Recent innovations in minimally invasive anterior and posterior lamellar keratoplasty

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Chapter 9

Summary and conclusions

BOWMAN LAYER TRANSPLANTATION

Today, penetrating keratoplasty (PK) and its cousin deep anterior lamellar keratoplasty (DALK) remain the standard of care for eyes with advanced keratoconus (KC) once visual acuity becomes unacceptable and/or contact lens intolerance develops (Chapters 1,2, and 5).[1,2] And while the outcomes of these operations are often described as "good," many unresolved challenges remain.[3,4]

Specifically, many recipients of both surgeries are young at the time of their operations, in some cases extremely so, rendering the procedures more technically challenging and the postoperative care more difficult, especially if there is some coexisting cognitive or behavioral limitation (which is not altogether uncommon).[5–8] Young eyes also tend to be phakic: in the first few years after transplantation, cataracts may develop. As a result, lens extraction may be necessary, potentially risking the graft's health in the process.[9,10] Children already suffer poorer graft survival than adults,[11] but even if the statistics were identical, still it is very likely that young patients will "outlive" their first transplant and therefore require re-operation(s). And because the outcomes of second and third transplants tend to be inferior to the first, many patients who seem—initially—to do well with both surgeries may, ultimately, experience problems.[12] This is especially true given that advanced KC is found in patients with severe ocular surface disorders, many of which are exacerbated by PK/DALK and their large incisions, sutures, and the neurotrophic corneas they produce.[13,14] Beneath the ocular surface, additional wound healing problems may also be found, since the stroma at the junction between the graft and the recipient probably never securely heals, predisposing these eyes to inadvertent traumatic rupture and ongoing ectasia at the tissue interface (and thereby "recurrence" of their disease).[15]

All of these difficulties are fundamental problems intrinsic to DALK and PK themselves and therefore not likely to be cured by refinements to operative technique or instrumentation (Chapter 2). The solution may instead require an entirely new surgical approach, possibly one that abandons the idea of exchanging or replacing the recipient cornea with donor tissue. To this end, recently there has been a strong push to intervene early against eyes with mild KC in the hopes of arresting progression before PK or DALK (and their attendant complications) become necessary. Both ultraviolet-crosslinking (UV-CXL) and intracorneal ring segments (ICRS) have been evaluated for this purpose, each with demonstrated success. Nevertheless, many eyes are not candidates for either operation. Those with corneas steeper than 58 diopters (D) or thinner than 400µm, for example, may be ineligible for both ICRS and UV-CXL according to published safety guidelines.[16,17] Further, in the US, ICRS are not approved in patients younger than 18 years old, and UV-CXL - while recently legalized - is not yet widespread.[16,17]

Other exclusions also apply: corneas with prior herpetic disease are disqualified from UV-CXL, and a history of recurrent erosions excludes ICRS placement.[16,17] Overall, it may

be fair to say that, for various reasons, many patients with "active" or "ongoing" KC are ineligible for these therapies, and therefore may continue to progress.[18] Eventually, contact lens intolerance might develop. Many patients then receive either PK or DALK and be subject to possible complications.

What has been badly needed is an operation to arrest keratoconic progression in eyes poorly suited for UV-CXL or ICRS, before PK or DALK become necessary.[18-20]For this reason, in 2014, we began our investigation into a new operation known as Bowman layer (BL) transplantation (Chapter 3).[21] One of the most sensitive and specific manifestations of KC is the fragmentation of the BL, an insult that critically destabilizes the surrounding cornea, predisposing it to ongoing ectasia. As a result, we reasoned that an isolated BL transplant might flatten the cornea into a more normal architecture and bolster it against further deformation.

For our first surgeries, we chose only patients with extremely advanced KC, all with maximum keratometry values ≥70D. The operation itself was performed by manually dissecting a midstromal pocket, limbus-to-limbus, 360° within the recipient cornea, then implanting an isolated BL graft. All surgeries in this initial series were uneventful with no complications, except in two cases that experienced an intraoperative perforation of Descemet Membrane during the dissection. In the initial 10 eyes operated with this technique, by one year after surgery, neither spectacle nor contact lens corrected visual acuity significantly changed from pre- to postoperative.[21] However, recipient corneas were flattened by an average of 8–9 D, and in all cases, disease progression was arrested and comfortable contact lens wear was preserved or restored.[21]

Since our original study, we have operated on a growing number of additional patients with the same technique both in the Netherlands and also now in the United States (Chapter 4).[22,23] Overall, the surgery seems effective in >90% of eyes at halting ongoing ectasia (now with a mean follow up period of greater than 3 years, and with some patients now 5 years after surgery). Moreover, a slight average improvement in spectacle corrected visual acuity has been observed (from 20/400 to 20/125). Likely, these gains reflect a "normalizing" of the ocular surface since – after BL implantation – the cornea's higher order visual aberrations (especially spherical aberration) significantly diminished.[24] In addition, no known postoperative complications have been observed. Specifically, no ocular surface matters have arisen (likely because the technique employs no surface incisions and no sutures), nor have there been any occurrences of either cataract formation or allograft reaction. In fact, because the BL transplant is acellular,[25] graft rejection may significantly less likely.[19,23] Therefore, much fewer (and possibly no) steroids may be required postoperatively, eliminating a major source of postoperative risk.

So far, our experience with Bowman layer transplantation has led us to believe that the operation may be a promising way to arrest keratoconic progression, even in those

eyes ineligible for other procedures. Longer and larger study with additional patients will be necessary, but it is possible that with continued effort, we may continue in the tradition of endothelial keratoplasty by abandoning the idea of full thickness corneal transplantation and, instead, choose a more limited and specific corrective intervention.

DESCEMET MEMBRANE ENDOTHELIAL KERATOPLASTY (DMEK)

For corneal endothelial disorders, several different techniques have been in existence, and Descemet Membrane Endothelial Keratoplasty (DMEK) may have superseded its predecessor, Descemet Stripping (Automated) Endothelial Keratoplasty (DS(A)EK), as the procedure of choice for this condition (Chapter 6).[26] With a graft consisting exclusively of an isolated Descemet membrane and its attendant endothelium, DMEK effects a one-to-one replacement of donor for diseased tissue, resulting in the near complete anatomic restoration of the recipient cornea (Chapter 6).[26]

Immediately postoperatively, the measured endothelial cell density of a DMEK graft displays a sharp decline, consistently measured at approximately 35% of the preoperative value (Chapter 7).[27,28] Although this decline is frequently expressed as "cell loss" resulting from intraoperative tissue manipulation, this explanation may be overly simplistic, and other factors may also be involved, for example: cell migration/redistribution from the graft onto surrounding areas of recipient posterior stroma.[29] Nevertheless, by six months after surgery, the rate of cell density decline appears to stabilize at a low level (around 5% per year). This pattern closely resembles that seen after DS(A)EK, and differs from the cell density trends seen after Deep Lamellar Endothelial Keratoplasty (DLEK) and PK, which both show an indefinite, linear decline in cell density in perpetuity.[30-32]

The average best corrected visual acuity (BCVA) after DMEK is 20/25 (0.8), which is usually achieved by three months postoperatively and with little entailed hyperopic shift.[33] This contrasts with the average visual acuities, recovery times, and refractive shifts after both PK and DS(A)EK: after PK, BCVA averages only 20/40 (0.5), is delayed by one year, and commonly entails severe astigmatism; after DS(A)EK, BCVA is averages 20/30, is delayed by 6 months, and entails twice as much hyperopic shift as DMEK.[34] However, DMEK's visual results are limited by the condition of the anterior corneal surface and by the lens status of the recipient eye. Specifically, longstanding corneal edema may produce anterior stromal scarring/ fibrosis, which may not entirely resolve after DMEK.[35] Therefore, early endothelial replacement before these changes develop may be advisable. (Otherwise, contact lens fitting may mitigate some of these abnormalities.) In addition, while phakic and pseudophakic patients seem to achieve the same average visual results after surgery, the "extremes" of good vision are more commonly found in phakic eyes, suggesting some optical advantage in preserving the natural lens (Chapter 8).[36]

Unlike phakic eyes undergoing DS(A)EK, cataract formation is not the rule after DMEK, possibly as a result of the lower post-operative steroid burden entailed. In our series only 4% of phakic eyes undergoing DMEK required subsequent phacoemulsification within a two-year follow up period.[36] However, phakic eyes receiving DMEK do display a unique susceptibility to air-bubble induced angle closure glaucoma, in which the air-fill left postoperatively pushes against the lens, which responds by tilting forward and closing off the trabecular meshwork.[37] To prevent this occurrence, phakic eyes are best left with a smaller air-fill at the conclusion of their operation: only 50% of the volume of the anterior chamber, rather than 75%, as recommended in pseudophakic eyes. Interestingly, phakic eyes treated in this manner do not seem to display a higher percentage of postoperative graft detachments than their pseudophakic counterparts, suggesting that the postoperative air-fill may be less critical to graft adherence than is currently believed.[36]

Because DS(A)EK involves a stroma-stroma interface at the junction of donor and recipient tissues, and because this interface may be highly reflective and irregular, the optical quality of the transplanted eye may suffer. Other reasons for poor visual acuity after D(A)EK include: stromal "waves" in the donor lenticule stemming from a curvature mismatch between the recipient's cornea and the graft; and recipient Descemet membrane "remnants" left in the interface. As a result of these three factors, some eyes which receive an uncomplicated DS(A)EK operation, experience a normal postoperative course, and present with clear and well attached grafts may, nevertheless, achieve unsatisfying visual results.[38] Re-operating on these eyes to replace their DS(A)EK grafts with DMEKs has been shown to result in substantial visual improvements in these cases, likely because DMEK grafts - being devoid of stroma - fit better against the recipient posterior cornea and induce less scarring. Moreover, separate studies have independently demonstrated that - when operated with both techniques - patients subjectively prefer the vision in their DMEK eye.[39] Altogether, these results confirm the underlying philosophy of DMEK surgery: that the operation returns the eye to a nearly-normal anatomy, unlike PK, DLEK, and even DS(A)EK.[40] Preliminary results have also been returned from a modified form of DMEK, known as Hemi-DMEK, in which a single, oversized, circular DMEK graft is divided in two, and each hemi-circular graft is then implanted in a different recipient.[41-43] Because approximately the same number of cells is transplanted with each of the two Hemi-DMEK grafts as with one "regular" DMEK graft, and because the donor tissue is likewise positioned in the same location against the recipient cornea, the rate and extent of visual recovery would be expected to be similar between the two operations, which is confirmed in our initial results. A possible, theoretical advantage of Hemi-DMEK over standard/ conventional DMEK is that, by dividing each donor tissue in two, Hemi-DMEK may double the pool of available tissue for transplantation. From Hemi-DMEK the next steps remain unsettled. The operation may progress to "Quarter-DMEK" in which the

donor tissue is again divided in two.[44] Alternatively, we may proceed with injections of cultured human endothelial cells, as is currently being trailed, or even "keratoplasty-free" solutions, that totally abandon the concept of donor material altogether.[45,46]

CONCLUDING REMARKS

The past two decades have seen an explosion of new keratoplasty techniques, a historically unparalleled flurry of activity which, ironically, may be superseded in the near future by the complete end of "keratoplasty" as a concept. Corneal grafts have steadily gotten smaller, thinner, and more peculiar. This applies to both transplants for the anterior, and the posterior, corneal surfaces. The logic motivating these innovations has been consistent: minimally invasive substitutions are to be preferred over wholesale replacements of corneal tissue. As new, tailored, lamellar operations have grown in popularity worldwide, we may be approaching a point where "transplantation" itself becomes unnecessary. Already, successful reports "descemetorrhexis only" treatments for patients with Fuchs Dystrophy are accumulating,[45] and in Japan, promising results with injectable endothelial cells are likewise emerging.[46]

Our former experience with Descemet Membrane Endothelial Transfer (DMET) demonstrated that - in eyes with Fuchs Dystrophy - recipient corneas would still clear (albeit over a longer time period) if an isolated DMEK graft were merely injected into the anterior chamber and placed into contact with the recipient posterior cornea without being unfolded.[47] The mechanism for this corneal clearance has been shown to be endothelial cell migration, although it is not presently known whether these cells are migrating out from the donor tissue, or in from the recipient periphery, stimulated by the presence of the donor graft. Regardless, the concept sticks that replacing a dysfunctional endothelial layer with a similarly positioned donor graft may be unnecessary, and that we might achieve the desired effect in a simpler and safer manner by some other intervention. If so, then this would mean that "keratoplasty" as a technique may soon be finished, at least for endothelial surgeries. For disorders of the anterior cornea, the introduction of UV-crosslinking and intracorneal ring segments have already cut heavily into the number of transplants being performed, and the BL transplantation may continue this trend away from PK and DALK. As a result, this may be simultaneously the most exciting - and possibly uncertain - time in history to be a corneal surgeon. And despite all the foregoing speculation about the future of corneal transplantation, it could also be some unforeseen advance that carries the profession forward.

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