Today's Practice refractive fundamentals

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Anatomically targeted procedures avoid the removal of healthy corneal tissue and replace or address only the diseased layer.

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Attempts at corneal transplantation in humans using both animal donor cornea and human graft tissue began in the 1800s. Richard Kissam, MD, reported the first corneal transplant in a human in 1838; this was a xenograft transplantation, with the donor cornea of a live pig grafted into a human recipient eye. Arthur von Hippel, MD, performed the first lamellar keratoplasty in 1886, grafting a full-thickness rabbit cornea into the lamellar bed of a young woman, and he is credited with the invention of the mechanical trephine for corneal procedures.

In 1905, Eduard Zirm, MD, performed the first successful human penetrating keratoplasty (PKP) on a 45-year-old farm laborer with bilateral alkali injuries. A few decades later, Vladimir Filatov, MD, introduced techniques for corneal grafts using cadaver donors and advanced the development of trephines. In the 1930s and 40s, Ramon Castroviejo, MD, developed the double-bladed knife and square graft technique with overlying sutures.

With the combined efforts of all these key figures, PKP became the dominant corneal transplantation procedure for decades. The procedure had a shorter operating time than other keratoplasty techniques and provided excellent outcomes as defined by graft clarity; PKP can yield a more than 90% clear graft rate at 5 years postoperative.

However, complications have also been associated with PKP, including poor refractive outcomes, high regular and irregular astigmatism, and unpredictable corneal power. PKP has also been associated with a risk of intraocular complications, poor wound healing, delayed visual rehabilitation, rupture, endothelial rejection, and endothelial cell loss. Historically, approximately 25% of all PKP eyes undergo endothelial rejection reaction, and 5% to 10% of all grafts fail due to endothelial rejection.

Over the past decade, there has been a changing paradigm in corneal surgery. The focus has shifted away from full-thickness grafts and toward anatomically targeted procedures that avoid the removal of healthy corneal tissue and replace or address only the diseased layer (Figure 1). These procedures include deep anterior lamellar keratoplasty (DALK) to address stromal disease; a variety of endothelial keratoplasty (EK) procedures, including Descemet stripping endothelial keratoplasty (DSEK), Descemet stripping automated endothelial keratoplasty (DSAEK), and Descemet membrane endothelial keratoplasty (DMEK) for endothelial disease; and ocular surface stem cell transplantation for epithelial disease. This article outlines the fundamental aspects of each approach.

ENDOTHELIAL KERATOPLASTY

One of the most significant advances in corneal surgery has been the introduction of EK techniques. The surgical treatment of endothelial failure is the leading indication for keratoplasty (40% to 50% of cases). Common indications for EK include Fuchs dystrophy, pseudophakic edema, aphakic edema, and regrafts for endothelial failure.

Melles et al reported the preliminary clinical results of posterior lamellar keratoplasty in 2000. In seven sighted human eyes, a deep stromal pocket across the cornea was created through a 9.0-mm superior scleral incision.

TAKE-HOME MESSAGE

- The focus has shifted away from full-thickness grafts and toward anatomically targeted procedures that avoid the removal of healthy corneal tissue and replace or address only the diseased layer.
- Anatomically targeted procedures include DALK to address stromal disease; EK procedures such as DSEK, DSAEK, and DMEK for endothelial disease; and ocular surface stem cell transplantation for epithelial disease.
- The future of ocular surface transplantation may include conjunctival stem cell replacement, the development of nonantigenic donor tissue, ex vivo expansion of limbal cells, and recipient-derived bone marrow pluripotent stem cells.
sion. A 7.0- or 7.5-mm posterior lamellar disc was excised and replaced by a donor posterior disc of the same size. No suture fixation of the graft was performed, but a scleral incision suture was placed. In 2004, Melles et al described descemetorhexis, a technique to excise Descemet membrane from a recipient cornea; they concluded that Descemet membrane could be excised in a controlled fashion without damaging the posterior corneal stroma. This maneuver quickly created a recipient stromal bed to facilitate implantation of a donor posterior lamellar disc in posterior lamellar keratoplasty.

The advantages of EK over PKP include a minimal change in refractive error, avoiding increased higher-order aberrations; a small, secure wound; a stronger and more stable eye; faster recovery; elimination of corneal graft sutures; and earlier surgical intervention. DSEK can also be performed in patients with Fuchs corneal dystrophy and cataract.

Several developments have been introduced to improve the outcomes of EK, including DSEK insertion devices, thin DSEK techniques, and DMEK. DSEK insertion devices allow easy placement of tissue, even as thin as 70 μm, through an incision of less than 4.0 mm. Examples of these devices include the Tan EndoGlide (Angiotech), EndoSaver (Ocular Systems Inc.), and Busin Glide (Moria).

**Ultrathin DSAEK.** Massimo Busin, MD, presented a new approach to DSAEK aimed at utilizing ultrathin grafts (UT-DSAEK). Busin et al recently published 2-year outcomes of a prospective, consecutive, interventional case series of patients undergoing UT-DSAEK for endothelial decompensation. Donor preparation was performed using a microkeratome-assisted double-pass technique. At 3 months postoperative, mean corneal graft thickness was 78.28 ±28.89 μm. The percentage of patients achieving BCVA of 20/20 or better at 3, 6, 12, and 24 months was 12.3%, 26.3%, 39.5%, and 48.8%, respectively.

**DMEK.** The advantages of DMEK are that it eliminates stroma from the graft, using the thinnest tissue possible; should result in the best visual acuity possible with a transplant procedure; and uses smaller incisions with less residual refractive error. The disadvantages include difficulty of tissue preparation, resulting in a high rate of tissue loss; increased graft detachment rate; increased endothelial cell loss due to tissue preparation; difficulty of tissue insertion due to the flimsy donor tissue; and graft detachments.

In a prospective study by Guerra et al, DMEK was performed alone (n = 110) or combined with either phacoemulsification and IOL implantation (n = 23) or pars plana vitrectomy (n = 3). The investigators found...
that 41% of patients achieved a BCVA of 20/20 or better, 80% achieved 20/25 or better, and 98% achieved 20/30 or better. There was a 4.2% graft creation failure rate, 62.0% rebubble rate, and 8.0% primary failure rate. Endothelial cell loss at 1 year was 36 ±20%.

**Future endothelial replacement.** Currently, DSEK techniques yield excellent results. Thin DSEK yields better visual outcomes than traditional DSEK. Although DMEK may result in the best visual outcomes, complication rates are much higher than with thin DSEK.

There is a need to develop methods for eye banks to cut reproducible, thin grafts in the range of 60 to 80 μm. Studies are needed to determine the best procedure—DMEK versus thin DSEK—and to assess whether thin DSEK produces visual outcomes similar to those of DMEK and whether the complications of DMEK can be reduced.

**DEEP ANTERIOR LAMELLAR KERATOPLASTY**

DALK is indicated in patients with corneal stromal disease and a functional endothelium. In this population, the procedure has several advantages over PKP. DALK retains the host endothelium, eliminating endothelial rejection, reducing endothelial cell loss over time, and prolonging graft survival. DALK is also associated with a decreased incidence of intraoperative complications, stronger corneal wounds, and less astigmatism.

However, several factors have served as barriers to the adoption of DALK. Retained stroma leads to interface haze and decreased visual acuity. DALK is also associated with a longer surgical time than PKP, a steep learning curve, and lower reimbursement. Additionally, some surgeons are in denial that the procedure is better than PKP.

**Return to lamellar keratoplasty.** The concept of deep

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**Evolution of Keratoplasty**

<table>
<thead>
<tr>
<th>Year</th>
<th>Procedure</th>
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<tbody>
<tr>
<td>1840</td>
<td>Xenograft</td>
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<tr>
<td>1860</td>
<td>Lamellar keratoplasty</td>
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<tr>
<td>1906</td>
<td>Penetrating keratoplasty</td>
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<tr>
<td>1990</td>
<td>Ocular surface transplantation</td>
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<tr>
<td>2000</td>
<td>Endothelial keratoplasty</td>
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<tr>
<td>2002</td>
<td>Deep anterior lamellar keratoplasty</td>
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<tr>
<td>2004</td>
<td>Boston KPro</td>
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<tr>
<td>2009</td>
<td>Biosynthetic cornea</td>
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Figure 1. The focus of corneal surgery has shifted away from full-thickness grafts and toward anatomically targeted procedures.
lamellar corneal dissection leaving Descemet membrane intact was first proposed by Von Walther and described further by Franz Muhlbauer in 1842. Use of full-thickness donor corneal tissue without any dissection through the corneal stromal tissue was proposed for lamellar keratoplasty by Hallermann in 1959. He further proposed both full-thickness donor graft with endothelium and full-thickness donor graft without endothelium over a deeply dissected corneal stromal recipient bed for lamellar keratoplasty.

In the 1960s to 1970s, additional techniques were developed for DALK, such as Malbran’s peeling-off approach. In 1984, Eduardo Arenas Archila, MD, described the use of intrastromal air for dissection. In 2002, Anwar et al described the big-bubble technique, the first procedure to achieve a quick and repeatable baring of Descemet membrane in anterior lamellar keratoplasty.

DALK versus PKP. Bahar et al reported a comparative case series of 30 keratoconic eyes that underwent DALK or PKP. Both groups achieved similar visual outcomes, but patients in the PKP group experienced more postoperative astigmatism, endothelial cell loss, and rejection episodes. Patients in the DALK group had a shorter time to suture removal.

Shimazaki et al conducted a randomized clinical trial comparing DALK and PKP in 26 eyes with stromal scarring and corneal dystrophy. Both groups had similar visual outcomes; however, patients in the DALK group had higher endothelial density, and those in the PKP group had higher postoperative intraocular pressure (IOP).

Javadi et al conducted a randomized clinical trial including 77 keratoconic eyes that underwent DALK or PKP. Both groups had similar visual and refractive outcomes; however, the PKP group had a longer duration on steroids and more rejection episodes, and the DALK group had no endothelial rejections and earlier suture removal.

Sarnicola et al conducted a retrospective study of 660 consecutive DALK procedures in 502 patients with a mean follow-up of 4.5 years (range, 6 months to 10 years). Average graft survival rate was 99.3%. Endothelial cell loss averaged 11.0% at final follow-up. Endothelial cell density was unchanged between 6 months postoperative and the last follow-up visit.

OCULAR SURFACE TRANSPLANTATION

Severe ocular surface disease (OSD) and stem cell deficiency are conditions that result in loss of limbal and/or conjunctival epithelial stem cells. Etiologies may be

1. traumatic or toxic, including chemical (alkali or acid), thermal, toxic (mitomycin C), and contact-lens–induced,

2. inflammatory, including Stevens-Johnson syndrome and ocular cicatricial pemphigoid, and

3. congenital, including aniridia or other dermatologic conditions.

An important lesson in severe OSD is not to perform routine keratoplasty for limbal stem cell deficiency. All keratoplasties will fail due to recurrence of the ocular surface failure. The patient will then be immunologically sensitized to corneal antigens and have a worse prognosis for ocular surface transplantation.

In 1964, Jose Barraquer, MD, described an autograft technique in which transplantation of epithelial limbal and conjunctival-corneal tissue from the patient’s fellow eye improved the outcome of keratoplasty procedures in eyes that had sustained thermal injuries. Richard Thoft, MD, described conjunctival transplantation in 1977 and keratoepithelioplasty in 1984 and 1990. Various techniques for limbal transplants were described in the late 1980s through mid-1990s, including limbal autograft transplantation, limbal allograft transplantation, and conjunctival limbal allograft transplantation.

At the Cincinnati Eye Institute/University of Cincinnati, our OSD team has worked to improve the outcomes of ocular surface transplantation. We have developed a classification of OSD and proposed a standard nomenclature for OSD transplantation procedures so that investigators can compare techniques. We have also developed an immunosuppression protocol based on organ transplantation that is safe and effective and devised new surgical techniques specific to the extent of ocular surface damage.

In cases of severe bilateral ocular surface failure, patients may be treated with (1) ocular surface transplantation (keratoplasting), (2) the Boston Keratoprosthesis (KPro), or (3) osteo-odontokeratoprosthesis.

KPro. The Boston KPro artificial cornea has evolved over the past 50 years under the leadership of Claes Dohlman, MD, PhD, at the Massachusetts Eye and Ear Infirmary. Advantages of the keratoprosthesis include a single operation (no staged keratoplasty required) that is technically similar to PKP, no need for immunosuppression (and therefore no concern regarding medical issues), and no risk of rejection. Additionally, a poor ocular surface does not interfere with vision.

Disadvantages of the Boston KPro include an inability to accurately measure IOP, the need for lifelong close follow-up, and the risk of complications that can lead to loss of the eye (corneal melts, infectious keratitis, and endophthalmitis). Caution must be taken in cases of severe dry eye.

At the Cincinnati Eye Institute, we conducted a retrospective chart review of 105 patients (126 eyes) who received the Boston KPro. Nineteen cases of corneal melts were identified; of these, 12 had a preoperative diagnosis of severe OSD. Ten cases of infectious keratitis were identified, nine of which had a preoperative diagnosis of severe OSD. Of three cases of endophthalmitis that were identified, two had a preoperative diagnosis of severe OSD. This review showed that the complication rate was worse in eyes with severe OSD.
THE FUTURE

Overall, the future of ocular surface transplantation is likely to include conjunctival stem cell replacement; the development of nonantigenic donor tissue; ex vivo expansion of limbal cells, whether from fellow eye, relative, or postmortem source; and recipient-derived bone marrow pluripotent stem cells as a source of ocular surface tissue. Some recent investigations hold promise for future development:

Cultured endothelial cells. Kinoshita et al39 successfully transplanted cultured monkey corneal endothelial cells into monkey eyes via a collagen type 1 carrier sheet. At 6 months, corneal clarity was maintained and the endothelial cell count ranged from 1,992 to 2,475 cells/mm².

Biosynthetic cornea. In 2008, recombinant human collagen corneal substitutes were implanted as deep lamellar grafts in 10 patients in Sweden. All implants were stable at 4 years, and six patients had improved vision. No immune reactions have occurred.30

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