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Amniotic Membrane Grafts to Reduce Pterygium Recurrence

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Purpose: To demonstrate the long-term outcome of pterygium surgery with adjunctive amniotic membrane transplantation (AMT) and intraoperative mitomycin C (MMC) in a large case series.

Methods: Medical records were retrieved for this noncomparative retrospective study of all patients who had pterygium excision with adjunctive AMT and intraoperative MMC, from October 2010 to June 2016 with at least 6 months of follow-up.

Results: There were a total of 556 eyes of 535 patients (291 males and 244 females) with average age of 51.9 ± 13 years who had pterygium excision (527 primary and 29 recurrent). For an average follow-up period of 17.3 ± 0.8 months (range 6–74 months), corneal recurrence occurred in 20 eyes (3.6%) and conjunctival recurrence in 12 (2.2%) in a total of 32 eyes (5.8%). Eleven eyes (2%) underwent reoperation. Other complications included granuloma (0.5%), diplopia (1.1%), and steroid-induced ocular hypertension (4.3%).

Conclusions: Adjunctive use of AMT and short exposure of MMC can reduce recurrence after pterygium surgery. The procedure is less tedious and less time consuming, resulting in early recovery while saving the conjunctiva for future surgeries.

Key Words: amniotic membrane, fibrin glue, mitomycin C, pterygium, recurrence

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Pterygium is a wing-shaped superficial overgrowth on the ocular surface, which is characterized by inflammation, fibrovascular conjunctival proliferation, and invasion of the corneal surface.[1–3] It is presumably due to ultraviolet-induced damage to the limbal stem cells[3,4] and hence considered as focal limbal stem cell deficiency.[5] Surgical excision is indicated for either optical or cosmetic reasons. In the former, visual disturbances are caused by irregular astigmatism, blocking of the visual axis, or restricted ocular motility.

The most daunting challenge of pterygium surgery is the high incidence of recurrence, as high as 88% with simple excision involving an uncovered bare sclera. Surgical techniques in more recent years, in which scleral defects are covered with conjunctival autograft or cryopreserved amniotic membrane (CAM) with or without mitomycin C (MMC), have resulted in much better outcomes, with less than 10% recurrence rates and minimal complications postoperatively.[6–8] However, some debate still continues regarding which graft offers the better outcome.[9–11]

The purpose of this retrospective analysis is to provide compelling long-term evidence that CAM grafts, combined with short exposure to MMC, can reduce recurrence and complications after pterygium surgery. To the best of our knowledge, this is the largest sample size reported with a long-term follow-up.

METHODS

Study Design and Participants

The study was approved and supported by a grant from the Kaiser Permanente Southern California Regional Research Committee and was conducted in accordance with the Health Insurance Portability and Accountability Act (HIPAA) and Declaration of Helsinki. In this noncomparative retrospective study, the medical records of all patients who had pterygium excision with adjunctive amniotic membrane transplantation (AMT) and MMC by the same surgeon (R.R.) from October 2010 to June 2016, at the Southern California Kaiser Permanente Medical Center, Panorama City, were reviewed. A total of 535 patients were identified during the study interval, and all of them had completed at least 6 months of follow-up. Tables 1–3 summarize the data collected regarding demographic characteristics, type of pterygium (primary or recurrent), surgical technique, postoperative complications, pterygium recurrence, and reoperation.

Surgical Technique

Ocular surface inflammation, dryness, and exposure were addressed before surgery (Fig. 1). Tetracaine hydrochloride (Tetravisc 0.5%, Ocusoft) was applied as preoperative anesthesia. The eye was draped, lid speculum placed, and superior and inferior limbal 6-0 Vicryl (Ethicon, Somerville, NJ) traction sutures were inserted to retract the globe

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TABLE 1. Study Population Baseline Characteristics and Results by Sex

	Female	Male	Total	
	n = 254 (45.7%)	n = 302 (54.3%)	N = 556	*P*
Overview of pterygium surgeries, n (%)				
Recurrent pterygium	17 (6.7)	15 (5)	32 (5.8)	0.384
Corneal recurrence	9 (3.5)	11 (3.6)	20 (3.6)	0.3368
Conjunctival recurrence	8 (3.1)	4 (1.3)	12 (2.2)	0.3368
Same eye reoperation*	4 (1.6)	7 (2.3)	11 (2)	0.5308
Bilateral eyes†	20 (7.9)	22 (7.3)	42 (7.6)	0.7934
Double pterygium with a double graft	4 (1.6)	11 (3.6)	15 (2.7)	0.1339
Postoperative complications, n (%)				
Conjunctival granuloma	1 (0.4)	2 (0.7)	3 (0.5)	0.6668
Diplopia	3 (1.2)	3 (1)	6 (1.1)	0.831
Ocular hypertension	8 (3.1)	16 (5.3)	24 (4.3)	0.2144
Perioperative treatment,‡ n (%)				
Pred Forte	155 (61)	189 (62.6)	344 (61.9)	0.7061
Fluorometholone	2 (0.8)	3 (1)	5 (0.9)	0.7977
Demographic characteristics				
Age at surgery, yrs, mean (SD)	51.5 (13.22)	52.3 (12.75)	51.9 (12.96)	0.4737
Race/ethnicity, n (%)				0.3634
White, non-Hispanic	13 (5.1)	18 (6)	31 (5.6)	
Black, non-Hispanic	1 (0.4)	3 (1)	4 (0.7)	
Hispanic	218 (85.8)	264 (87.4)	482 (86.7)	
Asian, non-Hispanic	20 (7.9)	17 (5.6)	37 (6.7)	
Other, non-Hispanic	2 (0.8)	0 (0)	2 (0.4)	

*The number of duplicate eye reoperations is included in the number of recurrences.
†Both left and right eyes.
‡Within 1 week of surgery.

TABLE 2. Study Population Baseline Characteristics and Results by Age (<50 Years vs. ≥50 Years)

	<50 yrs	≥50 yrs	Total	
	n = 257 (46.2%)	n = 299 (53.8%)	N = 556	*P*
Overview of pterygium surgeries, n (%)				
Recurrent pterygium	22 (8.6)	10 (3.3)	32 (5.8)	0.0085
Corneal recurrence	14 (5.4)	6 (2.0)	20 (3.6)	0.0307
Conjunctival recurrence	8 (3.1)	4 (1.3)	12 (2.2)	0.0307
Same eye reoperation*	9 (3.5)	2 (0.7)	11 (2.0)	0.0168
Bilateral eyes†	22 (8.6)	20 (6.7)	42 (7.6)	0.4051
Double pterygium with a double graft	7 (2.7)	8 (2.7)	15 (2.7)	0.9721
Postoperative complications, n (%)				
Conjunctival granuloma	3 (1.2)	0 (0.0)	3 (0.5)	0.061
Diplopia	2 (0.8)	4 (1.3)	6 (1.1)	0.5243
Ocular hypertension	4 (1.6)	20 (6.7)	24 (4.3)	0.003
Perioperative treatment,‡ n (%)				
Pred Forte	174 (67.7)	170 (56.9)	344 (61.9)	0.0086
Fluorometholone	2 (0.8)	3 (1.0)	5 (0.9)	0.7792
Demographic characteristics				
Age at surgery, yrs, mean (SD)	40.7 (6.80)	61.6 (8.40)	51.9 (12.96)	<0.0001
Patient sex, n (%)				0.2602
Female	124 (48.2)	130 (43.5)	254 (45.7)	
Male	133 (51.8)	169 (56.5)	302 (54.3)	
Race/ethnicity, n (%)				0.0002
White, non-Hispanic	11 (4.3)	20 (6.7)	31 (5.6)	
Black, non-Hispanic	1 (0.4)	3 (1)	4 (0.7)	
Hispanic	238 (92.6)	244 (81.6)	482 (86.7)	
Asian, non-Hispanic	5 (1.9)	32 (10.7)	37 (6.7)	
Other, non-Hispanic	2 (0.8)	0 (0)	2 (0.4)	

*The number of duplicate eye reoperations is included in the number of recurrences.
†Both left and right eyes.
‡Within 1 week of surgery.

temporally. This offered better exposure and juxtaposition, to help close the conjunctival–Tenon gap. Subconjunctival 2% lidocaine with 1:100,000 epinephrine (lidocaine, Accutome) was then injected under the pterygium. The pterygium was excised with sharp Westcott scissors and avulsed off the cornea with Weck-Cell sponge (Beaver-Visitec, Waltham, MA). A motorized burr was used to further dissect pterygium off the Bowman corneal layer. Tenon fibrovascular tissue was excised. The bipolar cautery was then used for moderate hemostasis and adherence of the conjunctival–Tenon gap, taking care not to overcauterize around the rectus muscle. Segmented Weck-Cell sponges soaked in 0.02% MMC were placed subconjunctivally for 30 seconds, removed, and then the surgical field was rinsed copiously with balanced salt solution several times to avoid any residue. Weck-Cell sponges were used to dry the bare sclera. The CAM (AmnioGraft; Bio-Tissue, Miami, FL) was cut in an elliptical shape at least 2 mm over the defect size, placed with the sticky stromal side down, and pushed toward the conjunctival–Tenon gap before gluing. A small amount of fibrin glue (Tisseel; Baxter, Glendale, CA) was injected consecutively under the graft, then "squeegied" across the graft with a muscle hook toward the cornea, taking care to maintain the graft position. The edge toward the cornea was trimmed with Vannas scissors so as not to cover the pupil margin. Then, the gap edge and the graft corneal edge were reglued with a tiny layer of additional glue. Subconjunctival cefazolin and dexamethasone were injected, and finally, the eye was patched.

During the course of the study, 2 modifications in the surgical technique were made. The first modification was the reduction of the time of MMC exposure from 60 to 90 seconds for the first 179 cases to 20 to 30 seconds for the remaining cases because 3 (0.5%) eyes of the former developed scleral thinning. No scleral thinning was encountered thereafter. The second modification was to discontinue

TABLE 3. Study Population Baseline Characteristics and Results by Age (<40 Years vs. ≥40 Years)

	<40 yrs	≥40 yrs	Total	
	n = 94 (16.9%)	n = 462 (83.1%)	N = 556	*P*
Overview of pterygium surgeries, n (%)				
Recurrent pterygium	5 (5.3)	27 (5.8)	32 (5.8)	0.8421
Corneal recurrence	5 (5.3)	15 (3.2)	20 (3.6)	0.1849
Conjunctival recurrence	0 (0)	12 (2.6)	12 (2.2)	0.1849
Same eye reoperation*	4 (4.3)	7 (1.5)	11 (2)	0.082
Bilateral eyes†	14 (14.9)	28 (6.1)	42 (7.6)	0.0031
Double pterygium with a double graft	2 (2.1)	13 (2.8)	15 (2.7)	0.7082
Postoperative complications, n (%)				
Conjunctival granuloma	2 (2.1)	1 (0.2)	3 (0.5)	0.0211
Diplopia	0 (0)	6 (1.3)	6 (1.1)	0.2666
Ocular hypertension	2 (2.1)	22 (4.8)	24 (4.3)	0.252
Perioperative treatment,‡ n (%)				
Pred Forte	62 (66)	282 (61)	344 (61.9)	0.3708
Fluorometholone	0 (0)	5 (1.1)	5 (0.9)	0.311
Demographic characteristics				
Age at surgery, yrs, mean (SD)	33.3 (5.03)	55.7 (10.56)	51.9 (12.96)	<0.0001
Patient sex, n (%)				0.6402
Female	45 (47.9)	209 (45.2)	254 (45.7)	
Male	49 (52.1)	253 (54.8)	302 (54.3)	
Race/ethnicity, n (%)				0.1023
White, non-Hispanic	4 (4.3)	27 (5.8)	31 (5.6)	
Black, non-Hispanic	0 (0)	4 (0.9)	4 (0.7)	
Hispanic	89 (94.7)	393 (85.1)	482 (86.7)	
Asian, non-Hispanic	1 (1.1)	36 (7.8)	37 (6.7)	
Other, non-Hispanic	0 (0)	2 (0.4)	2 (0.4)	

*The number of duplicate eye reoperations is included in the number of recurrences.
†Both left and right eyes.
‡Within 1 week of surgery.

Vicryl closure of the conjunctival–Tenon gap because the first 14 eyes developed exuberant postoperative conjunctival injection, which was reversed in all 14 eyes, with the use of postoperative prednisolone acetate drops. The remaining 542 eyes (97.5%) underwent exclusively nonsutured gap closure with the cautery and fibrin glue. The AM was pushed up to help secure the gap and mechanically block regrowth.

Postoperative Care

Postoperative treatment included topical prednisolone 6 times daily for 2 months in tapering dosage, and a quinolone antibiotic was used 4 times per day for 1 week. Patients were examined 1 day, 1 week, 1 month, 3 months, 6 months postoperatively, and as needed thereafter. Complications such as pyogenic granuloma, inclusion cysts, epithelial defects, and dellen formation were recorded. Recurrence was defined as conjunctival if fibrovascular regrowth was limited to the conjunctiva and as corneal if tissue growth extended to the cornea across the limbus.[12]

RESULTS

There were a total of 535 patients [291 males and 244 females; age (mean ± SD) 51.9 ± 13 years] who underwent pterygium excision with combined MMC and AMT. From the 535 patients, there were a total of 556 eyes, which included 527 (94.8%) eyes with primary pterygium and 29 (5.2%) eyes with recurrent pterygium. Surgery was uneventful in all cases. No dislodgement of AM followed application of fibrin glue without sutures.

For the average maximum follow-up period of 17.3 ± 0.8 months (range 6–74), recurrence occurred in 32 eyes (5.8%), of which 12 eyes (2.2%) had conjunctival recurrence and 20 eyes (3.6%) had corneal recurrence. Eleven eyes that experienced corneal recurrence (2%) underwent reoperation; however, the eyes with conjunctival recurrence did not require surgery. There was no statistically significant difference in recurrence rates by sex (Table 1); however, the recurrent cases were predominantly in patients younger than 50 years (Table 2). The likelihood of pterygia occurring in both eyes was more frequent in younger age groups. Fourteen of the 94 pterygium patients younger than 40 years had pterygia in both eyes (Table 3), which was statistically significant ($P = 0.003$). Because the majority of the study population was of Hispanic origin, no significant conclusions could be derived regarding the ethnic background.

Other postoperative complications include conjunctival granuloma (0.5%), diplopia (1.1%), and ocular hypertension (4.3%). Ocular hypertension was primarily attributable to postoperative steroid use and was successfully managed with a combination of antihypertensive drops and a switch from prednisolone acetate to fluorometholone steroid drops. Ocular hypertension was more likely to occur in patients older than 50 years. Three (0.5%) eyes developed scleral melting when MMC was used for 60 to 90 seconds. However, no scleral thinning was encountered after reducing the exposure time to 20 to 30 seconds. Suture-related conjunctival vascularization was noted in 14 eyes (2.5%), which was resolved with postoperative prednisolone acetate drops. This vascularization was not observed in the remaining cases after elimination of the sutures. No graft dehiscence after gluing was observed in any of the 556 eyes over the 6 years of the study.

DISCUSSION

Ocular surface inflammation plays an important role in pterygium growth and recurrence. Clinical recognition of causes leading to inflammation and appropriate therapies should be regarded as an adjunctive measure in pterygium management. In this study, we achieved a considerably low

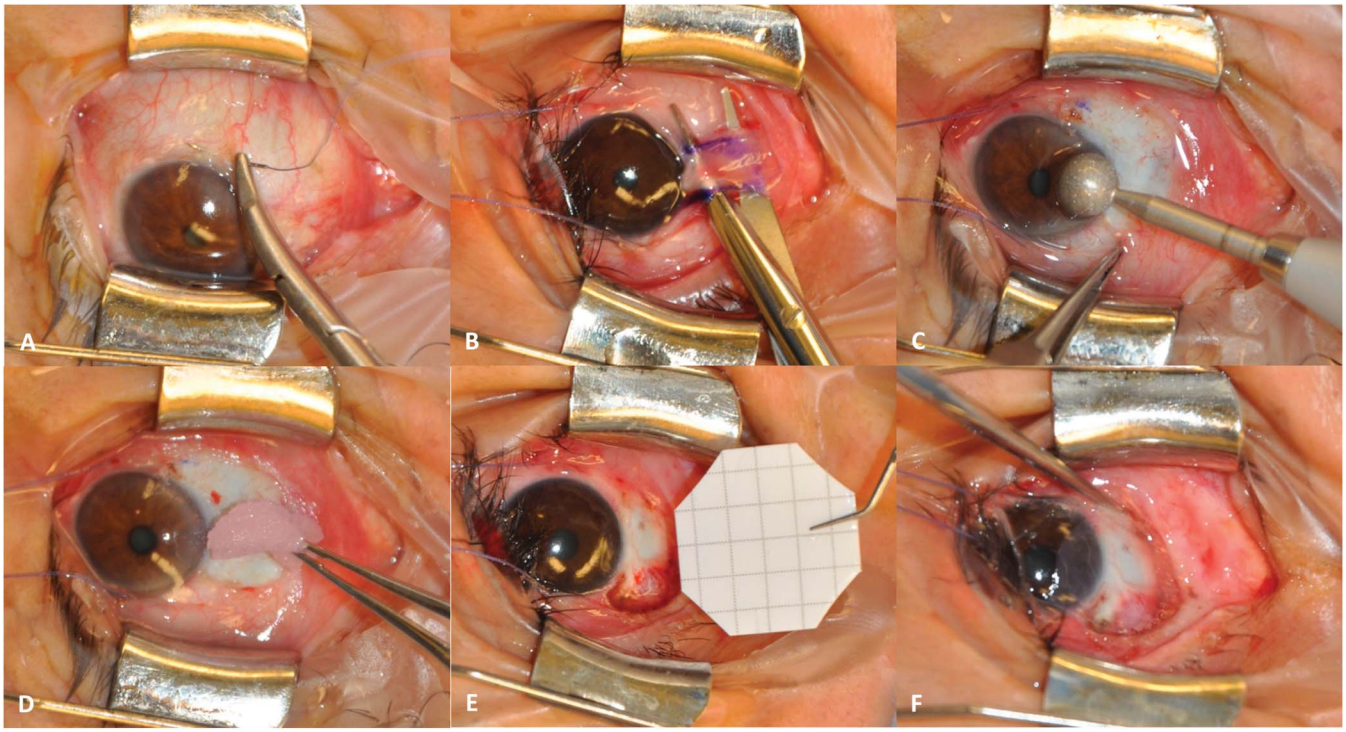

FIGURE 1. Key surgical steps. A, Traction suture. B, Pterygium excision. C, Polishing the cornea with a diamond burr. D, MMC application to the truncated edge of pterygium. E, AmnioGraft cut to size. F, After securing the AmnioGraft and sealing the gap, the edge is pushed up to secure the gap to prevent recurrence.

recurrence rate (3.6%) by reducing surgical manipulation during pterygium excision, reducing MMC exposure time, using a CAM graft, and using fibrin glue in lieu of sutures. With further close follow-up, we were able to eliminate the risk of postoperative inflammation.

This study provides several reasons to take a fresh look at pterygium surgical options. The most important reason is the large sample size. In addition, the amniotic membrane (AM) graft technique used in this study is straightforward and consistent throughout the entire study duration. It is also potentially an easier and shorter procedure than the alternatives because the technique obviates the need for preparing a conjunctival autograft of sufficient quality and thinness for optimal grafting after removal of the Tenon layer. AM stromal matrix has been found to be effective in suppressing the expression of TGF-β signaling and myofibroblast transformation of normal ocular surface fibroblasts[13] and pterygium body fibroblasts.[14] This finding supports the idea that CAM can be used to substitute conjunctival autografts in pterygium surgery.[15–19] In fact, Ma et al[18] retrospectively evaluated the efficacy and safety of AMT compared with conjunctival autograft and topical 0.02% MMC, after excision of primary pterygium [AM (80), conjunctival autograft (56), and MMC (54)]. There was no significant difference in recurrence rates (AMT = 3.8%, conjunctival autograft = 5.4%, and MMC = 3.7%) among these 3 groups. Although the recurrence rates are comparable in the literature, the AMT procedure is less tedious and less time consuming, while also saving the conjunctiva, especially if it is needed for future glaucoma surgery.

The recurrence rate has also been shown to be correlated with the preoperative pterygium morphology, surgical technique, and age, of which the latter was also confirmed in this study.[6,9] Recently, ocular Demodex infestation was also identified as an overlooked risk factor for pterygium recurrence, presumably by perpetuating chronic inflammation mediated by Th17 lymphocytes. Therefore, control of inflammation incited by ocular demodicosis before and after surgery is also important for reducing recurrence and should be considered as a strategy in managing pterygium growth and recurrence.[20]

The surgical technique is probably the single most important factor influencing recurrence. In a prospective study, Prabhasawat et al[16] first reported a recurrence rate of 10.9% in primary pterygium (n = 54) after excision and AMT. Solomon et al[17] subsequently modified the technique of AMT and achieved a low recurrence rate of 3% in 33 cases of primary pterygium. Another surgical parameter is the use of MMC. Amano et al[21] showed a statistically significant reduction in the recurrence rate when using intraoperative 0.04% MMC (8.7%) instead of β-irradiation (23%). Furthermore, reducing the MMC concentration and exposure time can effectively reduce recurrence while minimizing side effects. In this study, an exposure time of 20 to 30 seconds was effective and without the previously noticed complications of scleral thinning.[18,22] To further reduce such a complication, MMC was applied over the truncated fibrovascular tissue, in the gap between the conjunctival edge and the underlying Tenon layer. This approach reduces MMC dosage and avoids overspill to the

entire ocular surface. Another key step is to seal the gap between the conjunctiva and Tenon using fibrin glue and advance the AM to create a stronger barrier against further recurrence.[23]

Finally, long-term postoperative steroid use, which is essential for postoperative graft maintenance, will benefit from future enhancement of antiinflammatory effects and further reduction of side effects. Secondary steroid-induced ocular hypertension can hopefully be eradicated in the future without compromising steroid potency.

In conclusion, this study clearly shows that CAM imparts remarkable resilience against further regrowth. Coupled with short exposure to MMC, CAM should be considered an optimal choice for pterygium surgery, and the surgeon can confidently quote low recurrence statistics to his or her patients. Once mastered, the procedural time of this surgical option is potentially shorter, and it is technically easier to perform than conjunctival autografting.

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