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REVIEW

Conjunctival and Limbal Conjunctival Autograft vs. Amniotic Membrane Graft in Primary Pterygium Surgery: A 30-Year Comprehensive Review

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ABSTRACT

Introduction: The purpose of this study is to compare the "real-life" effectiveness of amniotic membrane graft (AMG) and conjunctival (CAT) or limbal conjunctival (LCA) autograft in the management of primary pterygium.

Methods: Human-based studies on primary pterygium surgery that were published between 1993 and 2022 with at least 3 months of follow-up were identified, and only those that were retrospective were included. The global recurrence rate of pterygium was assessed for each surgical technique separately. Specific recurrence rates taking into consideration the fixation technique (glue versus sutures) were also measured.

Results: 35 real-life retrospective subgroups comprising a total of 3747 eyes were included in the final review. The mean global recurrence rates for CAT, LCA and AMG were 7.61%, 5.50% and 9.0%, respectively. Recurrences were less common for patients who received fibrin glue (5.92%, 2.56% and 3.60%) than for those who received sutures (8.99%, 6.03% and 23.0%) for the three groups, respectively. Surgical techniques combining CAT or LCA with AMG yielded an even lower global recurrence rate (1.83%).

Conclusion: AMG seems like a reasonable option that could be considered in primary pterygium surgery, especially when glued to the underlying sclera. Combining AMG with other treatment modalities such as CAT or LCA seems to offer an interesting alternative in terms of recurrence.

Keywords: Primary pterygium; Recurrence; Amniotic membrane; Conjunctival autograft; Limbal conjunctival autograft; Real-life; Review

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Key Summary Points

Why carry out this study?

Surgery is the only option to remove a pterygium, and several surgical techniques have been developed over the years to try and reduce the pterygium recurrence rate.

Randomized controlled trials and meta-analysis have failed to show a statistical superiority of conjunctival autograft or limbal conjunctival autograft over amniotic membrane graft for primary pterygium surgery.

The purpose of this review was to compare the "real-life" effectiveness of these three surgical techniques in terms of pterygium recurrence based on the retrospective published data in the literature.

What was learned from the study?

Conjunctival autograft, limbal conjunctival autograft and amniotic membrane graft all seem like reasonable options that could be considered in primary pterygium surgery.

Amniotic membrane graft can be particularly useful in the case of subsequent glaucoma surgery or in the case of double-headed pterygia; the recurrence rate is lowest when the membrane is glued to the sclera.

New data suggest that combining amniotic membranes with conjunctival autograft or limbal conjunctival autograft can yield very low recurrence rates, but further studies are needed to confirm these results.

INTRODUCTION

Pterygium is a UV-sunlight-induced benign abnormal growth of epithelial and fibrovascular tissue migrating towards the central cornea [1]. Its global prevalence increases with age, ranging between 3% and 19.5% (mean of 12%) [2]. Impaired vision, induced astigmatism, and recurrent inflammation are among the common complications of a pterygium [3]. Even though medical treatment is crucial to relieve eye irritation and discomfort, surgical treatment remains the only option to remove a pterygium. Indications for surgical intervention include loss of vision secondary to induced astigmatism or to the involvement of the central part of the cornea; a restriction in ocular motricity; cosmetic problems; and suspicious features which can reveal an underlying squamous cell carcinoma [4].

Several surgical modalities for the treatment of pterygia have been developed over the years, ranging from the bare sclera technique first documented by Celsus in 25 AD to the PERFECT technique (pterygium extended removal followed by extended conjunctival transplant) described by Hirst et al. in 2009 [5, 6]. Growth over the cornea is proposed to be due to a destruction of the barrier limbal tissue, which forms the basis for the inclusion of limbal stem cells in the limbal conjunctival autograft (LCA) technique, with lower recurrence rates for both primary and secondary pterygia [7]. Recently, human amniotic membranes have gained increased popularity for the management of many ocular surface disorders, including coverage of the conjunctival defect after pterygium excision, or even for their use in combination with other techniques such as conjunctival autograft [8]. However, the efficacy of amniotic membrane graft (AMG) in preventing recurrences varies widely in the literature and depends on the surgical procedure, fixation technique, adjuvant treatment and/or study population.

Meta-analysis and systemic reviews of randomized controlled trials (RCTs) have failed to show a statistical superiority of LCA over AMG for primary pterygium surgery [9, 10].

Furthermore, RCTs have strict inclusion criteria and may not be representative of patients seen in routine clinical practice. Therefore, the place of AMG in the surgical therapeutic arsenal remains to be defined. The main objective of this review is to compare the "real-life" effectiveness of free conjunctival autograft (CAT) with LCA, AMG and combined surgical techniques in terms of pterygium recurrence based on the retrospective published data in the literature, providing new insights and perspective for the management of this very common disease.

METHODS

Surgical Procedures

Currently used surgical techniques all consist of dissecting the head of the pterygium from the cornea, resecting the conjunctiva and tenon capsule, and covering the bare sclera with biological tissue, whether with conjunctival autograft or with a human amniotic membrane.

Conjunctival Autograft

This surgical technique was first described by Gómez-Márquez in 1931 [11]. After excision of the pterygium under local anesthesia, the bleeding can be controlled with optional light cautery. Lidocaine 2% or saline is used to separate the conjunctiva from the underlying tenon capsule and harvest a free CAT from the superior temporal bulbar conjunctiva of the same eye (an area of the conjunctiva protected from UV exposure). The free graft is placed at the site of pterygium excision and fixed to the underlying sclera and at the limbus using nylon or vicryl sutures or is glued using biological fibrin glue. The graft harvest site does not need to be covered as it re-epithelializes on its own [12].

Limbal Conjunctival Autograft

Limbal autografting was first described by Barraquer and Strampelli in 1964 in the World Cornea Congress [13]. Pterygium surgery with LCA is performed similarly to the technique described above. However, at the time of graft harvesting, blunt dissection is continued anteriorly towards the peripheral cornea for about 1 mm beyond the limbus to include limbal stem cells [14].

Amniotic Membrane Graft

AMG is a newer technique than CAT and LCA that has been used increasingly since 1995 [15]. After excision of the pterygium, the bare sclera area is covered with an amniotic membrane placed with the stromal side facing down (inlay). It is then fixed to the surrounding conjunctiva either by biologic glue or by interrupted 8–0 or 9–0 vicryl sutures [8].

Search Methods

A search of PubMed was first performed in January 2022 using the keywords ("Primary Pterygium" OR "Primary Pterygium Recurrence") AND ("Conjunctival Autograft" OR "Limbal Conjunctival Autograft" OR "Amniotic Membrane"); this retrieved 111 results (58 CAT, 20 LCA, 27 AMG and 6 combined techniques).

All studies published between 1993 and 2022 with at least 3 months of follow-up were eligible, but only those reporting real-life retrospective data and that were not RCTs or subgroup analyses of RCTs were selected (Fig. 1). Two reviewers independently assessed the included studies for potential sources of bias. One author independently extracted data from the included studies regarding year and country of publication, study population, time of follow-up, surgical technique, fixation technique, use of mitomycin C (MMC), post-operative treatment, definition of recurrence and mean recurrence rate. For papers with both primary and recurrent pterygia, only primary pterygium data were included, and recurrence rates were recalculated accordingly. Also, for papers describing different surgical techniques, every subgroup was reported separately.

This article is based on previously conducted studies and does not contain any new studies

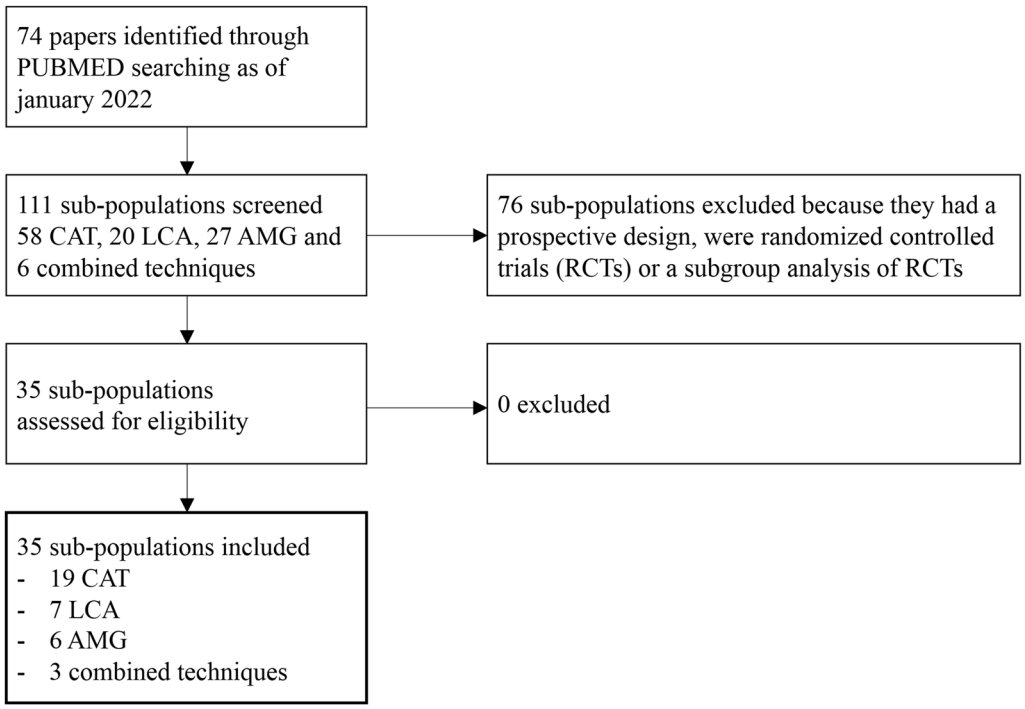

Fig. 1 Flow diagram of the identification and selection process of the papers for the literature review of conjunctival autograft (CAT), limbal conjunctival autograft (LCA) and amniotic membrane graft (AMG) in primary pterygium surgery

with human participants or animals performed by any of the authors.

Statistical Analysis

This was an observational descriptive analysis. No statistical analysis was made.

Outcome of Interest

The primary outcome for this review was the recurrence rate of the pterygium. Definition of recurrence varied between publications, depending on whether it was exclusively conjunctival or extended onto the cornea. Only corneal recurrence rate was reported in this review, and this was defined as a new fibrovascular overgrowth reaching and exceeding the limbus in 26 subgroups [16–35]; a growth > 1 mm or more anterior to the limbus in 7 subgroups [20, 27, 36–39]; and a growth > 1.5 mm or more anterior to the limbus in 1 subgroup [28].

RESULTS

This section is divided into subsections that treat the results of each surgical technique separately. Overall, 35 subgroups comprising a total of 3747 treated eyes met all the inclusion criteria and were included in the final review. Mean pterygium recurrence was assessed globally (global recurrence rate; Fig. 2), taking into account all included papers, and was then recalculated for each fixation technique separately (specific recurrence rate; Fig. 3). Except for one publication by Okoye et al. [33], all included papers had a minimum follow-up of 6 months (range, 3–48 months).

Conjunctival Autograft

Between 1993 and 2022, 16 publications about CAT met all the inclusion criteria and were included in the review [16–28, 37–39]. None of the papers had adjuvant MMC used peroperatively. For three papers, different fixation techniques or surgical variations were analyzed

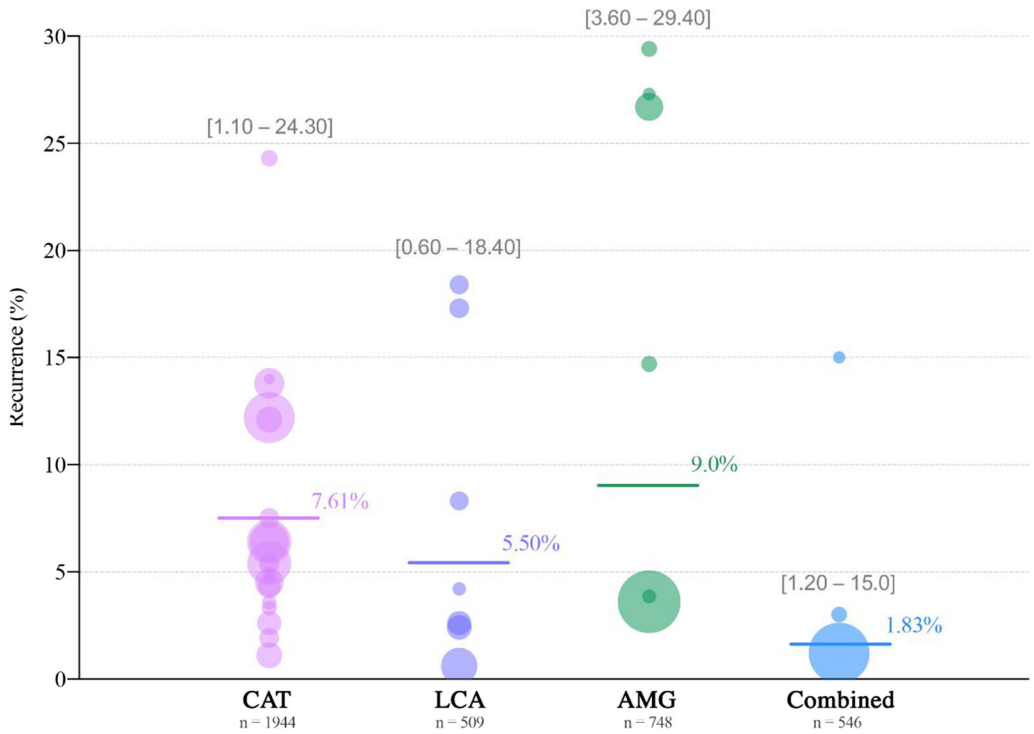

Fig. 2 Bubble plot of overall real-life primary pterygium recurrence rates following different surgical techniques. Each point corresponds to a subgroup of included patients, and the size of the point reflects the number of subjects in each subgroup. The mean overall recurrence rate for each technique is shown as a line and the margin between brackets. *CAT* conjunctival autograft, *LCA* limbal conjunctival autograft, *AMG* amniotic membrane graft, *Combined* techniques combining CAT or LCA with AMG

separately. Of the 1944 eyes included, 148 had a recurrence of their pterygium throughout their follow-up (the mean follow-up was 16 months). The mean global recurrence rate for CAT was 7.61% (range 1.10–24.3%).

Among the included subgroups, nine (1034 eyes) used nylon or vicryl sutures for graft fixation and ten (895 eyes) used fibrin glue. The mean specific recurrence rates were 8.99% and 5.92%, respectively (Table 1).

Limbal Conjunctival Autograft

Seven subgroups of six papers were included in the LCA analysis, summing to a total of 509 eyes with a mean follow-up of 17.7 months [27–32]. Only one paper had MMC 0.02% used peroperatively for 2 min. Pterygium recurred in 28 patients. The mean global recurrence rate for LCA was 5.50% (range 0.60%–18.40%).

Among the included subgroups, 6 (431 eyes) used nylon or vicryl sutures for graft fixation, and 1 study (78 eyes) used fibrin glue. The mean specific recurrence rates were 6.03% and 2.56%, respectively (Table 2).

Amniotic Membrane Graft

Six retrospective studies about AMG in primary pterygium excision met all the inclusion criteria and were included. MMC 0.02% was used for 30 seconds in one study. 748 eyes were followed up for a mean of 11.8 months. The mean global recurrence rate for AMG was 9.0% (range 3.60–29.40%).

Among the included studies, 5 (221 eyes) used nylon or vicryl sutures for amniotic membrane fixation, and one large cohort of 527 eyes used fibrin glue. The mean specific

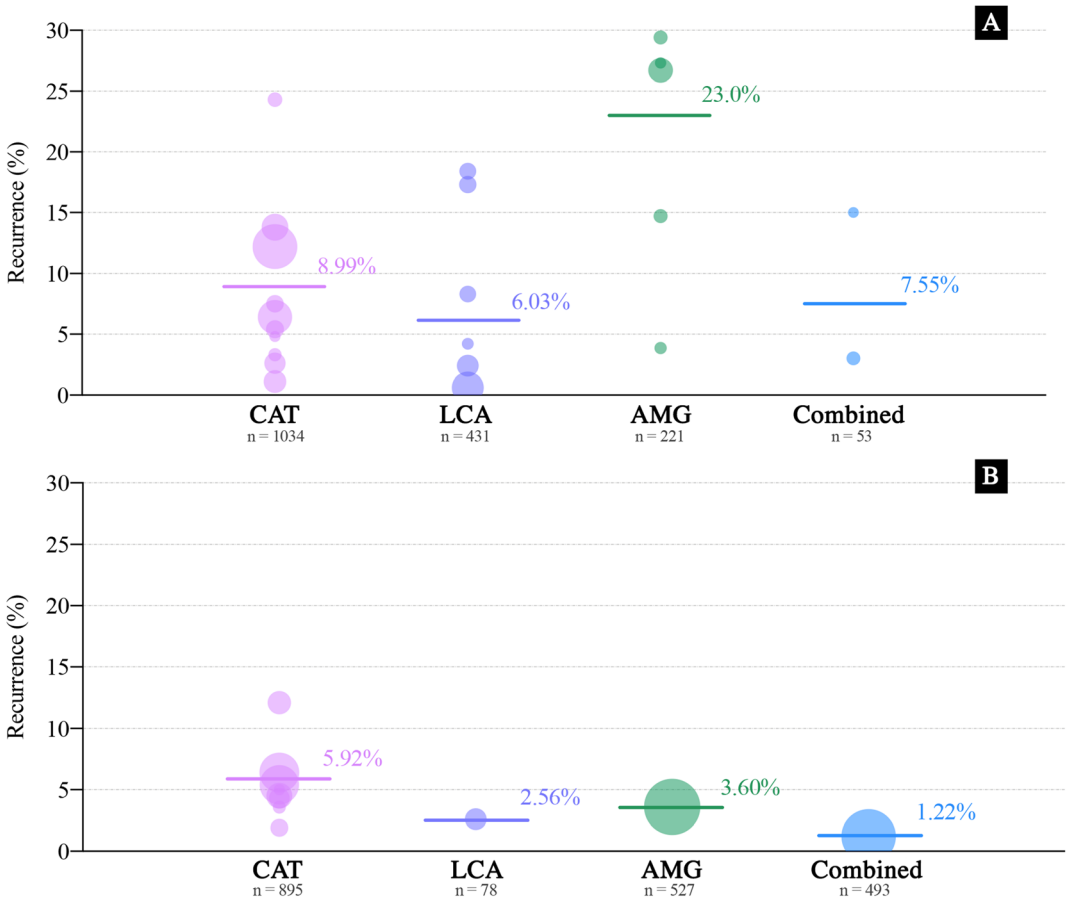

Fig. 3 Bubble plot of specific real-life primary pterygium recurrence rates following different surgical techniques using either sutures **A** or fibrin glue **B**. Each point corresponds to a subgroup of included patients, and the size of the point reflects the number of subjects in each subgroup. The mean specific recurrence rate for each technique is shown as a line and the margin between brackets. *CAT* conjunctival autograft, *LCA* limbal conjunctival autograft, *AMG* amniotic membrane graft, *Combined* techniques combining CAT or LCA with AMG

recurrence rates were 23.0% and 3.60%, respectively (Table 3).

Combined Techniques

In 2005 and 2018, two papers retrospectively reported the combined use of CAT with AMG placed epithelial side up (inlay) under the conjunctiva or epithelial side down (overlay) over the conjunctival graft [25, 28]. More recently, Shusko et al. [36] described a newer surgical technique combining LCA with a lyophilized AMG inserted into a subconjunctival pocket created around the surgical excision site. None of the studies used adjuvant MMC peroperatively. The mean global recurrence rate for combined surgeries, assessed based on these 3 studies (547 eyes), was 1.83% (range, 1.20–15.0%) after a mean follow-up of 15.5 months.

Two studies (53 eyes) used nylon 10–0 and/or vicryl 8–0 sutures for graft fixation, while Shusko et al. (493 eyes) used fibrin glue. The mean specific recurrence rates were 7.55% and 1.22%, respectively (Table 4).

Table 1 Summary of the papers published between 1993 and 2022 assessing the "real-life" efficacy of conjunctival autograft for primary pterygium surgery

Year	Author (journal)	City/state, country	Duration of follow-up, months (mean ± SD)	Surgical technique	*N*	Type of fixation used	Adjuvant use of MMC	Postoperative treatment	Recurrence rate	Definition of recurrence
1993	Riordan Eva et al. (Eye)	London, England	15	Conjunctival autograft	15	–	–	–	14.00%	Fibrovascular proliferation outreaching the limbus
1997	Prabhasawat et al. (Ophthalmology)	Florida, United States	24.4 ± 20.9	Conjunctival autograft	78	Vicryl 8–0 or 9–0 sutures	–	CTC + AB, 1 month	2.60%	Fibrovascular proliferation outreaching the limbus
2000	Ma et al. (BJO)	Taoyuan, Taiwan	22.8 ± 18.2	Conjunctival autograft	56	Vicryl 8–0 sutures	–	CTC + AB 2-4x/d	5.40%	Fibrovascular proliferation outreaching the limbus
2003	Syam et al. (Ophthalmology)	Brighton, England	27.3	Conjunctival autograft	30	Vicryl 8–0 sutures	–	CTC + AB 4x/d, 4 weeks	3.30%	Fibrovascular proliferation outreaching the limbus
2005	Fernandes et al. (Eye)	Hyderabad, India	6.4 ± 8.8	Conjunctival autograft	345	Nylon 10–0 + vicryl 8–0 sutures	–	CTC 6 weeks + AB 1 week	12.20%	Fibrovascular proliferation outreaching the limbus > 1.5 mm
2005	Koranyi et al. (Acta Ophthalmol Scand)	Stockholm, Sweden	23.0 ± 20.0	Conjunctival autograft	123	Sutures	–	CTC 6x/d 6 weeks + AB 2x/d 1 week	13.8% at 6 months	Fibrovascular proliferation outreaching the limbus
2005	Koranyi et al. (Acta Ophthalmol Scand)	Stockholm, Sweden	23.0 ± 20.0	Conjunctival autograft	258	Biologic glue	–	CTC 6x/d 6 weeks + AB 2x/d 1 week	5.4% at 6 months	Fibrovascular proliferation outreaching the limbus > 1 mm
2005	Mejia et al. (Cornea)	Medellin, Columbia	9	Conjunctival autograft	88	Nylon 10–0 sutures	–	CTC 3x/d 2 weeks	1.10%	Fibrovascular proliferation outreaching the limbus > 1 mm
2008	Bahar et al. (Curr Eye Res)	Ontario, Canada	9.0 ± 2.6	Conjunctival autograft	70	Biologic glue	–	CTC + AB 4x/d 4 weeks	4.30%	Fibrovascular proliferation outreaching the limbus
2008	Bahar et al. (Curr Eye Res)	Ontario, Canada	9.8 ± 4.5	Conjunctival autograft	91	Biologic glue	–	CTC + AB 4x/d 4 weeks	12.10%	Fibrovascular proliferation outreaching the limbus
2010	Sarnicola et al. (Cornea)	Grosseto, Italy	24	Conjunctival autograft	111	Biologic glue	–	CTC + AB 4x/d 2 weeks	4.50%	Fibrovascular proliferation outreaching the limbus
2011	Nieuwendaal et al. (Cornea)	Amsterdam, Netherlands	Minimum of 12 months	Conjunctival autograft	28	Biologic glue	–	CTC tapered over 3 months + AB 2 weeks	3.57%	Fibrovascular proliferation outreaching the limbus
2014	Cagatay et al. (Postgrad Med)	Kars, Turkey	21.5 ± 5.3	Conjunctival autograft	53	Vicryl 8–0 sutures	–	CTC + AB 4x/d 4 weeks	7.50%	Fibrovascular proliferation outreaching the limbus > 1 mm

Table 1 continued

Year	Author (journal)	City/state, country	Duration of follow-up, months (mean ± SD)	Surgical technique	*N*	Type of fixation used	Adjuvant use of MMC	Postoperative treatment	Recurrence rate	Definition of recurrence
2014	Cagatay et al. (Postgrad Med)	Kars, Turkey	22.1 ± 5.2	Conjunctival autograft	53	Biologic glue	–	CTC + AB 4x/d 4 weeks	1.90%	Fibrovascular proliferation outreaching the limbus > 1 mm
2015	Boucher et al. (Can J Ophthalmol)	Ottawa, Canada	12	Conjunctival autograft	20	Biologic glue	–	CTC 4x/j 3 months + AB 4x/d 1 week	5.00%	Fibrovascular proliferation outreaching the limbus > 1 mm
2018	Bilge et al. (Saudi J Ophthalmol)	Istanbul, Turkey	11.7	Conjunctival autograft	21	polypropylene 8–0 sutures	–	CTC + AB 4x/j 4 weeks	4.8% at 6 months	Fibrovascular proliferation outreaching the limbus
2018	Arriola-Villalobos et al. (JFO)	Madrid, Spain	7.82 ± 8.23	Conjunctival autograft	264	Biologic glue	–	CTC + AB 5x/d tapered over 5 weeks	6.40%	Fibrovascular proliferation outreaching the limbus > 1 mm
2018	Malla et al. (Int J Ophthalmol)	Nanjing, China	Minimum of 12 months	Conjunctival autograft	37	Vicryl 8–0 sutures	–	CTC + AB 3x/d tapered over 1 month	24.30%	Fibrovascular proliferation outreaching the limbus
2019	Röck et al. (Med Sci Monit)	Tübingen, Germany	12	Conjunctival autograft	203	Vicryl 8–0 and 9–0 sutures	–	CTC 4x/d tapered over 3 months + AB 4x/d 2 weeks	6.4% at 12 months	-

N number of eyes included in the study, *MMC* mitomycin, *CTC* corticosteroids, *AB* antibiotics

Table 2 Summary of the papers published between 1993 and 2022 assessing the "real-life" efficacy of limbal conjunctival autograft for primary pterygium surgery

Year	Author (journal)	City/state, country	Duration of follow-up, months (mean ± SD)	Surgical technique	*N*	Type of fixation used	Adjuvant use of MMC	Postoperative treatment	Recurrence rate	Definition of recurrence
2005	Mejia et al. (Cornea)	Medlin, Columbia	9	Limbal conjunctival autograft	24	Nylon 10–0 sutures	–	CTC 3x/d 2 weeks	4.20%	-
2005	Fernandes et al. (Eye)	Hyderabad, India	6.4 ± 8.8	Limbal conjunctival autograft	52	Vicryl 8–0 + nylon 10–0 sutures	–	CTC 6 weeks + AB 1 week	17.30%	Fibrovascular proliferation outreaching the limbus
2012	Han et al. (Ophthalmologica)	Seongnam, Korea	18.9 ± 9.2	Limbal conjunctival autograft	82	Vicryl 8–0 + nylon 10–0 sutures	–	CTC + AB 4x/d 1 month	2.40%	-
2015	Masters et al. (Cornea)	Tennessee, USA	46.4 ± 49.8	Limbal conjunctival autograft	176	Vicryl 8–0 + nylon 10–0 sutures	–	CTC + AB 4x/d 1 week then 2x/d 2 weeks	0.60%	Fibrovascular proliferation outreaching the limbus
2018	Hwang et al. (BMC Ophthalmology)	Gyeonggi-do, Korea	19 ± 4.9	Limbal conjunctival autograft	78	Biologic glue	0.02% 2 min	CTC + AB 4x/d 1 month	2.60%	Fibrovascular proliferation outreaching the limbus
2020	Yang et al. (Graefes Arch Clin Exp Ophthalmol)	Kangwon, Korea	12	Limbal conjunctival autograft	48	Vicryl 8–0 + nylon 10–0 sutures	–	CTC + AB 4x/d 1 month	8.30%	Fibrovascular proliferation outreaching the limbus
2020	Yang et al. (Graefes Arch Clin Exp Ophthalmol)	Kangwon, Korea	12	Limbal conjunctival autograft	49	Vicryl 8–0 sutures	–	CTC + AB 4x/d 1 month	18.40%	Fibrovascular proliferation outreaching the limbus

N number of eyes included in the study, *MMC* mitomycin, *CTC* corticosteroids, *AB* antibiotics

Table 3 Summary of the papers between 1993 and 2022 assessing the "real-life" efficacy of amniotic membrane graft for primary pterygium surgery

Year	Author (journal)	City/state, country	Duration of follow-up, months (mean ± SD)	Surgical technique	*N*	Type of fixation used	Adjuvant use of MMC	Postoperative treatment	Recurrence rate	Definition of recurrence
2005	Fernandes et al. (Eye)	Hyderabad, India	6.4 ± 8.8	AMG inlay	105	Vicryl 8–0 + nylon 10–0 sutures	–	CTC 6 weeks + AB 1 week	26.70%	Fibrovascular proliferation outreaching the limbus
2013	Okoye et al. (Niger J Clin Pract)	Andra Prand., India	3	AMG inlay	26	Vicryl 8–0 sutures	–		3.85%	Fibrovascular proliferation outreaching the limbus
2013	Kurna et al. (Eur J Ophthalmol)	Istanbul, Turkey		AMG	22	Vicryl 8–0 + nylon 10–0 sutures	–	–	27.30%	Fibrovascular proliferation outreaching the limbus
2018	Rosen et al. (Cornea)	California, USA	17.3 ± 0.8	AMG inlay	527	Biologic glue	0.02% 30 s	CTC 6x/d tapered over 2 months + AB 4x/d 1 week	3.60%	Fibrovascular proliferation outreaching the limbus
2018	Malla et al. (Int J Ophthalmol)	Nanjing, China	Minimum of 12 months	AMG-L inlay	34	Vicryl 8–0 sutures	–	CTC + AB 3x/d tapered over 1 month	29.40%	Fibrovascular proliferation outreaching the limbus
2019	Röck et al. (Med Sci Monit)	Tübingen, Germany	12	AMG inlay	34	Vicryl 8–0 + 9–0 sutures	–	CTC 4x/d tapered over 3 months + AB 4x/d 2 weeks	14.7% at 12 months	-

N number of eyes included in the study, *MMC* mitomycin, *AMG* amniotic membrane graft, *AMG-L* lyophilized amniotic membrane graft, *CTC* corticosteroids, *AB* antibiotics

Table 4 Summary of the papers between 1993 and 2022 assessing the "real-life" efficacy of combined surgical procedures for primary pterygium surgery

Year	Author (journal)	City/state, country	Duration of follow-up, months (mean ± SD)	Surgical technique	N	Type of fixation used	Adjuvant use of MMC	Postoperative treatment	Recurrence rate	Definition of recurrence
2005	Fernandes et al. (Eye)	Hyderabad, India	6.4 ± 8.8	Conjunctival autograft + AMG inlay under the conjunctiva	20	Vicryl 8–0 + nylon 10–0 sutures	–	CTC 6 weeks + AB 1 week	15.00%	Fibrovascular proliferation outreaching the limbus
2018	Malla et al. (Int J Ophthalmol)	Nanjing, China	Minimum of 12 months	Conjunctival autograft + AMG-L overlay	33	Vicryl 8–0 sutures	–	CTC + AB 3x/d tapered over 1 month	3.00%	Fibrovascular proliferation outreaching the limbus
2020	Shusko et al. (Clin Ophthalmol)	Florida, USA	28	Conjunctival-limbal autograft + AMG-L under the conjunctiva	493	Biologic glue	–	CTC 4x/d 2 weeks then tapered + AB 1 week	1.20%	Fibrovascular proliferation outreaching the limbus > 1 mm

N number of eyes included in the study, *MMC* mitomycin, *AMG* amniotic membrane graft, *AMG-L* lyophilized amniotic membrane graft, *CTC* corticosteroids, *AB* antibiotics

DISCUSSION

Pterygium recurrence is a complication of pterygium surgery. Even though the predicting factors are not fully understood, some have been identified, including ethnicity (Hispanic and dark-skinned patients), younger age, current active growth, preexisting disfiguration of the lacrimal caruncle, ocular motility restriction, ocular surface inflammation and genetic predisposition [40]. Surgery-related factors have also been studied. They include appropriate removal of the proliferative epithelial cells that alter the corneal limbal stem cells; thorough removal of the subconjunctival fibrovascular tissue with or without the use of adjunctive therapies; appropriate covering of the bare sclera; and adequate postoperative inflammation control [4].

Although several surgical techniques to cover the surgical site have been described over the years, CAT, LCA and AMG have gained worldwide acceptance. In this "real-world" review of 35 subgroups of patients, comprising a total of 3747 primary pterygia, we compared the effectiveness of these techniques with respect to pterygium recurrence. Meta-analysis and systemic reviews have already been conducted and did not show a statistical superiority of LCA over AMG or the converse [9, 10]. A meta-analysis of 13 RCTs in Cornea (878 eyes) compared LCA to other surgical techniques in primary and recurrent pterygia [9]. It excluded non-randomized, non-controlled trials and those combining two different techniques. The authors found that the recurrence rate of LCA was not statistically different than that of AMG, with an odds ratio of 0.96 for primary pterygia. Similarly, a Cochrane systemic review published in 2017 did not show any superiority of CAT or AMG for primary pterygia at 3 and 6 months (6 RCTs, 538 eyes and 10 RCTs, 1021 eyes, respectively), with a relative risk of 0.58 (0.27–1.27) at 6 months [10]. On the other hand, another meta-analysis published in 2012 showed different results, with a superiority of the CAT technique over AMG (hazard ratio 0.30) [41]. However, the paper included both RCTs and retrospective cohorts, including a

study by Tananuvat et al. [42] with an abnormally high recurrence rate (40.9%) for patients treated with AMG fixated with vicryl 8.0 sutures, which are known to be pro-inflammatory. According to the authors, this particularly high recurrence rate could be partly explained by the high sun exposure of the studied population, which was mainly composed of agricultural workers in a tropical area.

In our review, the real-world recurrence rates for AMG, CAT and LCA were 9.0%, 7.61% and 5.50%, respectively. Amniotic membranes have several biological properties, including anti-angiogenic, anti-inflammatory and anti-fibrotic effects. Also, because of their structure and low immunogenicity, they work as a substrate for conjunctival epithelial adherence, migration, and differentiation [43]. Different mechanisms by which amniotic membranes can reduce pterygium recurrence have been described. Wound healing can be generally considered an inflammatory process in its earlier stages. The use of an amniotic membrane provides an anti-inflammatory environment and promotes epithelialization [44]. Also, the stroma of the amniotic membrane is thought to inhibit tissue growth factor beta (TGF-β) signaling and reduce extracellular matrix production [28]. When placed directly in contact with the Tenon's fibroblasts, it suppresses myofibroblast differentiation and reduces scarring [45]. Amniotic membranes can therefore be considered an alternative to conjunctival grafting without compromising efficacy. In our review, only one study used lyophilized amniotic membranes [25], and further studies are therefore needed to compare their efficacy to that of cryopreserved ones in pterygium management. However, it is noteworthy that experimental studies have shown that lyophilized and cryopreserved membranes have similar amounts of the major growth factors that play a role in epithelial healing [46–48], and recent clinical studies showed similar rates of superficial ulcer healing for the two types of membranes [49]. Furthermore, a comparative study showed that both can be safe and effective adjunctive treatments for primary pterygium over a 22-month follow-up [50].

The recurrence rate after surgery does not depend solely on the biomaterial used, but also on the concomitant use of adjunctive treatments such as MMC and/or on the fixation technique [51].

In our review, MMC 0.02% was used in only two subgroups of patients. However, wide variations of the recurrence rates were found when sutures and fibrin glue were treated separately. Despite its anti-inflammatory effect, the fixation of the amniotic membrane with vicryl sutures yielded very high specific recurrence rates (23.0%), but MMC was used in none of these studies. In fact, a meta-analysis by Song et al. showed that amniotic membrane transplantation with MMC was associated with lower recurrence rates compared to amniotic membrane alone, but the fixation technique was not specified in the paper [52]. It should be noted, however, that the use of MMC for primary pterygium surgery is arguable, and the lowest effective concentration and contact time should be employed in order to limit possible side effects [53].

In our review, vicryl sutures were used more frequently than nylon 10–0, except for the LCA technique where the two were combined. This is probably due to the fact that vicryl sutures have the advantage of being absorbed within 60 days, eliminating the need for suture removal. While both types of sutures can cause a conjunctival reaction in the postoperative period, vicryl ones are known to be pro-inflammatory and to enhance the TGF-β pathway [54], promoting myofibroblast transformation and pterygium recurrence. Human fibroblasts, on the other hand, produce a fibrin clot that promotes tissue adhesion and minimizes inflammation [55]. The recurrence rate of AMG fixated with fibrin glue is lower than that of CAT and similar to that of LCA (3.60%). Even though only one monocentric study was included, it reported the results of a large cohort of 527 eyes (535 patients) from a high-risk population with a mean follow-up duration of 17.3 months. The reason why sutures are more inflammatory when associated with AMGs rather than with conjunctival grafts remains unclear. One possible explanation could be that, unlike CAT, which does not require an

inflammatory re-epithelialization phase, a sutured AMG requires both a conjunctival epithelial healing phase and a suture resorption phase, which are both associated with inflammation.

Associating AMG with fibrin glue for primary pterygia has a double advantage: the use of AMG preserves the conjunctiva of the patient in case they require a future glaucoma procedure or in case of recurrences, and the use of fibrin glue reduces surgical time and minimizes postoperative discomfort and inflammation [56, 57]. However, it is noteworthy that fibrin glue is more expensive than sutures and is not available in certain countries or surgical settings.

Recent evidence suggests that the combination of AMG with CAT or LCA can achieve an even lower recurrence rate than what can be achieved with either technique alone. In our review, the mean recurrence rate for papers combining CAT or LCA with AMG was the lowest (1.83%), and dropped even further to 1.22% when the biomaterial was glued, offering what is possibly the best available surgical option to date. Further evaluation will be required to confirm these results.

Different surgical techniques combining AMG with conjunctival graft for primary pterygia have been described over the years. In their large cohort of 989 eyes, Fernandes et al. described 20 patients in which the CAT was harvested and transferred to the recipient bed over the AMG with the epithelial side up and then anchored to the surrounding conjunctiva with 8–0 vicryl sutures, with a 15% recurrence rate [28]. In 2011, Taylan et al. prospectively followed 30 patients with primary pterygia treated with excision followed by an inlay AMG to cover the conjunctival side of the bare sclera combined with a narrow-strip CAT to cover the limbal part of the bare sclera; both tissues were fixated using fibrin-glue tissue adhesive (recurrence rate 6.67%) [58]. Other surgical techniques have also been described, including CAT with an overlay cryopreserved or lyophilized AMG (recurrence rates of 7.10% and 3.00%, respectively); mini simple limbal epithelial transplantation followed by an overlay AMG (recurrence rate of 2.50%); and more recently, LCA and dehydrated AMG inserted into a subconjunctival pocket created around the periphery of the excision site in 493 eyes (recurrence rate of 1.20%) [36, 59–61].

Regardless of the technique used, extensive removal of the Tenon can be beneficial. In fact, Hirst et al. followed 1000 consecutive patients (806 primary pterygium) undergoing extended pterygium removal encompassing the Tenon layer followed by an extended conjunctival transplant, and noted a near-zero recurrence rate [62]. The extent of Tenon resection is barely described in the different studies. This could be a confounding factor when interpreting their results.

Our review has several limitations. "Real-life" observational studies better represent real-life patients but have a lower level of evidence than interventional trials. Data from such papers can be statistically poor because of their retrospective design but also due to their heterogenicity. In fact, the follow-up time and the definition of recurrence varied widely between authors. We tried to compensate for this bias and to strengthen the relevance of our findings by analyzing a significant number of papers. Also, except for one paper, the follow-up was at least 6 months for all studies and reached 46 months for Masters et al. [30]. We tried to homogenize the different recurrence definitions by recalculating the corneal recurrence rate for all papers. Some factors, such as ethnicity, sun exposure or surgeon's experience, could still have affected our results. Moreover, our review only considered the pterygium recurrence rate, not the postoperative esthetic appearance. Other complications have been reported in the literature, such as graft dehiscence, graft detachment and granulomas. Finally, another limitation would be the small sample of patients in some subgroups. Nevertheless, this bias was minimized by the overall number of included eyes (3747 eyes).

CONCLUSIONS

In conclusion, based on our review, AMG seems like a reasonable option that could be considered in primary pterygium surgery. It can be

used alone, glued to the underlying sclera with its epithelial side up, with the advantage of preserving the patient's conjunctiva, particularly in the case of subsequent glaucoma surgery or in the case of double-headed pterygia. If the AMG is to be sutured, the use of thinner 10.0 sutures with MMC is encouraged, but physicians should be aware of its various side effects. The combination of AMG with CAT or LCA seems to yield very low recurrence rates, but further studies are needed to confirm these results.

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REFERENCES

1. Malozhen SA, Trufanov SV, Krakhmaleva DA. Pterygium: etiology, pathogenesis, treatment. Vestn Oftalmol. 2017;133(5):76–83.
2. Rezvan F, Khabazkhoob M, Hooshmand E, Yekta A, Saatchi M, Hashemi H. Prevalence and risk factors of pterygium: a systematic review and meta-analysis. Surv Ophthalmol. 2018;63(5):719–35.
3. Chu WK, Choi HL, Bhat AK, Jhanji V. Pterygium: new insights. Eye (Lond). 2020;34(6):1047–50.
4. Shahraki T, Arabi A, Feizi S. Pterygium: an update on pathophysiology, clinical features, and management. Ther Adv Ophthalmol. 2021;13:25158414211020150.
5. Hille K, Höh H, Gross A, Ruprecht KW. Prospective study of surgical therapy of pterygium: bare sclera technique vs. free conjunctiva-limbus transplant. Ophthalmol Z Dtsch Ophthalmol Ges. 1996;93(3):224–226.
6. Hirst LW. Prospective study of primary pterygium surgery using pterygium extended removal followed by extended conjunctival transplantation. Ophthalmology. 2008;115(10):1663–72.
7. Clearfield E, Muthappan V, Wang X, Kuo IC. Conjunctival autograft for pterygium. Cochrane Database Syst Rev. 2016;2(2):CD011349.
8. Jirsova K, Jones GLA. Amniotic membrane in ophthalmology: properties, preparation, storage and indications for grafting—a review. Cell Tissue Bank. 2017;18(2):193–204.
9. Zheng K, Cai J, Jhanji V, Chen H. Comparison of pterygium recurrence rates after limbal

conjunctival autograft transplantation and other techniques: meta-analysis. Cornea. 2012;31(12): 1422–7.

10. Clearfield E, Hawkins BS, Kuo IC. Conjunctival autograft versus amniotic membrane transplantation for treatment of pterygium: findings from a cochrane systematic review. Am J Ophthalmol. 2017;182:8–17.

11. Gómez-Márquez J. New operative procedure for pterygium. Arch Oftal Hisp-Am. 1931;31:87–95.

12. Kositphipat K, Tananuvat N, Choovuthayakorn J. Results of pterygium excision adjunct with conjunctival autograft transplantation for primary pterygium by ophthalmology trainees. Int Ophthalmol. 2016;36(5):615–21.

13. Daya SM. Conjunctival-limbal autograft. Curr Opin Ophthalmol. 2017;28(4):370–6.

14. Mery G, Maalouf T, George JL, Angioi K. Limbal-conjunctival autograft in pterygium surgery. J Fr Ophtalmol. 2010;33(2):92–8.

15. Meller D, Pauklin M, Thomasen H, Westekemper H, Steuhl KP. Amniotic membrane transplantation in the human eye. Dtsch Arzteblatt Int. 2011;108(14): 243–8.

16. Riordan-Eva P, Kielhorn I, Ficker LA, Steele AD, Kirkness CM. Conjunctival autografting in the surgical management of pterygium. Eye (Lond). 1993;7(Pt 5):634–8.

17. Prabhasawat P, Barton K, Burkett G, Tseng SC. Comparison of conjunctival autografts, amniotic membrane grafts, and primary closure for pterygium excision. Ophthalmology. 1997;104(6): 974–85.

18. Ma DH, See LC, Liau SB, Tsai RJ. Amniotic membrane graft for primary pterygium: comparison with conjunctival autograft and topical mitomycin C treatment. Br J Ophthalmol. 2000;84(9):973–8.

19. Syam PP, Eleftheriadis H, Liu CSC. Inferior conjunctival autograft for primary pterygia. Ophthalmology. 2003;110(4):806–10.

20. Koranyi G, Seregard S, Kopp ED. The cut-and-paste method for primary pterygium surgery: long-term follow-up. Acta Ophthalmol Scand. 2005;83(3): 298–301.

21. Bahar I, Kaiserman I, Weisbrod M, McAllum P, Slomovic A. Extensive versus limited pterygium excision with conjunctival autograft: outcomes and recurrence rates. Curr Eye Res. 2008;33(5):435–40.

22. Sarnicola V, Vannozzi L, Motolese PA. Recurrence rate using fibrin glue-assisted ipsilateral conjunctival autograft in pterygium surgery: 2-year follow-up. Cornea. 2010;29(11):1211–4.

23. Nieuwendaal CP, van der Meulen IJE, Mourits M, Lapid-Gortzak R. Long-term follow-up of pterygium surgery using a conjunctival autograft and Tissucol. Cornea. 2011;30(1):34–6.

24. Bilge AD. Comparison of conjunctival autograft and conjunctival transposition flap techniques in primary pterygium surgery. Saudi J Ophthalmol. 2018;32(2):110–3.

25. Malla T, Jiang J, Hu K. Clinical outcome of combined conjunctival autograft transplantation and amniotic membrane transplantation in pterygium surgery. Int J Ophthalmol. 2018;11(3):395–400.

26. Röck T, Bramkamp M, Bartz-Schmidt KU, Röck D. A retrospective study to compare the recurrence rate after treatment of pterygium by conjunctival autograft, primary closure, and amniotic membrane transplantation. Med Sci Monit. 2019;25:7976–81.

27. Mejía LF, Sánchez JG, Escobar H. Management of primary pterygia using free conjunctival and limbal-conjunctival autografts without antimetabolites. Cornea. 2005;24(8):972–5.

28. Fernandes M, Sangwan VS, Bansal AK, et al. Outcome of pterygium surgery: analysis over 14 years. Eye Lond Engl. 2005;19(11):1182–90.

29. Han SB, Hyon JY, Hwang JM, Wee WR. Efficacy and safety of limbal-conjunctival autografting with limbal fixation sutures after pterygium excision. Ophthalmologica. 2012;227(4):210–4.

30. Masters JS, Harris DJ. Low recurrence rate of pterygium after excision with conjunctival limbal autograft: a retrospective study with long-term follow-up. Cornea. 2015;34(12):1569–72.

31. Hwang HS, Cho KJ, Rand G, Chuck RS, Kwon JW. Optimal size of pterygium excision for limbal conjunctival autograft using fibrin glue in primary pterygia. BMC Ophthalmol. 2018;18(1):135.

32. Yang H, Lee Y, Hyon J, Kim K, Han S. Efficacy of bevacizumab injection after pterygium excision and limbal conjunctival autograft with limbal fixation suture. Graefes Arch Clin Exp Ophthalmol. 2020;258(7).

33. Okoye O, Oguego N, Chuka Okosa C, Ghanta M. Short term results of pterygium surgery with adjunctive amniotic membrane graft. Niger J Clin Pract. 2013;16(3).

34. Kurna S, Altun A, Aksu B, Kurna R, Sengor T. Comparing treatment options of pterygium: limbal sliding flap transplantation, primary closing, and amniotic membrane grafting. Eur J Ophthalmol. 2013;23(4).

35. Rosen R. Amniotic membrane grafts to reduce pterygium recurrence. Cornea. 2018;37(2).

36. Shusko A, Schechter B, Hovanesian J. Pterygium surgery utilizing limbal conjunctival autograft and subconjunctival amniotic membrane graft in high-risk populations. Clin Ophthalmol Auckl NZ. 2020;14.

37. Cagatay HH, Gokce G, Ekinci M, Koban Y, Daraman O, Ceylan E. Long-term comparison of fibrin tissue glue and vicryl suture in conjunctival autografting for pterygium surgery. Postgrad Med. 2014;126(1): 97–103.

38. Boucher S, Conlon R, Teja S, et al. Fibrin glue versus autologous blood for conjunctival autograft fixation in pterygium surgery. Can J Ophthalmol. 2015;50(4):269–72.

39. Arriola-Villalobos P, Cifuentes-Canorea P, Peraza-Nieves J, et al. Fibrin glue conjunctival autograft for primary pterygium: Overall outcomes and outcomes in expert versus trainee ophthalmologists. J Fr Ophtalmol. 2018;41(4).

40. Nuzzi R, Tridico F. How to minimize pterygium recurrence rates: clinical perspectives. Clin Ophthalmol Auckl NZ. 2018;12:2347–62.

41. Li M, Zhu M, Yu Y, Gong L, Zhao N, Robitaille M. Comparison of conjunctival autograft transplantation and amniotic membrane transplantation for pterygium: a meta-analysis. Graefes Arch Clin Exp Ophthalmol. 2012;250(3).

42. Tananuvat N, Martin T. The results of amniotic membrane transplantation for primary pterygium compared with conjunctival autograft. Cornea. 2004;23(5):458–63.

43. Walkden A. Amniotic membrane transplantation in ophthalmology: an updated perspective. Clin Ophthalmol Auckl NZ. 2020;14:2057–72.

44. Kogan S, Sood A, Granick MS. Amniotic membrane adjuncts and clinical applications in wound healing: a review of the literature. Wounds Compend Clin Res Pract. 2018;30(6):168–73.

45. Ti S, Tseng S. Management of primary and recurrent pterygium using amniotic membrane transplantation. Curr Opin Ophthalmol. 2002;13(4).

46. Rodríguez-Ares M, López-Valladares M, Touriño R, et al. Effects of lyophilization on human amniotic membrane. Acta Ophthalmol (Copenh). 2009;87(4).

47. Koh J, Shin Y, Oh J, et al. The expression of TIMPs in cryo-preserved and freeze-dried amniotic membrane. Curr Eye Res. 2007;32(7–8).

48. Füst A, Pállinger E, Stündl A, et al. Both freshly prepared and frozen-stored amniotic membrane cells express the complement inhibitor CD59. Sci World J. 2012;815615.

49. Memmi B, Leveziel L, Knoeri J, et al. Freeze-dried versus cryopreserved amniotic membranes in corneal ulcers treated by overlay transplantation: a case-control study. Cornea. 2022;41(3).

50. Kim HJ, Kim SH. The comparative study of clinical results between cryopreserved and lyophilized amniotic membrane transplantation after surgical excision of primary pterygium. Invest Ophthalmol Vis Sci. 2010;51(13):2404.

51. 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(12):CD011308.

52. Yin-Wei S, Ai-Hua Y, Xiao-Jun C. Effectiveness of amniotic membrane transplantation combined with mitomycin C in the treatment of pterygium: a meta-analysis. Int J Ophthalmol. 2010;3(4):352–5.

53. Mearza AA, Aslanides IM. Uses and complications of mitomycin C in ophthalmology. Expert Opin Drug Saf. 2007;6(1):27–32.

54. Lock AM, Gao R, Naot D, Coleman B, Cornish J, Musson DS. Induction of immune gene expression and inflammatory mediator release by commonly used surgical suture materials: an experimental in vitro study. Patient Saf Surg. 2017;11:16.

55. Flavell SJ, Hou TZ, Lax S, Filer AD, Salmon M, Buckley CD. Fibroblasts as novel therapeutic targets in chronic inflammation. Br J Pharmacol. 2008;153(Suppl 1):S241–246.

56. Hong-Wei P, Jing-Xiang Z, Chun-Xia J. Comparison of fibrin glue versus suture for conjunctival autografting in pterygium surgery: a meta-analysis. Ophthalmology. 2011;118(6):1049–54.

57. Karalezli A, Kucukerdonmez C, Akova YA, Altan-Yaycioglu R, Borazan M. Fibrin glue versus sutures for conjunctival autografting in pterygium surgery: a prospective comparative study. Br J Ophthalmol. 2008;92(9):1206–10.

58. Taylan Sekeroglu H, Erdem E, Dogan NC, Yagmur M, Ersoz R, Dogan A. Sutureless amniotic membrane transplantation combined with narrow-strip

conjunctival autograft for pterygium. Int Ophthalmol. 2011;31(6):433–8.

59. Ghanavati SZ, Shousha MA, Betancurt C, Perez VL. Combined conjunctival autograft and overlay amniotic membrane transplantation; a novel surgical treatment for pterygium. J Ophthalmic Vis Res. 2014;9(3):399–403.

60. Sabater-Cruz N, Martinez-Conesa E, Vilarrodona A, Casaroli-Marano RP. Lyophilized amniotic membrane graft for primary pterygium surgery: preliminary results. Cell Tissue Bank. 2022;23(2):401–6.

61. Jha A, Simba A. Conjunctival autograft versus combined amniotic membrane and mini-simple limbal epithelial transplant for primary pterygium excision. J Ophthalmic Vis Res. 2022;17(1):4–11.

62. Hirst L. Long-term results of P.E.R.F.E.C.T. for pterygium. Cornea. 2021;40(9):1141–1146.