Current Techniques and Novel Treatments in Ocular Surface Reconstruction

BY MITCHELL C. SHULTZ, MD

Over the past decade, significant advances have been made in the field of ocular surface reconstruction. Tissue adhesives, allograft materials, and stem cell research all play a vital role in surgeons' ability to restore a more natural corneal and conjunctival surface in eyes with a variety of disorders that affect the ocular surface. Although the most common procedure ophthalmologists perform is the removal of sight-threatening and cosmetically unacceptable pterygia, they also manage limbal stem cell deficiency, delayed epithelial closure following trauma or surgery, symblepheron after blepharoplasty of the lower lid, chemical burns or systemic diseases such as Stevens Johnson syndrome and ocular cicatricial pemphigoid, and challenging corneal perforating injuries. This month's installment of "Peer Review" focuses on the most current articles available on this fascinating topic. Several have excellent graphics that demonstrate the techniques the authors discuss.

I was fascinated to learn about techniques such as the preoperative subconjunctival injection of mitomycin C (MMC) combined with delayed bare-sclera excision of pterygia that has recurrence rates similar to the more popular and expensive techniques that include intraoperative MMC (with increased risks of corneal and scleral toxicity) and amniotic membrane (AM) grafts. In a perfect world, surgeons would provide patients with the latest and most technically advanced modalities for the management of pterygia. Instead, the reality of managed care, accountable care organizations, and a restricted Medicare budget will dictate how physicians spend their patients' health care dollars. It should be noted that the surgical management of primary and recurrent pterygia is different around the world, and I hope that the selection of articles presented herein will assist readers' clinical decision-making process. Although I believe that health care reform is going to affect ophthalmologists mostly in a negative way, surgeons must not compromise their ideals to serve corporations and must continue to advocate for their patients' best interest.

With regard to limbal stem cell deficiency, research is providing exciting alternatives to cadaveric allograft tissues, which require lifelong systemic immunosuppressive therapy. The use of umbilical cord stem cells, which are considered ethically acceptable to religious and governmental advocacy groups, appears to be promising when these cells are combined with the transplantation of human AMs.

I hope you enjoy this installment of "Peer Review," and I encourage you to seek out and review the articles in their entirety at your convenience.

TISSUE ADHESIVES

Shehadeh-Mashor et al retrospectively evaluated the safety and efficacy of combining fibrin glue with a conjunctival autograft and MMC in 28 cases of recurrent pterygium. The investigators applied MMC 0.02% for 2 minutes after excising the pterygium. Then, they used Tisseel tissue glue (Baxter International, Inc.) to fixate the conjunctival autograft. Recurrent pterygium occurred in one case over a mean follow-up period of 26.5 months. The recurrence rate was 3.5%, graft dehiscence occurred in two cases, and one case required intervention with additional Tisseel tissue glue and sutures.[1] A study by Sarnicola et al concluded that fibrin glue-assisted ipsilateral conjunctival autograft is safe and efficacious and that it is associated with a low rate of recurrence. One hundred eleven eyes of 92 patients treated for primary

pterygium were retrospectively evaluated for recurrence rate and intraoperative and postoperative complications. The recurrence rate after 2 years was 4.5% (n = 5), with only one case of donor site granuloma and no other significant postoperative complications.[2]

Nassiri et al described a technique for harvesting thin limbal grafts from cadaveric corneoscleral rims and a sutureless method to secure the grafts to the recipient eye using fibrin glue. The retrospective study included 19 eyes of 16 patients with bilateral limbal stem cell deficiency. Fifteen eyes underwent a cadaveric keratolimbal allograft, three eyes underwent sectoral keratolimbal allograft (180° only), and one eye underwent conjunctival-limbal autograft. The donor grafts were fixated using only fibrin glue to secure the limbal allografts to the recipient eye. In patients with complete limbal stem cell deficiency, two donor corneas under 50 years of age and less than 5 days old with large scleral rims (greater than 3 mm) and as much conjunctiva as possible were required for complete coverage.

The surgeon prepared the recipients by removing all abnormal epithelium and fibrovascular pannus, while the ophthalmologist performed a 360° peritomy to undermine and dissect underlying adhesions. Three 180° donor grafts were placed in close proximity to one another to cover the entire bed, and then they were fixated with Tisseel fibrin glue. After the grafts were in place for 2 to 3 minutes, the surgeon trimmed excess fibrin glue and loose conjunctiva from the donor grafts. The host conjunctiva was then approximated to the donor grafts.

The mean time for epithelial healing was 8.4 ±4 days. At the last follow-up, 15 of 19 eyes had a stable ocular surface, and four eyes had developed graft failure, which was diagnosed 7.5 months postoperatively. Significant improvement in visual acuity from baseline was demonstrated in 78.9% of eyes. To prevent graft failure, the surgeon used the Cincinnati protocol with a regimen consisting of systemic steroids, tacrolimus, and mycophenolate. The study's authors highly recommended comanaging patients with an organ transplant team.[3]

PREOPERATIVE SUBPTERYGIAL MMC INJECTION

In a prospective, randomized study, Mandour et al evaluated 91 eyes of 91 patients with primary pterygia. Group 1 included 48 patients who underwent bare-sclera excision of the primary nasal pterygium 1 month after a subconjunctival injection of 0.1 mL of 0.15 mg/mL MMC into the body of the pterygium. Group 2 included 43 patients who underwent pterygium excision followed by conjunctival-limbal sutured autographs. Recurrent pterygium occurred in two eyes (4.2%) in group 1 compared with four eyes (9.3%) in group 2. None of the patients in group 1 developed a persistent epithelial defect, dellen, or signs of scleral melting at any time during the postoperative follow-up. According to the authors, the subconjunctival injection of MMC decreased complications of persistent corneal or conjunctival defects, reduced toxicity to the corneal endothelium, which can occur with the topical intraoperative application of MMC, and resulted in technically easier and short operative times.[4]

SODIUM HYALURONATE GEL

Jun et al conducted a prospective, randomized study that examined the safety benefits of using a gel formulation of MMC instead of sponges soaked in the conventional solution. MMC gel was prepared by mixing sodium hyaluronate gel and trypan blue. Fifty consecutive patients were randomized to the gel group or the solution group. The researchers measured endothelial cell counts with a noncontact specular microscope at 0, 1 week, and 1, 3, and 6 months. Although there was no significant difference in cellular density between the two groups during the study, the researchers hypothesized that the increased molecular density of sodium hyaluronate (800 kDa+) helped to prevent MMC from diffusing through the cornea and sclera, minimizing toxicity, and that trypan blue helped to identify the location of the material to prevent unwanted exposure to the adjacent tissues.[5]

TOPICAL 0.05% CYCLOSPORINE

In a prospective, controlled study, Turan-Vural et al randomized 36 eyes of 34 patients with primary pterygium into two groups of 18 eyes each (group 1, 18 patients; group 2, 16 patients). A bare-sclera technique was used for all eyes in both groups. In group 1, 0.05% cyclosporine was administered every 6 hours postoperatively for 6 months. Patients in group 2 did not receive cyclosporine treatment. Pterygium recurred in four patients in group 1 (22%) and in eight patients in group 2 (44%). The preoperative size of pterygium was not considered to be statistically significant in regard to the postoperative outcome ($r = .343$, $P > .05$). The authors proposed that, unlike in normal conjunctival tissue, there are elevated T lymphocyte levels in pterygial tissue, and these cells play an important role in the mediation of pterygium pathogenesis.[6]

ADJUNCTIVE LOW-DOSE β RADIATION

Viani el al evaluated the effectiveness and safety of a single, low, postoperative dose of β irradiation (β-RT) in pterygium. The researchers compared conjunctival autograft (CAG) surgery with CAG plus adjuvant

β-RT in a randomized clinical trial. The study included 116 eyes with primary pterygium. Eight patients were lost to follow-up.; mean follow-up for the remaining 108 patients was 18 months (range, 8-33 months). All patients had CAG harvested from the superior bulbar conjunctiva. The β-RT group received 10 Gy of β-RT in a single dose after CAG. Pterygium recurred in five eyes (9.2%) in the CAG plus β-RT group compared with 12 eyes (22%) in the CAG group. The study's authors recommended longer-term follow-up to address fears about late tissue damage related to β-RT.[7]

GRADING SYSTEM

Liu et al reported a new system of grading for the management of recurrent pterygia. They evaluated 32 eyes of 30 patients who were treated consecutively between January 1, 2002, and December 31, 2010. Their surgical technique involved recession of the pterygium; sealing the gap; covering exposed medial rectus muscle by AM, conjunctival autograft, or oral mucosal graft; and covering bare sclera with AM. Main outcome measures were recurrence, diplopia, and caruncle morphological characteristics. Caruncle grading strongly correlated with residual conjunctiva (P = .01), severity of diplopia (P = .001), and overall success rate (P = .05). Transplanting AM alone was more successful when there was 27.8 ±10 mm of residual conjunctiva. During the mean follow-up of 27.5 ±20.5 months, 30 of 32 eyes (94%) achieved total success without recurrence, 17 of 21 eyes (81%) with preoperative abnormal caruncles returned to normal, one eye (3%) developed a recurrence and was lost to follow-up, and one eye (3%) was left with a depressed caruncle and residual diplopia on adduction.[8]

SURGICALLY INDUCED NECROTIZING SCLERITIS

A rare complication of pterygium surgery is the development of surgically induced necrotizing scleritis (SINS). Yamazoe et al reported a case of SINS that occurred in a 68-year-old man who underwent uncomplicated surgery with excision and placement of a conjunctival autograft. The patient had no prior history of systemic disease, and intraoperative MMC was not used. On postoperative day 17, the conjunctival graft was noted to be avascular, with a new corneal epithelial defect present. The graft and sclera melted despite continued treatment with topical steroids and antibacterial agents. Bacterial and fungal cultures were negative, as were tests for rheumatoid factor and antinuclear antibody. The diagnosis of SINS was suspected, and the patient was started on oral prednisone 20 mg per day. Although the initial results were positive, the patient could not tolerate oral prednisone due to nausea. Surgical resection of the necrotic tissue was performed, followed by the creation of a conjunctival flap with Tenon capsule to cover the defect, and the graft was well accepted. Treatments for SINS were also discussed in the article and included immunosuppression with systemic steroids, cyclophosphamide, or tacrolimus; surgical intervention, including resection of necrotic tissue; AM transplantation; and scleral or corneal tissue patch grafts.[9]

MODIFIED SYMBLEPHARON RING WITH AM PATCH GRAFT

In a prospective, randomized study, Liang et al observed 75 patients with grade 3 to 6 acute ocular burns. The patients were randomly divided into two groups. Thirty-nine eyes received the sutureless AM patch with a modified symblepharon ring. The other 36 eyes received the conventional, sutured AM patch as a control. The mean epithelialization time was significantly shorter in the sutureless group (14.03 ±7.36 days compared with 23.06 ±10.87 days). Complete epithelialization occurred in 71.79% of eyes in the sutureless group compared with 47.22% of eyes in the sutured group. Symblepharon formation was noted in 38.46% of eyes in the sutureless group, significantly less than the 61.11% of eyes in the sutured group. Corneal neovascularization occurred in 53.85% of eyes in the sutureless group compared with 72.22% of eyes in the sutured group. The investigators concluded that this modified method was simple, minimally invasive, and atraumatic; provided symptomatic relief; and promoted effective wound healing.[10]

PHOTOCHEMICAL TISSUE BONDING AND AMs

In a rabbit model, Gu et al and Verter et al independently reported on a novel, light-activated, tissue-bonding technique for sealing AMs over the cornea (Verter) and for attaching AM grafts to limbal stem cells and then to the cornea (Gu). Using 0.1% rose bengal and 150 J/cm^2 at 532 nm, Verter demonstrated rapid bonding of AM grafts to the cornea. Alternatively, Gu used 0.1% rose bengal and an irradiance of 0.4 W/cm^2 to deliver 80 J/cm^2. The bonding treatment was nontoxic to keratocytes but slightly reduced the migration of corneal epithelial cells on amnion ex vivo. In a comparison to sutured techniques, Gu also demonstrated that this light-activated cross-linking produced better outcomes with improved corneal transparency as well as decreased inflammation, vascularization, and scar formation. Both authors concluded that this rapid light-activated technique produces a strong,

immediate bonding between amnion and the cornea through singlet oxygen ($^1O_2$) activated protein-protein cross-linking. The authors suggested further evaluation for ocular surface strategies for corneal lacerations that are difficult to suture, pterygium excision, corneal melt syndromes, forniceal reconstruction, and composite limbal stem cell and amnion grafts.[11,12]

STEM CELLS LINING THE UMBILICAL CORD

Reza et al proposed the use of umbilical cord stems cells for ocular surface reconstruction, because they are less immunogenic, nontumorigenic, highly proliferative, and ethically acceptable compared with embryonic stem cells prohibited in the United States. The investigators performed ex vivo expansion of limbal stem cells on human AM (HAM) substrate. The limbal stem cells expressed vital markers, including HES1, ABCG2, BMI1, and CK15 as well as adhesion-associated molecules integrin-α6, -α9, -β1, collagen-IV, and lamin. These sheets (competitive local exchange carrier-muc-HAM) similarly expressed CK3 and CK12, which are cytokeratins specific to the cornea. The sheets were transplanted onto rabbit corneas that were denuded of all corneal epithelial and limbal cells. Eyes that received these competitive local exchange carrier-muc-HAM transplantations formed well-laminated five- to seven-layer-stratified epithelium with a smooth surface. The nontransplant group exhibited hypercellular changes (seven to nine layers thick and irregular), and the HAM-transplant-alone group developed a thin epithelium with multiple infiltrating inflammatory cells. The study's authors proposed that this mechanism could benefit patients with bilateral limbal stem cell deficiency for whom autologous limbal stem cell transplantation is not possible.[13] ■

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