REVIEW/UPDATE

Surgical techniques and adjuvants for the management of primary and recurrent pterygia

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The removal and rate of recurrence of pterygium have been discussed for years. The disorder is highly associated with environmental factors, and recurrence rates can be unacceptably high and cannot be successfully predicted. New techniques and graft preparations and postoperative management strategies are helping to reduce the recurrence rates and provide an ocular surface that is near ideal for future cataract or refractive surgery. This review discusses the advantages and disadvantages of various treatment strategies.

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Pterygium is a noncancerous elastotic degeneration of the conjunctiva that extends past the limbus and eventually grows over the cornea. It is usually nasal, but it can grow temporally or in both directions and may or may not occur bilaterally (Figure 1). Recurrence following simple surgical removal is common. Further, environmental factors play a significant role, especially in people who work in direct sunlight or under windy or extremely bright conditions or live in regions with high snowfall levels because of the reflective nature of fresh snow.[1–8]

It is now well accepted that ultraviolet (UV) light has a substantial role in the pathogenesis of pterygium,[8–12] even if the exact causes remain unknown. A better understanding of the disorder, including the molecular biology and pathogenesis, may lead to better medical and/or surgical treatments and a lower rate of recurrence. This is of particular importance as the aging population develops cataracts. Pterygia are known to distort keratometry readings and may induce astigmatism[13,14]; treatment in those cases should involve pterygia removal separately from cataract extraction.

The American Society of Cataract & Refractive Surgery Cornea Clinical Committee evaluated the current literature and reviewed the current options for pterygium treatment. This review summarizes the current literature on this topic and the experience of the authors and our colleagues.

Prevalence and Geographic Distribution

Prevalence rates of pterygia range from 7% to 15%,[9,15] with reports of pinguecula higher than 70% in some populations.[15] Lifetime sun exposure (UV radiation) is thought to be the primary causative factor for pterygium,[16,17] but other risks include increasing age, male sex, and rural residency as in China, Pakistan, the Amazon region in Brazil, and Barbados.[8] The prevalence rate is generally much higher in countries closer to the equator.[18,19] Conversely, wearing sunglasses or hats to avoid direct sun exposure to the eyes seems to have a protective effect.

Some occupations (including welders and outdoor laborers) have higher rates of pterygia, supporting the role of environmental exposure.[20–22] The UV radiation causes focal limbal defects, which are the main pathogenic factor in pterygia.[23]

Although the environment may be the leading causative factor, it is far from the only cause. Detorakis and Spandidos[17] suggest a 2-fold cause and effect with viral infections (such as human papilloma virus or herpes simplex virus) secondary to genetic predisposition for pterygia.

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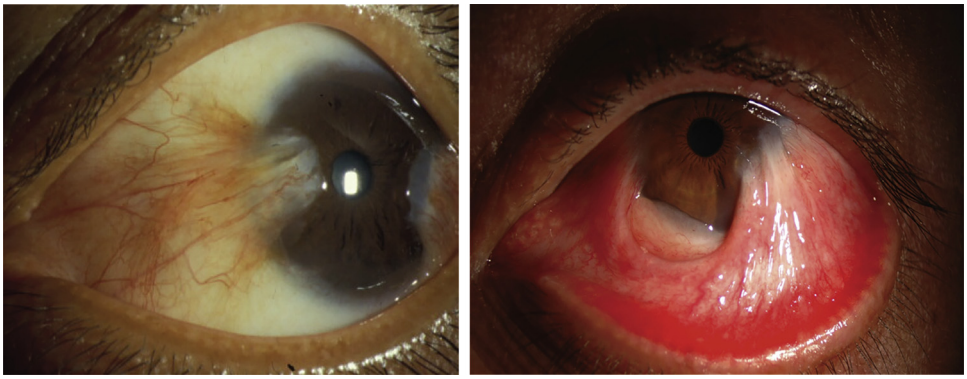

Figure 1. Examples of pterygia. Photo credit: Terry Kim, MD.

Some studies suggest a genetic factor, noting some genes associated with DNA repair are crucial for pterygium development.[24] Chronic irritation coupled with actinic damage are likely responsible for the fibrovascular reaction typical of pterygium.[16] Cytokines, growth factors, and matrix metalloproteinase are involved in the pathogenesis of pterygium,[12] and UV exposure is known to induce their proinflammatory aspects. However, studies of the genetic variant contributions are limited in patient numbers and should be interpreted with caution.

As might be expected with a disorder that has a large environmental component, direct medical and surgical costs to a nation's healthcare budget can be significant.[25]

Actinic Damage and Manifestations

Pterygia have histologic components similar to those associated with other photoaged disorders, including epidermal proliferation, inflammatory infiltrates, activated fibroblasts, accumulation of elastin, glycosaminoglycans, and extracellular matrix remodeling.[8] Hill and Maske[16] report 2 epidemiologic surveys in South Africa showing that pterygium is not closely linked to other actinic disorders such as pinguecula and climatic droplet keratopathy. They suggest the differences are a result of the chronic inflammation associated with pterygia.

Similar to pterygia, conjunctival epithelial malignancies are thought to be related to UV exposure. However, it is unusual for a malignancy to be mistaken for a pterygium given the distinct clinical difference in their appearances. For this reason, clinicians who are treating a typical-appearing pterygium surgically need not routinely submit the excised specimen for pathologic evaluation because this practice generally represents a significant and unnecessary cost to the healthcare system.

Recurrence and Its Predictors

Pterygium recurrence can be as high as 89% even after initial surgical management.[26] Pterygium removal with a conjunctival or amniotic graft is associated with a decreased recurrence risk of 5% to 10%. Biomarkers and predictors of recurrence of this disorder are neither well understood nor well defined.

Recurrence is likely multifactorial, with patient-attributed factors (genetics, environment) and/or surgeon-attributed factors (treatment methods).[27] Race is also likely to play a role in the recurrence of pterygia, with 1 study and much clinical experience suggesting higher rates among Hispanics and other darker-skinned groups.[28]

Tan et al.[29] suggest a grading system based on the visibility of episcleral vessels to indicate lesion thickness. Based on categorization, the degree to which pterygia were nontranslucent was a significant risk factor in recurrence when the pterygia were managed initially by scleral excision. A recent review found bare sclera excision resulted in substantially higher recurrence rates than excision accompanied by adjuvants.[30] Some authors think that excising the Tenon tissue under the edge of the conjunctiva during dissection can reduce recurrence rates; techniques that involve more than simply baring the sclera involve removal of the subconjunctival fibrosis and Tenon tissue.

Pterygium recurrence cannot be successfully predicted based on histologic or immunohistologic parameters alone.[31] However, several biologic characteristics are associated with recurrence.[8] We believe that biomarkers must undergo further evaluation before a uniform statement on their usefulness in a clinical setting as a predictor of recurrence can be made.

Treatment strategies for pterygium will probably continue to target multiple pathways rather than a single pathway. There are several visually relevant reasons to treat pterygia, among them the potential that the advancing cap (or the body) may encroach on the visual axis and reduce vision, that the pterygium can induce major against-the-rule (ATR) astigmatism, and that it can induce diplopia by restricting extraocular movement. In the cataract population, a pterygium can distort keratometry readings and the induced astigmatism it causes may be along the axis of the pterygium.[13,14] In both cases, we recommend removing pterygia larger than 2.0 mm first and waiting for the cornea to stabilize before performing cataract surgery. Simultaneous cataract and pterygium surgery is generally safe and effective, but accuracy can be best described as moderately predictable.[32] Kamiya et al.[32] suggested that a significant myopic shift can occur postoperatively and postulate steepening of the cornea after pterygium removal as the cause and that the degree of myopic shift is correlated to the size of the pterygium. Gulani and Dastur[33] reported 63% of 30 patients achieved a corrected distance visual acuity of 6/12 postoperatively, but both

with-the-rule and ATR astigmatism were well over 1.0 diopter (D) at 6 months. Kamiya et al.[32] reported only 48% of eyes within ±0.5 D (82% within ±1.0 D) of the targeted correction.

HISTORICAL APPROACHES TO SURGERY

The management of pterygium dates back to ancient Greece, where both the disorder and the management were frequently mentioned in the medical literature. One of the earliest mentions of surgical approaches to pterygium management dates to 25 AD, when Celsus described a needle and thread passing under and raising the pterygium, which was then excised with a knife.[34] In the 1500s, surgery was advised in rare cases only and recurrence was common even after "you have done everything in your power to cure it."[35,36]

Until the 1930s, numerous surgical techniques were suggested but none had overwhelming success or efficacy; these techniques included excision, incision, cauterization, transplantation, redirection, surgical division or splitting, inversion, irradiation, coagulation, rotation, and chemical treatment.[37] Excision with simple conjunctival closure was the most common; the pterygium was shaved off the cornea, affected conjunctiva removed from the limbus to the caruncle, and the defect closed with sutures. Redirection, in which surgeons would transplant the pterygium head away from the cornea, was widely used in the earlier parts of the 20th century, and a modification first described by McReynolds in 1902[38] became the most popular option.[36] As with other techniques, results were sometimes unsatisfactory and recurrence rates high.[39]

Recent History

By the mid-1900s, the bare sclera technique had evolved. In this method, the pterygium head is completely excised along with some of the adjacent abnormal nasal bulbar conjunctiva and Tenon tissue that was under the abnormal nasal bulbar conjunctiva. The surrounding normal bulbar conjunctiva was then sutured directly to the sclera, leaving an area of bare sclera several millimeters in width adjacent to the limbus.[37] The initial procedure was fairly simple and had few complications, but recurrence was high.[29,40] Although the technique is still used today, most surgeons opt to combine it with adjunctive therapies (radiation or antimetabolite treatment) to reduce recurrence rates.

Beta radiation was popularized in the 1970s, predominantly in the United States and Australia, and typically performed with strontium-90 after the bare sclera procedure.[37] The recurrence rates for pterygium excision with beta irradiation ranged from 0.5% to 52%, and complications included conjunctivitis, punctate keratitis, cataract, scleromalacia, infectious scleritis, and (rarely) endophthalmitis.[41,42]

Triethylene thiophosphoramide (thiotepa), a radiomimetic alkylating agent, was also used as an early adjunctive treatment for pterygium. In this treatment, multiple daily doses were necessary over a 4- to 6-week period and recurrence rates were low (ranging from 3% to 28%).[43,44] Although reported complications were low, thiotepa use diminished as other therapies gained support.

Sliding or Pedicle Grafts

When not using simple conjunctival closure, surgeons have used a variety of techniques, including sliding conjunctival flaps, pedicle flaps or grafts, conjunctival Z-plasty, conjunctivoplasty, and conjunctival relaxing incisions.[37] Sliding flap techniques minimize the defect by mobilizing and repositioning the surrounding normal conjunctiva. In some cases, a conjunctival autograft or amniotic membrane is placed in the remaining bulbar conjunctival defect, but this has been most useful if an insufficient amount of donor graft tissue is available to completely cover and close the defect after pterygium removal.[37]

Historical Approaches to Grafting

Graft tissue use during pterygium surgery was first reported in the late 1800s, but it was not until Thoft's[45] landmark study of the use of conjunctival autografts for various corneal and conjunctival surface disorders that graft surgery became popular.[46] Kenyon et al.'s technique[47] combining pterygium surgery with conjunctival autograft is still in widespread use today, 30 years after it was first reported. Other graft methods, including split-thickness skin graft, lamellar corneal graft, and amniotic membrane graft, have been described but not widely accepted (although recent techniques involving amniotic membrane grafts are changing that perception).

Techniques for conjunctival autograft transplantation have remained unaltered since Kenyon et al.[47] and Kenyon and Fava[48] first described it, with the notable exception of using fibrin tissue adhesive in lieu of sutures. Specific surgical recommendations are presented below.

Postoperative management typically includes a fluoroquinolone antibiotic and corticosteroid and nonsteroidal antiinflammatory drug (NSAID) treatment. Surgeons must ensure the steroid, antibiotic, and NSAID are dosed according to their labeled indications to control inflammation and pain and prevent infection. Dosing specifics will depend on which commercial product physicians choose, and the Cornea Clinical Committee does not endorse any specific product. The antibiotic and NSAID are generally discontinued at 1 week; however, the steroid must be continued and titrated to avoid potential rebound inflammation. At 1 month, if excessive inflammation persists, subconjunctival injection of triamcinolone 0.3 mL into the grafted area can be considered.[48]

SURGICAL ADHESIVES

Fibrin sealants have been used for decades. The first reported human use was for skin graft fixation in the 1940s. More recently, fibrin sealants have been used as an adjunct to hemostasis in cardiovascular surgery and trauma.[49–52]

United States regulators approved fibrin sealant in 1988, although not for ophthalmology. Because sutures are known to be a cause of tissue reaction and inflammation, numerous ophthalmic surgeons use fibrin sealant in an off-label use.

With fibrin sealant, fibrinogen is activated by thrombin. The adhesive capacity of the fibrin glue mimics the coagulation cascade.[53–55] During the coagulation cascade, factor X is activated and selectively hydrolyzes prothrombin to

thrombin. In the presence of thrombin, fibrinogen is converted to fibrin.

When mixed, the individual components of fibrin sealant—fibrinogen sealer protein, fibrinolysis inhibitor, and a thrombin and calcium chloride solution—mimic the human clotting cascade.[56] After the solutions come in contact with each other, the surgeon has 10 to 60 seconds to manipulate the glue, depending on the thrombin concentration.

Available Products

Currently, in the U.S., 2 companies have commercially available fibrin sealant products: Baxter Healthcare (Tisseel and Artiss) and Johnson & Johnson (Evicel). The chemical differences between the products were described by Hardten.[57] Tisseel fibrin sealant can be refrigerated in the freeze-dried form or can be purchased as frozen prefilled syringes. Chemically, Tisseel is composed of clottable protein (75 to 115 mg), fibrinogen (70 to 110 mg), plasma fibronectin (2 to 9 mg), factor XIII (10 to 50 IU), and plasminogen (40 to 120 mg). The small blue bottle contains bovine-derived aprotinin solution (3000 KIU/mL). The white bottle has thrombin 4 from a bovine source and is freeze dried (500 IU/mL). The small black bottle contains a calcium chloride solution of 40 mmol/L. After the vials are warmed, aprotinin (a fibrinolysis inhibitor) is added to the sealer concentrate vial, followed by warming and stirring. The second component is prepared by injecting the calcium chloride into the vial of thrombin. Those preparing the vials must use separate syringes to avoid premature clotting. The vapor-heated form has a bovine fibrinolysis inhibitor solution, whereas the Tisseel kit has a synthetic fibrinolysis inhibitor solution. Adhesion occurs when the 2 solutions are merged. Generally, the more concentrated the thrombin solution, the faster the clot forms.

Artiss fibrin sealant was first approved as an adherent of autologous skin grafts to surgically prepared wound beds resulting from burns. It is also available as a freeze-dried kit or as a prefilled frozen syringe. Once Artiss is reconstituted, time is critical: The product must be used within 4 hours, and the surgeon has approximately 60 seconds to manipulate the tissue prior to polymerization after a typical dilution. The amount of fibrinogen in the sealer protein solution is 100 mg/mL, and the synthetic fibrinolysis inhibitor is 3000 KIU/mL. Human albumin is also in this solution. In the thrombin solution, approximately 4 units/mL of human thrombin are present along with 40 mmol/mL of calcium chloride. Vapor heating and solvent/detergent treatment processes are used to reduce the chances of viral transmission.

Evicel fibrin sealant was initially approved for hemostasis in patients having surgery. One vial of the frozen solution contains fibrinogen at a concentration around 70 mg/mL, and the other has thrombin at a concentration around 1000 IU/mL. The sealant is stored at temperatures below −18°C. Once thawed, the vials should be used within 24 hours if kept at room temperature. Evicel contains no bovine protein components.

Fibrin glue was first used in conjunctival surgery in the mid-1980s. Its major use today in conjunctival surgery is after pterygium removal, although it has been used in strabismus surgery, corneal surgery (for corneal perforations, melts, corneal ulcers), glaucoma surgery (sealing leaking blebs, closing scleral flaps), cataract surgery (sealing incisions or securing haptics to the sclera), and vitreoretinal surgery (sealing full-thickness macular holes or for wound closure after retinal detachment surgery); as a fixation for lamellar grafts; and in the management of recurrent epithelial ingrowth after laser in situ keratomileusis surgery.[57]

Reports of inflammation are substantially fewer with fibrin sealant than with suture closures; the glue shortens surgical times; and fibrin sealant purportedly provides greater postoperative comfort than sutures. Anecdotally, members of the committee have noted the presence of more pyogenic granulomas after the use of sutures than with fibrin sealant, although granuloma can occur after both closure techniques. Farid and Pirnazar[58] compared pterygium excision with conjunctival autograft using tissue adhesive versus polyglactin (Vicryl) sutures and found a decrease in recurrence rates in those who had tissue adhesive closure. The authors suggested that the proinflammatory degradation of absorbable sutures incited a greater recurrence risk.

Risks of Fibrin Adhesives

Fibrin adhesives are prepared from pooled donor sources, and there is an inherent risk for transmitted infection. However, numerous studies indicate this is a rare occurrence, with a low risk.[59–65] At the time of donation, donors are tested for viral markers and are tested again after 6 months. The fibrin products are typically sterilized by gamma irradiation or with solvent and/or detergent treatments. Anaphylactic reactions have been reported and attributed to the presence of aprotinin in the compounds.[66–68]

Informed Consent Elements

Surgeons may wish to inform patients that fibrin sealants are blood products produced from human blood. As part of the informed consent, surgeons may also disclose that although fibrin sealants are blood products, there are no reports of their causing or transmitting human immunodeficiency virus, viral hepatitis, or prion-mediated disease.[69,70] A similar informed consent is necessary when using amniotic membrane, as that is also biologic tissue.

MITOMYCIN, 5-FLUOROURACIL, AND OTHER ADJUVANTS TO PTERYGIUM SURGERY

Because the recurrence rate after pterygium surgery is high (reportedly as high as 89%),[41,71] numerous adjunctive therapies have been proposed to reduce the recurrence rate. Among these, mitomycin-C (MMC) and 5-fluorouracil (5-FU) are commonly used.

Background and Chemistry

First synthesized by Dushinski et al. in 1957,[72] 5-fluorouracil (5-FU) is a fluorinated pyrimidine antimetabolite. Exposing the cornea to 5-FU impedes the proliferation of conjunctival and Tenon capsule fibroblasts and also

impedes proliferation of corneal epithelial cells.[73] This inhibitory action is thought to decrease recurrence rates, but recurrence rates between 11.4% and 60.0% have been reported.[74]

Application and Surgical Use

In the largest reported series of 125 consecutive eyes with intraoperative 5-FU (25 mg/mL), pterygia recurred in 36%.[75] Higher doses of 5-FU (50 mg/mL) decreased recurrence rates to around 11%, but recurrence rates with conjunctival autograft are around 12%, giving no statistical advantage to one over the other.[74] Although there is little in the literature to support routine intraoperative 5-FU use, routine use seems to have a role in treating recurrent lesions.[76–78] Prabhasawat et al.[79] reported the results of an unmasked randomized prospective controlled clinical trial of 5-FU injection for "impending recurrent pterygium." The respective recurrence rates were 31.4% in controls, 7.7% with 5-FU, and 14.3% with triamcinolone.

Singh et al.[80] were the first to describe MMC as an adjunct to pterygium surgery. Mitomycin-C is an antibiotic and antineoplastic initially isolated from *Streptomyces caespitosus*. In the early 1960s, some suggested its adjuvant use for pterygium surgery, but the use of MMC for pterygium surgery did not gain popularity until the late 1980s.[74] Studies have shown favorable results with doses as low as 0.02% (decreasing recurrence rates from 32% to 7% in primary pterygia and from 45% to 9% in recurrent pterygia).[81]

Numerous comparative studies have indicated MMC is as efficacious as conjunctival autograft in preventing recurrence.[74] The bare sclera approach with MMC 0.02% for 5 minutes has been reported to decrease recurrence rates from 45% to 5% with no reported complications.[82] Others have reported recurrence rates of 4% to 6% using 0.02% to 0.04% MMC with the only complication being mild superficial keratitis; this led to the recommendation to use the lowest dose intraoperatively given the similar efficacy outcomes.[83] In that study, the surgical technique included rotation of a conjunctival flap over the excision site at the conclusion of each case.

Risks and Management of Complications

Complications have been reported with 5-FU use, but they have been minor and transient in pterygium surgery. However, in the 1980s, cicatricial ectropion with topical 5-FU and punctal-canalicular stenosis with systemic 5-FU were reported.[84,85] Complications with 5-FU are more commonly reported when 5-FU is used in glaucoma treatment and include persistent epithelial defects, spontaneous bleb rupture, and development of a bacterial ulcer leading to perforation. However, the doses used in glaucoma management (up to 105 mg over the course of 2 weeks) are 5 to 10 times higher than those suggested for pterygia (usually 10 to 20 mg). There may be toxicity even in lower doses, and the use of 5-FU is somewhat contraindicated in patients with previous or current corneal disorders.[74,86,87]

Mitomycin-C complications include subjective complaints of tearing, photophobia, and pain. In 1 study of pterygium surgery at very low doses (0.01%), no complications were reported beyond postoperative irritation.[88] However, several studies indicate severe complications can occur months after the initial treatment; the complications include cataract formation, anterior uveitis, scleral plaque and necrosis, corneal edema and ulceration, protracted pain, anterior chamber inflammation, and nonhealing conjunctival, corneal, and scleral defects.[74] Complication theories include the high cumulative dosing and predisposing conditions (such as acne rosacea, ichthyosis, and dry-eye syndrome).

Hayasaka et al.[89] described late complications (18 to 25 years after pterygium excision) in which all cases presented with calcified plaques at the excision site; at the time of surgical removal of the plaques, scleral thinning was discovered, necessitating scleral patch grafts. Dougherty et al.[90] described a case of severe corneoscleral melt necessitating lamellar graft placement in a patient who had received a 3-minute application of MMC 0.02% followed by a sliding conjunctival flap closure.

AMNIOTIC MEMBRANE

Amniotic membrane is the third innermost layer of the fetal membrane and is essentially a basement membrane graft with numerous growth factors.[91] It can facilitate the proliferation and differentiation of epithelial cells and has been shown to be nonimmunogenic.[91] The physical features of human amnion make it useful in various potential ophthalmic surgeries, including pterygium and other conjunctival reconstructive surgery.[92,93]

Principles for Use in Ocular Surface Surgery

The cytoskeleton of amniotic membrane cells contains intracellular filaments that are crucial in maintaining the structural integrity of the membrane and its junctional permeability. There is evidence that the enzymes responsible for prostaglandin synthesis are also in the amnion.[92]

Corneal stem cells are concentrated in the limbus and can divide and move in a centripetal fashion when stimulated by trauma; conversely, central corneal cells are unable to divide when injured.[94] The amniotic basement membrane has tight junctions, whereas the surface is covered with a combination of amorphous and microfibrillar structures with microprocesses that bind the membrane to the epithelial cells. A connective tissue layer lies below the basement membrane. This ultrastructure mimics the surface of normal conjunctival tissues, allowing amniotic membrane to be considered a viable substitute for conjunctival tissue.[95] The tight junctions maintain hydration, and the loose connective tissue covers the nerve endings that were exposed during surgery, thereby reducing postoperative swelling, pain, and recurrence of the pterygium (Figure 2).[92]

Amniotic membranes were first investigated for use in ophthalmic surgery during the early 1900s, but results were not encouraging and use dwindled until the latter part of the century when studies were carried out in the Soviet Union and Latin America.[92] Since then, amniotic

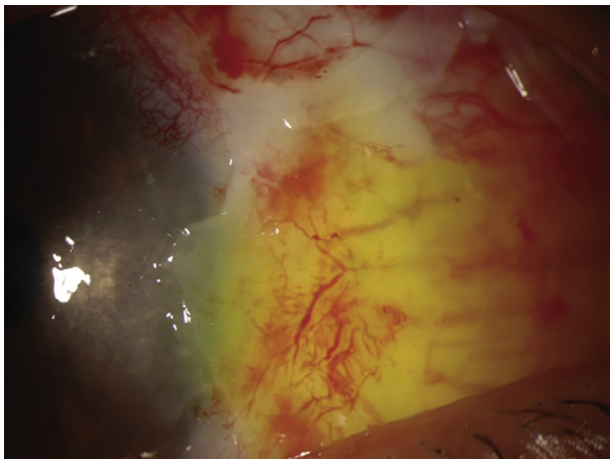

Figure 2. A post-pterygia eye after amniotic membrane transplant and Tisseel glue closure. Photo credit: Terry Kim, MD.

membrane has been shown to be beneficial during surgical reconstruction of the limbus after pterygium surgery. Covering the nerve endings reduces the patient's postoperative pain. Further, the basal lamina and stromal architecture of the amniotic membrane resembles that of human conjunctiva. This similarity makes amniotic membrane a particularly attractive replacement. It features an impermeable basal lamina that prevents evaporation and loss of electrolytes from the scleral bed; the basal lamina itself serves as a platform to grow healthy conjunctival and corneal epithelial cells.[92] The membranes act as a barrier, sometimes referred to as a "substrate that allows restoration of the normal limbal stem cells," while preventing abnormal conjunctival stem cells from flourishing.[93]

Properties

In the early iterations, conventional preparation used glycerol, tissue culture media, and freezing temperatures. In the 1980s, Muldachev used a conjunctival substitute in pterygium surgery and described less inflammatory response, less redness and edema, reduced incidence of recurrence, less pain, and faster recovery in patients who were operated on with this particular allotransplant. The allotransplant was later identified as amniotic membrane.[92] Initial results in 23 patients with recurrent pterygia, bullous keratopathy, corneal ulcers, dermoid reconstruction, reconstruction of symblepharon, and corneal dellen were promising.[96] Amniotic membrane in both frozen and dehydrated forms are now commercially available. Although surgeons have preferences as to the type of amniotic membrane, no consensus exists on which form is associated with lower rates of pterygium recurrence.

Available Types of Amniotic Membranes

Biotissue, which provides Amniograft, removes and separates the amniotic membrane from the chorionic membrane and preserves it in a solution of glycerol and tissue culture medium in a 50% solution prior to freezing at −80°C. The tissue is brought to room temperature in the operating room and rehydrated before use.

Innovative Ophthalmic Products (now part of Katena Surgical) developed Ambiodry, which does not require refrigeration or special devices for transportation. It is preserved inside a sterile envelope and boasts a shelf life of 2 years. Serologic testing excludes contaminated tissue, and dehydration preserves the tissue. A drying fixture embosses texture onto the final graft to identify the stromal and basement membrane sides. After the membrane is cut and double packaged, electron beam sterilization is applied. After being moistened with a balanced salt solution or human tears, the membrane behaves like a naturally occurring biologic membrane. Thickness varies depending on which version is used (Ambiodry2 versus Ambio5). BioD, LLC, also offers a dehydrated extracellular

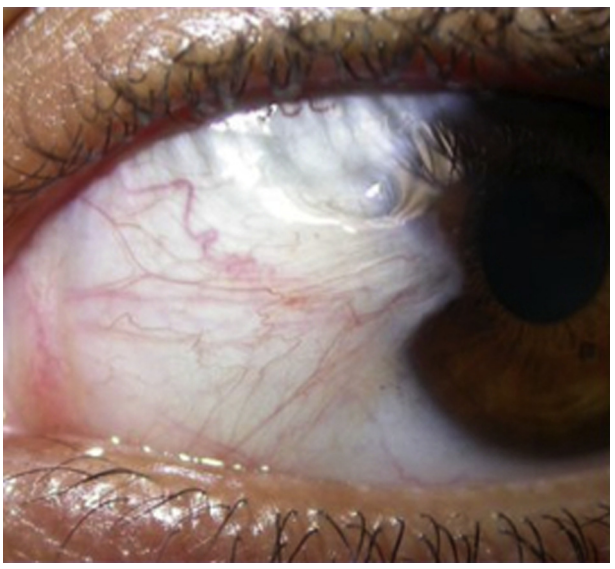

Figure 3. Pterygium before excision and conjunctival autograph. Photo credit: John A. Hovanesian, MD.

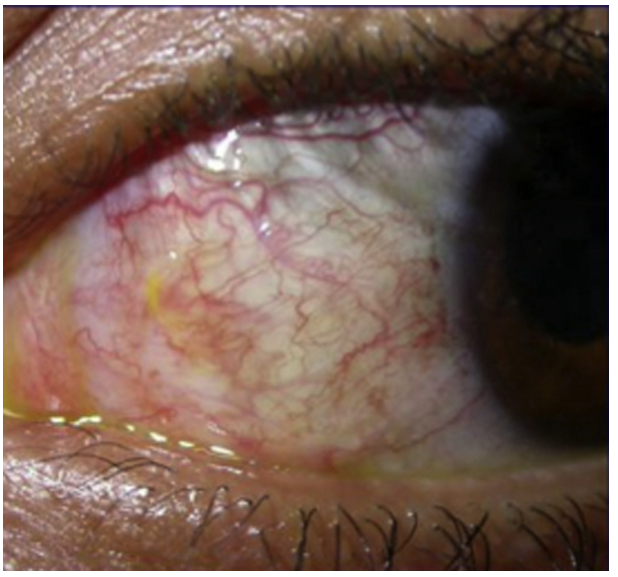

Figure 4. Pterygium after excision with conjunctival autograft. Photo credit: John A. Hovanesian, MD.

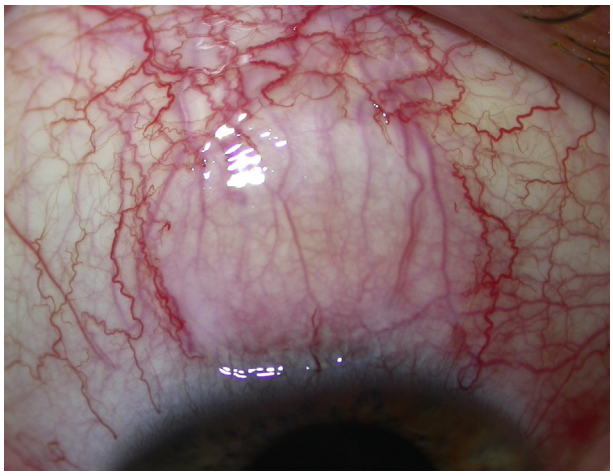

Figure 5. The graft donor site at the superior limbus with mild chemosis, demonstrating the presence of retained Tenon fascia, evidence that a thin graft had been harvested from this location. Photo credit: John A. Hovanesian, MD.

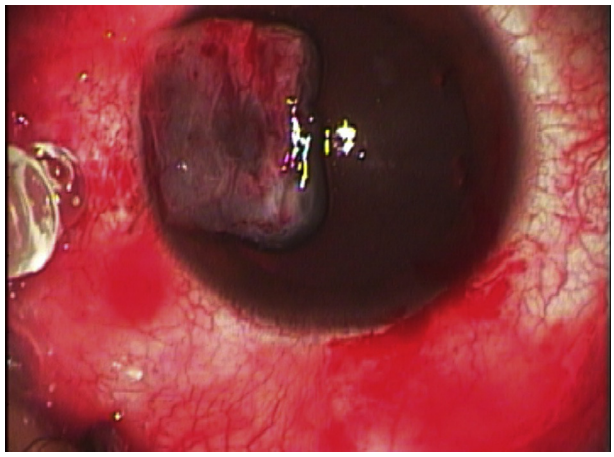

Figure 6. The free conjunctival autograft positioned adjacent to the pterygium excision site with the stromal side facing the surgeon and the limbal sign adjacent to the limbus at the excision site. Photo credit: John A. Hovanesian, MD.

membrane allograft derived from human amniotic tissue under the trade name BioDOptix.

PTERYGIUM EXCISION WITH CONJUNCTIVAL AUTOGRAFT

Pterygium excision with conjunctival autograft uses the patient's adjacent conjunctiva to fill the void left by the excised pterygium (Figures 3 and 4).[47,97] When a conjunctival autograft is used for pterygium excision, the preferred surgical technique is to remove the pterygium body from the bulbar conjunctival using a scissors and a forceps, excising most of the Tenon fascia down to bare sclera without excessive manipulation of the rectus muscle.[A] Particular care should be taken to excise the Tenon fascia under the free edges of the conjunctiva as this is the source of fibroblastic proliferation leading to recurrence. The leading edge or head of the pterygium can be avulsed or carefully dissected from the corneal surface, preserving Bowman membrane to maintain a healthy, intact corneal surface. The pterygium specimen can then be placed in formalin and submitted for pathology to confirm the diagnosis. (This may be necessary only in cases in which the clinical history and examination do not clearly support the diagnosis of a pterygium.) A diamond pterygium burr (not the type that is manufactured for corneal foreign-body and rust-ring removal) may be helpful in removing residual attachments of pterygium to leave a smooth corneoscleral junction. A sharp blade can also be held perpendicular to the surface and scraped parallel to the limbus to restore a surface that will provide an acceptable cosmetic appearance and functional surface to graft conjunctiva. In cases of recurrence or extensive scarring, it is particularly important to identify and isolate the rectus muscle; a muscle hook can be used to avoid damage.

The resulting conjunctival defect can be measured to determine the appropriate size for a graft, which is usually harvested from the superior or inferior bulbar conjunctiva. Graft edges can be marked with ink or small marks made with low-temperature cautery. This ensures the intended graft size is achieved and provides a mark to prevent unintentional graft inversion.

Use of a thin conjunctival graft is recommended as this avoids excessive chemosis in the graft and minimizes scarring in the donor site (Figure 5). To obtain a thin graft, the eye can be ducted to expose the full donor site and a small snip made with a blunt Westcott scissors at a graft edge away from the limbus. A spring-action Westcott scissors can be inserted through this small opening to bluntly dissect the conjunctival surface from Tenon fascia over the entire area of the graft. One blade of the scissors then placed through the small opening can extend the opening to the limbus to define the graft's lateral margins, leaving the limbal edge attached to the cornea. The donor site can be closed with a suture or fibrin adhesive or left open to heal without grafting or wound closure.

The graft can be placed directly on the bare sclera site and sutured in place. Most surgeons use 5 to 8 interrupted sutures for this. Fibrin sealant can also be used to secure the graft. In the latter case, the graft is placed on the cornea with the stromal side exposed and the epithelium touching the corneal epithelium. The limbal side of the graft should be adjacent to the limbal side of the pterygium excision site (Figure 6). A drop of the thrombin portion of fibrin sealant is applied to the bare sclera of the excision site, and a small portion (less than a drop generally) of the fibrinogen component is applied to coat the stromal side of the autograft. Two smooth-tipped forceps are used to grasp the autograft and invert it onto the excision site. This mixes the 2 components of the fibrin adhesive and aligns the limbus of the autograft to the limbus of the excision site.

Dilution of thrombin has been widely used by ophthalmic surgeons to slow the polymerization of fibrinogen to fibrin, allowing greater time to manipulate tissues. Dilution to 1:10 or 1:100 with a balanced salt solution is commonly practiced. To dilute to 1:10 concentration, 0.1 cc of thrombin and 0.9 cc of a balanced salt

solution are drawn into a single syringe, which is agitated to mix the components. To dilute to 1:100 concentration, 0.9 cc of the thrombin solution just described is discarded and another 0.9 cc of a balanced salt solution is drawn into the syringe and mixed. Using diluted thrombin does not reduce the tensile or shear strength of the polymerized fibrin sealant.[27,98] Undiluted fibrin sealant will polymerize within approximately 20 seconds, so it is important to align and stretch the edges of the graft to approximate the edges of the conjunctiva defect in a short period.

A therapeutic soft contact lens can be used to cover a large corneal epithelial defect. Alternatively, some surgeons place a small portion of fibrin adhesive on the deepithelialized surfaces to serve as a biologic bandage. The eye can be patched and shielded over a steroid and NSAID eyedrops.

Al Fayez[99] compared limbal and conjunctival autograft transplantation in advanced and recurrent pterygia. Limbal transplantation appeared more effective than free conjunctival transplantation in recurrent pterygia, but no statistically significant differences were found in advanced pterygia. Al Fayez[100] found the same outcomes in a much larger prospective parallel group study in 224 eyes that presented with recurrent pterygia.

Conjunctival autograft transplantation is not without potential downsides. It can make closing the large conjunctival defects difficult, and the technique mandates that conjunctiva be reserved for the possibility of glaucoma filtering surgery.[101] In patients who present with an increased likelihood of needing glaucoma filtration surgery in the future, harvesting the conjunctival autograft from an inferior bulbar location might be better.

Because of graft suturing, this method has the disadvantage of a relatively longer surgery than the bare sclera technique. It also carries the risk for complications such as pyogenic granuloma formation and giant papillary conjunctivitis, as well as significant patient discomfort after surgery.[102]

Finally, although rare, the graft can mechanically displace or become lost. Avascular stromalysis of the sclera is directly related to excessive or misapplied MMC use.[48] However, since the recurrence rate is only 5%, even in recurrent cases involving cicatricial strabismus, the technique should be at the forefront of management strategies.[48]

PTERYGIUM EXCISION WITH AMNIOTIC MEMBRANE GRAFTING

The less-than-stellar outcomes with previous techniques and the high recurrence rates have necessitated exploration of other surgical techniques to remove pterygium. The American Medical Association's Current Procedural Terminology code for amniotic membrane transplantation for ocular surface reconstruction is 65780. As of February 2015, more than 800 peer-reviewed articles on the ocular use of amniotic membrane, highlighting novel and therapeutic applications, had been published. Because amniotic membrane grafts have virtually no size limitation, fibrotic tissue can be extensively excised, which may contribute to the favorable surgical outcomes.[101]

Anatomic Considerations

Between 20 and 30 ophthalmic transplants can be performed with 1 placenta. The 2 most commonly used types of amniotic membrane are described above. However, outside the U.S. and other western countries, fresh and unpreserved membrane is often used within days or weeks of donation.

The anatomic makeup of amniotic membrane seems contradictory as amniotic membrane contains both inhibitory and proinflammatory cytokines; that is, interleukin (IL)-6 and IL-8 are proinflammatory and IL-10 and IL-1ra antiinflammatory, yet both are present in the amniotic membrane.[103] Different donors will likely yield differences in the amniotic membrane itself. The thickness and morphology of the donor membrane is affected by its original location. The variation in thickness may affect the integration of the membrane with other ocular surface tissues. Age, race, parity, gravidity, and duration of gestation may contribute to variability of specimens.[101]

Preparation of Tissue

After the pterygium head is undermined and separated at the limbus and dissected toward the central cornea with a Westcott scissors, an additional 1.0 to 2.0 mm margin of conjunctival tissue must be dissected to expose the bare sclera (Figure 7). The amniotic membrane is then cut within its surgical packaging to the appropriate size. When the membrane is prepared, the basement membrane should be on top, away from the sclera. When using Ambiodry2, for example, this is easily achieved; if the surgeon can read the letters "IOP," the membrane is in the correct position. When frozen amniotic membrane is used, the stromal side is stickier than the basement membrane side.[B]

Use of Fibrin Adhesive and Best Practices for Fixation

Fibrin glue can be prepared by the surgical assistant. If surgeons use Tisseel VH, the surgical assistant prepares the 2 components while the pterygium is being surgically removed. The adhesive can be administered to the ocular surface in 1 of 2 ways to form the fibrin clot. In the first

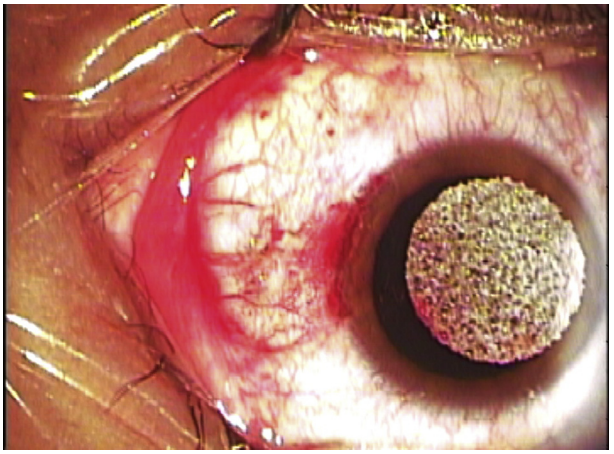

Figure 7. Excising a pterygium in preparation for placement of an amniotic membrane graft is facilitated by excising an additional 1.0 to 2.0 mm margin of conjunctiva to expose bare sclera. Photo credit: John A. Hovanesian, MD.

method, the 2 components are combined in the Y-connector of a Duploject syringe (supplied in the kit), and 10 drops are purposely wasted to ensure both components of adhesive are flowing at the tip. One drop is then injected under the amniotic membrane. A smooth instrument is used to rapidly position and smooth the membrane. The coagulum (fibrin clot) starts forming in 5 to 7 seconds, achieves 70% of the final tensile strength in 10 minutes, and is at full strength in 2 hours.[A] Altering the concentrations of the individual components will provide flexibility in setting times.

In the second method, 1 drop of the fibrinogen component of the sealant is placed on the scleral bed. The membrane must be placed several millimeters below the surrounding conjunctival tissue as the fibroblasts that can lead to recurrence are typically found here. Thrombin is placed on top and around the edges of the membrane to activate it. This should keep the membrane in position for weeks.[104]

In both methods, the speculum is removed and antibiotic–steroid ointment applied over the treated eye, which is then patched and shielded.

Postoperative Management and Results

Compared with a suturing technique, the use of fibrin glue causes less discomfort postoperatively (see above). Complications can arise if surgeons use too much glue or if excess product is left under the graft inadvertently. If the glue was not distributed evenly, the graft will appear edematous during the early postoperative period. The graft may retract if parts of the underlying sclera did not receive fibrin glue.

PTERYGIUM EXCISION WITH CONJUNCTIVAL AUTOGRAFT AND AMNIOTIC MEMBRANE

To further reduce the recurrence rate, amniotic membrane has been used in a simple adjunctive procedure performed with pterygium excision and conjunctival autograft.[27] The combined use of a conjunctival autograft and placement of an amniotic membrane is usually reserved for high-risk cases that involve large or inflamed pterygia or recurrences of pterygia.[101]

The combined technique places a small strip of amniotic membrane in the subconjunctival space surrounding the pterygium excision followed by placement of a conjunctival autograft (Figure 8). In this subconjunctival location, the amniotic membrane is thought to function as a biologic depot of antifibrotic and antiinflammatory material that prevents pterygium recurrence. Fibrin adhesive is used to secure the conjunctival autograft and the amniotic membrane.[27]

Surgical Technique

In the combination surgery, the pterygium is excised with an additional 1.0 mm margin of conjunctival tissue to expose the bare sclera. A space is created beneath the conjunctiva surrounding the excision site, tunneling approximately 5.0 mm into the tissue on 3 sides, ensuring the space remains superficial to most of the Tenon fascia, the medial rectus muscle, and tendon.[C] The conjunctival autograft is prepared from the superior bulbar conjunctiva of the same eye and remains attached at the limbus superiorly.

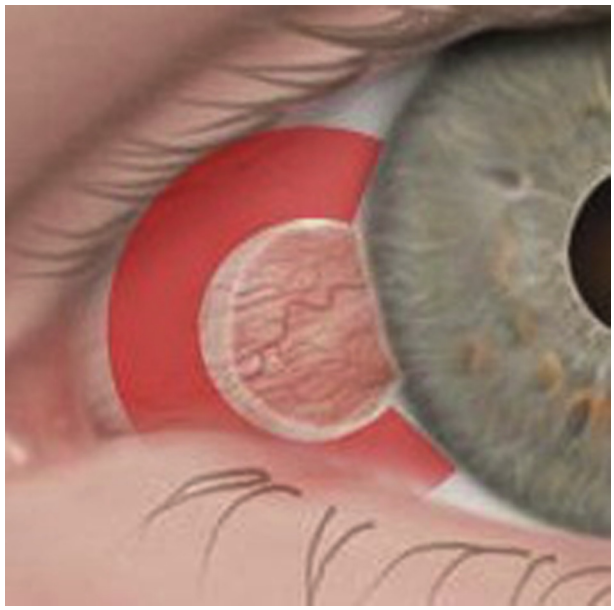

Figure 8. A strip of amniotic membrane placed in the subconjunctival space surrounding the pterygium excision site in the location highlighted in red. Photo credit: John A. Hovanesian, MD.

A potential advantage to this technique is that either cryopreserved or freeze-dried amniotic membrane can be used. In both cases, the membrane is cut into a C-shaped graft large enough to surround the conjunctival defect.

In this technique, fibrin tissue adhesive preparation differs from the standard preparation.[27] The components are not transferred to the syringe after preparation; rather, a scrub nurse draws approximately 0.1 cc of each component into 2 separate sterile 1.0 cc syringes through a sterile 18-gauge needle, minimizing the air entry into the syringe. Next, 0.9 cc of a balanced salt solution is added to the thrombin-filled syringe and the syringe is inverted several times to facilitate mixing.

A 0.12 forceps is recommended for lifting the conjunctiva, and a small amount of fibrinogen is applied to the undersurface of the conjunctiva (to keep the amniotic membrane in place); thrombin is not applied. In the freeze-dried amniotic membrane method, a balanced salt solution or fibrinogen solution can be placed on a section of surgical drape to facilitate hydration of the amniotic membrane graft; this step can be eliminated with the wet form of amniotic membrane. The hydrated amniotic membrane graft is placed directly on the bare sclera and brought into the subconjunctival space. The concept is to create a subconjunctival amniotic membrane area that surrounds the bare sclera but does not cover it. Edges of the overlying conjunctiva are lifted and advanced toward the limbus to cover any exposed remnants of the transplanted amniotic membrane. The presence of the fibrinogen, mixed with small amounts of thrombin in the patient's own blood, will ensure the edges stay in place.[27]

The conjunctival autograft, which remains attached to the superior limbus, is now reflected onto the cornea (epithelium to epithelium) and cut free from the superior limbus. The limbal side of the graft has to be oriented to

the limbus; a small droplet from the diluted thrombin syringe is applied to the bare sclera, and a small droplet from the fibrinogen syringe is applied to the underside of the graft. The graft is then flipped onto the bare sclera, which allows the 2 adhesive components to mix.[27]

After surgery, a topical fluoroquinolone antibiotic is applied 4 times a day for 1 week. Prednisolone acetate 1.0% is started 4 times a day and tapered over 4 weeks. A topical NSAID to control pain is recommended for 1 to 3 days immediately postoperatively.[27]

It is possible for patients to present with 2-headed pterygium. These cases can be treated with a conjunctival autograft obtained from the superior and/or inferior fornix, using a subconjunctival implant of amniotic membrane for 1 or both sites.

Postoperative Complications and Management

A retrospective analysis of 100 patients who had the combined procedure found a 1% recurrence rate after a 6-month follow-up, and all the conjunctival and amniotic membrane grafts remained viable and in place.[105]

COMPLICATIONS OF PTERYGIUM SURGERY

Postoperative complications are not common in pterygium removal and can be attributed to the surgical technique itself or to any of the possible adjuvants used.[106] It has been generally accepted that pterygium recurrence rates are substantially less with conjunctival or limbal autografts than with the bare sclera technique, but complications persist.[30] Topical antibiotics, lubricants, and analgesics are routinely used in the immediate postoperative period, and all patients should be examined postoperatively.[107,108]

Early Complications

Various early postoperative complications have been reported after pterygium removal relative to the surgical removal technique and postoperative medication used. The use of MMC postoperatively has led to reports of wound dehiscence and corneal epithelial defects.[109] This has been traditionally noted when MMC has been used topically. The ASCRS Cornea Clinical Committee therefore currently supports intraoperative rather than topical postoperative use of MMC to treat pterygium.

Although several other immediate complications are associated with pterygium surgery (including reactionary hemorrhage leading to excessive bleeding, graft edema, hematoma below the graft, or corneal scarring), they are usually not vision threatening and resolve quickly. Excessive bleeding can be managed via pressure bandages, graft edema resolves with topical treatment, and hematomas should be examined under the microscope and then evacuated under a block. Depending on the depth of corneal involvement, scars can be observed or may require lamellar keratoplasty later. Localized epithelial defects are noted in nearly every initial postoperative examination and heal within 24 hours.[106] Similarly, conjunctival chemosis may be noticed but resolves spontaneously.[106]

Suture-related complications can be reduced by using monofilament nylon in lieu of polyglactin sutures. Fibrin adhesives can eliminate suture-related complications.

Improperly harvesting or securing the conjunctival autograft may be a risk factor for the development of a Tenon cyst, especially if the graft was harvested with a thick Tenon layer or if the wound edges are imbricated after graft placement. Treatment/resolution occurs via excision of the cyst followed by conjunctival closure.[106]

It should be noted that conjunctival donor site can be used for subsequent surgeries (recurrent pterygia) provided the first dissection was performed carefully, with minimal disruption of Tenon fascia, and there is minimal fibrosis.

Late Complications

Recurrence is considered a significant late complication of initial pterygium surgery and often happens within a few months. The more repeatedly a recurrence happens in a particular eye, the more difficult the treatment, as the recurrence is often accompanied by increased conjunctival inflammation and faster corneal involvement.[40,106,110]

Scleral ulceration is a potential long-term complication after the bare sclera technique.[111] In the same report, the use of beta irradiation to prevent recurrence of pterygia was a significant cause of iatrogenic ocular disease. Ptosis, symblepharon, and iris atrophy have been reported after irradiation use in pterygium excision.[106] Ptosis often resolves spontaneously but does take several months. If symptomatic, the symblepharon release can be performed and the patient should be put on topical lubricants.[106]

Antimetabolite-Related Complications

It is well documented that MMC can reduce the recurrence rate to less than 10%, but severe postoperative complications include corneal edema, perforation, scleral calcification, corectopia, iritis, sudden-onset mature cataract, severe secondary glaucoma, incapacitating photophobia, and pain, although the complications have been associated with poor patient selection and overuse of MMC.[80,88,112] If strict patient-inclusion criteria are applied, stringent patient monitoring until reepithelialization can reduce MMC-related postoperative complications.[82,88,113]

Scleral dellen as a result of delayed conjunctival wound closure has been reported after bare sclera excision with MMC.[114] Other reported complications include temporary and prolonged discomfort, tearing, hyperemia, subconjunctival hemorrhage, wound dehiscence, and pigment accumulation after a single dose of intraoperative MMC.[106] It is now recommended that only patients with high-risk pterygia receive intraoperative MMC.[106]

Overuse of antimetabolites can also lead to scleral complications. These include necrotizing scleritis and scleral thinning with perforation.

MANAGING RECURRENCE

Minimizing pterygium recurrence is crucial to prevent vision loss, as advanced or recurrent pterygia eventually result in loss of corneal transparency in the visual axis.

High recurrence rates have led to the abandonment of several surgical techniques, and debate on the optimal technique is ongoing. Postoperative alterations in peripheral corneal topography, persistent wetting defects, and chronic irritation and inflammation after surgery may also increase the likelihood of pterygium recurrence.[115] Inflammation coupled with persistent vascularity is often an indication of recurrence. Recurrent pterygia continue to move toward the limbus, eventually moving onto the corneal surface.

Recurrent pterygia differ histopathologically from primary pterygia,[116] have higher rates of recurrence with subsequent surgical interventions, and must be considered a different entity than primary pterygia. Recurrent pterygia are also considered more aggressive clinically and therefore more likely to cause visual deficits and other complications.[115]

Simple Recurrence

Once a patient has been treated for primary pterygia, vigilant monitoring during the first postoperative months is critical to minimize the risk for recurrence: While 50% of recurrences appear in the first 4 months, 97% appear within the first 12 months.[117] Although conjunctival autografts have been shown to reduce recurrence rates in both primary and recurrent pterygia to less than 5%, recurrence can be a result of inadequate peripheral dissection, insufficient graft size, thick graft with Tenon tissue, and graft retraction due to inadequate fixation.[36] Similarly, recurrence rates after pterygia surgery using an amniotic membrane graft may be slightly higher than surgery using a conjunctival autograft, but recurrence rates with the 2 graft types are similar when appropriate dissection and/or other adjunctive therapies are performed.[115]

If persistent inflammation remains during the early postoperative period, reinitiation of topical steroids is commonly used to deter recurrence. Topical steroids can be used to quiet the inflammation and tapered slowly, and side effects of continued steroid use (intraocular pressure increases, steroid-induced cataract formation) must be discussed. Adjunctive use of commercially available topical NSAIDs should also be considered as studies have shown they can slow epithelial migration and are as effective as some topical steroids in treating inflamed pterygia and pinguecula.[118] Although the topical NSAIDs rarely induce side effects, their efficacy in recurrent pterygium has not been proven.[115]

Topical cyclosporine 0.05% has been used in the management of pterygium excision patients and early recurrences[119] and has been evaluated in its native form or compounded at a higher concentration (1.0% or 2.0%).[115] Topical tacrolimus and interferon alpha-2b and subconjunctival 5-FU have also been advocated for early pterygia recurrence[77,120,121]; the use of topical MMC has been discussed and the potential risks in the treatment of recurrent pterygia and of primary pterygium are the same.

Local steroid injections have shown efficacy in about 50% of cases of recurrence, and they are typically delivered subconjunctivally adjacent to the pterygium recurrence in the oblique quadrants, carefully avoiding the interpalpebral fissure.[115] (Patients may complain about the cosmetic appearance of a white depot.) However, there are no large randomized controlled clinical trials to confirm the efficacy of local steroid treatment for recurrent pterygium. The off-label use of topical and subconjunctival bevacizumab has been evaluated successfully in the treatment of recurrent pterygia, but further study is warranted.[115]

It is not uncommon for patients with recurrent pterygia to have concomitant lid disease or ocular rosacea. Medications that inhibit matrix metalloproteases should be considered, including oral doxycycline and/or topical tetracycline.

Because there is a higher risk for recurrence in advanced and recurrent pterygia that involved the optical zone, performing the pterygium excision alone at the initial surgery and then corneal surgery (including lamellar keratoplasty, phototherapeutic keratectomy, or penetrating keratoplasty) after recurrence is avoided may be optimal.

Recurrent pterygia are more difficult to excise as scarring is already present, which can not only obliterate tissue planes but also increase the risk for extraocular muscle damage.[36] In cases of extensive scarring, primary closure techniques are unreliable; sliding or pedicle flaps can sometimes be effectively used.[115]

Complex Recurrence (Symblepharon, Loss of Fornix Structure)

In cases of aggressive pterygium recurrence or recurrent pterygia that extend more centrally than the initial pterygium, surgical management should be considered as a first-line option, with a 4- to 6-month delay from the initial surgery.

When using a conjunctival autograft, using an oversized graft (1.0 to 2.0 mm) in both dimensions and the superior conjunctiva can minimize the risk for symblepharon and fornix shortening.

Advanced recurrent pterygium can be devastating to the normal anatomy of the ocular surface with the formation of symblepharon and/or fornix shortening or obliteration. The restricted extraocular movement coupled with the decreased visual acuity may result in diplopia and require extensive surgical intervention to maximize outcomes.[115]

Complete dissection of previous symblepharon and scarring is mandatory. The symblepharon should be completely freed flush with the ocular surface to completely remove the adhesions and minimize the resultant epithelial defects on the palpebral conjunctiva while minimizing the excision of normal conjunctival tissue. The freed conjunctival surface can then be retracted into the fornix and fixated with full-thickness sutures through the tarsus and palpebral conjunctiva. Isolation of the adjacent rectus muscle with careful dissection of any associated fibrosis is recommended to avoid inadvertent damage, to release any restriction present preoperatively, and to prevent extraocular muscle restriction postoperatively. Once complete, a large conjunctival autograft, amniotic membrane graft, and/or buccal mucosal graft may be used to reconstruct the ocular surface.[115]

There is often minimal normal conjunctiva, requiring the use of amniotic membrane or buccal mucosal grafts to cover the resultant defects after dissection. These buccal mucosal grafts are efficacious but not often used because of their inferior appearance compared with conjunctival autograft or amniotic membrane.[36] To avoid postoperative hypertrophy, surgeons should obtain a very thin flap free of submucosal tissue when using buccal mucosal grafts. Complete coverage of any outstanding defect is recommended, and severe cases may warrant deep extension into the fornix where the graft may fold over itself to cover the palpebral conjunctiva. Sutures are recommended over fibrin adhesive or cautery to fixate the graft along the lid margin and to prevent symblepharon reformation. A limbal conjunctival flap or autograft in conjunction with the amniotic membrane graft can be performed to supply epithelial cells to cover the large graft and provide an additional barrier to recurrence.[36,122] The surgical time increases when this reconstruction technique is used. The superiority of the technique over amniotic grafting alone has not been established well enough to justify its use in all cases.[115]

Symblepharon rings and/or bandage contact lenses in conjunction with a large temporary tarsorrhaphy may be useful in preventing reformation; each is removed about 6 to 8 weeks postoperatively, and frequent topical steroids with a slow taper should be used. Aggressive lubrication also is recommended to encourage epithelialization of the bulbar and palpebral conjunctiva and prevent reformation.

DISCUSSION

The treatment of pterygium continues to evolve, as does the management of recurrence. The ASCRS Cornea Clinical Committee advocates the use of any of the techniques described in this review. Individual surgeons will have preferences based on many parameters, and the various techniques described have been used successfully to manage primary or recurrent disease.

We also strongly advocate that surgeons leave a clean corneal surface and take the necessary steps to minimize manipulation and trauma during pterygium removal to reduce the risk for postoperative inflammation that may lead to recurrence. We believe that the more surgeons understand pterygium and the various treatment techniques, the lower the recurrence rates will be.

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