Options and Adjuvants in Surgery for Pterygium

A Report by the American Academy of Ophthalmology

Stephen C. Kaufman, MD, PhD,[1] Deborah S. Jacobs, MD,[2] W. Barry Lee, MD,[3] Sophie X. Deng, MD, PhD,[4] Mark I. Rosenblatt, MD, PhD,[5] Roni M. Shtein, MD[6]

Objective: To assess the outcomes and safety of current surgical options and adjuvants in the treatment of primary and recurrent pterygium.

Methods: Literature searches of the PubMed and the Cochrane Library databases were last conducted in January 2011 using keywords and were restricted to randomized controlled trials reporting on surgical intervention for pterygium. The searches were limited to articles published in English and yielded 120 citations. Citation abstracts, and if necessary the full text, were reviewed to identify randomized controlled trials that reported recurrence as an outcome measure and had a mean follow-up of at least 6 months. Fifty-one studies comparing bare sclera excision, conjunctival or limbal autograft, intraoperative mitomycin C, postoperative mitomycin C, and amniotic membrane transplantation for primary and recurrent pterygia fit these inclusion criteria.

Results: Four studies demonstrated that the conjunctival or limbal autograft procedure is more efficacious than amniotic membrane placement. Use of conjunctival or limbal autografts or mitomycin C during or after pterygium excision reduced recurrence compared with bare sclera excision alone in most studies of primary or recurrent pterygium. The outcomes of conjunctival or limbal autograft were similar to outcomes for intraoperative mitomycin C in the few studies that directly compared the 2 techniques. There is evidence that increased concentration and duration of exposure to intraoperative mitomycin C is associated with increased efficacy. Of the adjuvants studied, only mitomycin C was associated with vision-threatening complications, including scleral thinning, ulceration, and delayed conjunctival epithelialization; there is some evidence of increasing complications with increased concentration and duration of exposure. There is conflicting evidence as to whether increasing age is protective against recurrence, but the morphologic features of the pterygium were shown to affect the recurrence rate.

Conclusions: Evidence indicates that bare sclera excision of pterygium results in a significantly higher recurrence rate than excision accompanied by use of certain adjuvants. Conjunctival or limbal autograft was superior to amniotic membrane graft surgery in reducing the rate of pterygium recurrence. Among other adjuvants, there is evidence that mitomycin C and conjunctival or limbal autografts reduce the recurrence rate after surgical excision of a pterygium. Furthermore, the data indicate that using a combination of conjunctival or limbal autograft with mitomycin C further reduces the recurrence rate after pterygium excision compared with conjunctival or limbal autograft or mitomycin C alone. Additional studies are necessary to determine the long-term effects, optimal route of administration, and dose and duration of treatment for mitomycin C. Factors such as availability of resources, primary or recurrent status of pterygium, age of patient, and surgeon or patient preference may influence the surgeon's choice of adjuvant because there are insufficient data to recommend a specific adjuvant as superior.

Financial Disclosure(s): Proprietary or commercial disclosure may be found after the references.
Ophthalmology 2013;120:201–208 © 2013 by the American Academy of Ophthalmology.

The American Academy of Ophthalmology prepares Ophthalmic Technology Assessments to evaluate new and existing procedures, drugs, and diagnostic and screening tests. The goal of an Ophthalmic Technology Assessment is to review systematically the peer-reviewed literature for clinical efficacy and safety. After review by members of the Ophthalmic Technology Assessment Committee, other Academy committees, relevant subspecialty societies, and legal counsel, assessments are submitted to the Academy's Board of Trustees for consideration as official Academy state-

ISSN 0161-6420/13/$–see front matter
http://dx.doi.org/10.1016/j.ophtha.2012.06.066

ments. The purpose of this assessment is to evaluate results from randomized controlled trials published in the English language literature about the outcomes and safety of current surgical options and adjuvants in the treatment of primary and recurrent pterygium.

Background

A pterygium is a wing-shaped fibrovascular conjunctival growth extending onto the cornea that was described as early as 1000 BC by Susruta, the first recorded ophthalmic surgeon.[1] Throughout the centuries, medical treatment for pterygium made use of relatively benign agents such as bile and urine and more toxic agents such as lead acid, mercuric lanolin, radiotherapy, thiotepa, 5-fluorouracil, and, more recently, mitomycin C in a search for a safe and effective therapy. Surgical therapies in the past made use of materials such as thread or horse hair, which were used as a Gigli saw to remove the pterygium,[2] and, more recently, conjunctival or limbal autografts and amniotic membrane transplants. Surgical approaches to pterygium are described in the review by Hirst,[2] including the bare sclera technique that has been the basic model for pterygium surgery. In bare sclera excision, the pterygium is excised from the cornea, conjunctiva, and underlying Tenon's tissue, leaving bare sclera exposed.[3] With recurrence rates after surgical excision reaching as high as 88% in certain populations,[4] the goal of using the various combinations of surgical options and adjuvants is to remove the pterygium and to prevent recurrence. The presence of a pterygium is "disturbing to both the patient because of its unsightly appearance and the surgeon because of its tendency to recur."[5]

Regulatory Considerations

The administration of mitomycin C in pterygium surgery is considered an off-label use by the Food and Drug Administration (FDA). Because mitomycin C is classified as a group 2B carcinogen (possible for human) by the International Agency for Research on Cancer, waste (including tissues or other items that come into contact with the chemical) must be disposed of in accordance with federal, state, and local environmental control regulations.

Cryoprotected and then fresh-frozen amniotic membrane—as used in 2 randomized clinical trials reviewed for this assessment[6,7]—has FDA approval for wound repair, for healing, and as a covering. In 2 additional studies, the amniotic membrane was prepared on site from fresh samples that were stored in tissue culture media.[8,9] A dry-stored amniotic membrane has FDA approval for use as a human tissue graft in ophthalmic applications, but no controlled comparison studies were available at the time of the literature search.

Tissue adhesives such as medical-grade fibrin tissue adhesive have FDA approval in other fields of medicine; however, fibrin tissue adhesive in ophthalmic applications is considered off-label use by the FDA.

Resource Requirements

Pterygium surgery can be performed in a minor procedure room using only local anesthesia, depending on the comfort of the patient and surgeon and the complexity of the case. Cases performed in an operating room because of surgical complexity and surgeon or patient preference may require a preoperative physical examination; laboratory testing; topical, regional, or general anesthesia; and monitored anesthesia care. Mitomycin C requires compounding by a pharmacist under sterile conditions and special handling. Amniotic membrane must be procured in advance of the surgery, and fresh-frozen amniotic membrane requires storage in a freezer or refrigerator.

Operating room time and surgeon's time are factors that may determine which procedure a surgeon will select for a particular patient. Duration of the procedure varies widely with the skill of the surgeon, complexity of the procedure chosen, patient cooperation, and anesthesia requirements. Bare sclera excision with no adjuvant therapy treatment likely can be performed in fewer than 30 minutes. Use of intraoperative mitomycin C adds 5 to 10 minutes to the surgical procedure compared with approximately 20 additional minutes needed to suture a conjunctival or limbal autograft or amniotic membrane transplant. The use of tissue adhesives may shorten this time. In addition, 20 minutes generally is required to harvest the graft if conjunctiva is used. The longer and more complex the procedure, the more likely the surgeon is to require anesthesia support, thereby further increasing the length of the procedure and resources required. The literature reports that procedures using conjunctival or limbal autografts require approximately 1.5 hours.[10]

Questions for Assessment

The goal of this assessment was to address the following questions:

1. What are the recurrence rates of different surgical options and adjuvants for treating primary and recurrent pterygium?
2. Which surgical options and adjuvants are safest for treating primary and recurrent pterygium?

Description of Evidence

Literature searches were conducted in October 2004, October 2008, and January 2011 in PubMed and in the Cochrane Library without date restrictions. The MeSH term *pterygium* was used as well as truncated text word search terms *pterygi* and *pterigi*. In the PubMed search, the Cochrane highly sensitive search strategy for identifying controlled clinical trials was used in combination with the other search terms,[11] yielding 120 unique citations. Abstracts for these citations were reviewed for inclusion by the lead author (S.C.K.) using the following criteria: randomized controlled trial involving participants of any age with primary or recurrent pterygia who underwent bare sclera excision, am-

niotic membrane transplantation, conjunctival autograft, limbal autograft, intraoperative or postoperative mitomycin C, or a combination thereof as interventions. Beta irradiation, used mainly in Australia,[12] was excluded from review. Reports with mean follow-up of fewer than 6 months were excluded from the analysis to avoid underestimation of recurrence rates.

When it was not possible to determine whether a study met inclusion criteria from the abstract, the full text of the article was obtained and reviewed. Articles that were not in English were excluded from consideration. Of the 120 citations retrieved, 51 studies[3,4,6–10,13–56] were determined to meet the inclusion criteria. Studies were characterized as to whether they included only subjects with primary pterygium, only subjects with recurrent pterygium, or both. These groupings are presented in Table 1A–C (available at http://aaojournal.org). The tables include tabulation of the intervention for each arm of trial, number in each arm, mean follow-up with the range in months, definition of recurrence, recurrence rate for each arm, and statistical significance of the difference in recurrence rate between arms if reported. Study populations and subpopulations also were characterized and grouped so that studies comparing the same 2 arms could be compared regardless of whether participants had primary pterygium, recurrent pterygium, or a mixture. These groupings are presented in Tables 2 through 7 (available at http://aaojournal.org). Table 8 (available at http://aaojournal.org) presents the rates of vision-threatening complications with tabulation of surgical option or adjuvant, complication, and rate of complication.

Seventeen trials[4,13–28] examined the efficacy of bare sclera excision; in some of these trials, the free conjunctival edge was sutured to the underlying sclera. Fourteen trials included the adjuvant of a conjunctival or limbal autograft that was sutured over the bare sclera after pterygium excision.[4,6,10,20,22,26,29–34,39,40] A translational autograft taken from superior conjunctiva[41] and placed over the exposed sclera was the most common type of autograft used in these trials. A bridge[20] or sliding[30] graft of superior conjunctiva pulled over to cover exposed sclera was used in two trials, and a rotational graft (in which the conjunctival portion of the pterygium is excised, rotated 180 degrees, and sutured to the sclera) was used in another trial.[31] Two studies included limbal stem cells with the conjunctival or limbal autograft,[10,29] referred to herein as *limbal autograft*. Six trials using fibrin tissue adhesive to secure the graft have been published.[42–47]

Twenty-one trials used mitomycin C of different concentrations applied during surgery for various amounts of time to the bare sclera after pterygium excision.[10,14–17,21,24,25,27,28,30,33–37,48–51,56] Thirteen trials examined the efficacy of mitomycin C drops of different concentrations applied after surgery to the eye, using various dosing schedules.[4,13,17–19,23,30,33,35–38,48]

Two trials compared cryopreserved amniotic membrane grafts, sutured to the exposed sclera, with the bare sclera technique during the removal of the pterygium.[6,7] Two additional studies compared the use of nonfrozen amniotic membrane to cover the region of bare sclera with conjunctival or limbal autograft coverage of the bare sclera.[8,9] None of the trials specified the use of freeze-dried amniotic membrane. Two studies compared the use of a nonspecific type of amniotic membrane with the use of conjunctival or limbal autografts during pterygium excision surgery.[40,49]

Wide variation in protocols prohibits the direct comparison of results from the various randomized trials. Studies varied with respect to populations evaluated, classification of pterygium, the indication for surgery, excision of the entire pterygium or partial excision, the definition of recurrence, and postoperative care. Furthermore, surgical technique was not entirely standardized for a given option or adjunctive treatment. Many studies using mitomycin C during surgery did not use a sham agent for the control.[13,15,17–19,21,23,24,26–28,49,51,52,56] Only a limited number of studies reported that observers were masked to the treatment option.[4,14,16,24,25] Eight studies reported results for primary and recurrent pterygia together.[15–17,21,22,35,37,38] The selection criterion of a mean follow-up of at least 6 months allowed for studies to have variable follow-up intervals. Ideally, Kaplan-Meier survival analysis would be used to address more appropriately variable follow-up, but the data as presented do not permit such an analysis. Another limitation was that concealment of treatment allocation was inadequate or was not used in many studies, which increases the risk of selection bias.

Published Results

Various modifications to the surgical technique of bare sclera excision and adjuvants have been studied, including translational conjunctival or limbal autograft and use of mitomycin C. More recent methods also have been examined, including comparing autograft with mitomycin C, comparing amnion graft with autograft, as well as these methods combined with mitomycin C.

Translational Conjunctival or Limbal Autograft Compared with Bare Sclera Excision

Pterygium recurrence rates after translational conjunctival or limbal autograft were compared with the rates for bare sclera excision in 5 randomized controlled clinical trials (Table 2).[4,20,22,26,39,40] Five studies reported statistically significant reductions in recurrence rates for primary pterygium using conjunctival or limbal autograft when compared with bare sclera excision,[4,20,26,39,40] and 2 studies found a statistically significant reduction in recurrence for participants undergoing surgery for recurrent pterygium as well. Another trial of mixed primary and recurrent pterygia did not find a statistically significant difference in recurrence between the 2 techniques ($P>0.10$),[22] although there was a trend toward lower recurrence in the autograft group. The data from these studies indicate that translational conjunctival or limbal autograft reduces pterygium recurrence compared with bare sclera excision for both primary and recurrent pterygia.

Intraoperative Mitomycin C Compared with Bare Sclera Excision

Seven studies[14,15,21,25,27,28,48] compared intraoperative mitomycin C with bare sclera excision (Table 3). Four randomized trials[14,25,28,48] of primary pterygium reported that all concentrations of intraoperative mitomycin C, from 0.002% to 0.04% administered for 3 to 5 minutes, significantly (all $P \leq 0.045$) reduced pterygium recurrence compared with bare sclera excision. Another randomized trial[21] demonstrated reduction of recurrence in a range of exposures of mitomycin C of 0.02% to 0.04% administered for 3 to 5 minutes.

Two studies reported recurrence rates after surgery for recurrent pterygium.[21,27] Statistically significant reduction in recurrence using intraoperative mitomycin C 0.02% for 4 to 5 minutes was demonstrated compared with bare sclera excision.[27] This is corroborated in the other study in which 3 minutes of exposure to 0.02% mitomycin C reduced recurrence less in patients with recurrent pterygium compared with longer durations of exposure.[21] Another study reported a statistically significant reduction in the recurrence rate for primary and recurrent pterygia combined using intraoperative mitomycin C 0.02% applied for 3 minutes compared with bare sclera excision ($P = 0.03$).[15]

The study by Lam et al[21] was the only trial in this assessment that studied the use of intraoperative mitomycin C at varying concentrations and durations (0.02% and 0.04% applied for 3 or 5 minutes); in other studies, this seemed to have the greatest therapeutic benefit[15,27,28] for treating both primary and recurrent pterygia. All concentrations and durations of mitomycin C reduced pterygium recurrence compared with bare sclera excision. The study had several limitations: there were a limited number of patients in the recurrent pterygium treatment group, the authors did not separate the results for primary and recurrent cases, and they did not compare recurrence rates between treatment groups.

These studies comparing the use of intraoperative mitomycin C with bare sclera excision indicate that intraoperative mitomycin C reduces pterygium recurrence for primary pterygia. The most commonly used concentration of mitomycin C was 0.02% (0.2 mg/ml), and the most common duration of treatment was 3 minutes. Further studies are needed to determine the optimal concentration and exposure time and whether the mitomycin C should be applied to the bare sclera, Tenon's membrane, or the underside of the conjunctiva.

Postoperative Mitomycin C Compared with Bare Sclera Excision

Three studies[4,13,23] compared recurrence rates with the use of postoperative topical mitomycin C with bare sclera excision (Table 4). In 2 studies, postoperative mitomycin C (0.02% twice daily for 5 days) after primary pterygium excision reduced recurrence compared with bare sclera excision.[4,13] A higher concentration of mitomycin C (0.04% 3 or 4 times daily for 7 days or more) resulted in a reduced proportion showing recurrence ($P = 0.005$) compared with bare sclera excision.[13] One study of primary pterygium reported no recurrence using postoperative mitomycin C 0.04% 4 times daily for 2 weeks.[23] Data from all 3 studies indicate that the use of postoperative mitomycin C reduces pterygium recurrence compared with bare sclera excision for primary pterygia.

Intraoperative Mitomycin C Compared with Postoperative Mitomycin C

Six randomized controlled clinical trials[30,33,35–37,50] compared recurrence rates using various protocols that incorporated intraoperative or postoperative mitomycin C of different durations (Table 5). Studies of primary pterygia alone[33,36,50] or combined with recurrent pterygia[35,37] reported no significant differences in the use of intraoperative or postoperative mitomycin C.

Mitomycin C Compared with Conjunctival or Limbal Autograft

Six of the 8 randomized trials for primary pterygium that contrasted the use of postoperative mitomycin C (0.02% twice daily for 5 days[32]) or intraoperative mitomycin C (0.02% for 2.5 minutes,[34] 0.04% for 3 minutes,[33,56] 0.02% for 2 minutes,[49,51,52] or 0.02% for 3 minutes[48]) with translational conjunctival or limbal autograft reported no significant differences in recurrence rates (Table 6). Two studies comparing mitomycin C (0.04% for 3 minutes[53] and 0.02% for 2 minutes[56]) with conjunctival or limbal autograft demonstrated a significantly lower recurrence rate in the conjunctival or limbal autograft group. Two studies compared recurrence after pterygium excision and conjunctival or limbal autograft alone with recurrence after excision and conjunctival or limbal autograft combined with intraoperative mitomycin C 0.02% or 0.04% for 3 minutes, postoperative mitomycin C 0.02% 3 times daily for 7 days or 0.04% 3 times daily for 14 days,[30] or intraoperative mitomycin C 0.02% for 1 minute.[48] Combining conjunctival or limbal autograft with any mitomycin C application resulted in a significant reduction in pterygium recurrence compared with conjunctival or limbal autograft alone ($P \leq 0.001$). There are no data to suggest whether intraoperative or postoperative mitomycin C is more efficacious when combined with a conjunctival or limbal autograft. One potential limitation of this comparative analysis results from the different methods used during the application of the intraoperative mitomycin C (mitomycin C on filter paper or sponge applied to the bare sclera or Tenon's membrane).

Amniotic Membrane Compared with Conjunctival or Limbal Autograft

Four randomized clinical trials examined pterygium recurrence rates after using amniotic membrane grafts compared with conjunctival or limbal autograft groups.[6,40,49,53] The type of amniotic membrane used was not specified in all studies. All 4 studies demonstrated a lower pterygium recurrence rate in the conjunctival or limbal autograft group ($P < 0.05$), which suggests that the conjunctival or limbal

autograft procedure is more efficacious than amniotic membrane use.

Other Combinations of Adjuvants for Recurrent Pterygium

A study of treatments for recurrent pterygium reported no statistically significant difference in recurrence using conjunctival or limbal autograft with intraoperative mitomycin C 0.02% for 3 minutes compared with limbal autograft.[10] Another trial of recurrent pterygium reported no difference in recurrence rates when amniotic membrane was used alone versus with the concurrent use of intraoperative mitomycin C 0.025% for 3 minutes.[7] A single study suggests that there is an advantage to a combination of adjuvants in surgery for primary pterygium. The treatment group that underwent the combined use of a conjunctival or limbal autograft with intraoperative mitomycin C had a statistically significantly lower incidence of pterygium recurrence compared with the other treatment groups: intraoperative mitomycin C alone (0.02% for 3 minutes), conjunctival or limbal autograft alone, and intraoperative sodium chloride 0.9% as a control. There is insufficient evidence to recommend any combination of adjuvants in surgery for recurrent pterygium.

Age, Pterygium Morphologic Features, and Recurrence

Eight randomized controlled trials reported the statistically evaluated association of age at the time of surgery and pterygium recurrence.[4,6,7,10,22,29,33,34] No significant association of age with recurrence was reported in studies of amniotic membrane with and without intraoperative mitomycin C ($P = 0.20$),[7] conjunctival autograft and conjunctival or limbal autograft (P = nonsignificant),[29] or amniotic membrane and conjunctival autograft ($P = 0.28$).[6]

In contrast, a statistically significant association of age and pterygium recurrence was reported in 5 randomized clinical trials (Table 7).[4,10,22,33,34] One study reported that the effect of age was statistically significant ($P = 0.006$) after controlling for pterygium type and treatment group.[4] In general, patients with recurrent pterygia were a decade younger than those who did not experience recurrence in any given study. There is conflicting evidence as to whether younger age is associated with an increased probability of recurrence in surgery for pterygium. One study found a statistically significant direct correlation between the recurrence rate and the morphologic grade (fleshiness) of the pterygium.[26]

Published Results: Safety of Surgical Options and Adjuvants

This part of the assessment addresses the safety of the various options and adjuvants. Complications are categorized as vision threatening or non-vision threatening.

Vision-Threatening Complications

Vision-threatening complications, including scleral thinning or ulceration, delayed conjunctival epithelialization, iritis, and symblepharon, are presented in Table 8.

Scleral Thinning or Ulceration. No ulceration occurred over the follow-up period for any trial using conjunctival or limbal autograft (total of 677 eyes) or amniotic membrane transplantation (total of 92 eyes).[4,6,7,9,10,22,25,26,29–34,42,46,49,50,52,53,57] There were no other cases of ulceration reported for another 493 eyes that underwent bare sclera excision from the other trials reviewed for this assessment.[4,17,24,26–28,42,56]

Use of intraoperative and postoperative mitomycin C was associated with reports of scleral ulceration (Table 8) ranging from 2% to 19% of eyes in which intraoperative mitomycin C 0.02%[17,37,49,50] and 0.04%[21,56] was used. Scleral ulceration occurred at proportions that ranged from 5% to 19% of eyes when postoperative mitomycin C 0.02% was applied twice daily for 5 days,[17] 0.02% applied 4 times daily for 7 days,[33] and 0.04% applied 3 times daily for 7 days.[18] The incidence of scleral thinning or ulceration after postoperative mitomycin C 0.02% applied twice daily for 5 days and intraoperative mitomycin C 0.02% applied for 5 minutes was significantly higher compared with bare sclera excision ($P<0.001$) or compared with 1 drop of mitomycin C 0.02% at the end of surgery ($P = 0.0001$).[17] Two studies reported greater rates of scleral thinning and ulceration with increasing intraoperative[21] or postoperative[18] mitomycin C concentration and longer duration of application.[18,21] Intraoperative exposure to mitomycin C offers the advantage of direct monitoring of mitomycin C exposure when compared with postoperative regimens, which require patient adherence, but this advantage has not yielded lower complication rates in studies published thus far.

Delayed Conjunctival Epithelialization. Delayed epithelialization was associated only with mitomycin C use in the trials reviewed. Delayed epithelialization, defined as re-epithelialization that did not occur until 2 to 3 weeks or more after surgery, was reported when intraoperative mitomycin C 0.02% was applied for 5 minutes, with an incidence of 4% (1 of 24 eyes)[4] and 5% (2 of 38 eyes).[36] Delayed epithelialization also occurred with use of intraoperative mitomycin C 0.04% for 3 or 5 minutes, but not mitomycin C 0.02% for 3 minutes.[21] Delayed epithelialization of 1 to 2 months occurred with postoperative mitomycin C 0.02% 4 times daily for 5 days in 6% of eyes (2 of 34).[36] One trial reported a statistically significant decrease in delayed re-epithelialization (defined as healing in 3 to 4 weeks) using a single drop of intraoperative mitomycin C 0.02% compared with mitomycin C 0.02% twice daily for 5 days ($P = 0.003$) or intraoperative mitomycin C 0.02% for 5 minutes ($P = 0.004$).[17] It cannot be determined from the available results whether intraoperative or postoperative mitomycin C use is associated with greater rates of delayed epithelialization.

Iritis. Anterior chamber reaction occurred only after mitomycin C use. Iritis was reported after intraoperative mitomycin C 0.01% for 5 minutes in 3% (2 of 66 eyes)[14] and after postoperative mitomycin C 0.02% 4 times daily

for 7 days in 3% (1 of 40 eyes)[37] and mitomycin C 0.005% 4 times daily for 2 weeks in 1% (2 of 156 eyes).[35]

Symblepharon. Symblepharon formation was reported in 2% to 10% of cases after bare sclera excision alone and with conjunctival or limbal autograft, postoperative mitomycin C, and amniotic membrane alone or combined with intraoperative mitomycin C (Table 8). No trials using intraoperative mitomycin C alone reported symblepharon formation.

Non–Vision-Threatening Complications

Corneal Dellen. Corneal dellen was a complication reported after use of all adjuvants except amniotic membrane transplantation (Table 8). Corneal dellen occurred with translational conjunctival or limbal autograft (1% to 6% of eyes),[4,26,31] bare sclera excision (3%[20] to 5%[16] of eyes), intraoperative mitomycin C 0.02% (3% to 6% of eyes),[15,16,36] and postoperative mitomycin C 0.02% (2%[51] to 9%[36] of eyes).

Postoperative Astigmatism. Severe astigmatism occurred in 6% of cases (2 of 31) after bare sclera excision in 1 study.[18]

Pyogenic Granuloma. Conjunctival pyogenic granuloma occurred after the use of conjunctival or limbal autograft,[8,10] bare sclera excision,[4,14,19,20,27] intraoperative[14,25,27,34,36,51] and postoperative[4,19,36] mitomycin C, and amniotic membrane alone[34,55] or combined with intraoperative mitomycin C.[7] In one study, pyogenic granuloma occurred more frequently in cases using higher concentrations of mitomycin C.[17]

Potential Long-Term Considerations

None of the trials included in the assessment addressed potential long-term complications such as the effect of mitomycin C on the ocular surface or cornea or the effect of either mitomycin C exposure or conjunctival or limbal autograft on the success of subsequent glaucoma surgery, should it be required.

Mitomycin C-Associated Symptoms

Ocular pain, foreign body sensation, and photophobia are common symptoms after bare sclera excision, with or without concurrent use of intraoperative or postoperative mitomycin C, or conjunctival or limbal autografts.[10,15,17,21,24,25,31,36–38] These symptoms occur less frequently with conjunctival or limbal autografts[20] and more frequently with the use of mitomycin C[15,28] compared with the bare sclera technique. Substantial irritation required stopping postoperative mitomycin C use in 7% of eyes (1 of 15)[23] and in 2% of eyes (1 of 64[4]).

Summary

Conjunctival or limbal autograft and mitomycin C used during or after surgery were more efficacious than bare scleral excision in reducing the rate of recurrence after surgery for both primary pterygium and recurrent pterygium. Studies demonstrated a lower pterygium recurrence rate in the conjunctival or limbal autograft group compared with amniotic membrane grafts alone. Most studies demonstrated that conjunctival or limbal autograft had similar efficacy to intraoperative mitomycin C for primary and recurrent pterygium. There may be a benefit to using both conjunctival or limbal autograft and mitomycin C. An overview of the studies suggests that higher exposure (dose or duration) to intraoperative and postoperative mitomycin C is associated with greater efficacy along with an increased risk of complications.

Scleral ulceration and delayed conjunctival epithelialization were associated with both intraoperative and postoperative mitomycin C use, and there is evidence that increased complications are related directly to increased concentration and extent of exposure. Scleral thinning or ulceration was not reported after conjunctival or limbal autograft and occurred rarely after bare scleral excision.

There is conflicting evidence as to whether increasing age is protective against recurrence.

In conclusion, there is evidence to suggest that the use of an adjuvant in surgery for primary and recurrent pterygium is warranted to achieve a lower recurrence rate. Although bare sclera excision may have advantages as far as having the fewest resource requirements, evidence presented here indicates that it is an inferior procedure and is associated with the highest recurrence rate. Among the adjuvants, mitomycin C and conjunctival or limbal autografts resulted in fewer recurrences. Conjunctival or limbal autograft was superior to amniotic membrane graft surgery in reducing the rate of pterygium recurrence. Furthermore, the data indicate that using a combination of conjunctival or limbal autograft with mitomycin C reduces the recurrence rate after pterygium excision compared with conjunctival or limbal autograft or mitomycin C alone. Considering that these adjuvants are not mutually exclusive, further randomized controlled trials are warranted to demonstrate whether the combination of conjunctival or limbal autograft and mitomycin C is a beneficial treatment. Because the efficacy of mitomycin C seems to increase with exposure and safety seems to decrease with exposure, there is a clear need for further studies to identify the optimal route of administration and dose and duration of treatment with mitomycin C. Factors such as availability of resources, primary or recurrent status of pterygium, age of patient, and surgeon or patient preference may influence the surgeon's choice of adjuvant because there are insufficient data to recommend a specific adjuvant or combination of adjuvants as superior for each specific case.

Future Research

Additional randomized controlled trials in pterygium surgery are required to assess the comparative safety and efficacy of conjunctival or limbal autograft, techniques to excise Tenon's membrane, various exposure times and techniques associated with the use of mitomycin C, newer adjuvants such as amniotic membrane transplantation, anti-inflammatory treatments, anti-vascular endothelial growth factor agents, tissue adhesives, and combinations of these adjuvants.[54,57,58] Use of a uniform, consistent grading scale

for pterygium such as the one proposed by Tan et al[26] would aid in the evaluation of these options and adjuvants in surgery for pterygium. Certainly, more studies are required to determine exactly what degree of mitomycin C exposure offers the greatest combination of safety and efficacy. Further characterization of risk factors for recurrence may help to identify cases in which higher exposures to mitomycin C are warranted. A standard postoperative medication regimen (typically topical antibiotics and corticosteroids) will help to compare the results between studies. Newer surgical excision techniques for pterygium removal may prove to be beneficial, but randomized controlled studies are needed to assess new techniques. Finally, continued study of the pathophysiologic basis of occurrence and recurrence may lead to other therapeutic options in the treatment of pterygium.[59]

References

1. Rosenthal JW. Chronology of pterygium therapy. Am J Ophthalmol 1953;36:1601–16.
2. Hirst LW. The treatment of pterygium. Surv Ophthalmol 2003;48:145–80.
3. D'Ombrain A. The surgical treatment of pterygium. Br J Ophthalmol 1948;32:65–71.
4. Chen PP, Ariyasu RG, Kaza V, et al. A randomized trial comparing mitomycin C and conjunctival autograft after excision of primary pterygium. Am J Ophthalmol 1995;120:151–60.
5. Townsend WM. Pterygium. In: Kaufman HE, Barron BA, McDonald MB, Waltman SR, eds. The Cornea. New York: Churchill Livingstone; 1988:461–84.
6. Tananuvat N, Martin T. The results of amniotic membrane transplantation for primary pterygium compared with conjunctival autograft. Cornea 2004;23:458–63.
7. Ma DH, See LC, Hwang YS, Wang SF. Comparison of amniotic membrane graft alone or combined with intraoperative mitomycin C to prevent recurrence after excision of recurrent pterygia. Cornea 2005;24:141–50.
8. Luanratanakorn P, Ratanapakorn T, Suwan-Apichon O, Chuck RS. Randomised controlled study of conjunctival autograft versus amniotic membrane graft in pterygium excision. Br J Ophthalmol 2006;90:1476–80.
9. Kucukerdonmez C, Akova YA, Altinors DD. Comparison of conjunctival autograft with amniotic membrane transplantation for pterygium surgery: surgical and cosmetic outcome. Cornea 2007;26:407–13.
10. Mutlu FM, Sobaci G, Tatar T, Yildirim E. A comparative study of recurrent pterygium surgery: limbal conjunctival autograft transplantation versus mitomycin C with conjunctival flap. Ophthalmology 1999;106:817–21.
11. Robinson KA, Dickersin K. Development of a highly sensitive search strategy for the retrieval of reports of controlled trials using PubMed. Int J Epidemiol 2002;31:150–3.
12. Troutbeck R, Hirst L. Review of treatment of pterygium in Queensland: 10 years after a primary survey. Clin Experiment Ophthalmol 2001;29:286–90.
13. Caliskan S, Orhan M, Irkec M. Intraoperative and postoperative use of mitomycin-C in the treatment of primary pterygium. Ophthalmic Surg Lasers 1996;27:600–4.
14. Cano-Parra J, Diaz-Llopis M, Maldonado MJ, et al. Prospective trial of intraoperative mitomycin C in the treatment of primary pterygium. Br J Ophthalmol 1995;79:439–41.
15. Demirok A, Simsek S, Cinal A, Yasar T. Intraoperative application of mitomycin C in the surgical treatment of pterygium. Eur J Ophthalmol 1998;8:153–6.
16. Frucht-Pery J, Ilsar M, Hemo I. Single dosage of mitomycin C for prevention of recurrent pterygium: preliminary report. Cornea 1994;13:411–3.
17. Gupta VP, Saxena T. Comparison of single-drop mitomycin C regime with other mitomycin C regimes in pterygium surgery. Indian J Ophthalmol 2003;51:59–65.
18. Hayasaka S, Noda S, Yamamoto Y, Setogawa T. Postoperative instillation of low-dose mitomycin C in the treatment of primary pterygium. Am J Ophthalmol 1988;106:715–8.
19. Kaimbo Wa Kaimbo D. Postoperative instillation of 0.04% mitomycin C in the treatment of primary pterygium in Zaire. Bull Soc Belge Ophtalmol 1996;261:107–10.
20. Kaya M, Tunc M. Vertical conjunctival bridge flaps in pterygium surgery. Ophthalmic Surg Lasers Imaging 2003;34:279–83.
21. Lam DS, Wong AK, Fan DS, et al. Intraoperative mitomycin C to prevent recurrence of pterygium after excision: a 30-month follow-up study. Ophthalmology 1998;105:901–4; discussion 904–5.
22. Lewallen S. A randomized trial of conjunctival autografting for pterygium in the tropics. Ophthalmology 1989;96:1612–4.
23. Mahar PS, Nwokora GE. Role of mitomycin C in pterygium surgery. Br J Ophthalmol 1993;77:433–5.
24. Mastropasqua L, Carpineto P, Ciancaglini M, et al. Effectiveness of intraoperative mitomycin C in the treatment of recurrent pterygium. Ophthalmologica 1994;208:247–9.
25. Panda A, Das GK, Tuli SW, Kumar A. Randomized trial of intraoperative mitomycin C in surgery for pterygium. Am J Ophthalmol 1998;125:59–63.
26. Tan DT, Chee SP, Dear KB, Lim AS. Effect of pterygium morphology on pterygium recurrence in a controlled trial comparing conjunctival autografting with bare sclera excision. Arch Ophthalmol 1997;115:1235–40.
27. Verma N, Garap JA, Maris R, Kerek A. Intraoperative use of mitomycin C in the treatment of recurrent pterygium. P N G Med J 1998;41:37–42.
28. Yanyali AC, Talu H, Alp BN, et al. Intraoperative mitomycin C in the treatment of pterygium. Cornea 2000;19:471–3.
29. Al Fayez MF. Limbal versus conjunctival autograft transplantation for advanced and recurrent pterygium. Ophthalmology 2002;109:1752–5.
30. Cardillo JA, Alves MR, Ambrosio LE, et al. Single intraoperative application versus postoperative mitomycin C eye drops in pterygium surgery. Ophthalmology 1995;102:1949–52.
31. Dadeya S, Malik KP, Gullian BP. Pterygium surgery: conjunctival rotation autograft versus conjunctival autograft. Ophthalmic Surg Lasers 2002;33:269–74.
32. Mahar PS. Conjunctival autograft versus topical mitomycin C in treatment of pterygium. Eye (Lond) 1997;11:790–2.
33. Manning CA, Kloess PM, Diaz MD, Yee RW. Intraoperative mitomycin in primary pterygium excision: a prospective, randomized trial. Ophthalmology 1997;104:844–8.
34. Sharma A, Gupta A, Ram J, Gupta A. Low-dose intraoperative mitomycin-C versus conjunctival autograft in primary pterygium surgery: long term follow-up. Ophthalmic Surg Lasers 2000;31:301–7.
35. Helal M, Messiha N, Amayem A, et al. Intraoperative mitomycin-C versus postoperative topical mitomycin-C drops for the treatment of pterygium. Ophthalmic Surg Lasers 1996;27:674–8.
36. Hosal BM, Gursel E. Mitomycin-C for prevention of recurrent pterygium. Ann Ophthalmol-Glaucoma 2000;32:107–9.

37. Oguz H, Basar E, Gurler B. Intraoperative application versus postoperative mitomycin C eye drops in pterygium surgery. Acta Ophthalmol Scand 1999;77:147–50.
38. Frucht-Pery J, Ilsar M. The use of low-dose mitomycin C for prevention of recurrent pterygium. Ophthalmology 1994;101: 759–62.
39. Kilic A, Gurler B. The efficiency of limbal conjunctival autografting in pterygium surgery. Eur J Ophthalmol 2006;16: 365–70.
40. Ozer A, Yildirim N, Erol N, Yurdakul S. Long-term results of bare sclera, limbal-conjunctival autograft and amniotic membrane graft techniques in primary pterygium excisions. Ophthalmologica 2009;223:269–73.
41. Kenyon KR, Wagoner MD, Hettinger ME. Conjunctival autograft transplantation for advanced and recurrent pterygium. Ophthalmology 1985;92:1461–70.
42. Jiang J, Yang Y, Zhang M, et al. Comparison of fibrin sealant and sutures for conjunctival autograft fixation in pterygium surgery: one-year follow-up. Ophthalmologica 2008;222:105–11.
43. Karalezli A, Kucukerdonmez C, Akova YA, et al. Fibrin glue versus sutures for conjunctival autografting in pterygium surgery: a prospective comparative study. Br J Ophthalmol 2008;92:1206–10.
44. Srinivasan S, Dollin M, McAllum P, et al. Fibrin glue versus sutures for attaching the conjunctival autograft in pterygium surgery: a prospective observer masked clinical trial. Br J Ophthalmol 2009;93:215–8.
45. Ratnalingam V, Eu AL, Ng GL, et al. Fibrin adhesive is better than sutures in pterygium surgery. Cornea 2010;29:485–9.
46. Kucukerdonmez C, Karalezli A, Akova YA, Borazan M. Amniotic membrane transplantation using fibrin glue in pterygium surgery: a comparative randomised clinical trial. Eye (Lond) 2010;24:558–66.
47. Hall RC, Logan AJ, Wells AP. Comparison of fibrin glue with sutures for pterygium excision surgery with conjunctival autografts. Clin Experiment Ophthalmol 2009;37: 584–9.
48. Frucht-Pery J, Raiskup F, Ilsar M, et al. Conjunctival autografting combined with low-dose mitomycin C for prevention of primary pterygium recurrence. Am J Ophthalmol 2006; 141:1044–50.
49. Keklikci U, Celik Y, Cakmak SS, et al. Conjunctival-limbal autograft, amniotic membrane transplantation, and intraoperative mitomycin C for primary pterygium. Ann Ophthalmol (Skokie) 2007;39:296–301.
50. Rahman A, Yahya K, Ul Hasan KS. Recurrence rate of pterygium following surgical excision with intraoperative versus postoperative mitomycin-C. J Coll Physicians Surg Pak 2008; 18:489–92.
51. Ari S, Caca I, Yildiz ZO, et al. Comparison of mitomycin C and limbal-conjunctival autograft in the prevention of pterygial recurrence in Turkish patients: a one-year, randomized, assessor-masked, controlled trial. Curr Ther Res Clin Exp 2009;70:274–81.
52. Biswas MC, Shaw C, Mandal R, et al. Treatment of pterygium with conjunctival limbal autograft and mitomycin C—a comparative study. J Indian Med Assoc 2007;105:200, 202, 204.
53. Besharati MR, Miratashi SA, Ahmadi AB. Pterygium surgery: amniotic membrane or conjunctival autograft transplantation. Int J Ophthalmol 2006;6:1258–62.
54. Ibanez M, Eugarrios MF, Calderon DI. Topical cyclosporin A and mitomycin C injection as adjunctive therapy for prevention of primary pterygium recurrence. Ophthalmic Surg Lasers Imaging 2009;40:239–44.
55. Fallah MR, Golabdar MR, Amozadeh J, et al. Transplantation of conjunctival limbal autograft and amniotic membrane vs mitomycin C and amniotic membrane in treatment of recurrent pterygium. Eye (Lond) 2008;22:420–4.
56. Koranyi G, Artzen D, Seregard S, Kopp ED. Intraoperative mitomycin C versus autologous conjunctival autograft in surgery of primary pterygium with four-year follow-up. Acta Ophthalmol 2012;90:266–70.
57. Fallah MR, Khosravi K, Hashemian MN, et al. Efficacy of topical bevacizumab for inhibiting growth of impending recurrent pterygium. Curr Eye Res 2010;35:17–22.
58. Mandalos A, Tsakpinis D, Karayannopoulou G, et al. The effect of subconjunctival ranibizumab on primary pterygium: a pilot study. Cornea 2010;29:1373–9.
59. Chui J, Di Girolamo N, Wakefield D, Coroneo MT. The pathogenesis of pterygium: current concepts and their therapeutic implications. Ocul Surf 2008;6:24–43.

Footnotes and Financial Disclosures

Originally received: June 8, 2012.
Final revision: June 8, 2012.
Accepted: June 26, 2012.
Available online: October 11, 2012. Manuscript no. 2012-853.

[1] Department of Ophthalmology, University of Minnesota, Minneapolis, Minnesota.

[2] Boston Foundation for Sight, Needham, Massachusetts.

[3] Piedmont Hospital and Eye Consultants of Altanta, Atlanta, Georgia.

[4] Jules Stein Eye Institute, University of California, Los Angeles, Los Angeles, California.

[5] Department of Ophthalmology, Weill Cornell Medical College, New York, New York.

[6] Department of Ophthalmology and Visual Sciences, University of Michigan, Ann Arbor, Michigan.

Prepared by the Ophthalmic Technology Assessment Committee Cornea and Anterior Segment Disorders Panel and approved by the American Academy of Ophthalmology's Board of Trustees February 25, 2012.

Financial Disclosure(s):
The author(s) have made the following disclosure(s):

Stephen C. Kaufman - Consultant - IOP Ophthalmics

W. Barry Lee - Lecturer - Bio-Tissue, Inc.

Funded without commercial support by the American Academy of Ophthalmology.

Correspondence:
Nancy Collins, American Academy of Ophthalmology, Quality Care and Knowledge Base Development, PO Box 7424, San Francisco, CA 94120-7424. E-mail: ncollins@aao.org.