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Update on Endothelial Keratoplasty

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New surgical techniques in endothelial keratoplasty (EK) have provided promising alternatives to the traditional “gold standard” treatment for endothelial dysfunction, penetrating keratoplasty (PKP). Compared with PKP, EK techniques allow for faster visual rehabilitation, a more predictable change in refractive power, a decrease in surgically-induced astigmatism, and a lower incidence of graft rejection. This issue of *Ophthalmology Rounds* reviews the literature and the advances surrounding preoperative considerations, techniques, and postoperative outcomes of endothelial keratoplasty as a surgical intervention for the treatment of endothelial dysfunction.

A brief history

EK was first proposed in the 1960s by Barraquer,^{1,2} who suggested an anterior approach via an anterior corneal flap; however, this technique resulted in significant postoperative astigmatism and suboptimal refractive outcomes. In 1998, EK in its modern form was pioneered in the Netherlands by Melles et al,³ as a posterior lamellar keratoplasty (PLK), in which a donor graft consisting of endothelium, Descemet membrane (DM), and posterior stroma were transplanted onto a recipient cornea whose posterior stroma was removed by a posterior approach in a closed anterior chamber. In 2004, Melles et al⁴ described Descemet stripping endothelial keratoplasty (DSEK), a method whereby only the DM and endothelium are dissected from the recipient eye. Subsequently, other authors⁵⁻⁷ described the use of a microkeratome to replace manual dissection in the preparation of the donor button, which has been termed Descemet stripping automated endothelial keratoplasty (DSAEK; Figure 1).

Recently, endothelial cells with DM as the isolated carrier have been successfully transplanted clinically. Melles et al⁸ first proposed the concept of what eventually became known as Descemet membrane endothelial keratoplasty (DMEK), and good results have been reported in several series.⁹⁻¹¹ Studeny et al^{12,13} reported the transplantation of donor DM attached to a peripheral stromal rim to facilitate tissue handling. Tappin¹⁴ designed a carrier device to insert donor DM into the anterior chamber through an 8.0-mm sutured incision, while others demonstrated how these techniques can result in improved visual acuity and faster visual rehabilitation.¹⁵

Direct comparisons of these methods should be tempered by the knowledge that significant differences exist in donor preservation media, patient populations, techniques, and the quality and freshness of available donor tissue. Nevertheless, comparisons are helpful in achieving a better understanding of the outcomes and complications resulting from these procedures.

Preoperative considerations

Indications

EK, in its various forms, was initially described for the treatment of Fuchs dystrophy and pseudophakic or aphakic bullous keratopathy. DSEK has since been successfully described in the setting of iridocorneal endothelial syndrome¹⁶ and after PKP graft failure.^{17,18} The indications for EK are expanding as a result of collective clinical experience and even in patients with conditions previously considered to be relative contraindications, reasonable visual rehabilitation is potentially possible. Several authors successfully performed DSAEK in a number of eyes with significant co-morbid conditions, such as the absence of an intact capsule-iris diaphragm, the presence of previous glaucoma filtering surgery, and tube shunts in the anterior chamber with good clinical results.

An intact posterior capsule is desirable, even if opacified, since an intact capsule is useful in maintaining a stable lens-iris diaphragm. This allows the air bubble to pressurize during the

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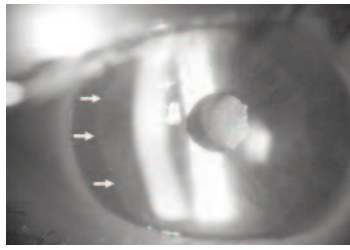
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positioning of the graft. Conversely, the presence of an open capsulotomy, aniridia, a history of vitrectomy, an anterior chamber intraocular lens (ACIOL), a trabeculectomy or a tube shunt, should alert the

Figure 1: Slit lamp photograph of DSAEK graft, postoperative Day 2



surgeon to the possible necessity of additional techniques to allow for the pressurization of the anterior chamber, which is an important step in achieving donor adherence. Expansile gases (eg, perfluoropropane [C3F8], sulfur hexafluoride [SF6]) have been utilized in these situations.¹⁹ In addition, it may be advantageous when planning shunts, to place the tube portion of a device either in the posterior chamber between the iris and the pseudophakic lens, or in the pars plana after a core vitrectomy is performed. A history of alpha antagonist (eg, tamsulosin) use may be important to note, since a floppy iris can cause difficulty in air bubble positioning and result in peripheral anterior synechiae (PAS; Figure 2).

Although deep stromal scarring with endothelial failure is perhaps best managed with a PKP, potentially, anterior scars in this setting can be treated less invasively with either a superficial or phototherapeutic keratectomy post-DSAEK. New imaging devices such as anterior segment optical coherence tomography (AS-OCT) are useful for delineating the extent and depth of ocular scarring prior to making such decisions (Figure 3).²⁰

Patients with infectious or inflammatory etiologies such as herpes simplex or herpes zoster virus (HSV/HZV) endotheliitis associated with neovascularization may carry a worse prognosis in comparison to noninflammatory conditions such as Fuchs dystrophy because penetrating grafts fair more poorly.

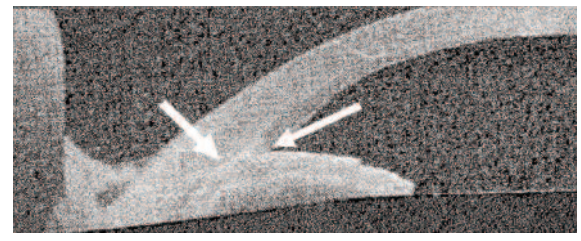
Combined procedures

In a case series of 200 patients, Price et al⁵ combined DSEK with another procedure in 93 patients, most commonly involving cataract surgery and vitrectomy. This and other series indicated that combined DSEK surgery had better visual outcomes and lower astigmatism, but higher endothelial cell losses compared with combined PKP procedures.

While the evidence on combined cataract surgery and DSEK remains inconclusive, intraocular lens calculations for DSEK patients should target a myopic final refraction to avoid postoperative hyperopic surprises. Several case series have demonstrated post-DSAEK refractive changes with a shift of approximately +1.25 D (range: +0.75 to +2.00).^{7,21-24} This hyperopic shift decreases with time; this is likely a product of a change in the differential peripheral/central graft edema that results in a shift in the posterior curvature of the graft (Figure 4).

Some suggest that special attention be given to DSEK after ACIOL implantation, since significant donor endothelial cell losses can occur in the event of graft dislocation due to endothelial-ACIOL touch.²⁵

Figure 2: Anterior segment optical coherence tomography (AS-OCT) of DSAEK graft with peripheral anterior synechiae (PAS)



Techniques

Donor graft preparation

Currently, the most commonly adopted DSAEK technique⁵⁻⁷ involves the use of a microkeratome for the preparation of the donor cornea. The Moria microkeratome and artificial anterior chamber are frequently used, since they are able to consistently create large diameter anterior stromal caps measuring approximately 400-450 μm in central depth with the available 300 μm and 350 μm heads. Larger diameter caps allow for larger donor grafts and have a greater tolerance for slight decentrations during trephination. The Barron disposable artificial anterior chamber is a viable, cost-effective alternative.

One of the main benefits of microkeratome dissection is that it results in a meniscus shape, resulting in dissection that is deeper in the periphery than centrally in the anterior lamellae. This produces a slightly more planar, less concave posterior stromal lenticule in comparison to that of a perfectly planar anterior cut. Microkeratome dissection is also quick compared with manual dissection. Price et al²⁶ found that microkeratome dissection reduced the risk of donor tissue perforation, provided faster visual recovery, did not alter the refractive outcome, and resulted, potentially, in a smoother intra-lamellar interface.

Femtosecond lasers are potentially useful in the preparation of the donor graft.²⁷ Cheng et al²⁸ demonstrated the feasibility of this technique, and subsequently compared the femtosecond laser-assisted DSEK (FS-DSEK) with PKP. In a prospective randomized study of 58 eyes, best-corrected vision, refractive astigmatism, and topographic cylinder were significantly lower after FS-DSEK compared with PKP at 6 months follow-up,²⁹ in addition, our group has had a positive experience with this technique 3 years postoperatively. EK donor preparation is likely to change with evolving experience, and as technologies such as the femtosecond laser become more refined for this purpose.

Figure 3: AS-OCT image of corneal stromal scar extending 110 μm into stroma

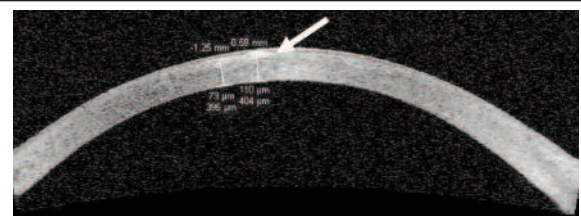
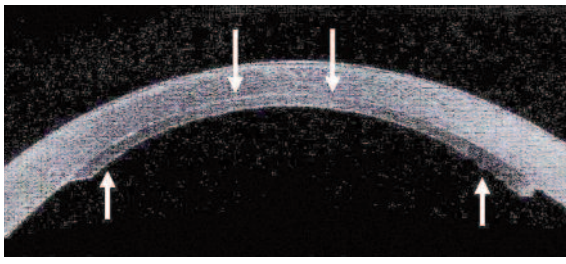


Figure 4: OCT of DSAEK graft, 6 months postoperatively



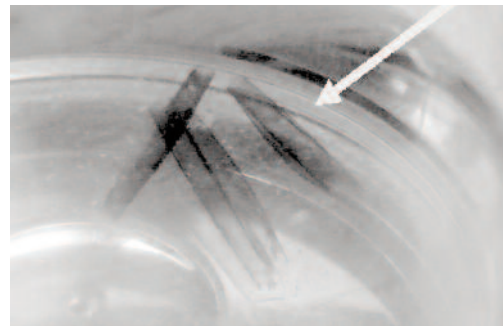
Harvesting and manipulating the fragile donor Descemet membrane remains a significant concern for DMEK. Melles et al¹⁰ demonstrated that corneoscleral buttons could be stored in a modified tissue culture medium for 2 weeks and, subsequently, the DM with endothelial cells could be manually dissected and implanted with clinical success. Lie et al³⁰ then demonstrated that DM carrying endothelial cells, excised after the corneoscleral button was stored in tissue culture for 1 week, could be stored for up to 4 additional weeks of organ culture.

Busin et al³¹ successfully demonstrated in 6 patients another method for DMEK tissue preparation and storage in tissue culture medium, whereby a “big bubble” technique is used to separate DM and endothelium from the overlying stroma. Our group examined a similar technique by using Optisol as a storage medium (Figure 5). Studeny et al¹³ described an alternative method of donor preparation also using an air bubble technique that results in a graft 8 mm in diameter with a 2 mm-wide stromal rim, allowing for easier manipulation with the donor lamella. Comparing this method with deep lamellar endothelial keratoplasty (DLEK), Studeny found that visual outcomes in 15 patients were better in his DMEK group, although endothelial cell density was higher in the DLEK group at 1 year. The intrinsic tendency of the isolated DM endothelial grafts to scroll during storage can present a challenge as well as an opportunity during implantation (Figure 6). Although the scrolling allows for injection through a small incision, in 1 case the surgeon found it difficult to unscroll the tissue,¹⁰ and in 3 other cases the graft was found unfolded upside-down against the recipient bed.¹¹ The method Studeny used of retaining the stromal rim may be a useful technique to prevent such occurrences.

Figure 5: “Big bubble technique” for DMEK graft preparation



Figure 6: Scrolled DMEK grafts



Eyebank prepared tissue vs surgeon prepared tissue

Although microkeratome or femtosecond donor dissection is easier and faster than hand dissection, it requires a much larger capital investment. The preparation of DM endothelial grafts requires a similar investment in technical expertise and time. These costs can be minimized and the intraoperative surgical time reduced by having the dissections performed at an eyebank and delivered as precut tissue. However, there are also potentially surgical considerations with precut tissue. Centration of the donor cornea for trephination can be problematic in precut DSAEK tissue because it is difficult to identify the centre of the cornea due to stromal edema that occurs during storage after lamellar dissection and due to the lack of stromal markings.³² Endothelial cell loss is also an important concern during the storage of precut tissue, and there is evidence that retaining the anterior stromal cap may be protective.³³ Depending on the skill and expertise of the surgeon or technician, surgeon-cut tissue may encounter less manipulation during preparation, although a large precut series of 100 eyes demonstrated excellent clinical results.³⁴

One series³⁵ of 143 DSAEK cases demonstrated that preservation in Optisol™ of >3 days was associated with a 2-fold increase in the odds ratio of donor detachment, and >5 days was associated with a 3-fold increase. Thus, logistically it may be important for eyebanks to supply precut tissue such that this does not significantly affect preservation to surgery time. Nevertheless, several other authors^{36,37} report that preservation to surgery time does not significantly affect the incidence of dehiscence. Although there are significant potential costs, there are quality and efficiency advantages to precut and prepared tissue, especially for lower volume EK practices, but further studies are necessary to determine the true risks and benefits of eyebank prepared tissue.

Anesthesia

Although DSAEK was initially described with retrobulbar and peribulbar anesthesia, topical anesthesia with intracameral 1% nonpreserved xylocaine is adequate in most uncomplicated cases. This technique works especially well with corneal limbal incisions as opposed to scleral tunnel incisions or in combined procedures. Topical anesthesia obviates the risks associated with more invasive techniques, and allows for the monitoring of central artery status during anterior chamber pressur-

ization, since the patient is able to report symptoms intraoperatively and pupillary block postoperatively.

Preparation of the recipient bed

The use of either a Sinsky hook or a reverse Sinsky hook to score the area of stripping followed by either a 45° Descemet stripper or a microforceps grasper works well through a 1.0 mm paracentesis with a 25 G anterior chamber maintainer. Melles et al⁴ originally described descemetorhexis as a method for stripping Descemet membrane from the cornea, a technique similar to a capsulorhexis; alternatively, a bent 27 G needle can be effective for this purpose.¹⁴ Terry et al⁶ described the use of a cohesive viscoelastic (eg, sodium hyaluronate: Healon[®]) during the stripping procedure; however, a number of surgeons have suggested that the use of viscoelastic can often be associated with graft dislocation.¹⁰ Therefore, many surgeons limit the use of viscoelastics in EK to only the coating of the endothelium prior to donor insertion. The use of viscoelastics for stripping also requires an otherwise unnecessary irrigation/aspiration (I/A) device to completely clear the anterior chamber prior to donor insertion. Staining a viscoelastic may be an alternative to ensure its removal; however, there is evidence that certain lenses can absorb and retain vital stains such as Trypan blue. Nevertheless, dye staining can be useful to help visualize Descemet membrane, if the stripped portion of the membrane cannot be inspected in its entirety. In the setting of significant epithelial edema, removing the epithelium is useful for improved visualization during the DSAEK procedure.²⁶

Some have proposed that aside from visually significant guttata, the host Descemet membrane could conceivably be left intact in EK. In fact, Price et al¹⁶ argued that the strongest point of attachment in the setting of a failed PKP is at the level of Descemet membrane and he reported good visual results in this setting without actually stripping the recipient tissue of the Descemet membrane. The same group also described a circumferential area of corneal edema in the setting of bared corneal stroma, outside of the area covered by the graft that subsequently required many months to resolve.⁵ Histological evidence indicates that endothelial cell migration onto recipient cornea does not occur in posterior lamellar keratoplasty even up to 2.5 years postoperatively.³⁸ While Amano et al³⁹ demonstrated that the peripheral cornea contains precursor endothelial cells, Engelmann et al⁴⁰ suggested that Descemet membrane has inhibitory effects on the endothelium. There is no evidence, however, that retaining a peripheral edge of Descemet membrane increases the likelihood of donor detachment. In a cornea that is primarily edematous centrally, it may be preferable to strip an area slightly smaller than the graft.

Price et al⁵ advocated the use of full thickness vertical drainage incisions placed in the mid-periphery after insertion of the donor graft to drain interface fluid. These incisions are very helpful in decreasing the incidence of donor dehiscence, as

well as in aiding the drainage and repositioning of dehisced grafts postoperatively. Alternatively, replacing these incisions after Descemet stripping and before donor insertion, while the chamber is formed, allows for more controlled performance.

Corneal incision size

Melles et al⁴¹ initially described posterior endokeratoplasty with a 10-mm scleral incision. Decreasing the corneal incision size by folding the donor lenticule with forceps, however, results in significantly increased endothelial cell losses. Data on DLEK by Terry et al⁶ revealed that increased cell losses can occur between 1-2 years postoperatively in folded corneas that are greater than the initial cell losses associated with the trauma of folding the donor cornea.

The future of smaller incision DSAEK lies in less traumatic insertion techniques. Data on the use of a metal glide (Busin glide) through a 4.0-mm incision, which involved pulling a graft into the eye using a microforceps, demonstrated endothelial cell losses of only 23.5% at 1 year.¹⁵ This is an elegant technique that has great potential; others have used a modified Sheet glide for this purpose.⁴² Rootman et al⁴³ found that the glide technique resulted in a lower percentage of endothelial cell loss at 6 months postoperatively.

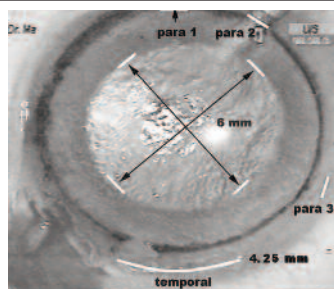
A long corneal limbal pocket with an external os of 4.25 mm and an internal os of 3.75 mm that enters approximately 0.5 mm inside the demarcation ring works well with the Busin glide. The corneal wound can often be left sutureless and, typically, the author hydrates both the main incision and the paracentesis with intracameral vancomycin; a typical incision layout is demonstrated in Figure 7.

Donor insertion and adhesion

Marking the donor stroma with a small asymmetric (eg, S or J) symbol prior to its insertion is helpful to confirm the donor orientation once it unfolds in the eye. Prior to insertion, the endothelium is coated with a layer of cohesive viscoelastic (Healon[®] or Provisc[®]). A case series that avoided the use of viscoelastic to protect the endothelium demonstrated an unacceptably high rate of graft failure and endothelial cell loss.¹⁹

With the Busin glide technique, the microforceps is inserted into the eye through the internal os of the corneal tunnel to grasp the donor graft, which is pulled through the incision with the prongs of the glide supporting the external incisional os. The flow rate of the anterior chamber maintainer is lowered to prevent the donor from being flushed out of the wound during insertion. The proximal portion of the donor can be tucked under the internal os of the incision to secure the graft into position and seal the corneal tunnel. The anterior chamber maintainer is then removed and filtered air is injected through one of the paracentesis ports with a 30 G needle. The bubble tends to help unfold the tissue and pressurize the anterior chamber.

Figure 7: Intraoperative incisions and markings on OS, temporal aspect at bottom



Published techniques on the duration of anterior chamber air pressurization range from 8 minutes⁵ to 1 hour.⁷ It makes intuitive sense that the optimal duration of pressurization may relate to the quality of the tissue, the endothelial pump function, and the duration of preservation.

Several maneuvers have been suggested to improve donor adhesion; for example, some advocate rolling a blunt instrument across the surface of the cornea and draining the interface fluid through vertical midperipheral corneal incisions.⁵ Others suggest peripheral stromal scraping,⁶ or leaving an air bubble in the eye for approximately 1 hour postoperatively,⁷ while some have incorporated the use of a retained suture hinge into their technique. The use of Tisseel fibrin glue has been described to improve donor adhesion;¹⁹ fibrin glue has been shown to be nontoxic in a rabbit model and prevents donor corneal button dislocation in an *in vitro* model.

At the conclusion of surgery, it is important to release some air and instill a long-acting mydriatic (eg, atropine) to prevent pupillary block glaucoma. The inferior border of the final bubble should be superior to the inferior border of the dilated pupil in order to prevent this complication.

Postoperative management

Topical steroids, antibiotics, nonsteroidal anti-inflammatory drugs (NSAIDs), and glaucoma medications are typically given postoperatively with careful instructions to not disturb the graft in the initial postoperative period. Since dislocation can be reproduced quickly and easily in the operating room from a simple rubbing motion,⁵ it is important to reinforce preoperative instructions to abstain from eye rubbing, keep a fox shield on at all times, and maintain a face-up position for the first several days postoperatively. When epithelial debridement is necessary, a high DK (penetration coefficient) bandage contact lens can be helpful.

Visual and refractive outcomes

Since the anterior cornea is untouched, EK typically results in a normal topographical surface postoperatively without significant surgically-induced irregular astigmatism. In contrast, 10%-15% of PKP patients require hard contact lenses to achieve best

corrected vision.⁴⁴ DSAEK provides more rapid visual recovery, and a reasonable best spectacle-corrected visual acuity (BSCVA) in the 20/40 range is generally achievable within 3 to 6 months of surgery.^{7,26,35} However, relatively few DSAEK patients achieve BSCVA of 20/20. Some postulate that subclinical stromal changes, such as interface haze and subepithelial fibrosis that occur in the setting of chronic corneal edema may limit visual potential; ultimately this may become the limiting factor in visual rehabilitation with isolated endothelial replacement. Larger amounts of corneal light scattering occur in DLEK than in PKP when measured by a scatterometer, which may reflect existing corneal changes. Patel⁴⁵ demonstrated that forward light scatter is associated with patient age, suggesting that the duration of endothelial dysfunction in the host cornea before DSEK may affect postoperative visual recovery.

The lack of donor stroma in DMEK may provide an even smoother donor surface and reduce interface scarring. Melles et al¹⁰ found in their series that 6 out of 10 DMEK eyes achieved a BSCVA of 20/40 or better, and 3 eyes reached 20/20 at 1 month, which was quicker than the typical visual recovery seen in DLEK or DSEK. This suggests that donor stroma also affects the rate of visual rehabilitation.

Graft dehiscence

While the most frequently cited complication of EK is graft dehiscence, much remains unknown about the factors involved in graft adhesion.^{5,35,46} Endothelial pump function, interface architecture, and surface tension may play important roles. The latency of endothelial function and the impact of preservation time on adhesion are also not well understood. The assumption that repeated graft dehiscence is due to graft failure may be incorrect, since nonfunctioning grafts can remain strongly adherent to the recipient cornea.³⁸ In addition, donor dehiscence can potentially be influenced by the size of the donor graft (possibly greater with 9-mm grafts), edge thickness, and cut asymmetry.

In the setting of complete donor dehiscence, air injected into the anterior chamber under a sterile technique, as in the original procedure, can be performed with requisite head positioning for the initial several days. Alternatively, this can be done at the slit lamp utilizing an inferior midperipheral drainage incision. In the presence of a small area of donor lenticule detachment, however, observation as opposed to re-bubbling the graft should be considered, since it is likely to seal with time. Intervention with re-bubbling in this scenario may not necessarily improve the partial dehiscence and will most certainly cause additional endothelial cell damage. Terry et al⁶ described a DSAEK case with partial dehiscence where re-bubbling left the area of dehiscence unchanged; however, the area of dehiscence resolved spontaneously after 6 weeks without further intervention. There have also been reports of spontaneous resolution in dislocated DLEK grafts up

to 1 month postoperatively.⁴⁷ However, prolonged sectoral areas of dislocation can often delay visual recovery for several months.

Graft rejection and endothelial cell loss

In a large multicentre endothelial transplant series of 199 eyes, Allan et al⁴⁸ reported a rejection rate of 7.5% within the first 2 years after DSEK or DLEK. This rate compares favourably with a rejection rate of 13% in a PKP series from the Swedish Corneal Graft Registry that was matched for most attributes except for a longer duration of topical steroid use in non-PKP patients.⁴⁸ Others have reported similar rates of graft rejection.⁴⁶

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