Postoperative Conjunctival Inflammation After Pterygium Surgery With Amniotic Membrane Transplantation Versus Conjunctival Autograft

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• PURPOSE: To compare the postoperative conjunctival inflammation around the surgical site after pterygium surgery using either amniotic membrane transplantation (AMT) or free conjunctival autograft.

• DESIGN: Prospective, randomized, interventional study.

• METHODS: Forty-two eyes of 42 patients with primary pterygium underwent surgical excision followed by removal of subconjunctival fibrovascular tissue and intraoperative application of 0.02% mitomycin C. Then, the patients were randomized to receive either AMT (21 eyes) or free conjunctival autograft (21 eyes), with sutures used in both groups. Main outcome measures included presence of host conjunctival inflammation around the surgical site at 1 month after surgery and also recurrence of pterygium.

• RESULTS: Twelve-month follow-up was completed in 39 eyes of 39 patients (19 in the AMT group and 20 in the conjunctival autograft group). At 1 month after surgery, different grades of host conjunctival inflammation were present in 16 eyes (84.2%) in the AMT group and in 3 eyes (15%) in the conjunctival autograft group ($P = .02$). Subconjunctival injection of triamcinolone was performed in eyes with moderate or severe inflammation, which included 12 eyes (63.1%) in the AMT group and 2 eyes (10%) in the conjunctival autograft group ($P < .001$). Conjunctival recurrence of pterygium was seen in 2 eyes (10.5%) in the AMT group and in 2 eyes (10%) in the conjunctival autograft group ($P = .92$). After surgery, pyogenic granuloma developed in 3 eyes (15.8%) in the AMT group and in 1 eye (5%) in the conjunctival autograft group ($P = .31$).

• CONCLUSIONS: After pterygium surgery, conjunctival inflammation was significantly more common with AMT than with conjunctival autograft. However, with control of such inflammation and intraoperative application of mitomycin C, similar final outcomes were achieved with both techniques. (Am J Ophthalmol 2011;152: 733–738. © 2011 by Elsevier Inc. All rights reserved.)

Accepted for publication Apr 6, 2011.

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PTERYGIUM IS CHARACTERIZED BY ENCROACHMENT of a fleshy fibrovascular tissue from bulbar conjunctiva onto the cornea. For a long time, pterygium has been considered a chronic degenerative disease[1]; however, there is increasing evidence implicating the proliferative and inflammatory nature of the lesion.[2] For example, proliferating cells have been shown in pterygium head,[3] and epithelial hyperplasia and exuberant fibrovascular tissue in the stroma have been demonstrated histopathologically.[4,5] There are also increased levels of inflammatory markers in pterygium.[6–8] In addition, it has been shown clinically that mitomycin C (MMC), which inhibits cellular proliferation, reduces pterygium recurrence after excision,[9–10] and also steroids are beneficial in halting progression of impending recurrent pterygium.[11,12]

Many surgical techniques have been developed for pterygium surgery. These include bare sclera, rotational conjunctival flap, free conjunctival autograft, and amniotic membrane transplantation (AMT). Furthermore, to reduce the recurrence rate after pterygium surgery, various adjunctive methods have been used, such as β irradiation and several chemical agents, including MMC, 5-fluorouracil, and thiotepa.[13] Various success rates have been reported for different surgical techniques[10,13,14]; however, it remains largely unclear why one technique has better results than another procedure.

One of the factors that may play a role in outcome of pterygium surgery is the postoperative conjunctival inflammation. It has been shown that persistent conjunctival inflammation around the surgical site is present in approximately 31% to 40% of cases after pterygium surgery with AMT,[15,16] and also it has been demonstrated that treatment of this inflammation improves the final postoperative outcome.[15] However, it is unknown whether such postoperative conjunctival inflammation is present after techniques of pterygium surgery other than AMT and whether it plays a role in their final outcome. To address the above-mentioned questions, this study was designed to compare the postoperative conjunctival inflammation around the surgical site of pterygium surgery in eyes with either AMT or free conjunctival autograft and to evaluate the possible role of this inflammation in the final outcome of pterygium surgery with these techniques.

0002-9394/$36.00
doi:10.1016/j.ajo.2011.04.013

TABLE. Clinical Findings of Patients with Primary Pterygium and Their Postoperative Outcome after Surgery with Either Amniotic Membrane Transplantation or Free Conjunctival Autograft

	Amniotic Membrane Group	Conjunctival Autograft Group	*P* Value
No. eyes	19	20	
Age (y)	42.8 ± 13.2	47.7 ± 15.7	.33
Gender (male/female)	10/9	12/8	.76
Pterygium morphologic features			.89
T1	4	5	
T2	8	9	
T3	7	6	
Postoperative complications			
Conjunctival inflammation grade			
0	3 (15.8%)	17 (85%)	.02
I	4 (21.1%)	1 (5%)	
II	7 (36.8%)	2 (10%)	
III	5 (26.3%)	0	
Pterygium recurrence			.92
Conjunctival recurrence	2 (10.5%)	2 (10%)	
Corneal recurrence	0	0	
Pyogenic granuloma	3 (15.8%)	1 (5%)	.31

METHODS

IN THIS PROSPECTIVE RANDOMIZED STUDY, 42 EYES OF 42 patients with primary nasal pterygium underwent surgical excision. The patients were randomized to receive either amniotic membrane transplantation (21 eyes; AMT group) or free conjunctival autograft (21 eyes; conjunctival autograft group). Furthermore, there was an additional randomization of pterygia in each group based on the morphologic features of pterygium, as described below.

Before surgery and at all visits after surgery, each patient underwent a complete ocular examination, including slit-lamp photography, measurement of best-corrected visual acuity, and assessment of intraocular pressure. Before surgery, the morphologic features of pterygium were graded according to what was described by Tan and associates.[17] In this grading, pterygia were graded as grade T1 (atrophic pterygium), in which episcleral vessels were unobscured by the body of pterygium, grade T3 (fleshy pterygium), in which episcleral vessels were totally obscured, and grade T2 (those between grades T1 and T3), with partially obscured episcleral vessels.

Before surgery, informed consent was obtained from each patient. All surgeries were performed by 1 surgeon (R.N.) under retrobulbar anesthesia. For surgery, the head and body of pterygium first were removed by a similar technique in all patients, with resection of the body at 2 mm in front of plica semilunaris. This was followed by removal of subconjunctival fibrovascular tissue for 2 mm beyond the conjunctival edges and polishing of the cornea with a diamond burr. After minimal cauterization of bleeding vessels, 0.02% MMC was applied both on the bare sclera and under the conjunctival edges by using pieces of Weck-Cel surgical sponge soaked in 0.02% MMC solution. Duration of MMC application depended on the preoperative grading of pterygium morphologic features, with a 1-minute application for grade T1, 3 minutes for grade T2, and 5 minutes for grade T3. After the eye surface was washed with 100 mL balanced salt solution, patients randomly received either an amniotic membrane graft (in the AMT group) or a free conjunctival graft (in the conjunctival autograft group) to cover the bare sclera. Cryopreserved amniotic membrane (Homapeyvand, Inc, Tehran, Iran) was used as a single layer with the stromal side down, attached with 10-0 nylon interrupted sutures. Free conjunctival autograft was harvested from the superotemporal bulbar conjunctiva with careful attention to avoid inclusion of any Tenon tissue. The graft was attached using interrupted 10-0 nylon sutures while keeping the proper limbal–forniceal orientation.

After surgery, all patients received an identical regimen of topical antibiotics for 2 weeks and tapering topical steroids for 3 months. The latter included 0.1% betamethasone 4 times daily for 1 month followed by 0.1% fluorometholone 4 times daily for 2 weeks, thrice daily for 2 weeks, twice daily for 2 weeks, and once daily for 2 weeks. Postoperative follow-up examinations were performed at 1 day, 1 week, 2 weeks, 1 month, and 3, 6, 9, and 12 months after surgery. Sutures were removed after 1 week in the conjunctival autograft group and after 2 weeks in the AMT group.

Presence of postoperative conjunctival inflammation around the surgical site was assessed at 1 month after surgery and graded as 0 (none), I (mild), II (moderate),

and III (severe), as described previously.[15] Eyes with grades II and III inflammation received a subconjunctival injection of 8 mg triamcinolone acetonide around the surgical site. Postoperative recurrence of pterygium was reported using a grading system described previously.[18] This grading included grade 1 as no recurrence, grade 2 as the presence of fine episcleral vessels without fibrous tissue in the surgical area, grade 3 as the presence of fibrovascular tissue in the surgical area but without invasion onto the cornea (conjunctival recurrence), and grade 4 as true recurrence in which the fibrovascular tissue invaded onto the cornea (corneal recurrence). Eyes with conjunctival recurrence of pterygium (grade 3) received either 1 single subconjunctival injection of 8 mg triamcinolone acetonide or 2 weekly intralesional injections of 5-fluorouracil.

Statistical analysis was performed using SPSS software version 15 (SPSS, Inc, Chicago, Illinois, USA). The chi-square test and Student *t* test were used to compare qualitative and continuous quantitative variables, respectively, between the AMT and conjunctival autograft groups. P values of .05 or less were considered to be statistically significant.

RESULTS

OF 42 EYES INCLUDED IN THIS STUDY, 12-MONTH FOLLOW-UP was completed in 39 eyes of 39 patients (22 men and 17 women) with a mean age of 45.6 ± 13.9 years (range, 19 to 83 years). These included 19 eyes in AMT group and 20 eyes in conjunctival autograft group. There were no statistically significant differences in age, gender, and grade of pterygium morphologic features before the surgery between the 2 groups (Table). Surgery was uneventful in all cases; secured attachment of both amniotic membrane and conjunctival autograft was obtained in all eyes after surgery.

At 1 month after surgery, examination revealed conjunctival inflammation around the surgical site in 16 eyes (84.2%) and 3 eyes (15%) in the AMT group and the conjunctival autograft group, respectively ($P = .02$; Table). In the AMT group, grading of this postoperative inflammation included grade I (mild) in 4 eyes (21.1%), grade II (moderate) in 7 eyes (36.8%), and grade III (severe) in 5 eyes (26.3%). However, in the conjunctival autograft group, the inflammation was grade I (mild) in 1 eye (5%) and grade II (moderate) in 2 eyes (10%). Subconjunctival injection of triamcinolone acetonide was performed in 12 eyes (63.1%) and 2 eyes (10%) in the AMT and conjunctival autograft groups, respectively ($P < .001$). This injection resulted in resolution of the inflammation in all of these eyes.

Grade 3 pterygium recurrence was seen in 2 eyes (10.5%) in the AMT group (at 3 and 6 months after surgery) and in 2 eyes (10%) in the conjunctival autograft group (at 3 and 12 months after surgery), with no statistically significance difference between the 2 groups ($P = .92$; Table). The 2 eyes with recurrence in the AMT group had either moderate (1 eye) or severe (1 eye) conjunctival inflammation at 1 month after surgery. The eyes with recurrence in the conjunctival autograft group had either no inflammation (1 eye) or moderate inflammation at the 1-month visit. The eyes with this conjunctival recurrence received either 1 single subconjunctival injection of 8 mg triamcinolone acetonide (2 eyes, 1 in each group) or 2 weekly intralesional injections of 5-fluorouracil (2 eyes, 1 in each group); in none did true corneal recurrence develop during the follow-up.

Pyogenic granuloma developed at the surgical site in 3 eyes (15.8%) in the AMT group and in 1 eye (5%) in the conjunctival autograft group ($P = .31$; Table). All pyogenic granulomata developed in the caruncular border of the graft. In the conjunctival autograft group, the superotemporal area where the conjunctival grafts had been harvested healed without any complication in all eyes. No complication related to amniotic membrane graft or conjunctival graft was seen in any eye during the postoperative follow-up. After injection of triamcinolone acetonide, increased intraocular pressure developed in 2 eyes that was controlled medically. No other steroid-induced complication was noted in any eye.

DISCUSSION

THIS PROSPECTIVE, RANDOMIZED STUDY SHOWED THAT after pterygium surgery, conjunctival inflammation was significantly more common with AMT than with conjunctival autograft. However, with control of this inflammation and intraoperative application of MMC, similar final outcomes were achieved with both techniques. Future studies are required to evaluate the role of postoperative conjunctival inflammation in surgical outcome with other techniques of pterygium surgery.

At 1 month after pterygium surgery, when the normal postoperative inflammatory responses were expected to be subsided, 84.2% of eyes in the AMT group and 15% of eyes in the conjunctival autograft group showed host conjunctival inflammation around the surgical site. The inflammation was significantly more common with AMT than with conjunctival autograft ($P = .02$). Such host conjunctival inflammation previously was reported after AMT for pterygium surgery[15,16] and also after AMT for conjunctivochalasis excision and fornix reconstruction.[19,20] Although suture-related inflammation has been noted after pterygium surgery with conjunctival autograft,[21,22] development of such persistent inflammation, which easily may be overlooked, after other techniques of pterygium surgery has been poorly described.

Solomon and associates reported an incidence of 31.5% of persistent host conjunctival inflammation after extensive pterygium surgery, AMT using sutures and intraoper-

ative subconjunctival injection of triamcinolone.[16] Our previous study of 27 eyes which had pterygium excision, MMC application, and AMT using either suture or fibrin glue with intraoperative triamcinolone injection in 11 eyes showed an incidence of 40.7% for such inflammation.[15] With MMC application but without intraoperative triamcinolone injection in the present study, the inflammation was present in 84.2% of eyes after AMT, which is remarkably higher than its incidence in previous studies. It seems that lack of intraoperative injection of triamcinolone might have resulted in the higher incidence of such inflammation in this study compared with previous ones. However, controlled studies are required to evaluate the role of intraoperative steroids in prevention of such inflammation.

Pathogenesis of this persistent postoperative conjunctival inflammation and the possible reasons for its higher incidence after AMT, which is known to have anti-inflammatory effects,[23] remain unclear. In addition, other factors that may play a role in this postoperative inflammation mostly are unknown. Previously, it was noted that after pterygium surgery with AMT, there is a higher incidence of such inflammation with suture use compared with fibrin glue (61.5% vs 21.4%, respectively).[15] In the present study, sutures were removed after 1 week in the conjunctival autograft group and after 2 weeks in the AMT group. Although the presence of such inflammation was evaluated at 1 month after surgery, longer duration of the suture stay in the AMT group might have caused inflammation that persisted even after their removal. However, presence of such inflammation even with fibrin glue[15] implicates the possible role of other factors. Mitomycin C, which is known to have antiproliferative action,[24,25] was used in all eyes in this study. Although it has been shown that MMC decreases conjunctival inflammation in eyes with allergic conjunctivitis,[26] it is unknown whether there is less postoperative conjunctival inflammation after pterygium surgery in eyes with MMC application compared with those without. In addition, future studies with large sample sizes are required to evaluate the role of other factors such as age, gender, pterygium morphologic features, and different surgical techniques in the incidence of such postoperative inflammation.

In our series of primary pterygium surgery with MMC application, conjunctival recurrence of pterygium developed with similar rates of approximately 10% in both groups during 12 months of postoperative follow-up. Several previous studies have compared the results of pterygium surgery using either conjunctival autograft or AMT. These have found that for pterygium surgery, AMT has recurrence rates equal to [27,28] or higher than[18,29–31] those of conjunctival autograft. However, none of these have used adjunctive intraoperative MMC, which has been proven to reduce the recurrence rate.[9,10] Therefore, it may seem that similar recurrence rates in the AMT and conjunctival autograft groups in our study in part may be related to this adjunctive MMC application in both groups. However, another factor that might have played a role in causing similar recurrence rates in both groups is the control of postoperative conjunctival inflammation.

In our previous retrospective study, it was shown that after pterygium surgery with MMC application and AMT, eyes with host conjunctival inflammation at 1 month after surgery had no recurrence if they received a subconjunctival triamcinolone injection; however, the eyes left untreated had a high chance for recurrence.[15] Even with conjunctival autograft, it has been demonstrated that there is a higher recurrence rate in patients who received inadequate postoperative topical steroids.[32] Therefore, it may be reasonable to think that higher recurrence rates of pterygium after excision with AMT compared with conjunctival autograft reported before[18,29–31] may be due to higher incidence of postoperative conjunctival inflammation after AMT, which had been overlooked and left untreated. Treatment of such inflammation, as was performed in our study, may result in similar recurrence rates of pterygium regardless of using either AMT or conjunctival autograft. Future studies are required to unravel other possible mechanisms playing a role in different outcomes of various surgical techniques for pterygium surgery.

Although subconjunctival injection of triamcinolone in our study resulted in resolution of the inflammation, the best postoperative method to treat inflammation and to prevent the recurrence remains unknown. In our study, 3 of 4 eyes with conjunctival recurrence of pterygium had conjunctival inflammation at 1 month after surgery, even though it was treated with triamcinolone injection. Although other factors may be involved, subclinical inflammation that persists even after triamcinolone injection may have an effect on causing recurrence. Furthermore, as previously has been demonstrated,[11,12] subconjunctival injection of 5-fluorouracil or triamcinolone in this study was able to halt progression of the conjunctival recurrence to the corneal recurrence of pterygium. Nevertheless, the roles of other anti-inflammatory agents and also anti–vascular endothelial growth factor agents[33] for treatment of such persistent postoperative inflammation require further studies.

Parallel to higher incidence of postoperative conjunctival inflammation, there was higher incidence of pyogenic granuloma after AMT compared with conjunctival autograft (15.8% vs 5%, respectively), although the difference was not statistically significant. This lesion, which is inflammatory, is caused by exuberant healing with fibrovascular proliferation. Although the higher incidence in the AMT group in this study may be the result of longer suture stay, a previous study did not reveal any correlation between its incidence and wound closure with or without sutures.[34]

The main limitation of our study was the small sample size. However, the postoperative follow-up was 1 year, which was long enough to evaluate pterygium recurrence.[16] Moreover,

randomization was performed not only for AMT or conjunctival autograft groups, but also for pterygium morphologic features, which have been shown to affect the surgical outcome.[17] Even with the small sample size, our data strongly suggest that postoperative conjunctival inflammation after pterygium surgery is significantly more common with AMT compared with conjunctival autograft, and treatment of such inflammation and intraoperative application of MMC may result in similar outcomes in these 2 groups regarding the pterygium recurrence.

THE AUTHORS INDICATE NO FINANCIAL SUPPORT OR FINANCIAL CONFLICT OF INTEREST. INVOLVED IN CONCEPTION AND design of study (A.K., R.N.); Data collection (H.G., R.N.); Analysis and interpretation of data (A.K., M.N., H.G.); Provision of materials, patients, or resources (M.J.B., H.H.); Statistical expertise (A.K., M.N.); Literature search (A.K., R.N., M.N.); Administrative, technical, or logistic support (MJB,HH); Writing the article (A.K., R.N., M.N.); Critical revision of article (H.H., M.J.B.); Final approval of article (A.K., M.J.B.). The protocol of the study was approved by the Institutional Review Board of Farabi Eye Hospital, Tehran, Iran.

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AJO History of Ophthalmology Series

Antarctic Eye Surgery

The first major surgery done in Antarctica was an enucleation, performed during the British Antarctic Expedition of 1907-09 commanded by Sir Ernest Shackleton. Aeneas Mackintosh was the second officer of the ship, the *Nimrod*. As the crew was unloading supplies, a lifting hook swung across the deck and struck his right eye. The expedition's two surgeons, Eric Marshall and Alistair Mackay, examined him and found the lens on his cheek and a portion of the retina protruding from the laceration.

Marshall decided to remove the eye. The patient was placed on the floor of the captain's cabin, on which the surgeons knelt. Mackay administered chloroform anesthesia with a towel. The only illumination was a single oil lamp. A retractor was improvised with a piece of rigging wire. The operation was uncomplicated and Mackintosh fully recovered.

Submitted by Robert M. Feibel from the Cogan Ophthalmic History Society.