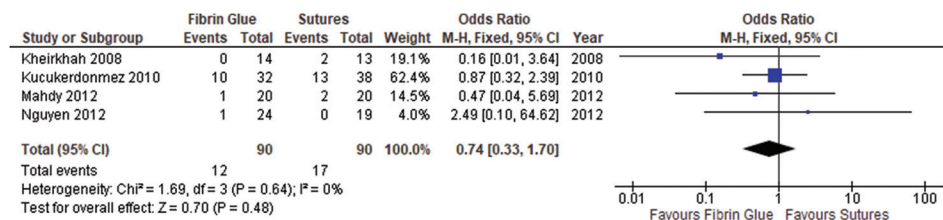


Figure 4: Forest Plot for Odds Ratio of Fibrin Glue versus Sutures – Pterygium Recurrence. Quantitative analysis showing no significant difference in the rate of pterygium recurrence between the fibrin glue group and the sutures group

enrolling 67 patients. There was no statistically significant difference seen in the OR analyses with a trend of a lower rate of pyogenic granuloma in the fibrin glue group (OR = 0.47, CI = 0.092.52, $P = 0.38$). A low level of heterogeneity was found among the studies ($I^2 = 0\%$, $P = 0.77$).

Surgical time

In Figure 6, surgical time was reported in two studies enrolling 97 patients. There was no statistically significant difference seen in the mean difference analyses with a trend of faster surgical time in the fibrin glue group (MD = -17.52, CI = -39.964.92, $P = 0.13$). A high level of heterogeneity was found among the studies ($I^2 = 87\%$, $P = 0.006$).

Secondary outcomes

Amniotic membrane transplant outcomes

Kheirkhah et al.^[7] found no statistically significant difference in the healing of the epithelial defect over the amniotic membrane in both groups. In addition, Kucukerdonmez et al.^[8] reported that fluorescein staining demonstrated complete epithelialization of the amniotic membrane graft within 7 days postoperatively in all patients. For the fibrin glue group, Kucukerdonmez et al.^[8] did not report any cases of graft dehiscence or detachment of the membrane during the follow-up period. Similarly, patients in the suture group had no suture-related complications which would require early suture removal or re-operation.

Time to recurrence

According to Kucukerdonmez et al.,^[8] no statistically significant difference was found in the time taken for the pterygium to reoccur between the fibrin glue group and the suture group.

Graft loss

According to Mahdy et al.,^[9] only one patient in the fibrin glue group experienced a loss of the amniotic membrane graft, compared to four patients who had sutures, with a significant difference between them ($P \leq 0.05$). In addition,

Kucukerdonmez et al.^[8] reported no cases of graft loss occurring in both groups.

Subconjunctival hemorrhage

According to Kheirkhah et al.,^[7] both groups did not report any complications of sub-graft hematoma or graft edema.

Methodological quality and risk of bias assessment

The Cochrane Collaboration’s tool was used to assess the quality of the RCTs included in the study [Table 2]. The Newcastle–Ottawa Scale was used to assess the quality of the cohort study by Kheirkhah et al.^[7] [Table 3], which demonstrated high scores in selection and outcome but a low score in comparability with an overall quality rating of good according to the AHRQ standards.^[12]

DISCUSSION

Fibrin glue showed a comparable effect to sutures, as shown by the findings of the analyses. The fibrin glue group showed superior a statistically significant improvement in postoperative conjunctival inflammation ($P = 0.0005$). In addition, a general trend favored the use of fibrin glue in terms of postoperative pain and discomfort, pterygium recurrence, pyogenic granuloma, and surgical time. Heterogeneity among included studies was low for all the outcomes ($I^2 = 0\%$) except for the surgical time, which was high. For secondary outcomes, fibrin glue was associated with significantly fewer cases of postoperative graft loss. No statistically significant difference was found in terms of the amniotic membrane transplant outcomes, time to recurrence, and subconjunctival hemorrhage.

An ongoing debate in the literature currently exists on whether the use of fibrin glue is superior to sutures for pterygium excision with AMT.^[7-10] Jiang et al.^[13] and Uy et al.^[14] compared the same interventions with CAG fixation. Both studies found that the fibrin glue group had significantly lower operating time, and lower postoperative pain and discomfort. In addition, Jiang et al.^[13] demonstrated that the sutures group had a

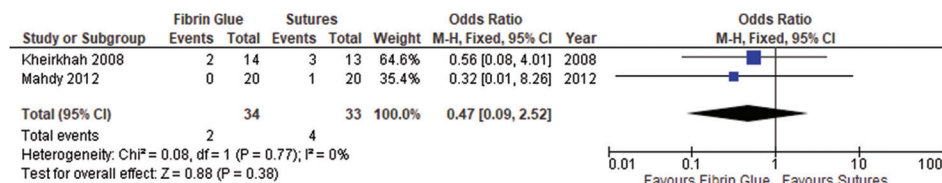


Figure 5: Forest Plot for Odds Ratio of Fibrin Glue versus Sutures – Pyogenic Granuloma. Quantitative analysis showing no significant difference in the rate of pyogenic granuloma between the fibrin glue group and the sutures group

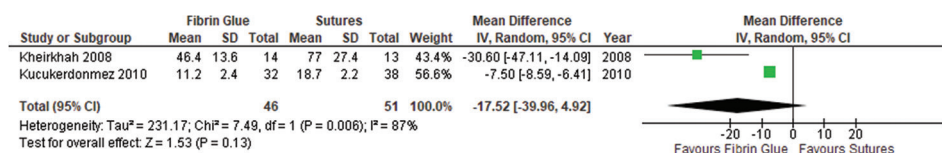


Figure 6: Forest Plot for Mean Difference of Fibrin Glue versus Sutures – Surgical Time. Quantitative analysis showing no significant difference in the surgical time between the fibrin glue group and sutures group

Table 2: Bias analysis of the randomized trials using the Cochrane collaboration's tool

Author (year)	Bias	Authors' judgment	Support for judgement
Kucukerdonmez <i>et al.</i> (2010) ^[8]	Random sequence generation (selection bias)	Low risk	Patients were randomized using a list created by a random number generator in a masked manner
	Allocation concealment (selection bias)	Unclear risk	No information was given
	Blinding of participants and personnel (performance bias)	Low risk	Patients were not informed about the surgical procedure they received, and the surgeon was instructed on which method to use only after he had completed the excision of pterygium
	Blinding of outcome assessment (detection bias)	Low risk	All patients were examined before and after the operation by an independent observer
	Incomplete outcome data (attrition bias)	Low risk	Consistency in numbers reported by the study and no missing data
	Selective reporting (reporting bias)	Low risk	All outcome data were reported
Mahdy and Wagieh (2012) ^[9]	Other bias	Low risk	Similar baseline characteristics in both groups
	Random sequence generation (selection bias)	Unclear risk	Insufficient information was given
	Allocation concealment (selection bias)	Unclear risk	No information was given
	Blinding of participants and personnel (performance bias)	Unclear risk	No information was given
	Blinding of outcome assessment (detection bias)	Unclear risk	No information was given
	Incomplete outcome data (attrition bias)	Low risk	Consistency in numbers reported by the study and no missing data
Nguyen <i>et al.</i> (2012) ^[10]	Selective reporting (reporting bias)	Low risk	All outcome data were reported
	Other bias	Low risk	Similar baseline characteristics in both groups
	Random sequence generation (selection bias)	Unclear risk	Insufficient information was given
	Allocation concealment (selection bias)	Unclear risk	No information was given
	Blinding of participants and personnel (performance bias)	Unclear risk	No information was given
	Blinding of outcome assessment (detection bias)	Unclear risk	No information was given
	Incomplete outcome data (attrition bias)	Low risk	Consistency in numbers reported by the study and no missing data
	Selective reporting (reporting bias)	Low risk	All outcome data were reported
	Other bias	Low risk	Similar baseline characteristics in both groups
	Other bias	Low risk	Similar baseline characteristics in both groups

Table 3: Newcastle–Ottawa Scale to assess the quality of nonrandomized studies

Author (year)	Selection (out of 4 stars)	Comparability (out of 2 stars)	Outcome (out of 3 stars)
Kheirkhah <i>et al.</i> (2008) ^[7]	****	*	***

higher recurrence rate than the fibrin group. These results are consistent with Ozdamar *et al.*^[15] who found that tissue glue had significantly less postoperative symptoms, which healed faster than vicryl sutures using CAG. Correspondingly, a meta-analysis by Pan *et al.*^[16] included seven RCTs comparing fibrin glue and sutures for pterygium surgery with CAG implantation. Although no statistically significant difference was noted in postoperative complications, fibrin glue significantly reduced the surgical time ($P = 0.0001$) and demonstrated fewer recurrence rates. Moreover, another meta-analysis by Romano *et al.*^[17] reported similar results, demonstrating a significant decrease in surgery time and recurrence rate favoring fibrin glue. Although Romano *et al.*^[17] found higher complication rates, such as graft dehiscence and graft loss in the fibrin glue group, the authors explained that it may be associated with graft preparation and the experience of the surgeon.

Pterygium recurrence remains a challenge and a source of disappointment to both patients and physicians following

pterygium surgery. Ti and Tseng^[18] showed that postoperative conjunctival inflammation directly correlates with pterygium recurrence as it can elicit the remaining pterygium body fibroblasts to become a more aggressive phenotype. Hence, its significance might be beyond just normal wound healing. Fibrin glue has proved its ability in reducing postoperative conjunctival inflammation post pterygium surgery in comparison to sutures, whether it was used to fixate conjunctival autograft or amniotic membrane transplantation.^[5,18] In contrast, Ti and Tseng^[18] and Suzuki *et al.*^[19] demonstrated that sutures can provoke inflammation, consequently leading the Langerhans cells to travel to the cornea, which increases the risk of recurrence. The amniotic membrane is said to have anti-inflammatory actions when implanted on the ocular surface.^[20] As a result, the recurrence rate could be lower, accompanied by fibrin glue. Viral infection remains a risk when transplanting amniotic membranes; however, there are no reported studies of such cases. Given the results from the best available evidence as well as the support from the clinical trials, fibrin glue could be used as an effective and safe option during pterygium surgery. However, sutures could be reserved for complex and high-risk cases.

A systematic approach was used in this review to provide a summary of the best available evidence and to assess the risk of bias in relevant studies.^[7-10] Based on the design and included population, the four included studies were standardized. The intervention and control groups were homogenous, comparing

fibrin glue and sutures. Therefore, this allows for a non-biased comparison. All of these allow a robust conclusion to be made from the best available evidence. However, inherent limitations should be acknowledged. Only four studies were identified, enrolling only a total of 180 subjects, which may not be sufficient to generalize the conclusions.

CONCLUSION

The findings of this meta-analysis suggest that fibrin glue is comparable to the sutures used in the pterygium surgery with amniotic membrane transplantation as it improves conjunctival inflammation and does not increase postoperative pain and discomfort, pterygium recurrence, pyogenic granuloma, and surgical time. Further studies should be performed to evaluate the efficacy of fibrin glue.

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Conflicts of interest

There are no conflicts of interest.

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