

Ocular Surface Transplantation

An overview of techniques, indications, and postoperative management.

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Severe ocular surface disease is one of the most challenging ailments in the realm of ophthalmology. Affected patients have profound visual loss, chronic inflammation of the ocular surface and cornea, chronic discomfort, and a poor prognosis for standard keratoplasty. Recent advancements in the various techniques of ocular surface transplantation have led to significant improvements in the overall success rate in the management of these patients.¹⁻¹⁰

Procedures for ocular surface transplantation can be divided into autografts and allografts. A conjunctival autograft takes tissue from the same eye or the fellow eye to manage a conjunctival deficiency. Limbal tissue is not used, because this method is not meant to treat limbal disease. In a conjunctival limbal autograft, a normal fellow eye is used as a donor for severe, unilateral limbal deficiency. When limbal disease is present in the fellow eye, it is important that the conjunctival graft include limbal tissue. For bilateral disease, an allograft procedure is required. The two main sources of donor tissue are cadavers and living relatives.

TECHNIQUES

Keratolimbal Allograft

The cadaveric donor procedure, also known as *keratolimbal allograft*, utilizes one or two donor corneoscleral rims in which peripheral cornea, a scleral rim, and a small conjunctival skirt are used to transfer limbal stem cells (Figure 1). The technique is readily available and affords a large quantity of limbal stem cells to be transferred to the recipient eye.

Living-Related Conjunctival Limbal Allograft

Living-related conjunctival limbal allograft is a surgical method in which normal limbal tissue and the conjunctival carrier are harvested from a patient's living relative and

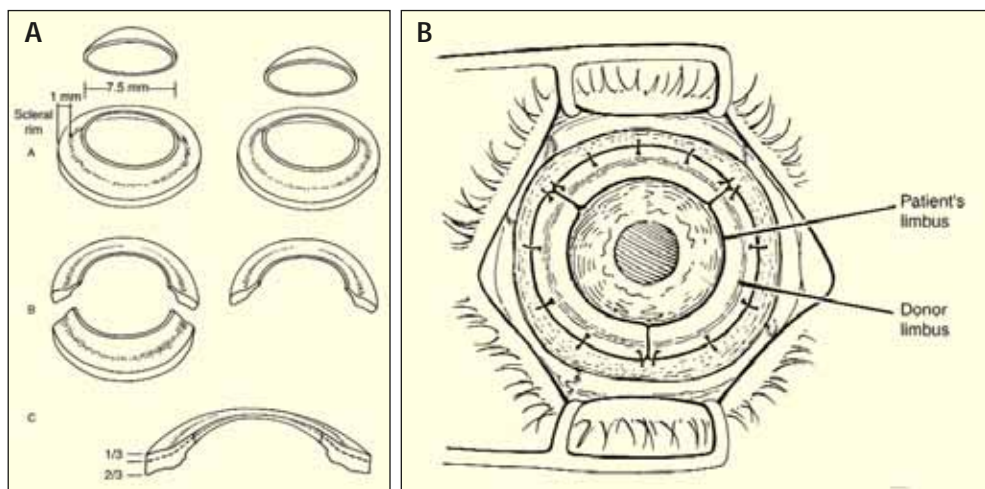


Figure 1. For keratolimbal allograft, the authors prepare tissue from a cadaveric donor for transplantation (A). Both corneas from the same donor are used to provide three lenticules of 6 clock hours of limbal tissue. The keratolimbal allograft method utilizes three donor limbal tissue crescents positioned at the limbus of the recipient's eye (B).

transplanted onto the diseased eye. Two trapezoidal limbal grafts, including approximately 6mm of the limbus and extending 5 to 8mm posterior to the limbus, are transplanted (Figure 2). This technique supplies conjunctival tissue as well as limbal cells. However, a smaller number of stem cells are transplanted when compared to the keratolimbal allograft procedure. Additionally, the living-related conjunctival limbal allograft depends on the availability of a relative who agrees to donate.

Ex-Vivo Expansion

Newer methods of stem cell transplantation utilize the technique of ex-vivo expanded limbal cells. Limbal tissue from a donor is expanded in culture before transplantation. Cells can come from a normal fellow eye, a living relative, or a cadaver. This technology is still being developed and is not utilized as commonly as the aforementioned allograft procedures.

Amniotic Membrane Transplantation

Amniotic membrane transplantation is also used in ocular surface reconstruction. The membrane is harvested from a human placenta and can be stored frozen for extended periods of time. These transplants can provide basement membrane that can then be utilized as a substrate for epithelial cell growth. Additionally, amniotic membrane can replace conjunctival tissue in which there are no conjunctival sources available. However, amniotic membrane transplantation alone does not provide stem cells and should not be used as a solitary procedure in patients with significant limbal stem cell deficiency.

POSTOPERATIVE MANAGEMENT

Compared to conventional penetrating keratoplasty, limbal allografts are associated with a significantly higher risk for rejection because the grafted tissue does not have the same immune privilege status as a central corneal graft. The vasculature of the limbal area allows the donor tissue greater access to the immune system. Also, most eyes with ocular surface disease have preoperative inflammation due to the disease state.

Our current immunosuppression protocol includes topical corticosteroids as well as topical cyclosporine. All patients receive systemic immunosuppression with three agents: (1) corticosteroids used 1mg/kg/day and tapered during a 6-month period; (2) tacrolimus, 1 to 4mg b.i.d.; and (3) mycophenolate, 500 to 1,000mg b.i.d. A multidrug regimen is necessary with limbal allograft transplantation to achieve adequate immunosuppression. Additionally, it allows the use of lower doses of individual medications, thereby reducing the risk for side effects. The level of immunosuppression can be justified

for this group of patients, because they are highly dependent on the survival of their grafts for functional vision. The necessary duration of immunosuppression depends on a patient's preoperative diagnosis, postoperative course, and whether the rejection of a transplant has occurred. The drug regimen is continued for at least 12 to 18 months for the vast majority of patients, with the corticosteroids reduced to less than 1mg/kg/day for the first 3 months postoperatively.

A number of patients, particularly those with noninflammatory disease such as aniridia, can successfully taper off all systemic immunosuppression at 12 to 18 months. However, patients with underlying inflammatory conditions such as Stevens-Johnson syndrome will often have signs of chronic inflammation and are at risk of rejection upon the discontinuation of systemic immunosuppression. If inflammation persists, or an impeded rejection reaction occurs, it may be necessary to maintain the patients on long-term immunosuppression.

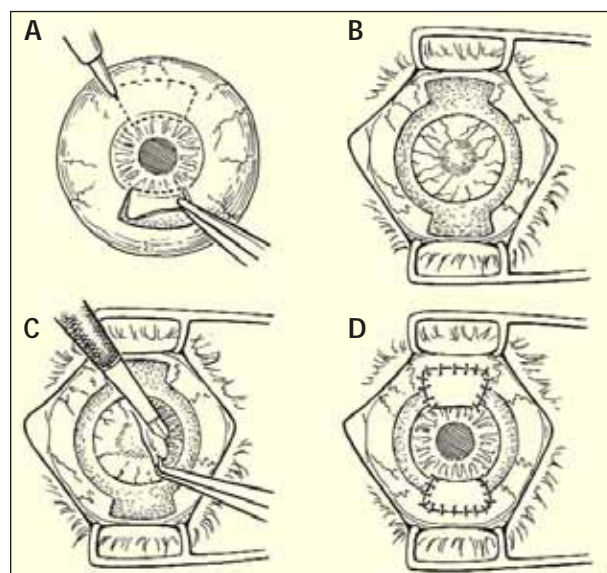


Figure 2. When performing the living-related conjunctival limbal allograft transplantation technique, tissue is harvested from a donor eye. The dimensions of the conjunctiva are marked using a gentian violet pen. Harvesting begins in the conjunctiva and proceeds anteriorly (A). To prepare the recipient for the donor tissue, the authors perform a 360° limbal conjunctival peritomy and allow the conjunctiva to recess. Recipient beds of 3 clock hours are created at the 12- and 6-o'clock meridian (B). Abnormal corneal epithelium and fibrovascular pannus are removed using necessary techniques (eg, peeling, blunt and sharp dissection) (C). Conjunctival allografts are transferred to corresponding anatomic positions on the recipient's eye and secured with 10-0 nylon sutures (D).

TABLE 1. AN ALGORITHM FOR THE TREATMENT OF PATIENTS WITH SEVERE OCULAR SURFACE DISEASE¹¹

Management of Glaucoma

Tube shunt for patients on more than one topical medication

Correction of Eyelid and Eyelash Abnormalities

Exposure: lagophthalmos, ectropion

Misdirected lashes: entropion, trichiasis, distichiasis

Suppression of Inflammation

Topical corticosteroids and cyclosporine A

Systemic immunosuppression

- Oral corticosteroids
- Tacrolimus or cyclosporine A
- Mycophenolate or azathioprine

Ocular Surface Transplantation

Conjunctival limbal autograft for unilateral disease

Keratolimbal allograft for bilateral limbal deficiency with minimal-to-moderate conjunctival disease

Living-related conjunctival limbal allograft for bilateral limbal deficiency with moderate-to-severe conjunctival disease

Combined conjunctival-keratolimbal allograft for bilateral limbal deficiency with severe conjunctival disease

Keratoplasty

Lamellar keratoplasty for patients with stromal opacification with normal endothelium

Penetrating keratoplasty for patients with stromal opacification with loss of endothelial function

RECOMMENDED TREATMENT ALGORITHM

Based on our experience with severe ocular surface disease, we have established a sequential paradigm for the management of patients with ocular surface disease (Table 1).

Glaucoma Management

On the patient's initial presentation to our clinic, we evaluate IOP. We recommend the aggressive management of elevated IOP by the early placement of a tube shunt in patients who are on more than one topical glaucoma medication. After stem cell transplantation, many patients experience an increase in their IOP. Moreover, their long-term use of multiple topical medications not only becomes less effective but can be toxic to the transplanted epithelial surface. Therefore, it is important that a patient's IOP be stable before ocular surface transplantation.

Eyelid Function

We evaluate the status of the eyelid and lashes before performing ocular surface transplantation. Patients with significant exposure, lagophthalmos, entropion, ectropion, trichiasis, or distichiasis are referred to the oculo-plastic service. Significant eyelid abnormalities can cause a breakdown of the epithelium and secondary microbial infection in patients with ocular surface disease. Oculo-

plastic procedures should improve the function of the eyelids as much as possible prior to ocular surface transplantation.

Ocular Surface Inflammation Management

Limbal allografts transplanted to an inflamed ocular surface have a significantly poorer prognosis than those in which the inflammation has been reduced. If significant conjunctival inflammation is present, topical and systemic immunosuppression should begin weeks to months before transplantation to improve the overall success rate of the procedure.

Ocular Surface Transplantation

Once the IOP stabilizes, lid anatomy and function are restored, and the ocular inflammation is reasonably controlled, ocular surface transplantation may be performed (Figure 3). The selection of technique is based on several factors. If the patient has unilateral disease, a conjunctival limbal autograft is the procedure of choice because it does not run the risk of failure secondary to immune rejection. For patients with bilateral disease, the most common choices of donor tissue are the cadaveric procedure (keratolimbal allograft) or the living-related conjunctival limbal allograft. For the vast majority of patients with limbal deficiency without extensive conjunctival disease, we advocate



Figure 3. A patient suffered a severe alkali injury (A). Three months after the authors performed a keratolimbal allograft, the patient achieved a normal corneal epithelium and experienced a regression of neovascularization (B). In another 3 months, the authors performed a successful penetrating keratoplasty (C).

the use of keratolimbal allograft because of the availability of cadaveric donor tissue and the increased quantity of stem cells available for transplantation.

If patients have extensive conjunctival disease, we believe the living-related conjunctival limbal allograft provides much needed healthy conjunctival cells in addition to limbal tissue. Most recently, we have combined keratolimbal allograft with living-related conjunctival allograft in patients who have the most severe ocular surface disease. This combination maximizes the advantages inherent to each procedure.

Keratoplasty

In patients whose IOPs are controlled, whose ocular lid function is reasonably healthy, and who have a stable ocular surface, we will consider keratoplasty as a means of visual rehabilitation. The vast majority of patients with a failed ocular surface have subsequent stromal scarring and loss of vision even if the ocular surface has been restored. These individuals then undergo a penetrating or a lamellar keratoplasty for visual rehabilitation. If there is significant stromal scarring but good endothelial function, a lamellar keratoplasty will reduce problems with endothelial rejection. If the endothelium is involved in the disease process, a penetrating keratoplasty is required.

SUMMARY

Ocular surface transplantation has changed greatly during the last decade. Patients with severe ocular surface disease now have a chance of obtaining reasonable visual function. Surgeons need not only address the corneal and ocular surface problems, but they must also aggressively treat glaucoma and oculoplastic problems prior to ocular surface transplantation. It is extremely important to control inflammation both pre- and postoperatively with systemic and topical immunosuppression to maximize outcomes.

Improvements in the success rates of transplantation procedures are still needed, because patients with the most severe ocular surface damage and total conjunctival

failure are not candidates for ocular surface transplantation. The development of conjunctival substitutes, as well as techniques to reverse severe keratitis sicca, will allow patients with total ocular surface failure the opportunity for visual recovery. ■

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