ENDOTHELIAL KERATOPLASTY: CLINICAL OUTCOMES IN THE TWO YEARS FOLLOWING DEEP LAMELLAR ENDOTHELIAL KERATOPLASTY (AN AMERICAN OPHTHALMOLOGICAL SOCIETY THESIS)

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ABSTRACT

Purpose: To evaluate the clinical outcome of small-incision, deep lamellar endothelial keratoplasty (DLEK) for the treatment of endothelial dysfunction.

Methods: A prospective series of 79 eyes that underwent DLEK by a single surgeon was evaluated. Best spectacle-corrected visual acuity (BSCVA), refractive astigmatism, and central endothelial cell density (ECD) were measured preoperatively and at 6, 12, and 24 months.

Results: Data was available on 78 eyes (99%) at 6 months, 77 eyes (97%) at 1 year, and 79 eyes (100%) at 2 years. Mean BSCVA preoperatively of 20/71 improved to 20/42 by 6 months and remained stable. Eliminating eyes with known retinal disease, BSCVA of 20/40 or better was present in 60% (40 of 67) of eyes at 6 months, 74% (49 of 66) of eyes at 1 year, and 79% (53 of 68) of eyes at 2 years. Refractive astigmatism preoperatively was .91 ±.78 diopters and was unchanged by surgery over time with results at 6 months of 1.11 ±.76 (P = .052, power = .43), 1 year 1.04 ±.80 (P =.287, power = .06), and 2 years 1.10 ±.70 (P =.467, power = .22). The mean donor ECD preoperatively was 2819 ± 225 (2389 to 3385) cells/mm^2, and this decreased by 26% at 6 months (2095 ± 380) (1097 to 2920) (P = .0001; 95% confidence interval [CI] = 643-809), 3% fewer at 1 year (2009 ± 393) (612 to 2723) (P = .054, power = .5), and 17% fewer at 2 years (1536 ± 547) (500 to 2546) (P < .001, 95% CI = 368-585). Complications included one primary graft failure and 4 dislocations into the anterior chamber.

Conclusions: DLEK provides improved vision and minimal refractive astigmatic change, but progressive ECD decrease over time is of concern.

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INTRODUCTION

Corneal transplantation has been used to treat corneal disease for over 100 years, with the first successful full-thickness human transplant performed by a private practice physician, Eduard Zirm, in 1905.[1,2] Full-thickness penetrating keratoplasty (PK) has been applied as the preferred therapy of visual loss due to corneal disease and has advanced dramatically over the past 25 years due to better surgical techniques, medications, and donor storage advances.[3] However, PK is a rather indiscriminate form of surgery, in that it replaces all layers of the cornea, regardless of the tissue layer that is responsible for the visual deficit. In the case of anterior stromal scars with healthy endothelium, a PK removes the scar but sacrifices the healthy endothelium. In the case of endothelial dysfunction due to disease or trauma, PK replaces the endothelium with healthy tissue, but sacrifices the normal corneal topography and also the structural integrity of the anterior corneal tissues.

Endothelial dysfunction requiring surgery most commonly occurs in the advancing stages of Fuchs endothelial dystrophy and following trauma from intraocular surgery. Other causes include inflammatory destruction of the endothelium, trauma to the virgin eye, and late endothelial failure in a previous PK. Over 50% of corneal transplants in the United States are done primarily to treat endothelial dysfunction (Eye Bank Association of America, Statistical Report, 2005). A surgical method that can selectively replace the diseased endothelial layer and leave the remaining tissue relatively undisturbed would have a large impact on the transplant community, and efforts in this direction have accelerated over the past 10 years.

In order to compare techniques of endothelial replacement surgery, it is worthwhile to consider what the ideal goals of endothelial transplant surgery should be. The ideal endothelial transplantation procedure should fulfill, on a practical level and by inherent design, 6 goals, which can be described as the following: (1) a smooth surface topography without significant change in astigmatism from preoperative to postoperative status, (2) a highly predictable and stable corneal power, (3) a healthy donor endothelium that resolves all edema, (4) a tectonically stable globe, safe from injury and infection, (5) an optically pure cornea, and (6) a surgical technique that is quickly and easily acquired.[4-6] It is tempting to add to the list a seventh goal of an antigen-neutral donor endothelium layer, but this goal is more a function of donor properties than surgical design. Each major development in endothelial replacement surgery can be judged in accord with its fulfillment of these goals.

PENETRATING KERATOPLASTY

The technique of PK is quite straightforward and involves the trephination of the recipient cornea, removing all layers, and leaving an "open sky" hole to be filled. This central hole defect is filled with a varied size donor button which has been cut with a similar trephination device. The wound is then closed watertight with sutures that remain in place for usually 1 year or longer. In replacing all of the layers of the cornea with a vertical corneal stromal wound and prolonged suture closure, PK surgery incurs optical and structural liabilities for the recipient eye.

Despite the advances in suture technique and wound construction, PK does not consistently achieve the first goal of endothelial replacement in that it does not provide for a consistently smooth topography without change in preoperative astigmatism. Initially the

donor corneal epithelium the day after PK is found to be partially or completely sloughed, leaving the immediate postoperative surface optically irregular and open to infection. However, even after the surface epithelium heals, the topography may still not smooth out, leaving many grafts with high levels of irregular astigmatism. Gross and associates[7] found that the surface irregularity index (SRI) measured by the TMS-1 (Tomey Technology, Cambridge, Massachusetts; software version 1.61) averaged 3.24 and the surface asymmetry index (SAI) averaged 1.69 after their PK surgery, much worse than the normal readings of about 1.0.[8] Even with a smoothly healed epithelium, the compressive effect of sutures makes corneal topography unpredictable and often leaves the surface curvature with higher levels of astigmatism than were seen preoperatively.[9-12] The average astigmatism with sutures still in place is between 3 and 6 diopters (D), and even in the best of hands can be much higher. Pineros and associates[13] found that over 42% of their grafts for Fuchs dystrophy had 5 D or more of astigmatism. Astigmatism levels can change dramatically after sutures have been removed, and astigmatism levels which cannot allow spectacles or contact lens corrections will require secondary surgeries such as relaxing incisions, wedge resections, or refractive laser correction.[13-19] Despite the advances in surgical techniques, the fact that no single technique of PK has been universally adopted and proven to consistently minimize astigmatism points to the inherent problems of wound management and topography control with PK surgery.

The second goal, a predictable and stable corneal power after transplantation, is poorly met by PK. The vertical stromal wound of PK is inherently weak and continues to undergo remodeling after suture removal. With wound instability, the corneal topography can continue to shift over time, changing the astigmatism but also changing the overall corneal dioptric power. The corneal power shifts of PK can be quite unpredictable, with the resultant induced myopia, hyperopia, and anisometropia problems exasperating for the surgeon and patient alike.[20] Combining cataract surgery with PK makes intraocular lens (IOL) calculations an educated guess at best and postoperative spherical equivalents ranging from -6.75 to +7.25 are not unusual.[21-22] Hayashi and Hayashi[23] recently performed a prospective study to evaluate the advantages of combining cataract surgery with PK vs sequential surgery of PK followed by cataract surgery months later. They found that in the combined procedure, the percentage of eyes that had a final refractive spherical equivalent that was within 2 D of the target refraction was only 39% (15 of 39) while the percentage of eyes in the sequential surgery group was significantly higher at 70% (16 of 23). (P = .03). Although there was a significant refractive advantage for the sequential group, patients in this group had to wait a year or more for their subsequent cataract surgery. These disadvantages of both surgical strategies for patients with cataracts and corneal disease continue the decades-long debate on whether it is better to do cataract surgery simultaneously with PK or as a sequential procedure.

The third goal, successful transfer of healthy donor endothelial cells, is well accomplished by PK surgery. The recent PK literature reports donor endothelial cell loss after PK surgery for low-risk keratoplasty groups. In 1998, Ing and associates[24] reported on 394 eyes that had a preoperative diagnosis of Fuchs dystrophy, keratoconus, or pseudophakic bullous keratopathy. The average endothelial cell density (ECD) at 1 year was 1958 ± 718 cells/mm^2, and this represented a donor endothelial cell loss of 34% ± 22% from the preoperative counts. At 3 years, the average cell count was 1376 ± 586 cells/mm^2, representing a 53% ± 19% cell loss from the preoperative counts. This study, however, reported cumulative findings over a number of years of transplantation, and therefore included corneal transplant cases that had been done before the advent of viscoelastics and modern preservation solutions such as Optisol GS (Chiron IntraOptics, Irvine, California). A more recent report by Bourne and associates[25] on just 9 eyes that had been preserved in Optisol GS solutions and underwent modern techniques of PK surgery showed only a 17% endothelial cell loss at 1 year after surgery. Looking at another large study of PK in low-risk patients, Langenbucher and associates[26] reported in 2002 on 187 Fuchs dystrophy and keratoconus patients. At 1 year after PK, their ECD was 1562 ± 540 cells/mm^2. At 2 years, the cell count had dropped to 1222 ± 520 cells/mm^2. This represents a progressive endothelial cell loss from 1 to 2 years of 22%. In 2004, Rheinhard and associates[27] evaluated the effect on donor cell survival in 101 patients with HLA matches or mismatches. Regardless of the tissue match, they found that the donor cell loss after PK at 2 years was 35% with an annual cell loss of about 18%. These two large studies, however, utilized organ culture storage media, and so may not be completely comparable to studies in the United States, which use short-term preservation media with cold storage. On the other hand, Frueh and Bohnke[28] compared Optisol to organ culture media for tissue preservation in 12 pairs of eyes and found slightly better endothelial survival for the organ culture group at 1 and 2 years after PK. In this same 2000 report they found a cell loss of 19% ± 18% at 1 year after PK and 34% ± 23% at 2 years after PK for the Optisol stored corneas. In addition, a prospective PK study by Lass and colleagues[29] compared Optisol to DexSol (Chiron IntraOptics, Irvine, California) corneal storage media and found that in 26 eyes that made it to the 1-year postoperative examination, the ECD was 2210 ± 797 cells/mm^2, which represented a 15.3 ± 24.9% cell loss from preoperative measurements.

The most recent study to prospectively evaluate endothelial survival after modern PK surgery was reported by Hayashi and Hayashi.[23] They looked at 62 eyes requiring PK for bullous keratopathy or scars and which also required cataract surgery. Simultaneous PK and cataract surgery was performed in 39 eyes and sequential surgery in 23 eyes. All of the eyes underwent PK using protective viscoelastic and modern techniques. They found that at 6 months the ECD in the simultaneous group had only decreased by 26%, yet the group that had cataract surgery after the PK had a decrease of ECD at 6 months after the cataract surgery of 35% (P = .03). At 1 year after all completed surgery, there was no difference in ECD decrease between the two groups, with a 37% to 39% cell loss. Long-term endothelial cell loss beyond 2 years postoperatively has been assessed, and Bourne[30] has shown that the endothelial cell count deteriorates over time, with cell counts of only 960 ± 470 cells/mm^2 at 10 years. His group has also shown relative cell stability from 10 to 15 years in surviving grafts, with Patel and associates[31] reporting that at 15 years postoperatively the mean ECD was 872 ± 348 cells/mm^2, representing a 71 ± 12% cell loss from preoperative measurements with an annual rate of cell loss similar to that seen with normal corneas. The endothelial cell loss after PK, therefore, can be highly variable between surgeons, ranging from an average of 15% to 37% at 1 year, and although the attrition rate appears to level off by 10 years, early high ECD

levels are desirable in endothelial transplantation to avoid late endothelial cell failure and the need for regrafting.

The fourth goal, providing a tectonically stable globe, safe from injury and infection, is not met by PK surgery. Even during the time of surgery, due to the large central hole created by recipient trephination, there is the increased risk of intraoperative expulsive hemorrhage with an "open sky" PK eye compared to the closed system of limbal incision surgery. In PK surgery, donor storage time reduces the fragile adherence of the donor epithelium, and it either partially or fully sloughs at the time of surgery or by postoperative day 1 in the majority of cases. This leaves the transplanted cornea transiently open to infection and stromal melt, until the surface heals, sometimes not completely for days or even weeks after surgery. In low-risk cases of PK for endothelial dysfunction, these short-term risks are relatively unimportant compared to the long-term risks of surface corneal sutures and an unstable stromal wound. The sutures used to close the PK wound are the primary culprits in the complications that can occur after PK surgery. Not only do the sutures cause optical problems with surface astigmatism, but they act as a nidus for vascularization, infection, wound melt, and graft rejection.[3,32-34] Graft loss and complications due to surface sutures has been reported as high as 11% to 14% of all grafts and may be even higher.[35] The vertical wound of PK is inherently weak and never heals to the same tectonic strength of the nonincised stromal tissue. The risk of traumatic globe rupture in the first 10 years postoperatively after PK has been reported to be 5.8% in a study by Elder and Stack.[36] Even years after PK surgery, minor blunt trauma can cause rupture of the wound with subsequent loss of the graft and even loss of the eye.[36,37] Nagra and associates[38] have recently reviewed 30 eyes repaired for wound dehiscence after PK and found that the mean time from PK to wound dehiscence was 7.5 years, with a range of 1 week to 31 years, emphasizing the lifelong risk of this disaster.

Clearly, in any surgery to replace the endothelial layer, it would be desirable to avoid disruption of the tectonic strength of the anterior stromal tissue if at all possible. The femtosecond laser is a high-technology tool that has shown great usefulness for precise stromal incisions and has been applied for creating Lasik flaps in refractive surgery for several years.[39-42] Recent technological advances with the femtosecond laser for cutting stromal tissue have now allowed surgeons to create customized laser trephination of the donor and the recipient cornea in PK surgery. With the laser, the surgeon is no longer limited to creating weak vertical incisions for PK, and instead can create more interlocking and mechanically stable patterns of incisions such as "zig-zag," "top hat," "mushroom," and any conceivable pattern desired to enhance wound stability (Price and Price, November 10, 2006, Federated Corneal Society Meeting, Las Vegas, Nevada). At this time, proof of concept with anecdotal clinical reports at meetings is the only evidence currently supporting this technology, but femtosecond laser trephination holds great promise in mitigating a current failing of traditional PK surgery.

The fifth goal, providing an optically pure cornea, is well accomplished by full-thickness PK. Unlike anterior lamellar keratoplasty, in PK surgery there is not a stromal interface, and if the surface irregularity of PK is eliminated, then an outcome of 20/20 visual acuity is not unusual. However, the reported average visual results after PK are variable and in the scientific literature are often influenced by nonexcluded, comorbidities, such as age-related macular degeneration, cystoid macular degeneration, and other factors. As a practical consideration, many surgeons also report their visual results as a percentage of eyes that achieve a level of visual acuity of 20/40 or better visual acuity as well as the percentage of eyes that have poor outcomes of 20/200 or worse. Reports of visual acuity of 20/40 or better after PK can range from 27% to 75% in different studies.[43-47] Barkana and associates[43] reported only 27% of 48 PK eyes with visual acuity of 20/40 or better, and nearly 33% of their eyes had poor visual acuity of 20/200 or worse after PK surgery. In a recent, retrospective study of 264 eyes with PK for the treatment of endothelial failure, Akpek and colleagues[44] found an average visual acuity of only 20/60 but, most disturbingly, reported that 29% of the eyes had worse than 20/200 visual acuity after surgery. In their patients with Fuchs dystrophy and average preoperative visual acuity of about 20/150, Jonas and associates[45] reported average postoperative visual acuities in 24 eyes (at 34 ± 25 months after PK) of about 20/48 with sutures in and 20/42 with sutures out. The percentage of eyes that achieved 20/40 or better was 58%. Claesson and colleagues[46] looked at 71 eyes with Fuchs dystrophy in their large, prospective graft registry study in Sweden and found that at 2 years, 54% of the eyes were 20/40 or better. Davis and associates performed the triple procedure in 47 eyes with Fuchs dystrophy, obtaining an average visual acuity at 2 years postoperatively and with sutures still present of about 20/43.[10] In this group, the number of eyes achieving 20/40 or better visual acuity was excellent at 70%. Similarly, Olson and associates[47] found in 20 PK eyes with short-term follow-up of only 4 to 12 months that there were 75% of eyes with visual acuity of 20/40 or better.

Two surgeons have found visual results that are distinctly better than these other groups.[18,48,49] Although Price found a 74% rate of 20/40 or better visual acuity in 157 PK eyes at 12 months, when this same group was retrospectively reviewed for 2 years after surgery, this favorable vision rate increased to 86% (101 of 117).[48] Similarly, in describing their technique of intraoperative running suture adjustment, Serdarevic and associates[18] achieved a laudable 100% of 16 eyes seeing 20/40 or better at 18 to 24 months after PK. Notably with these reports, Price and associates[48] and Serdarevic and associates[18] do not report in their papers the percentage of patients who could achieve 20/40 or better visual acuity before surgery. In addition, Serdarevic and associates excluded any patients with "other ocular abnormalities or previous ocular surgery," so it is possible that the differences observed between these studies and the rest of the literature at various time points after surgery may be due as much or more to patient selection than to technique.[18,48] Indeed, Claesson and colleagues, [46] in their huge study of 520 grafts at 2 years after PK, showed a strong association between preoperative visual acuity and the likelihood of obtaining postoperative visual acuities of 20/40 or better. The variable of preoperative visual acuity level therefore needs to be reported to make fair comparisons of studies looking at visual outcomes after any form of corneal transplantation.

The sixth goal, a procedure that is easily and quickly acquired, is generated from a practical viewpoint. If a procedure is so difficult that it can be performed by only a few surgeons, or is so difficult to learn that it is not worth the time, effort, or money to the

surgeon to do so, then that procedure is unlikely to become mainstream. As the technology and techniques of PK have advanced dramatically over the past 25 years,[3] PK has become technically easier to perform, and transfer of skills for PK surgery occurs regularly in many residency and fellowship training programs. This is one of the strong points of PK surgery.

Penetrating keratoplasty has evolved over the past century into a highly successful surgical solution to patients suffering from blinding corneal disease. However, while the incidence of clear grafts is higher than ever before, the ability of PK to fulfill only 3 of the 6 ideal goals of endothelial replacement surgery has spurred surgeons to search for an alternative form of transplantation.

ENDOTHELIAL KERATOPLASTY

Anterior Flap Technique

The concept of the surgical selective replacement of the corneal endothelium was first published by Jose Barraquer in 1951.[50] In his presentation, he diagrams his "queratoplastia laminar posterior" as beginning with the creation of a square shaped anterior lamellar flap. The flap is then retracted, a circular trephine is used to excise the posterior tissues, the donor posterior tissue is placed, and then the square flap is sutured into place. The technique was described, but no clinical data was given. In 1956 Charles Tillett[51] of Charlotte, North Carolina, reported the first successful "posterior lamellar keratoplasty" for the treatment of endothelial dysfunction. In his technique, he began with a 180-degree, nonperforating incision in the peripheral cornea, created a lamellar plane from limbus to limbus for 360 degrees, then retracted the proximal portion of this "half-flap" to gain access for excision of the distal posterior tissues. After scissors excision of the posterior recipient tissues, he sutured the donor posterior tissue into place to the recipient limbus with mattress sutures, and then sutured the overlying "half-flap" back down. His case report was successful with a clear recipient cornea 1 year later, but the vision ultimately was lost to glaucoma. No further clinical reports are found in the literature over the next several decades, but animal work continued in the flap technique of posterior lamellar keratoplasty (PLK), as shown in a report by Frank Polack in 1965.[52]

The flap creation technique of PLK was resurrected over the past decade by surgeons utilizing the now familiar automated microkeratome for creation of the recipient flap, as well as the donor tissue. This technological advance promised the same optical interface as can be created for refractive surgery, as well as easy access to the posterior stromal tissue. With the investigations, various new names and acronyms were applied to the flap technique of selective endothelial keratoplasty.

Jones and Culbertson described the technique in 1998 and called it *endothelial lamellar keratoplasty* (ELK) (Jones DT, Culbertson WW, ARVO meeting, 1998, Abstract). Busin and colleagues[53] described a similar technique in 2000 and termed it *endokeratoplasty* (EKP). Azar and associates[54] reported the technique in 2001 and called it *microkeratome assisted posterior keratoplasty*. Finally, outside the United States, Ehlers and associates[55] reported the technique with 4 patients and called it *posterior corneal grafting*, while Guell and associates[56] called the procedure the same name it was given decades earlier, *posterior lamellar keratoplasty*. Regardless of the name, the techniques of microkeratome flap access to the endothelial layer are similar and quite straightforward. The common goal with the flap techniques is to replace the diseased endothelium and posterior tissue, taking advantage of the exquisitely smooth lamellar interface created by the microkeratome, and so avoid the interface optical irregularities commonly found in other anterior lamellar manual procedures.[57,58] For convenience of discussion, all of the procedures using a flap technique for posterior lamellar grafting will be referred to by the Culbertson name of ELK.

The general technique of ELK begins with a microkeratome flap with a diameter of at least 8.5 mm and a thickness of at least 130 μm. The flap is then retracted and the stromal bed exposed for trephination. The diameter of the recipient trephine is limited by the diameter of the flap, with diameters of 6.0 to 7.0 mm most commonly reported. The recipient stromal button is trephined, excised with standard corneal scissors, and then an "open sky" access to the anterior chamber and other intraocular structures is obtained. Concurrent cataract extraction, vitrectomy, IOL exchange, or iris surgery can all be performed with the standard techniques and instruments as are used with PK. The donor tissue originally was transplanted as a full-thickness graft, but the procedure evolved to attempt to match the thickness of the graft to the thickness of the resected posterior recipient tissue.[53,54,56] The anterior portion of the donor tissue is resected utilizing an artificial anterior chamber and a microkeratome to produce the proper thickness donor posterior disc. The original procedure was done with the same diameter size donor button as the diameter of the recipient excised tissue. It was later advocated that the donor diameter be oversized by 0.25 to 0.50 mm.[53-56] Once the donor tissue is secured into place with one or more sutures, the microkeratome-created anterior flap is placed back into position and the edges of the flap are sutured down into position with either multiple interrupted sutures or a running suture. The surface sutures are removed in weeks to months, much faster than with a standard PK.

Published clinical data on the flap technique in the peer reviewed journals is very limited, therefore information on ELK can only be gleaned from other sources as well. The success and challenges of this procedure can be evaluated in the context of achieving the ideal goals of endothelial replacement surgery.

The first goal of endothelial replacement surgery, astigmatic stability and surface smoothness, has not been uniformly achieved with the flap technique. The best spectacle-corrected visual acuity (BSCVA) of the 4 patients reported by Ehlers and associates[55] was only 20/125 to 20/400, and they felt that this poor vision was from high irregular astigmatism induced by the type of microkeratome used to make the flap. The average astigmatism reported by Busin and colleagues[53] for the 7 cases of endothelial keratoplasty at 5 to 7 months postoperatively was 2.6 ± 0.8 D, and this resulted in a range of BSCVA of 20/40 to 20/100. Their corneal topography maps have also shown significant irregular astigmatism that may limit the visual outcome. Culbertson has reported visual acuities after ELK of between 20/25 and 20/80 in a series of 12 eyes, with a range of astigmatism between 1.25 and 8.0 D (personal communication, William Culbertson, MD, June 27, 2002). Unfortunately, there are no other clinical reports to evaluate the short- or long-term

astigmatic outcomes of this procedure. Recent laboratory work with cadaver eyes by Pirouzmanesh and associates[59] has shown that the use of tissue adhesive for stabilizing the flap results in a mean astigmatic change of only 1.13 D. While these laboratory results are encouraging, clinical application and validation have not been done with this modification.

The second goal of a stable and highly predictable corneal power is even more elusive with the flap technique. In his first clinical case report,[54] Azar found severe flattening of the postoperative topography resulting in 16 D of induced hyperopia. In laboratory cadaver eye testing, Li and associates[60] found that the corneal power after ELK changed from preoperative an average of 0.30 ± 1.52 D for grafts oversized by 0.5 mm and up to an average of -10.30 ± 6.29 D of flattening for same size grafts. Busin and associates[53] have had the greatest success in minimizing ELK corneal power changes and reported a range of -1.0 to -4.0 D spherical equivalents.

It is difficult to determine the success of the flap technique in accomplishing the goal of safe and plentiful donor endothelial cell transfer. While anecdotally the flap technique has been successful in providing clear corneas, there is very little data available to determine the true endothelial survival rate with this procedure. No reports on endothelial cell survival after flap surgery are available from Azar[54] or Busin and associates.[53] Culbertson has reported on a series of 12 eyes of his ELK patients that had early postoperative cell counts averaging 1693 with a range of 994 to 2168 cell/mm^2. There was one eye with primary graft failure (personal communication, William Culbertson, MD, June 27, 2002). The single published report of endothelial cell survival after flap approach surgery is from Ehlers and associates,[55] who reported cell counts in their 4 cases ranging between 1200 and 2300 cells/mm^2. Silk and associates found that the procedure resulted in 21% graft loss (3 of 14) due to endothelial cell failure, and in the 11 grafts that did not fail, the average endothelial cell count was not reported. They concluded that the procedure needs further modification to reduce endothelial damage (Silk W, ARVO meeting, 2002, Abstract). Finally, the maximum diameter of the posterior disc with ELK surgery is problematic. The larger the posterior donor disc, the more endothelial cells can be transplanted. However, with ELK surgery the diameter of the donor disc needs to be significantly smaller than the flap, and the flap needs to be sutured down at the edges. To avoid the complications of sutures into the vascularized limbus and conjunctiva, the flap may be limited to 9- or 10-mm diameter. This may place a practical limit on the donor diameter to a maximum of 8 mm or less. This may be why there are no reports with ELK surgery of recipient trephinations greater than 7.0 mm. Until further prospective clinical reports of endothelial survival in ELK surgery are published, the effectiveness of this procedure in fulfilling the goal of safe donor endothelial transfer is unknown.

It is difficult to assess the long-term tectonic stability of the globe in ELK surgery, as reports with this procedure provide only 6 to 12 months follow-up, and no trauma has been reported. However, the short-term stability and safety of the stromal wounds in ELK can be evaluated. In the 4 patients reported by Ehlers and associates,[55] all 4 patients suffered epithelial ingrowth into the interface and required surgery to remove the epithelial nests. In their series of seven patients, Busin and associates[53] had one patient that had epithelial ingrowth that caused flap melt and required cutting off the flap. In his series of 14 patients, Silk had 3 patients that required regrafting for endothelial failure and 3 patients that had significant wound leaks requiring further surgery (Silk W, ARVO meeting, 2002, Abstract). Such a high incidence of early postoperative complications may be explained by the technical difficulty of the procedure requiring a learning curve, but may also point to an inherent instability of the flap edges and vertical stromal wounds following the procedure.

An optically pure cornea is achieved after microkeratome lamellar dissections in refractive surgery, and so it is reasonable to assume that this would be the case following the dissections of the ELK procedure, utilizing the same technology. However, despite the clear corneas that can sometimes be achieved in ELK surgery, consistent optical clarity has not been established. In fact, the single case report by Azar and associates[54] stated that their ELK patient achieved 20/50 visual acuity 1 year after surgery, but that dropped off to 20/100 at 2 years due to haze in the interface. There are no published reports of 20/20 visual acuity following ELK surgery, and the interface created by the microkeratome in this application may not be as optically clear as we see in refractive surgery.[61]

The final goal, a transplant procedure that is quickly and easily acquired, would seem to apply to ELK surgery. The flap technique for replacement of the endothelium utilizes familiar technology and a straightforward approach. Published papers and abstracts on ELK up to this time, however, report results that have been disappointing in their fulfillment of the other ideal goals of endothelial replacement, and the incidence of vision-threatening complications is high. ELK remains an interesting but unproven technique, and although scattered laboratory work continues,[59] clinical application of this technique appears to have been abandoned.

Limbal Incision Technique

Another technique for selective endothelial replacement utilizes a limbal incision, avoiding surface corneal incisions, sutures, and flap creation. This procedure has undergone rapid evolutionary changes over the past 7 years, with the addition and proliferation of new names and acronyms with each surgical revision.

History, Acronyms, and Techniques. The first concept of a truly limbal-based method of endothelial transplantation was presented by Ko and associates in 1993 (Ko W, ARVO Meeting, 1993, Abstract). They performed an animal study with rabbits whereby they made a limbal scleral incision, created a deep lamellar pocket, cut out the posterior corneal tissue, and then sutured in a posterior lamellar corneal button. The grafts were successful in about half of the animal eyes, but this work went relatively unnoticed. The importance of this study was that it avoided any surface corneal incisions or flaps and preserved the normal surface topography. In 1998 Gerrit Melles[62] of the Netherlands published his work with cadaver and animal eyes and described his development of a limbal incision–based "posterior lamellar keratoplasty." In his technique, he used a 9.0-mm incision at the limbus, and with specialized instruments that he designed, he created a deep lamellar pocket, limbus to limbus. He then slipped a 7- to 7.5-mm circular trephine into the pocket and trephined out the posterior cornea using a trephine and special scissors. The entire dissection and resection process was done under air, without the benefit of viscoelastics, and was difficult to the extreme. A similar technique was

used to prepare the donor tissue on whole cadaver eyes, with the exception that a donor trephine was used to cut the desired donor tissue from the endothelial side after the pocket had been formed, and the corneal-scleral donor cap had been removed from the donor globe. The tissue was then transferred onto a spatula, inserted into the eye, and then stabilized with an air bubble placed into the anterior chamber. The insight which Melles provided was that the transplanted donor tissue did not require sutures to keep it attached to the recipient bed. With this new technique, Melles was able to avoid the two inherent liabilities of PK surgery—surface corneal sutures and vertical stromal wounds. He performed the first human limbal incision PLK in the world and published this as a case report in 1999.[63]

In 1998 Mark Terry of the United States read the published animal work by Melles[62] and began his own laboratory research to further develop the technique.[6,64,65] Terry and his associate, Paula Ousley, redesigned the instruments and validated the extensive use of Healon viscoelastic (Advanced Medical Optics, Santa Ana, California) to make the procedure easier and safer. They also established manual techniques for preparation of the donor tissue for EK using an artificial anterior chamber rather than whole cadaver eyes. They published their laboratory work and named their modified procedure "deep lamellar endothelial keratoplasty" (DLEK) to distinguish it from the flap technique of endothelial keratoplasty, which was also commonly called PLK.[64,65] Terry[66] established a prospective, institutional review board–approved protocol and performed the first human limbal incision DLEK in the United States in March 2000 and subsequently published early results from the first two patients. Independently, Melles[4] and Terry[67] continued their own laboratory work and clinical series and began to train other surgeons in their techniques.

In 2002 Melles reduced the size of the recipient incision from 9-mm length to only 5 mm to provide greater structural integrity to the globe and reduce the risk of induced astigmatism from a large limbal incision. This modification also required folding of the donor tissue for insertion, raising the concern about short- and long-term endothelial damage with this new technique. Melles' initial case report of "sutureless" PLK surgery showed proof of concept with a clear graft and good vision at 1 week postoperatively, but the measured ECD was substantially lower than that of his prior large-incision cases.[4,68] Terry[69] adopted the small-incision approach by Melles for DLEK and called it "small-incision DLEK" and began a large prospective trial of this modified technique, with special attention to documenting the acute endothelial cell loss that might occur. Other surgeons and researchers, such as Thomas John,[70] Rajesh Fogla,[71] Bernard Seitz,[72] Kaz Soong,[73] and many others continued to work and publish on modifications to the DLEK technique that would make the surgery easier or more automated with high technology to replace the manual dissections.[74,75] Laboratory work also has continued in the development of automated methods of donor preparation, including the use of automated microkeratomes and femtosecond lasers, for all forms of endothelial keratoplasty surgery.[76-79] This work has been directed at improving the smoothness of the donor side of the interface, as well as documenting the endothelial cell damage that can occur in cutting the tissue.

In his continuing laboratory work with endothelial keratoplasty, Melles designed a technique for the selective removal of Descemet's membrane. He published this work in 2004 and he termed this procedure PLK with "Descemetorhexis."[80] The advantage of this modification was felt to be that it would provide for a smoother interface on the recipient side than what could be found with a manual deep stromal dissection. In addition, this modification eliminated the recipient deep lamellar dissection from the procedure, making the procedure easier and safer. The donor tissue could then be placed directly onto the recipient bed, which had been stripped of the diseased Descemet's membrane. Although not published, he performed this modification of his PLK surgery on several patients with success and reported on this at subspecialty meetings in 2003, prior to the publication of his laboratory studies.[6,81] The selective removal of Descemet's membrane with placement of the donor graft directly on the posterior surface of the full-thickness recipient was a faster and easier procedure than either PLK or DLEK and quickly gained acceptance. The procedure was popularized here in the United States by Frank Price of Indianapolis, who renamed the procedure "Descemet's stripping with endothelial keratoplasty" (DSEK) and in 2005 published the first cases reported in a peer-reviewed journal.[82] The DSEK procedure underwent another name change as surgeons began to use the microkeratome not only for DLEK surgery, but also for DSEK. Mark Gorovoy of Florida popularized the use of the microkeratome to prepare the donor tissue in DSEK surgery and renamed the procedure "Descemet's stripping automated endothelial keratoplasty" (DSAEK). He published the results of his first 16 patients with good early visual results but a high complication rate with dislocation of the tissue in 25% (4 of 16) of his cases.[83] By utilizing the microkeratome to prepare the donor tissue, and eliminating all manual lamellar dissections, the surgical skill level required for the DSAEK form of limbal endothelial keratoplasty was significantly reduced from what was required for PLK or DLEK surgery, and this procedure gained further general acceptance. Price and Terry have both independently reported on different technique modifications with DSEK surgery to reduce complications,[84,85] and Terry and associates[85] have elucidated with scanning electron microscopy studies the histology which may underlie the higher dislocations found in DSEK compared to DLEK. Finally, Price and Price[86] have recently applied DSEK surgery to the treatment of endothelial failure in eyes with a previous PK with good success, and this has significantly expanded the application possibilities of this surgery. Nieuwendaal and associates [87] also recently have reported performing DSEK surgery using tissue that they "precut" with lamellar dissection of the cornea on the whole globe, excise the corneal-scleral cap, and then store at room temperature in organ culture media until use 10 or more days later. The use of precut tissue prepared by certified Eye Bank technicians is now rapidly gaining widespread acceptance here in the United States using Optisol-GS (Bausch and Lomb, St Louis, Missouri) for short-term cold storage, but the Melles group is the first to report the use of precut tissue in the peer-reviewed literature.[87]

In an attempt to provide a true anatomically accurate result with endothelial keratoplasty, Melles[88] experimented in the laboratory with Descemetorhexis followed by pure Descemet's membrane transplantation and published his initial laboratory techniques with cadaver eyes. He recently described further cadaver eye work with a modified technique, but most important, he describes the first

successful clinical application of his technique in a case report. He named this anatomic replacement procedure "Descemet's membrane endothelial keratoplasty" (DMEK).[89] In this technique, Descemet's membrane with healthy donor endothelium is stripped from the donor tissue with minimal trauma, rolled up and placed into a specialized, small-incision injector, injected into the anterior chamber, unrolled with irrigation, and placed up into position onto the stripped recipient bed with an air bubble for support. Melles reports only 1-week follow-up data on this single case, but the visual recovery to 20/20 was rapid, and the ECD measured at 1 week was 2350 cells/mm^2. Clinical attempts at pure Descemet's membrane transplantation have also been done by Michael Tappin using a specialized air-injection spatula for insertion of the nonfolded donor Descemet's membrane through a large incision. He has named his technique "true endothelial cell transplantation," or "Tencell."[90] The early results with the Tencell technique show some success in obtaining a clear cornea, but the endothelial failure rate is currently too high for general use. Until long-term data on more eyes are reported and the success of these procedures in the hands of other surgeons is established, DMEK and Tencell remain truly investigational procedures.

Fulfillment of Ideal Goals of Endothelial Keratoplasty. Over the past several years, the data available on the various limbal incision endothelial keratoplasty procedures has been rapidly expanding. These techniques can now be judged according to the extent that they fulfill the 6 goals of endothelial keratoplasty surgery.

The first goal of providing for a smooth surface postoperatively without significant change in astigmatism appears to be well accomplished by the DLEK/PLK and DSEK/DSAEK endothelial keratoplasty procedures. In his largest clinical report of 9.0-mm incision PLK surgery, Melles[4] found that the postoperative astigmatism in the 6 eyes that made up the group was 1.54 ± .81 D, and no range or preoperative values were given. Melles[68] has had no series reported of small-incision PLK, but the single case report he published demonstrated an eye with 1.0 D of refractive astigmatism at 1 week and 1.75 D at 1 year. Terry and Ousley[67] reported, in their initial series of 8 eyes with large-incision (9-mm length) DLEK, the results of an average refractive astigmatism of 2.28 ± 1.03 D (range, 1.0 D to 3.75 D). This represented an average increase from preoperative levels of astigmatism of 1.13 ± 1.5D. The largest report on large-incision DLEK surgery is the prospective study by Terry and Ousley[91] on 36 eyes. They had 100% follow-up data at 6 months and demonstrated a postoperative refractive astigmatism of 1.63 ± .97 D (range, 0 to 4.0 D). This represented an increase from preoperative levels of astigmatism of only .39 ± 1.32 D, which was reported as not statistically significantly different. (P = .035). The stability of large-incision DLEK was evaluated by Ousley and Terry[92] in a separate paper, which analyzed 20 eyes in this group at the 2-year protocol visit. They found a refractive astigmatism of 1.76 ± .66 D (range, .75 to 3.0 D) at 2 years after surgery, reported as not statistically different from the 1-year value of 2.04 ± 1.05 D (range, 0.00 to 4.0 D). (P = .239) Terry and Ousley have provided a prospective evaluation of a large number of eyes following small-incision (5-mm-length incision) DLEK surgery. While data was initially available on the first 25 eyes in their series, which demonstrated 1.31 ± .59 D (range, .25 to 2.5D) of astigmatism at 6 months,[69] they have recently increased the series to 62 eyes.[91] They found similar findings of low astigmatism of 1.18 ± .74 D (range, 0 to 3.75 D) at 6 months in this larger group, and once again without significant increase in astigmatism levels from the preoperative values of .97 ± .71 D (range, 0 to 2.75 D). Terry and Ousley have not reported any 1- year or 2-year astigmatism data on their small-incision DLEK cases. Fogla and Padmanabhan reported on their initial 15 small-incision DLEK cases,[71] and similar to the reports by Terry and Ousley found a low average refractive astigmatism of 1.46 ± 1.21D (range, .5 to 4.0 D) at 6 months postoperatively. Amayem and colleagues[93] have shown that DLEK surgery can be performed even in cases of severe corneal bullous edema with preoperative visual acuity ranging from a best vision of count fingers to light perception. In their report on just 6 eyes receiving large-incision DLEK surgery, refractive astigmatism at 6 months averaged 2.0 ± 1.6 D (range, .5 to 4.0 D) and at 1 year was 2.2 ± 1.4 D (range, 1.0 to 4.0 D), similar to the amplitudes of astigmatism found by other surgeons performing DLEK in less severely affected eyes.[71,92] From these studies, it appears that DLEK/PLK surgery does not significantly increase the refractive astigmatism and results in astigmatism at 6 months in most cases of between 1 and 2.5 D of astigmatism. This level of astigmatism is well within what can be corrected with spectacles rather than resorting to gas permeable contact lenses, corneal relaxing incisions, or laser refractive surgery.

Another measure of the success of DLEK/PLK surgery in restoring the smoothness of the recipient corneal surface is the indices of SRI and SAI, which are calculated by the software of the TMS-1 corneal mapping system.[8] Terry and Ousley[69] have shown in 20 cases of large-incision DLEK that the SRI is relatively normal at 1.16 ± .41 (range, .57 to 2.13) at 1 year after surgery and remains stable at 1.13 ± 44 (range, .63-2.39) at 2 years after surgery. (P = .763). Consistent with surface smoothing, the SAI in this group was 1.05 ± 1.09 (range, .26-4.86) at 1 year after surgery and .76 ± .59 (range, .29-2.37) at 2 years after surgery. In a separate report on small-incision DLEK, Terry and Ousley[69] reported the corneal map indices at 6 months after surgery in 25 eyes. The mean SRI was normal at 1.01 ± .47 (range, .32-2.35) and the SAI was also normal at .94 ± 1.01 (range, .23-4.86), and these values were considerably better than the preoperative SRI of 1.86 and SAI of 2.05 in that series. (P = .001). The only other report on TMS-1 topography indices after DLEK is by Fogla and Padmanabhan,[71] who reported an excellent SRI of .72 ± .44 (range, .04-1.33) and SAI of .83 ± .52 (range, .26-1.73) 6 months after their small-incision DLEK in 15 eyes.

There are no prospective studies currently in print on DSEK or DSAEK surgery, but the retrospective studies are encouraging for minimizing postoperative astigmatism. Price and Price[82] found an average of 1.5 ± .94 D of refractive astigmatism at 6 months on their initial 50 DSEK cases. In their subsequent report comparing their DSEK to DSAEK cases, they increased the number of DSEK cases analyzed to 98 at 6 months and found a similar astigmatism postoperatively of 1.50 ± 1.0 D (range, 0 to 4.5 D).[94] This was not statistically different than the preoperative values of 1.5 ± 1.3 D (range, 0-5.5) (P = .81). Recently, Gorovoy[83] reported on his 16 initial DSAEK cases and found that the range of preoperative refractive astigmatism was between 0 and 1.75 D, whereas the postoperative refractive astigmatism between 3 and 12 months postoperatively was in a wider range of between 0 and 4.25 D. No

averages or statistical analysis were done on this data. Price and Price[94] demonstrated in their retrospective review of 93 DSAEK cases that the mean postoperative astigmatism at 6 months was also quite low at 1.5 ± 1.2 D (range, 0-5.0 D). Nieuwendaal and associates[87] reported on using organ culture medium preserved precut donor tissue in 22 eyes undergoing DSEK surgery. There were 3 eyes in which the donor tissue failed and would not attach, and that left 19 eyes for analysis. The postoperative refractive astigmatism at least 6 months postoperatively averaged 1.7 ± 1.0 D (range, 0-3.0 D). Preoperative refractive astigmatism data were not available. There are no corneal mapping indices, such as SRI or SAI performed, in any published DSEK or DSAEK series. From these studies, it appears that the DSEK/DSAEK procedures yield a similar level of low postoperative average astigmatism, as is found in DLEK surgery.

The second goal, providing for a stable and predictable corneal power after endothelial replacement surgery, appears to be well met by the various EK procedures. The key to having a refractive spherical equivalent that is near emmetropia after endothelial keratoplasty lies in the ability of the surgery to retain the same keratometry readings before and after surgery. If this can be accomplished, then the IOL calculation for combined "triple" procedures (transplant, cataract extraction, and IOL placement) becomes far more accurate than what we have experienced with PK surgery.[10,11,13] If the eye already is pseudophakic, then restoration of the keratometry to what it was before the onset of epithelial edema will also return the eye to the target refraction of the original cataract surgery. The keratometry readings after large-incision PLK by Melles[4] in just 6 eyes ranged between 41.25 and 47.50 D. No preoperative data were given, so it is unknown if there was much change in corneal power from preoperatively to postoperatively, but these values of keratometry are certainly in the normal range. The PLK surgery in this Melles report[4] resulted in a range of postoperative refractive spherical equivalents of between +.50 D and -1.75 D in 5 pseudophakic eyes, with one eye excluded that was intentionally left aphakic. Ousley and Terry[92] reported on the stability of 20 large-incision DLEK eyes between 1 and 2 years after surgery and found that there was no significant change from the keratometry readings of 43.20 ± 1.8 D (range, 38.10-45.40) at 1 year to the keratometry readings at 2 years of 43.60 ± 1.80 D (range, 39.50-47.70). (P = .25) This surgery resulted in a postoperative refractive spherical equivalent of -.19 ± 1.52 D (range, -3.75 to +2.38 D) at 1 year and of -.37 ± 1.27 D (range, -3.88 to +1.50 D) at 2 years after large-incision DLEK. This was reported as not significantly different from the preoperative spherical equivalents, which ranged from -5.75 to +6.00 D, and the spherical equivalent was considered stable by the investigators between the 1 and 2 years of observation (P = .156). Fogla and Padmanabhan[71] found after small-incision DLEK in 15 eyes that the mean keratometry reading preoperatively of 40.30 ± 4.73 D (range, 30.10-45.50) became over 3 D steeper postoperatively after DLEK surgery with keratometry values of 43.6 ± 1.93 D (range, 39.50-46.90). They attributed this change in keratometry to the corneal edema and contact lens wear preoperatively, which may have been causing abnormal flattening of the corneal topography prior to surgery. Nonetheless, even with this preoperative uncertainty, the investigators found that the postoperative spherical equivalent was quite good at -.08 D with a range of +2.0 to -2.0 D. In their report on their first 25 eyes with small-incision DLEK surgery, Terry and Ousley[69] found that the cornea actually flattened by about 1 diopter after surgery with a preoperative mean keratometry of 44.30 ± 2.30 D (rang, 38.20-49.50) to a postoperative mean keratometry of 43.30 ± 1.10 D (range, 40.60-45.10) (P = .032). They also attributed this change in mean keratometry to the resolution of preoperative edema as well as to the difficulty in obtaining good keratometry readings in some eyes with extensive preoperative epithelial edema. Nonetheless, Terry and Ousley found that the preoperative spherical equivalent of -.320 ± 1.29 D (range, +1.70 to -2.75) did not significantly change 6 months after small-incision DLEK surgery with a resultant mean spherical equivalent of -.75 ± 1.25 D (range, -2.63 to +2.00) (P = .61).

The predictability and stability of the corneal power after the various Descemet's membrane stripping procedures should be similar to the closely related DLEK and PLK procedures. Price and Price[82] found in their retrospective study of 50 DSEK eyes that the preoperative spherical equivalent of -.36 ± 1.4 D (range, -3.25 to +3.75) did not significantly change after DSEK, with a postoperative spherical equivalent of +.17 ± 1.5 D (range, -2.90 to +4.25) (P = .10). They did not report keratometry readings. The later report of Price and Price[94] on 98 DSEK eyes found that the spherical equivalent preoperatively was -.68 ± 1.60 D (range, -6.60 to 3.75) and that it increased by .66 D to -.09 ± 1.6 D (range, -5.6 to 4.25) postoperatively at 6 months (P = .0007). In analysis of their 93 DSAEK eyes, the investigators found no significant change from the preoperative spherical equivalent of .15 ± 1.60 D (range, -4.50 to 5.40) to the 6-month postoperative spherical equivalent of .23 ± 1.80 D (range, -3.50 to +4.75) (P = .82). Once again, keratometry values were not given in this retrospective study using postoperative data from multiple follow-up clinics.[94] In the retrospective DSAEK report by Gorovoy [83] of 15 eyes with postoperative refractions, analysis of spherical equivalents was not done and keratometry was not reported. An analysis of his raw data on refractions, however, reveals that the average spherical equivalent preoperatively was -.25 D with a range of -1.88 D to +1.50 D, whereas postoperatively at 1 year the mean spherical equivalent was -.12 with a range of -3.38 D to +1.86 D. The report by Nieuwendaal and associates[87] on their precut tissue DSEK series also did not report keratometry data nor did it contain spherical equivalent analysis. An analysis of their raw data on postoperative refractions, however, reveals that the average spherical equivalent in their series postoperatively was +.37 D with a range of -3.50 D to +2.75 D. No preoperative data on refractions are given, however, and so stability of refraction from preoperatively to postoperatively with their DSEK technique cannot be assessed.

The third goal, the ability of endothelial keratoplasty procedures to restore the normal corneal hydration of the recipient through the transfer of healthy donor endothelial cells, has been critically evaluated. Melles and associates[4] reported a postoperative donor ECD of 2520 ± 340 cells/mm^2 (range, 2110 to 2980 cells/mm^2) at about 9 months after large-incision PLK surgery in just 6 eyes. Because he used fresh, whole globes as donors, no preoperative cell counts were available to determine the percentage of donor ECD loss. In their report on 10 large-incision PLK eyes, Van Dooren and associates[95] found an average ECD of 2366 ± 357 cells/mm^2 (range, 1167 to 2969) 6 months after surgery, and they calculated a 17% cell loss based on the preoperative ECD of the mate donor

cornea. Terry and Ousley[91] have reported on the largest prospective series in the literature of large-incision EK surgery and found that the ECD at 6 months after 36 large-incision DLEK eyes was 2189 ± 440 cells/mm^2 (range, 1167 to 2897 cells/mm^2), which represented a 23% cell loss from preoperative values. Terry and Ousley[91] also reported that in 62 small-incision DLEK eyes, the donor ECD at 6 months was 2112 ± 420 cells/mm^2 (range, 1097 to 3202 cells/mm^2), which represented a 25% cell loss from preoperative values. There was no statistical difference between the large-incision cases that did not fold the tissue and the small-incision cases that did fold the tissue at the early 6-month postoperative measurements (P = .392). Fogla and Padmanabhan[71] reported on 15 cases of small-incision DLEK and found a 6-month mean ECD of 1732 ± 514 cells/mm^2 (range, 638 to 2341), which represented a 15% cell loss from preoperative donor measurements.

Data on longer-term endothelial survival after EK is sparse. Van Dooren and associates[95] found a 26% cell loss at 1 year after large-incision PLK surgery in 9 cases, and Ousley and Terry[92] found a similar 28% cell loss at 1 year after large-incision DLEK surgery in 20 eyes. At 24 months after large-incision PLK surgery, Van Dooren and associates[96] reported a 46% cell loss in these same 9 eyes, whereas Ousley and Terry[92] reported a 36% cell loss on their 20 eyes at 2 years after large-incision DLEK surgery.

There are even fewer data available on endothelial survival after DSEK or DSAEK surgery. In their report of DSEK surgery using their own precut tissue in organ culture media, Nieuwendaal and associates[87] report on 15 eyes with varying follow-up of 6 to 8 months (n = 7), 13 to 18 months (n = 6) and 26 to 27 months (n = 2). The short-term follow-up group averaged a decrease from preoperative donor ECD to postoperative ECD of 31% (range, 14% to 46%), the intermediate follow-up group averaged a decrease in ECD of 38% (range 0% to 64%), and the 2 eyes that were 2 years out from surgery had a decrease in ECD of 25% in one eye and 54% in the other. Gorovoy[83] reports on his first 16 cases that there was a 40% cell loss from preoperative donor measurements at just 7 to 12 months after DSAEK surgery, with a mean ECD of just 1714 cells/mm^2 (range, 987 to 2994) postoperatively. While these case numbers are small, there is a trend for the DSEK and DSAEK procedures to show a higher cell loss earlier postoperatively than most prior reports for either PK or DLEK surgery. Further good prospective data are needed on the latest iterations of EK surgery to know if this relative increase in early endothelial cell loss is real.

The fourth goal, a tectonically stable globe safe from injury or infection, would seem to be well met by all of the various forms of limbal-based EK surgery. During the time of EK surgery, the intraocular pressure is better controlled in this relatively closed system than in standard PK surgery where the presence of a large anterior hole in the eye presents a dangerous interval of time for choroidal hemorrhages to occur. There would seem to be less of a tendency to have wound leaks (and the accompanying worries of wound infections, endophthalmitis, and so on) after EK surgery compared to PK surgery due to the location and configuration of the wound, as well as the protective covering of conjunctiva that can easily cover the limbal wound. When the scleral limbal incision is sutured, it heals as a beveled, vascularized wound, which by its nature is more resistant to later trauma than a vertical, nonvascularized corneal wound, such as that found with PK. The 9-mm-long large-incision DLEK surgeries would be expected to have the same tectonic strength and resistance to trauma of an extracapsular cataract surgery wound, whereas the 5-mm-long small-incision DLEK wounds would likely be comparable to the wounds of scleral-tunnel cataract surgery. After DLEK surgery, there is rarely a corneal epithelial defect, and so the eye is better protected against infection in the first postoperative days. Finally, the absence of surface corneal sutures in EK surgery eliminates concerns of loose sutures causing vascularization, infection, and corneal melting as is found all too often in PK surgery.[32-35] To date, there have been no reports of globe rupture after EK surgery, wound infections, or other complications that would result from tectonic instability. There has been an anecdotal report of intrastromal interface infection following DLEK surgery (John T, ARVO Abstract, 2003), and this patient did require a therapeutic PK to cure the infection. Overall, by largely preserving the limbal architecture and most, if not all, of the recipient corneal stromal tissue, EK surgery has great advantages over PK surgery in protecting the globe during and after the transplantation procedure.

The fifth goal, providing an optically clear cornea for the best possible visual result, is currently the greatest challenge for EK surgery. By its very nature, EK surgery creates a horizontal donor-recipient interface that overlies the visual axis of the recipient eye. In anterior lamellar surgery, we have learned that a deep stromal interface of this nature can limit the final average visual results to about 20/40 or worse visual acuity.[96] The interface after DLEK may be similar to those anterior lamellar procedures, and the interface after DSEK and DSAEK surgery may be only somewhat different. In addition, most, if not all, of the recipient stromal tissue and epithelium (with often thickened basement membrane) is left behind after EK surgery, and if this tissue has any haze or opacification, it can interfere with the patient's vision in the long term. Finally, the thickness and placement of the donor tissue can affect the wound healing, and this in turn can affect the ultimate vision. Donor tissue folds, striae, donor Descemet's membrane detachments, and donor scars that transect the visual axis of the recipient have all been reported with EK surgery, presenting a unique new set of complications to be confronted in corneal transplant surgery.[97-99] A review of the visual results following uncomplicated EK surgery can shed light on the usual optical clarity of the cornea after this unique surgery.

In their first series of PLK eyes, Melles and associates[4] reported on 6 eyes that attained postoperative visual acuity of between 20/20 and 20/80. The first 8 eyes with large-incision DLEK reported by Terry and Ousley[67] attained postoperative visual acuity of between 20/25 and 20/70 at 6 months. When these two investigators expanded the large-incision DLEK series to 20 eyes and looked at the vision in the longer term,[92] they found that the average visual acuity at 1 year postoperatively was 20/50 (range, 20/25-20/200) and at 2 years, 20/48 (range, 20/25-20/200). Amayem and colleagues[93] performed large-incision DLEK on 6 eyes with severe visual loss (at the level of count fingers or worse), and were able to improve the visual acuity postoperatively to a range of 20/40 to 20/200. Fogla and Padmanabhan[71] reported an average visual acuity of 20/50 (range, 20/20-20/120) at 7 months in 15 eyes after their small-incision DLEK surgery. Terry and Ousley[91] have reported the largest prospective series of EK eyes, and in their 6-month postoperative report on 62 small-incision DLEK cases, they found an average visual acuity of 20/42 (range, 20/20-20/200). None of these studies excluded

eyes with comorbid disease such as age-related macular degeneration or cystoid macular edema, and so it is difficult to tell to what degree the interface and residual recipient tissue changes are interfering with the ultimate visual outcome following these EK surgeries.

The visual results after DSEK and DSAEK surgery are reported largely in a retrospective manner and often have included data gathered by multiple physicians at multiple clinics. However, in these reports the investigators have tried to separately report the visual results of eyes with and without comorbid disease that would influence visual acuity. Price and Price[82] reported the average visual acuity at 6 months after their first 50 cases of DSEK as 20/50 (range, 20/25 to count fingers). When they removed the 12 eyes with known retinal problems, the average visual acuity improved to 20/40 for the remaining 38 eyes at 6 months (no range given). When they expanded their series to 98 DSEK eyes,[94] the investigators found that the average visual acuity at 6 months was 20/42, with 55% of eyes seeing 20/40 or better. Removing eyes with comorbidity from the series, they found that the average visual acuity improved to 20/38, with 69% achieving 20/40 or better.[94] In their report of the 19 of 22 eyes that did not have primary graft failure after DSEK surgery, Nieuwendaal and associates[87] found that the BSCVA ranged between 20/20 and 20/100, with 53% (10 of 19) of the eyes seeing 20/40 or better. When the eyes with comorbidity are removed from the analysis, the average visual acuity was 20/36 with 62% (10 of 16) of the eyes seeing 20/40 or better. For DSAEK surgery, Gorovoy[83] reported an average BSCVA of 20/40 (range, 20/20-20/200) after DSAEK surgery in 16 eyes at 1 year, with 81% (14 of 16) seeing 20/40 or better. When the 2 eyes with retinal disease were removed from the analysis, the average BSCVA improved to 20/30 (range, 20/20-20/40), with 100% of the 14 eyes seeing 20/40 or better. The largest series in the literature on DSAEK surgery is by Price and Price,[94] who reported a retrospective review of 93 eyes at 6 months. They found that the average BSCVA was 20/40 with 69% (64 of 93) seeing 20/40 or better. Removing the eyes with comorbidity from the analysis, they found that the average visual acuity improved to 20/38, with 79% seeing 20/40 or better.

All of these studies demonstrate that rapid and practical visual acuity levels can be usually achieved with EK surgery. However, the paucity of 20/20 visual acuities and the 20% or higher number of eyes that see 20/50 or worse after surgery (even in the absence of comorbid disease) indicates that the interface and other factors related to this surgery dampen the corneal clarity or optical performance we have come to expect from transplant surgery and thus restrain the final visual acuity levels that can be obtained.

The first human limbal approach EK surgery was reported by Melles and associates in 1999 in the Netherlands, [63] and the first US cases of EK were performed by Terry in March of 2000.[66] Although the large-incision DLEK procedure using viscoelastic for space maintenance was easier than the PLK surgery using only air, the deep lamellar dissection and resection skills required for EK surgery were considered too difficult for general adoption of EK by most transplant surgeons. The sixth goal of having a new procedure that could be quickly and easily acquired did not occur until the manual stromal dissection portions of the EK were completely eliminated from the procedure. With the advent of DSAEK, and especially with the advent of tissue which is "pre-cut" by an Eye Bank technician, the surgeon no longer had to learn the delicate skills of deep stromal dissection, and subsequently the widespread utilization of EK surgery materialized. Although EK is still not considered an "easy" procedure, the main hurdles to becoming "mainstream" have now apparently been overcome and EK surgery has begun to be taught as an acceptable transplant procedure in a few fellowship and residency programs in the United States and elsewhere.

PURPOSE OF THIS CURRENT STUDY

There have been no published reports to date compiling the visual, astigmatic, topographic, pachymetric, and donor endothelial cell survival outcomes beyond the 6-month postoperative time frame in any single cohort report of small-incision endothelial keratoplasty. Although Ousley and Terry have reported on a prospective series of 20 cases of large-incision DLEK from 1 to 2 years postoperatively, none of their small-incision DLEK cases were included in that report.[92] Van Dooren and associates[95] have reported endothelial cell loss on a small case series of PLK cases from 6 months to 3 years postoperatively, but that report was on only 4 eyes with small-incision PLK and did not include any data on vision, refraction, or topography. Finally, there have been no papers on DSEK or DSAEK surgery that have provided data longer than the 6- to 12-month postoperative time frame, and all but one of these studies have been retrospective.[82-85,87]

This is the first report of multiple outcomes of small-incision DLEK surgery that extend out to the 2-year postoperative time frame. This is also the largest prospective series of small-incision DLEK surgery ever reported. Small-incision DLEK surgery was evaluated first to determine the specific data that support the visual rehabilitation at 6 months postoperatively and second to determine the stability of those outcomes over the first 2 years postoperatively. While the surgical technique of endothelial keratoplasty has now evolved from PLK to DLEK to DSEK/DSAEK surgery (and perhaps to DMEK), the data presented in this report can serve as a basis to judge the short- and long-term outcomes of these more recent modifications of selective endothelial replacement surgery.

METHODS

PROTOCOL

Health Insurance Portability and Accountability Act of 1996 (HIPAA) compliant clinical protocols and investigational surgical consent forms for small-incision (5.0 mm) DLEK surgery were approved by our hospital Institutional Review Boards, and enrollment of patients with endothelial decompensation was initiated. All study participants gave their written informed consent for surgery and for this study. The first case of small-incision DLEK surgery was performed on November 11, 2002, and the last case in this consecutive series was performed on October 19, 2004. Inclusion criteria for patients involved any eye with vision loss due to

endothelial dysfunction that otherwise would be considered for full-thickness PK. Vision loss was defined as a sufficient decrease of vision to interfere with a patient's significant activities of daily living. For many patients this meant that they were unable to see well enough to drive safely or read the newspaper for several hours in the morning until the corneal edema cleared later in the afternoon. Exclusion criteria included eyes that had significant anterior stromal scarring. Eyes with a history of cystoid macular edema, age-related macular degeneration, controlled glaucoma, and other comorbidities were not excluded.

Preoperative and postoperative measurements of BSCVA, manifest refraction, corneal mapping, corneal pachymetry, and central endothelial cell densities were dictated by the prospective protocol and were performed preoperatively and at 6, 12, and 24 months postoperatively.

There were 116 total eyes enrolled in this study during the specified time period. Of these 116 eyes, there were 23 eyes of patients that were referred from out of state. Most of the out-of-state patients returned for their 6-month postoperative visit, but for the 1- and 2-year visits, scattered data were returned by the referring out-of-state physician. There were 93 eyes that were from local patients. Of these local patients, there were 14 eyes of patients that had their preoperative examination performed with us and made at least one postoperative visit but did not complete their 2-year visit. This left 79 eyes of patients that had all of their examinations at our institution with at least 2 years follow-up solely at our institution.

The same Certified Ophthalmic Technician (COT) from my clinic performed all measurements at all time gates on protocol patients seen at our institution. The protocol called for measurements of the BSCVA and manifest refraction to be performed preoperatively and again at 6, 12, and 24 months postoperatively. On examinations performed in my clinic, the same COT performed all preoperative and postoperative vision testing of patients, using the same Snellen chart (in the same examination room) each time. Contrast sensitivity measurements were not performed. Refractive astigmatism calculations were taken directly from the manifest refraction without correction for any change in astigmatic axis from one examination to another. Refractive spherical equivalent data were taken as a direct calculation from the manifest refraction findings. Mean visual acuity for each time gate was computed using logarithmic acuity. It was then converted into Snellen acuity.

Corneal topography was performed by the same COT using the TMS-1 topography mapping device (Tomey Technology, Cambridge, Massachusetts; software version 1.61). The simulated keratometry of the TMS-1 software was used to determine the average keratometry value. Data regarding the smoothness of the corneal surface were entered using the standard mapping indices of Surface Regularity Index (SRI) and Surface Asymmetry Index (SAI) generated by the standard TMS-1 software. Corneal pachymetry was performed by the COT using an Ultrapach contact ultrasonic pachymeter with a 1-mm tip (Model ETI 500, Eye Technology, Inc, St Paul, Minnesota). At least three central corneal readings were taken at each examination, taking the middle reading of the three most consistent measurements.

Preoperative specular microscopy of the donor tissue was performed by certified technicians in Eye Bank Association of America (EBAA) certified eye banks. The vast majority of donor tissue came from the local Lions Eye Bank of Oregon, which used an EB-3000 XYZ Eye Bank specular microscope (HAI Laboratories, Inc, Lexington, Massachusetts). These preoperative cell counts were obtained using an apices digitized method and the manufacturer's calibrations for magnification. The apices of at least 100 cells from the endothelial images of each cornea were counted. Postoperative specular microscopy measurements of central ECD (Konan SP4000 noncontact specular microscope, Konan Medical Corp, Fairlawn, New Jersey) were performed in my clinic at 6, 12, and 24 months postoperatively. The same COT performed all postoperative testing of patients, using the same specular microscope each time. These postoperative cell counts were obtained using the manufacturer's calibrations for magnification and were counted with a fixed-frame method marking at least 50 to 100 cells for each image. Analysis of endothelial polymorphism and polymegathism was not performed. Specular ECD images that either could not be obtained due to poor patient compliance or were of poor quality to prevent the minimum number of cells to be marked, were not entered into the database.

SURGICAL PROCEDURE

All 116 small-incision DLEK cases were performed by me between November 11, 2002, and October 16, 2004. The major steps of the procedure are shown in Figure 1.

The small-incision DLEK procedure was performed in conjunction with cataract extraction by phacoemulsification technique in 58 (50%) of 116 cases. In all of these cases, the cataract surgery was performed initially from a superior approach through a 3-mm-wide scleral limbal incision. The only viscoelastic utilized for the phacoemulsification procedure was the cohesive viscoelastic Healon (Pfizer, New York, New York). Once the standard "phaco-chop" surgery was completed and the IOL was in place, the wound was sutured and the operation was begun for the DLEK procedure.

Recipient Preparation

For small-incision DLEK surgery, the operating microscope is positioned for the surgeon to be seated at the temporal side of the patient. A temporal limbal peritomy of the conjunctiva is performed with scissors allowing exposure of about 6-mm arc length of limbal tissue (about 3 clock hours). Prior to forming the DLEK scleral access incision, two clear corneal limbal stab incisions (about 1-mm diameter) are placed on either side of the peritomy area, to be used as access points to the anterior chamber later in the operation. Through one of the stab incisions, the cohesive viscoelastic Healon (Pfizer, New York, New York) is placed into the anterior chamber to replace the aqueous fully and to maintain normal pressure. I recommend against the use of Viscoat (Alcon, Fort Worth, Texas) or other dispersive viscoelastic materials during any portion of DLEK surgery as I believe that the dispersive viscoelastic materials can cause stromal interface coating with subsequent nonadherence and dislocation of the donor tissue. Separate laboratory studies that I performed with Healon Yellow (Pfizer) in 1999 demonstrated that the extremely cohesive nature of Healon

allows it to be completely removed from the anterior segment with simple irrigation and aspiration and does not allow Healon to coat the cut recipient stromal surface (unpublished data). I therefore recommend that only the very cohesive viscoelastic of Healon be used during DLEK surgery.

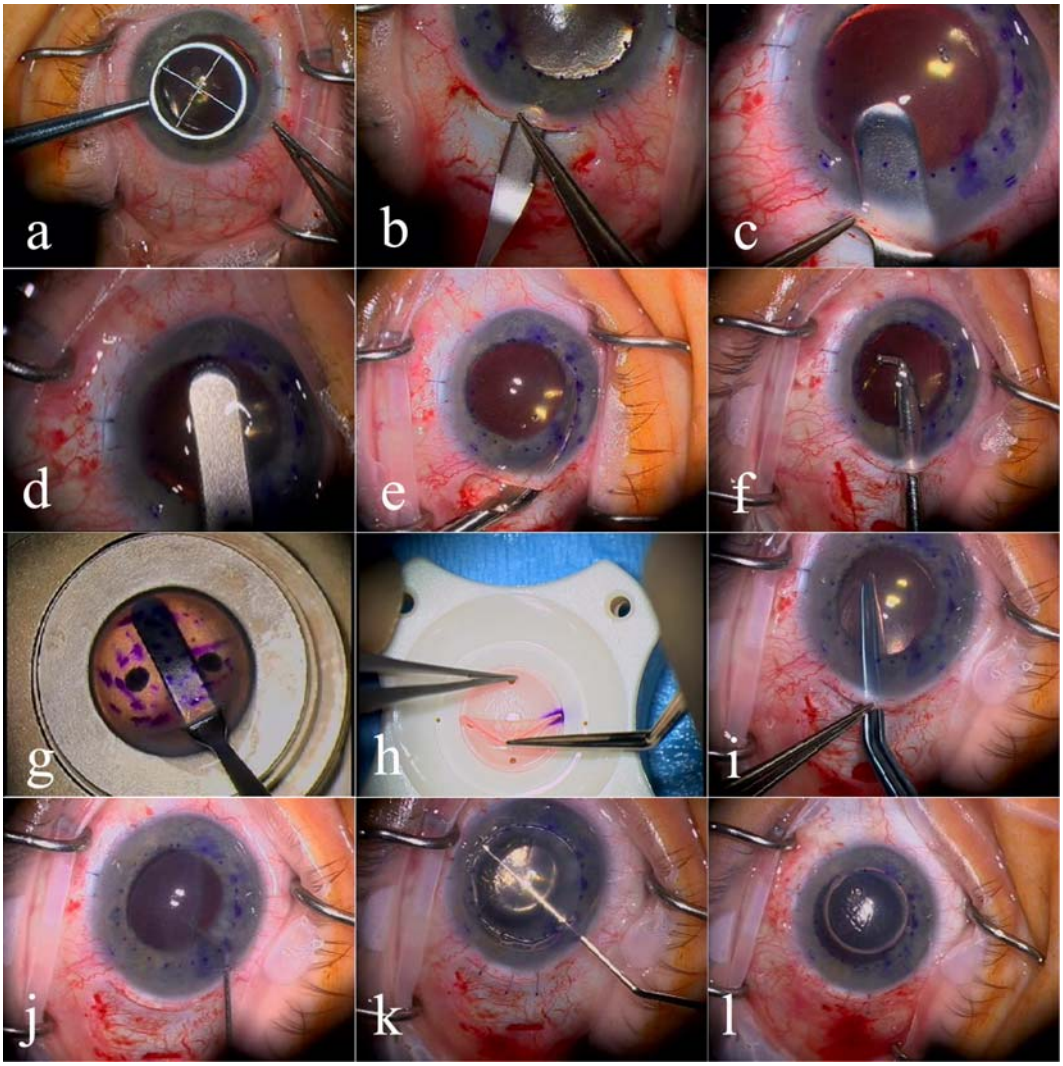

FIGURE 1

Surgical steps for small-incision deep lamellar endothelial keratoplasty (DLEK). *Top row*: Left, Surface of cornea is marked with an 8.0-mm circular template mark after anterior chamber is filled with Healon viscoelastic. Center, A 5.0-mm limbal scleral incision is made temporally, and a deep scleral cornea pocket is created. Right, A semisharp broad stromal dissector extends the deep lamellar pocket to the midpupillary zone. *Second row:* Left, A curved semisharp dissector extends the deep lamellar pocket distally to create a pocket 1 mm wider in diameter than the overlying template mark. Center, Specialized highly curved, low profile scissors are used to excise the posterior tissue, following the path of the overlying circular template mark. Right, All viscoelastic is removed from the eye with an irrigation-aspiration cannula. *Third row:* Left, Donor tissue is mounted onto an artificial anterior chamber, and after a 350-μm-deep limbal incision is made, the deep stromal dissection pocket is created, limbus to limbus. Center, The donor tissue is placed endothelial side up, punched with an 8.0-mm donor trephine, a Healon strip is placed on the central endothelium, and then the tissue is folded into a 60%/40% “taco” shape. Right, The donor tissue is inserted into the anterior chamber using special noncrushing forceps. *Bottom row:* Left, Irrigation from the paracentesis site deepens the chamber and the tissue unfolds spontaneously. Center, With the chamber filled with air and the wound closed, a reverse Sinskey hook is used to pull the recipient bed edges posterior to the donor edges. Right, At the close of the procedure, a 4-mm diameter or smaller air bubble is left in the anterior chamber, and a collagen shield with antibiotics and steroids is placed over the cornea and the eye patched until the next morning.

Prior to creating the deep lamellar pocket of DLEK, a template mark is placed on the corneal epithelial surface. A circular marker with a diameter of 8.0 or 8.5 mm (depending upon recipient corneal diameter and surgeon preference) is used to make a circular impression on the central epithelial surface. If the position and centration of the mark are acceptable to the surgeon, then it is accentuated with ink marks. This circle on the cornea is later used as a template for resection of the posterior recipient lamellar tissue.

A trifaceted, guarded diamond knife (Storz Ophthalmics, St Louis, Missouri) is then set to a depth of 350 μm, and a 5.0-mm-length incision is made approximately 1 mm posterior to the corneal limbus and concentric with it. A sharp crescent blade is then utilized to create a deep scleral-corneal lamellar pocket down to about 75% to 85% corneal depth along the entire length of the wound. Judgment of the initial depth of the pocket is based on inspection of the anterior lip thickness and by the clarity of the underlying stromal bed.

A specialized semisharp stromal dissector (straight Devers dissector, Bausch and Lomb, St Louis, Missouri) is then used to extend the pocket to the midpupillary region of the cornea, and then a curved stromal dissector (Devers Dissector-curved, Bausch and Lomb, St. Louis, MO) extends the pocket further. I prefer to have a pocket that extends at least 1 mm peripheral to the diameter of the surface template circular mark (ie, 10.0-mm pocket diameter for an 8.0-mm mark). This creates a large-area, deep lamellar corneal pocket. The dissection is accomplished with a slow and methodical sweeping motion of the Devers dissector heads, from central to peripheral tissue, and the surgeon can often see the reflections of Descemet's membrane wrinkling during the sweeping motion, which is an assurance that the depth of the dissection is adequate. It is important that the pocket stromal dissection be carried out over the entire desired area of the cornea, in order to allow adequate edge space for the donor disc.

The resection of the posterior recipient tissue begins by first entering the anterior chamber through the temporal scleral corneal pocket incision. A standard cataract surgery diamond blade with a 2.8-mm width was used. Entry into the anterior chamber is preferred at the exact corresponding position of the temporal edge of the surface template mark.

It is through this entry point that the recipient posterior resection is started utilizing special scissors designed for posterior lamellar tissue resection (Cindy I scissors, Bausch and Lomb, St Louis, Missouri). The first curved scissors (Cindy I) are placed with one blade in the anterior chamber and one blade in the stromal pocket. The scissors simply do a freehand cut, following the marks of the circular template on the overlying epithelial surface. The scissors have long, highly curved and low profile blades and are ideally suited for this procedure. Once the resection has progressed distally as far as comfortably possible, then the second specialized scissors are utilized for completion of the distal resection (Cindy II scissors, Bausch and Lomb, St Louis, Missouri). The second scissors (Cindy II) have long, low-profile blades that are set at nearly a right angle to easily complete the more difficult distal resection. Once the posterior recipient disc has been cut for the full 360 degrees, then the tissue is removed from the eye and placed on the corneal surface for inspection. It is washed with balanced salt solution (BSS, Alcon, Fort Worth, Texas) and dried with a sponge. The stromal surface is inspected for smoothness and the edges for regularity of cut, as well as the thickness of the resected tissue.

After removal of the recipient posterior tissue, the temporal scleral wound is temporarily closed with 1 interrupted 10-0 nylon suture. An irrigation/aspiration tip is then entered into the anterior chamber and extensive effort is expended to remove all of the viscoelastic from the eye. Absolutely no Healon should remain in the anterior chamber prior to insertion of the donor disc or the donor tissue will not stick in place. Therefore, care is taken to irrigate and aspirate the anterior chamber, pupillary area, angle, and even the peripheral pocket as necessary. Once the surgeon is confident that all Healon has been removed, then the pressure is left slightly soft and attention is turned to preparation of the donor.

Donor Preparation

The operating microscope is brought over to the separate donor table for preparation of the donor tissue. Because whole globes are rarely available here in the United States, an artificial anterior chamber is necessary for preparation of the donor posterior disc. A Bausch & Lomb (St Louis, Missouri) artificial anterior chamber that is all stainless steel and has dual irrigation/aspiration ports was used. The Optisol-GS preservation fluid (Chiron IntraOptics, Irvine, California) from the donor tissue container is pulled up in a syringe and is then used to fill the I/A ports of the artificial anterior chamber. The syringe is also attached to the port to be used to vary the pressure inside the chamber for the time of the resection. The standard donor cornea-scleral cap tissue is first coated with a thin layer of Healon on the endothelium. It is then placed endothelial side down onto the post of the artificial anterior chamber and oriented with the largest diameter of the cornea in the horizontal meridian. This meridian is marked with a marking pen so that the horizontal meridian of the donor tissue can be identified later in the procedure. The donor tissue is capped into place and the chamber is filled with Optisol-GS and the pressure normalized. An 8.5-mm diameter Barron suction recipient trephine (Katena Products, Denville, New Jersey) is placed onto the surface of the donor tissue and suction is applied. Trephination is carried out to about 60% depth with the trephine. It is noteworthy that after the blade touches the epithelial surface of the donor, it takes only about 4 or 5 quarter turns of the Barron trephine to reach this depth. This is much sooner than when the same trephine is used on the recipient in standard PK surgery. The trephine is then removed and the cut inspected for depth. Ideally, an 80% depth should be attained for the plane of the pocket of the donor tissue. Similar to the recipient disc preparation, the crescent blade is used to cut down to the 80% depth and this depth and pocket is then extended over the entire area of the cornea, all the way to the limbus, using the straight and curved special dissectors.

As an alternative to beginning the stromal pocket dissection with a measured trephine cut as described above, I also have used a diamond knife set to a depth of 350 μm to make an incision 3 or 4 clock hours in length in the peripheral donor limbal area. The

crescent blade is then used to cut to the deeper stromal tissue, and once the desired plane has been reached, then the special dissectors are used as described previously. This technique was used in about a third of the cases when the trephine could not hold suction on the mounted donor tissue.

After completing the deep stromal pocket formation, the cap of the chamber is gently rotated, taking care not to collapse the chamber, and the cap is removed. The donor tissue is then left on the post with a formed chamber. The scleral edges of the donor are gently lifted to release the tissue and the tissue is removed from the post, once again taking care not to collapse the chamber and damage the endothelium. After the tissue is lifted off the post, the endothelial side is gently irrigated with Optisol to remove excess Healon and prevent it from contaminating the stromal pocket during the next stage of the preparation.

The donor tissue is then placed endothelial side up onto a standard punch trephine block. A Barron donor punch (Katena, Denville, New Jersey) was used. The diameter of the punch used for the donor is the same size as the diameter of the recipient posterior disc resection.

Because the 5-mm wound of small-incision DLEK surgery is smaller than the 8.0-mm diameter of the donor disc, the donor tissue must be folded prior to insertion. To accomplish this, a very thin strip of Healon is placed onto the endothelial surface along the horizontal meridian of the donor button. Stabilizing the anterior edge of the donor button with a 0.12 forceps, the posterior stromal tissue edge is gently grasped with capsulorrhexis forceps (Bausch and Lomb, St Louis, Missouri). The posterior tissue is then gently folded with the endothelium on the inside protected by the layer of Healon, and it is folded into an asymmetric “taco” shape, in a 60% to 40% ratio, the most anterior side of the taco being 60% and the posterior side at 40%. The donor tissue is then brought over to the operative field still on the block.

Transplantation of the Donor Tissue

With the microscope in place, the temporary scleral suture of the superior wound is cut. The anterior chamber of the patient is then filled completely with BSS. The donor tissue is then brought into the field and specialized insertion forceps (Charlie insertion forceps, Bausch and Lomb, St. Louis, Missouri) are used to grasp the stromal surface of the donor tissue along the horizontal meridian. The specialized Charlie forceps are nontoothed fine forceps that only coapt at the distal tips. The Charlie forceps have a significant spacing along the blade’s length to prevent crushing of the donor tissue. The folded donor tissue is placed into the anterior chamber in one deft movement with the Charlie forceps, by inserting the donor tissue with the anterior 60% stromal side facing the recipient bed and the posterior 40% stromal side facing the iris. Again, the endothelial layer remains protected on the inside by Healon. The tissue can be gently prodded with the forceps along the stromal sides if centration of the tissue within the recipient bed needs to be improved. As the anterior chamber is deepened with irrigation of BSS from the right paracentesis site, the tissue gently opens up on its own, with the opening of the taco shape to the surgeon’s left. The 60% stromal side gently adheres to the overlying recipient bed with the 40% stromal edge lying nearly perpendicular to the iris plane.

Three sutures of 10-0 nylon are then used to close the scleral wound to secure the chamber. A cannula is placed through the left paracentesis incision and the tip placed onto the iris surface, between the folded donor sides, within the interior of the taco. BSS is then *gently* injected into the anterior chamber to fill the chamber and deepen it. Irrigation with BSS also loosens the Healon from the endothelial surface and helps to gently unfold the tissue. Because the donor tissue was folded into an asymmetric shape, the tissue invariably will spontaneously unfold in the correct orientation (ie, endothelium down), as long as the chamber is deep enough and there is no impediment. As the tissue begins to unfold, an air syringe is substituted, and an air bubble is gently injected between the lips of the unfolding donor tissue to complete the unfolding. More air is then injected into the anterior chamber to stabilize the tissue into position on the recipient stromal bed.

The donor disc may not be in perfect centration after insertion. If not, it can be positioned from either the endothelial side or the stromal side. A reverse Sinskey hook (Bausch and Lomb, St Louis, Missouri) is used for endothelial side positioning. The hook is placed through the stab incision, the peripheral endothelium is engaged, and the tissue is moved over to whatever position is desired. Care is taken, however, to minimize this maneuver and also to avoid the central posterior striae that can occur and can compromise vision. Once the tissue is in proper centration, it is critical to make sure that all of the donor edges are anterior to all of the recipient bed edges for 360 degrees. Visual inspection is not enough, and manual verification is mandatory. If any portion of the donor tissue edge lies posterior to the recipient rim, then the donor tissue will likely be dislocated the next morning or present with a significant space in the interface (secondary anterior chamber). To accomplish proper donor edge position, the anterior chamber is filled completely with air and a modified reverse Sinskey hook (Nick Pick, Bausch and Lomb, St Louis, Missouri) is placed through a stab incision into the anterior chamber. The distal tip of the Nick Pick is then lifted anteriorly and placed between the edge of the donor and recipient rim. The hook is then used to engage the recipient rim posterior stromal edge and then used to pull the edge posteriorly. With this maneuver, the air bubble in the anterior chamber immediately pushes the donor edge up anteriorly, into the recipient pocket, and on release of the Nick Pick, the recipient edge pops right up posterior to the donor edge. This “tire iron” maneuver is performed for 360 degrees, even when the donor tissue appears already in good position. This is done because even small strands of recipient stromal edge tissue can get caught in the edge interface and prevent adherence of the graft or act as a wick for aqueous into the interface, causing later dislocation.

Once the donor disc is in final position with good edge position, the air in the anterior chamber is removed and replaced with BSS. Care is taken to avoid intraoperative pupillary block by the air bubble in the anterior chamber, but if it occurs, simple suctioning of the air from the pupillary surface resolves the problem. Occasionally, air can get trapped behind the iris, giving the impression of posterior pressure with the iris coming forward to the donor edges. Again, suctioning with a cannula from the pupillary surface will resolve this

issue. The BSS placed into the anterior chamber creates a normal IOP and the chamber deepens. A small (3-mm-wide) air bubble is usually left in place to help further stabilize the donor disc position over the first 24 hours postoperatively.

The suture knots of the scleral incision are cut short and buried on the scleral side. The wound is checked to be watertight. The conjunctival peritomy is closed. A 24-hour collagen shield soaked in antibiotics and steroids is placed on the corneal surface at the close of surgery in order to deliver medication until the patch is removed the next day.

An occlusive patch and shield are gently placed, and the patient is brought to the recovery room. No specific positioning of the patient is done postoperatively. The patient is discharged from this outpatient procedure when fully recovered from anesthesia and seen in clinic the next day.

Postoperatively, the patient is put on a regimen of prednisolone acetate 1% drops and moxifloxacin antibiotic drops, both given 4 times a day, starting on the first day postoperatively. The antibiotic drops are discontinued at 2 weeks postoperatively, but the steroid drops are continued similar to our PK patients' regimen with a very slow taper schedule, down to 1 drop a day by 1 year postoperatively. After 1 year postoperatively, the steroid drops are usually continued at 1 drop a day if the eye is pseudophakic and no steroid related elevation in intraocular pressure has been seen.

STATISTICAL ANALYSIS

The data were analyzed using SPSS version 12.0. Descriptive statistics were computed and all variables were checked for and met with normality assumptions. Paired *t* tests were used to examine my local subjects on the following comparisons: (1) preoperative data to 6-month data, (2) 6-month data to 1-year data, and (3) 1-year data to 2-year data. A Multivariate Analysis of Variance (MANOVA) test was also performed. This MANOVA compared all measures at all time points for a subgroup of local patients. A MANOVA was chosen to help control the inflation of Type I error rate, in addition to justifying the use of my local patients (n = 79) as representative of the overall group (n = 116). Groups of the Student *t* test were then performed to examine cell counts and vision at each time gate of those patients that experienced postoperative interface fluid. Student *t* tests were also performed to analyze those with retinal comorbidity compared to those without on BSCVA at all time gates. A Pearson's correlation coefficient was also calculated between SRI, SAI, and BSCVA. Finally, a chi-squared test of independence was carried out to test the association between those patients that had 20/40 visual acuity or better at each time gate.

RESULTS

DEMOGRAPHICS AND FOLLOW-UP

The 116 eyes in this prospective, consecutive, nonrandomized series were from 104 patients, with a mean and standard deviation age at the time of surgery of 70 ± 10 years (range, 40-96 years). Sixty-three eyes (54%) were from females and 53 eyes (46%) were from males. Eighty-five eyes (73%) required DLEK surgery due to corneal edema from Fuchs endothelial dystrophy. Thirty-one eyes (27%) had no history of Fuchs dystrophy and required DLEK due to pseudophakic bullous keratopathy (30 eyes) or due to bullous keratopathy from trauma (1 eye). Two eyes had DLEK surgery for the indication of a failed prior DLEK graft (one late endothelial failure large-incision DLEK, and one primary graft failure small-incision DLEK). One eye in the series had an anterior chamber lens in place at the time of DLEK surgery, and this lens was left undisturbed. Five eyes had reduced vision due strictly to Fuchs dystrophy corneal edema and had a clear crystalline lens, with little or no cataract. In these eyes DLEK surgery was performed without cataract surgery, leaving the natural lens in place. The one eye with traumatic bullous keratopathy had a known, complex, traumatic cataract with zonular dehiscence and extensive posterior iris synechiae present preoperatively with an extremely edematous cornea and poor visualization of intraocular structures. Therefore, it was elected to perform cataract surgery at a later date in this eye, after the DLEK surgery had fully cleared the overlying recipient cornea. The preoperative and postoperative (after DLEK followed by cataract surgery) photographs of this eye are shown in Figure 2.

The results of all 116 cases are reported in Table 1 to show my total data collection. The data on the local patients that had all examinations at our institution from preoperative to 2 years (n = 79) are reported in Table 2 for consistent data collection across all time points. In-depth analysis of subgroups of this well-documented cohort of 79 eyes is shown in subsequent descriptive tables.

Total Study Group

Of the 116 eyes entered into the study, 113 eyes (97%) were available for examination at the 6-month protocol visit. At the 1-year protocol visit, 107 eyes (92%) were available for examination. There were 81 eyes (70%) that were examined for the 2-year protocol visit. Of the 35 eyes that did not make the 2-year visit, 24 eyes were from patients that were from, or had moved, out of state, and 9 eyes were from patients that had either died or were too ill to return. One eye had primary graft failure and was replaced 2 days after surgery. This first DLEK surgery was kept in the database for complications data but obviously did not make any of the protocol postoperative visits. The replacement surgery for this eye was entered as a separate data case and followed in the protocol. One eye had the DLEK graft replaced with another DLEK graft at 21 months postoperatively, prior to the 2-year protocol visit. Living patients with outcome data missing from the 2-year visit database were contacted, and all of the patients or their caregivers reported clear grafts with no gross change in their vision.

Local Patients Study Group

This group of patients was seen for all of their protocol visits here at our center. Of the 79 eyes in this group at preoperative examination, 78 (99%) were available for examination at the 6-month protocol visit. At the 1-year protocol visit, 77 eyes (97%) were available for examination. There were 79 eyes (100%) available for the 2-year protocol visit.

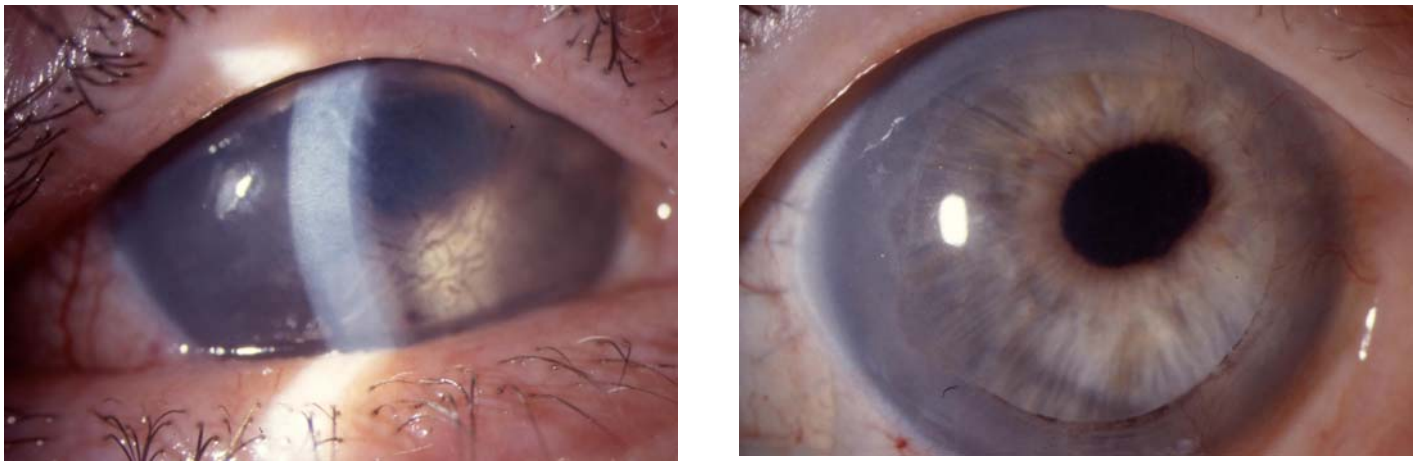

FIGURE 2

Deep lamellar endothelial keratoplasty (DLEK) surgery for the treatment of edema due to blunt trauma. Left, Preoperative appearance of severe edema following blunt trauma. Note extensive pigment coating posterior cornea accentuating the striate keratopathy. Preoperative vision was counting fingers at 2 feet. Right, Postoperative appearance of cornea with central clarity enabling subsequent cataract surgery. Peripheral surface pannus vessels are seen in the superior nasal quadrant. Spectacle visual acuity at 2 years after DLEK surgery (and after cataract surgery) was 20/30.

Subgroup 1. The protocol did not exclude patients with known retinal disease from receiving DLEK surgery. To evaluate visual acuity without this confounding variable, I analyzed the subset of my local patients that had no objective evidence of retinal disease (eg, age-related macular degeneration, prior history of cystoid macular edema) prior to their entry into the study. Of the 79 local patient eyes, 68 eyes (86%) met this criterion. Of the 68 eyes with no retinal disease, 67 eyes (99%) were available at 6 months, 66 eyes (97%) were available at 1 year, and 68 eyes (100%) were available at 2 years.

Subgroup 2. A subset of eyes was evaluated that had cataract surgery combined with their small-incision DLEK surgery. Out of the 79 local patient eyes entered into the protocol, 39 eyes (49%) had the combined "triple procedure" of DLEK plus phacoemulsification cataract surgery plus IOL implantation. Of these 39 eyes, 38 (97%) were available for the 6-month visit, 38 (97%) for the 1-year visit, and 39 (100%) for the 2-year visit.

Outcome Data: Endothelial Cell survival, BSCVA, Refractive Astigmatism, Average Keratometry, Corneal Mapping Smoothness Indices (SRI and SAI), Refractive Spherical Equivalent, and Pachymetry

In reporting and statistically analyzing the data, I first examined for a possible difference between my local patient group (n = 79) and my overall study group (n = 116). MANOVA testing found no statistically significant differences between the two (P = .321). Since the groups did not significantly differ in any of the multiple parameters, this justified using only my local patients for the in-depth analysis. I looked first at the change from preoperative measurements to 6-month measurements to determine the early rehabilitation effect of the surgery on the disease state. I then evaluated the stability of the outcome by comparing the 6-month measurements to the 1-year measurements, followed by a comparison of the 1-year measurements to the 2-year measurements.

Local Patients Study Group. The results from my *t* tests for the preoperative and postoperative outcome data on all measures for the local patient study group (n = 79) are given in Table 2. Critical to the treatment of endothelial dysfunction is the donor cell survival, and these data are given thoroughly in Table 2. The mean donor ECD preoperatively was measured at 2819 ± 225 cells/mm^2 and at 6 months postoperatively had fallen to 2095 ± 380 cells/mm^2, representing a 26% cell loss. (P = .0001; 95% confidence interval [CI] = 643-809) From 6 months to 1 year, the donor ECD did not significantly change, with only a 3% additional loss of cells (29% overall loss) to 2009 ± 393 cell/mm^2 (P = .054, power = .5). However, from 1 year to 2 years, the mean ECD decreased dramatically to 1536 ± 547 cells/mm^2 (500 to 2546) (P < .001, 95% CI, 368-585), representing a 16% further loss of endothelial cells from 1 to 2 years, with an overall 46% cell loss from preoperatively to 2 years after small-incision DLEK surgery.

The clinically important outcomes of vision, surface smoothness, and pachymetry all improved from before surgery to the 6-month postoperative visit. There was a highly significant improvement in the mean vision (and range of vision) from a preoperative BSCVA

of 20/71 (20/25 to 20/400) to 20/42 (20/20 to 20/200) 6 months after surgery (*P* = .0001;95% CI, .18-.3 logMAR). The number of cases that achieved 20/40 or better visual acuity increased as well from a preoperative level of 17% (13 of 79eyes) to a 6-month postoperative level of 57% (45 of 79). A chi-square test of independence found this improvement in vision to be significant (*P* = .001). Looking at the percent of eyes that attained visual acuity of 20/25 or better, 1% of eyes (1 of 79) had this level of vision at some time of the day preoperatively, and 10% (8 of 79) had this level of vision at 6 months. Conversely, preoperatively 17% of eyes had 20/200 or worse visual acuity, but after surgery, only 1 eye (1%) had this poor level of vision. Due to epithelial edema in many cases, the mean topography indices were highly irregular preoperatively with an SRI of 1.61 ± .85 (.05 to 3.35) and an SAI of 1.88 ± 1.5 (.15 to 5.83). With resolution of the edema, the SRI and SAI significantly improved at 6 months to a normal SRI of .913 ± .36 (.06 to 2.17) (*P* = .0001;95% CI, .5-.85) and a normal SAI of .781 ± .724 (.18 to 4.86) (*P* = .0001;95% CI, .77-1.14). The swollen preoperative recipient cornea had a mean thickness of 720 ± 81 μm (range, 588-939 μm). This significantly improved postoperatively to a thickness at 6 months of 590 ± 70 μm (461-816 μm) (*P* = .0001;95% CI, 103-144 μm). Interestingly, the average keratometry power was statistically significantly flatter from 44.83 ± 2.4 D (39.70-52.9) preoperatively to 43.41 ± 1.31D (40.13-46.41) postoperatively (*P* = .0001;95% CI, .83-1.94). This mean flattening of the cornea did not statistically significantly change the mean spherical equivalent, which was +.082 ± 2.1 D (-5.25 to +6.38 D) preoperatively and -.13+ ± -1.3 D (-3.75 to +4.25 D) postoperatively (*P* = .324, power =.14). Most important, there did not appear to be any induced astigmatism from DLEK surgery, with the mean refractive astigmatism at .91 ± .78 D (0.0-3.5 D) preoperatively and 1.11 ± .76 D (0 to 3.75 D) postoperatively (*P* = .052, power = .43).

TABLE 1. DEEP LAMELLAR ENDOTHELIAL KERATOPLASTY (DLEK): TOTAL CONSECUTIVE CASES

OUTCOME	PREOPERATIVE (n = 116)	6 MONTHS (n = 113)	12 MONTHS (n = 107)	24 MONTHS (n = 81)
BSCVA (logMAR)	m = 20/83 (.62) SD = .45 range = 20/25 - HM (.1-3)	m = 20/43 (.34) SD = .2 range = 20/20 - 20/200 (0.0-1)	m = 20/42 (.32) SD = .17 range = 20/20 - 20/200 (0.0-1)	m = 20/39 (.29) SD = .17 range = 20/20 - 20/200 (0.0-1)
% 20/40 or better	19%	52%	63%	71%
% 20/25 or better	2%	9%	9%	12%
% 20/200 or worse	22%	1%	1%	1%
Refractive astigmatism	m = 1.07 SD = .86 range = 0 - 4.5	m = 1.31 SD= .85 range 0 - 4.25	m = 1.28 SD= .8 range = 0 - 4.25	m = 1.21 SD= .6 range = 0 - 2.8
Average K	m = 44.42 SD = 2.3 range = 39.7 - 52.9	m = 43.35 SD = 1.4 range = 40.13 - 47	m = 43.43 SD = 1.43 range = 39.8 - 47.65	m = 43.48 SD = 1.4 range = 39.6 - 47.54
SRI	m = 1.62 SD = .9 range = .05 - 3.7	m = .87 SD = .38 range = .06 - 2.2	m = .7 SD = .42 range = .05 - 2.4	m = .6 SD = .4 range = .01 - 1.4
SAI	m = 1.82 SD = 1.45 range = .15 - 5.8	m = .77 SD = .73 range = .18 - 4.8	m = .7 SD = .55 range = .14 - 4.0	m = .76 SD = .55 range = .15 - 3.3
Refractive spherical equivalent	m = .02 SD = 2.33 range = -5.38 -6.38	m = -.3 SD = 1.4 range -6.75 -4.25	m = -.2 SD = 1.24 range = -3.5 - 3.0	m = -.22 SD = 1.3 range = -3.63 -2.4
Pachymetry	m = .72 SD = .09 range = .57 - .977	m = .59 SD = .07 range = .43 - .82	m = .57 SD = .08 range = .404 -.81	m = .59 SD = .08 range = .477 - .8

BSCVA, best spectacle-corrected visual acuity; HM, hand motion; m, mean; SAI, surface asymmetry index; SD, standard deviation; SRI, surface regularity index.

In analyzing the stability of the outcomes from 6 months to 1 year, I found that there was slight continued improvement in the reduction of the values of the SRI, which were statistically significant (SRI: *P* = .002;95% CI, .07-.3), but not clinically relevant. While a higher percentage of eyes was able to see 20/40 or better at 1 year (68%, 62 of 107) than at 6 months (57%, 59 of 113), there was not a statistically significant change in the mean BSCVA between 6 months and 1 year. (*P* = .262, power =.23). All other comparisons between 6-month and 1-year variables were not significantly different (SAI;*P* = .431, power =.13) (average K;*P* = .271, power =.21) (spherical equivalent;*P* = .497, power = .1) (refractive astigmatism;*P* = .287, power = .06) (pachymetry *P* =.153; power = .2).

Analysis of the stability of the outcomes from 1 year to 2 years showed that the most clinically relevant change in outcome (besides ECD drop) was in the pachymetry. The mean pachymetry increased from 580 ± 70 μm (455 to 806) to 590 ± 80 μm (477 to

800) between 1 and 2 years postoperatively (P = .025 (95% CI: ¯24 to ¯.2 μm). The only other statistically significant change was in the SRI. It continued to decrease, but although statistically significant, this was not clinically relevant. All other outcomes remained stable, and no statistically significant differences were found between any of the other variables (SAI;P = .596, power =.08) (average K;P = .803, power =.05) (spherical equivalent;P = .692, power = .06) (refractive astigmatism;P = .467, power = .22), and (BSCVA;P = .915, power =.1).

TABLE 2. DEEP LAMELLAR ENDOTHELIAL KERATOPLASTY (DLEK): LOCAL PATIENTS SUBGROUP

OUTCOME	PREOPERATIVE (n = 79)	6 MONTHS (n = 78)	12 MONTHS (n = 77)	24 MONTHS (n = 79)
BSCVA (logMAR)	m = 20/71 (.56) SD = .26 range = 20/25 - 20/400 (.1-1.3)	m = 20/42 (.32) SD = .16 range = 20/20 - 20/200 (0.0-1)	m = 20/40 (.30) SD = .16 range = 20/20 - 20/200 (0.0-1)	m = 20/38 (.28) SD = .16 range = 20/20 - 20/200 (0.0-1)
% 20/40 or better	17%	57%	68%	71%
% 20/25 or better	1%	10%	9%	12%
% 20/200 or worse	17%	1%	1%	1%
ECD	m = 2819 SD = 225 range = 2389 -3385	m = 2095 SD = 380 range = 1097 -2920	m = 2009 SD = 393 range = 612 -2679	m = 1536 SD = 547 range = 500 -2546
Refractive astigmatism	m = .91 SD = .78 range = 0 - 3.5	m = 1.11 SD = .76 range = 0 - 3.75	m = 1.04 SD = .8 range = 0 - 3.0	m = 1.10 SD = .7 range = 0 - 2.8
Average K	m = 44.83 SD = 2.4 range = 39.7 - 52.9	m = 43.41 SD = 1.31 range = 40.13 - 46.41	m = 43.5 SD = 1.4 range = 39.95-47.65	m = 43.47 SD = 1.41 range = 39.65 - 47.54
SRI	m = 1.61 SD = .85 range = .05 - 3.35	m = .913 SD = .36 range = .06 - 2.17	m = .73 SD = .43 range = .05 - 2.37	m = .6 SD = .4 range = .01 - 1.38
SAI	m = 1.88 SD = 1.5 range = .15 - 5.83	m = .781 SD = .724 range = .18 - 4.86	m = .72 SD = .6 range = .14 – 3.97	m = .761 SD = .54 range = .15 - 3.28
Refractive spherical equivalent	m = .082 SD = 2.1 range = -5.25 -6.38	m = -.13 SD = 1.3 range = -3.75 -4.25	m = -.28 SD = 1.24 range = -3.5 - 2.5	m = -.22 SD = 1.05 range = -3.25 -2.38
Pachymetry	m = .72 SD = .081 range = .588 -.939	m = .59 SD = .07 range = .461 - .816	m = .58 SD = .07 range = .455 -.806	m = .59 SD = .08 range = .477-.8

BSCVA, best spectacle-corrected visual acuity; ECD, endothelial cell density (cells/mm^2); m, mean; SAI, surface asymmetry index; SD, standard deviation; SRI, surface regularity index.

Subgroup 1. The descriptive preoperative and postoperative outcome data on all measures for the subgroup of eyes without retinal comorbidity as a confounding variable for vision are given in Table 3. The data on the subset of eyes without comorbidity nearly mimics the parent group of local patients' eyes (Table 2) in nearly every measurement taken with the exception of the visual acuity measures. When the confounding variable of retinal disease is removed, the resultant cohort of eyes of Table 3 shows a slightly better vision at each visit with a final mean visual acuity of 20/36 at 2 years with a tighter range of visual acuity of 20/20 to 20/80 than was found with the parent group. The eye in the vision category of 20/40 or better shows a related improvement compared to the parent group, with 78% of eyes reaching this good level of vision by 2 years out. Conversely, while 15% of eyes had 20/200 visual acuity or worse preoperatively, there were no eyes with this severe loss of vision by 2 years postoperatively.

Subgroup 2. The descriptive preoperative and postoperative outcome data on all measures for the subgroup of eyes that underwent a triple procedure is given in Table 4. The data on this subset of 39 eyes that underwent a triple procedure and had no coexisting retinal disease also nearly mimics the parent group of local patients' eyes (Table 2) in nearly every measurement taken. However, while the vision starts off better preoperatively (20/57) than the other subgroups, it also ends up better at 20/39, with 80% (30 of 38) of eyes seeing 20/40 or better. In addition, the spherical equivalent postoperative dioptric ranges are tighter with the triple procedure than the overall parent group, as expected when accurate preoperative keratometry can be obtained.

COMPLICATIONS

Complications reported here are from the entire cohort of 116 eyes.

Interface Fluid

The most common complication in the series was the presence of interface fluid on the first postoperative day. Eleven eyes (9%, 11 of 116) had fluid in the interface on the first postoperative day. Of these 11 eyes, however, there were only 4 eyes (3%, 4 of 116) where the donor tissue had dislocated into the anterior chamber. The remaining 7 grafts were still within the recipient bed. All 11 eyes were treated, however, with an air bubble, and all recovered full graft clarity and resolution of interface fluid. The data regarding BSCVA and ECD on the 7 eyes with interface fluid without graft dislocation and the same data on the 4 eyes with graft dislocation are shown in Table 5 and Table 6, respectively.

TABLE 3. DEEP LAMELLAR ENDOTHELIAL KERATOPLASTY (DLEK) LOCAL PATIENT EYES WITH NO COMORBID RETINAL DIAGNOSES: PREOPERATIVE TO TWO YEARS

OUTCOME	PREOPERATIVE (n = 68)	6 MONTHS (n = 67)	12 MONTHS (n = 66)	24 MONTHS (n = 68)
BSCVA (logMAR)	m = 20/69 (.54) SD = .27 range = 20/25 - 20/400 (.1-1.3)	m = 20/39 (.29) SD = .12 range = 20/20 - 20/60 (0.0-.48)	m = 20/38 (.28) SD = .15 range = 20/20 - 20/200 (0.0-1)	m = 20/36 (.26) SD = .13 range = 20/20 - 20/80 (0.0-.6)
% 20/40 or better	18%	60%	74%	79%
% 20/25 or better	2%	10%	10%	14%
% 20/200 or worse	15%	2%	2%	0%
ECD	m = 2833 SD = 225 range = 2389 - 3385	m = 2081 SD = .389 range = 1097 - 2920	m = 2015 SD = 381 range =612 - 2679	m = 1540 SD = 532 range = 514 - 2546
Refractive astigmatism	m = .86 SD = .74 range = 0.0 - 3.0	m = 1.05 SD = .7 range = 0 - 3.75	m = 1.0 SD = .71 range = 0 - 3.0	m = 1.06 SD = .7 range = 0 - 2.75
Average K	m = 44.78 SD = 2.42 range = 39.7 - 52.9	m = 43.42 SD = 1.4 range = 40.13 - 46.41	m = 43.5 SD = 1.5 range = 39.95 - 47.69	m = 43.5 SD = 1.5 range = 39.65 - 47.54
SRI	m = 1.56 SD = .83 range = .05 - 3.21	m = .894 SD = .32 range = .06 - 1.85	m = .72 SD = .39 range = .05 - 1.67	m = .56 SD = .32 range = .01 - 1.33
SAI	m = 1.81 SD = 1.52 range = .15 - 5.83	m = .66 SD = .34 range = .2 - 1.82	m = .67 SD = .5 range = .14 - 2.7	m = .75 SD = .54 range = .15 - 3.3
Refractive spherical equivalent	m = .02 SD = 2.01 range = -5.25 -6.38	m = -.1 SD = 1.2 range = -3.5 - 2.5	m = -.26 SD = 1.3 range = -3.5 - 2.5	m = -.26 SD = 1.02 range = -3.25 -1.88
Pachymetry	m = .72 SD = .084 range = .58 -.939	m = .59 SD = .071 range = .46 - .816	m = .59 SD = .07 range = .45 -.8	m = .6 SD = .08 range = .47 - .796

BSCVA, best spectacle-corrected visual acuity; ECD, endothelial cell density (cells/mm^2); m, mean; SAI, surface asymmetry index; SD, standard deviation; SRI, surface regularity index.

Primary Graft Failure

One eye had iatrogenic primary graft failure. This donor tissue was trephined eccentrically by the surgeon, and this resulted in a full-thickness edge on one side of the graft. Despite attempts at correcting the problem, the tissue did not survive transplantation and was replaced with a correctly prepared donor 2 days postoperatively. There were no problems with the replacement graft, and it was entered into the database. There were no other primary graft failures, yielding a 1% rate (1 of 116) of primary graft failures in this series.

Graft Rejection

At 2 years postoperatively, 56 of 81 eyes (70%) were on steroid drops and 24 of 81 (30%) of eyes were on no steroid drops. For the overall group of 116 eyes, 3 eyes had graft rejection episodes noted, and all grafts cleared with topical steroid treatment. Two of the eyes (eyes 88 and 101) had distinct keratic precipitates on the donor endothelium with overlying mild segmental stromal edema, but no confluent rejection line. The other eye (eye 103) had a few keratic precipitates, but no overlying edema. Graft rejections in these 3 eyes occurred at 1 year, 1.75 years, and 2.75 years after DLEK surgery. The BSCVA and ECD data on these 3 eyes is shown in Table 7.

Anterior Chamber Lens

One eye in the series had an anterior chamber lens, and this IOL was left in place. A limited anterior vitrectomy was required at the time of surgery, but other than this, there were no complications during surgery or postoperatively. The visual acuity improved from

20/60 preoperatively to 20/30 at 6 months postoperatively and remained at that level at the 1- and 2-year visits. The preoperative donor ECD was 2854 cells/mm^2 and at 6, 12, and 24 months postoperatively was 2077 cells/mm^2, 2051 cells/mm^2, and 2256 cells/mm^2, respectively.

TABLE 4. DEEP LAMELLAR ENDOTHELIAL KERATOPLASTY (DLEK): LOCAL PATIENT EYES WITH A "TRIPLE" PROCEDURE

OUTCOME	PREOPERATIVE (n = 39)	6 MONTHS (n = 38)	12 MONTHS (n = 38)	24 MONTHS (n = 39)
BSCVA (logMAR)	M = 20/57 (.46) SD = .18 range = 20/25 - 20/200 (.1 - 1.0)	m = 20/37 (.27) SD = .13 range = 20/20 - 20/80 (0.0 - .6)	m = 20/40 (.27) SD = .16 range = 20/20 - 20/200 (0.0 - 1)	m = 20/34 (.24) SD = .12 range = 20/20 - 20/60 (0.0 - .48)
% 20/40 or better	23%	67%	80%	80%
% 20/25 or better	3%	18%	13%	13%
% 20/200 or worse	5%	3%	3%	0%
ECD	m = 2825 SD = 229 range = 2415 - 3337	m = 2152 SD = 335 range = 1446 - 2920	m = 2107 SD = 276 range = 1438 - 2645	m = 1600 SD = 533 range = 623 - 2546
Refractive astigmatism	m = .8 SD = .7 range = 0 - 2.5	m = .93 SD = .58 range = 0 - 2.5	m = .96 SD = .64 range = 0 - 2.5	m = 1.13 SD = .66 range = 0 - 2.75
Average K	m = 44.61 SD = 1.95 range = 41.45 - 52.9	m = 43.47 SD = 1.16 range = 40.13 - 46.4	m = 43.4 SD = 1.1 range = 40.46 - 45.78	m = 43.56 SD = 1.35 range = 39.65 - 47.54
SRI	m = 1.42 SD = .73 range = .13 - 3.04	m = .81 SD = .32 range = .13 - 1.85	m = .7 SD = .38 range = .06 - 1.54	m = .52 SD = .30 range = .04 - 1.33
SAI	m = 1.50 SD = 1.29 range = .15 - 5.01	m = .62 SD = .39 range = .18 – 1.82	m = .602 SD = .3 range = .28 – 1.37	m = .7 SD = .57 range = .18 - 3.28
Refractive spherical equivalent	m = .621 SD = 2.0 range = -2.75 -6.38	m = -.12 SD = 1.14 range = -3.0 - 2.5	m = -.23 SD = 1.5 range = -3.5 – 2.5	m = -.33 SD = 1.12 range = -3.25 -1.88
Pachymetry	m = .7 SD = .08 range = .588 - .91	m = .59 SD = .07 range = .46 - .816	m = .59 SD = .07 range = .455 -.806	m = .6 SD = .081 range = .47 - .796

BSCVA, best spectacle-corrected visual acuity; ECD, endothelial cell density (cells/mm^2); m, mean; SAI, surface asymmetry index; SD, standard deviation; SRI, surface regularity index.

Repeat DLEK Corneal Transplantation

There were 2 cases where the DLEK corneal transplant was replaced with a second DLEK corneal transplant tissue, years after the original surgery. In one case (patient 69), the patient never achieved greater than 20/70 visual acuity despite completely normal retinal evaluation and extensive retinal testing. Two and a half years after the original DLEK surgery, the patient elected to receive a second DLEK graft where the donor was prepared with a microkeratome in an attempt to improve his vision. The data from the second DLEK graft is not included in this series, but the BSCVA was 20/80 at the 6-month follow-up visit. The other eye to receive a second DLEK graft (patient 113) developed late endothelial failure at 21 months after surgery, with a visual acuity of 20/200. This eye received a second DLEK graft (data of which is not included in this study), and the visual acuity improved to 20/30 by 3 months after the second surgery.

PK Replacement of DLEK Grafts

In 2 cases the DLEK graft was replaced with a standard full-thickness PK surgery, years after the original DLEK surgery. In one case (patient 69, described previously), the patient was still unhappy with his vision after the second DLEK surgery and elected to undergo a standard PK surgery, 9 months after his second DLEK surgery, 3.75 years after the first surgery. The PK surgery was uneventful, and 1 month later the patient's visual acuity is 20/80 by pinhole testing. In the second case (patient 53), the patient had improved from a BSCVA of 20/200 preoperatively to 20/50 at his 2-year visit with an ECD of 2234 cells/mm^2 and a clear graft. Exactly 3 years and 3 months after his DLEK surgery, the patient fell and hit his eye on the corner of a metal door. The globe ruptured along the DLEK wound and along the old extracapsular cataract surgery wound. Despite emergency repair, followed by PK, vitrectomy, and retinal repair, the vision remains at only bare light perception.

TABLE 5. DEEP LAMELLAR ENDOTHELIAL KERATOPLASTY (DLEK) PATIENTS WITH INTERFACE FLUID BUT NO DISLOCATION (n=7)*

PATIENT NO.	NO. OF DAYS POST-OPERATIVE	PRE-OPERATIVE ECD	PRE-OPERATIVE BSCVA (logMAR)	SIX-MONTH ECD	SIX-MONTH BSCVA (logMAR)	ONE-YEAR ECD	ONE-YEAR BSCVA (logMAR)	TWO-YEAR ECD	TWO-YEAR BSCVA (logMAR)
9	1	3151.000	20/60 (.48)	2660.000	20/40 (.30)	2307.000	20/40 (.30)	1757.000	20/40 (.30)
27	1	3337.000	20/80 (.60)	1930.000	20/25 (.10)	2063.000	20/30 (.18)	1252.000	20/40 (.30)
32	1	2701.000	20/40 (.3)	ND	ND	1259.000	20/30 (.18)	ND	ND
47	1	2557.000	20/200 (1.0)	2073.000	20/25 (.10)	2234.000	20/40 (.30)	2105.000	20/25 (.1)
60	1	2526.000	20/50 (.40)	2191.000	20/40 (.30)	2509.000	20/40 (.30)	1758.000	20/50 (.40)
68	1	2821.000	20/100 (.70)	2517.000	20/50 (.40)	2180.000	20/40 (.30)	1397.000	20/50 (.40)
84	1	2528.000	20/40 (.30)	1987.000	20/30 (.18)	1770.000	20/30 (.18)	1097.000	20/40 (.30)

BSCVA, best spectacle-corrected visual acuity; ECD, endothelial cell density (cells/mm^2); ND, no data.

*Results comparing local patient group (n=79) with interface fluid group using Student *t* test.

1. Donor ECD: *P* =.737, power = .14
2. Six-month ECD: *P* =.174, power = .928
3. One-year ECD: *P*=.103, power = .99
4. Two-year ECD: *P*=.457, power = .5
5. Preoperative BSCVA: *P*=.702, power = .133
6. Six-month BSCVA: *P*=.481, power = .55
7. One-year BSCVA: *P*=.487, power = .4
8. Two-year BSCVA: *P*=.009 (95% confidence interval, -.26 to +.1)

TABLE 6. DEEP LAMELLAR ENDOTHELIAL KERATOPLASTY (DLEK) PATIENTS WITH DISLOCATIONS (N=4)

PATIENT NO.	NO. OF DAYS POST-OPERATIVE	PRE-OPERATIVE ECD	PRE-OPERATIVE BSCVA (logMAR)	SIX-MONTH ECD	SIX-MONTH BSCVA (logMAR)	ONE-YEAR ECD	ONE-YEAR BSCVA (logMAR)	TWO-YEAR ECD	TWO-YEAR BSCVA (logMAR)
53	1	2867.000	20/50 (.40)	1761.000	20/50 (.40)	1916.000	20/50 (.40)	574.000	20/40 (.30)
59	1	3241.000	20/80 (.60)	1208	20/40 (.3)	1895	20/30 (.18)	1567	20/40 (.3)
49	1	2526.000	20/50 (.40)	1239.000	20/50 (.40)	1022.000	20/40 (.30)	759.000	20/30 (.18)
110	1	2799.000	20/80 (.60)	ND	20/70 (.54)	ND	20/50 (.40)	ND	ND

BSCVA, best spectacle-corrected visual acuity; ECD, endothelial cell density (cells/mm^2); ND, no data.

TABLE 7. DEEP LAMELLAR ENDOTHELIAL KERATOPLASTY (DLEK) PATIENTS WITH GRAFT REJECTION (n=3)

PATIENT NO.	NO. OF YEARS POST-OPERATIVE	PRE-OPERATIVE ECD	PRE-OPERATIVE BSCVA (logMAR)	SIX-MONTH ECD	SIX-MONTH BSCVA (logMAR)	ONE-YEAR ECD	ONE-YEAR BSCVA (logMAR)	TWO-YEAR ECD	TWO-YEAR BSCVA (logMAR)
88	2.75	2661.000	20/70 (.54)	2172.000	20/50 (.40)	ND	ND	ND	20/80 (.60)
101	1	2859.000	20/200 (1.0)	1928.000	20/40 (.30)	1592.000	20/50 (.40)	ND	ND
103	1.75	2879.000	20/400 (1.3)	ND	20/50 (.40)	ND	20/100 (.70)	ND	ND

BSCVA, best spectacle-corrected visual acuity; ECD, endothelial cell density (cells/mm^2); ND, no data.

Infectious Keratitis

There were no cases of bacterial or fungal keratitis in this series, but one eye did suffer an episode of herpes simplex keratitis 26 months after surgery. Although this resolved with therapy, the patient was left with a peripheral surface scar, which did not significantly impact his vision. There was no history of herpes simplex keratitis of the donor or evidence of herpes simplex events in the donor tissue. The recipient did have a history of oral outbreaks of herpes simplex but never an ocular outbreak. This eye is shown

in Figure 3. There were no cases of interface inflammation, such as the deep lamellar keratitis seen as a complication with LASIK surgery.

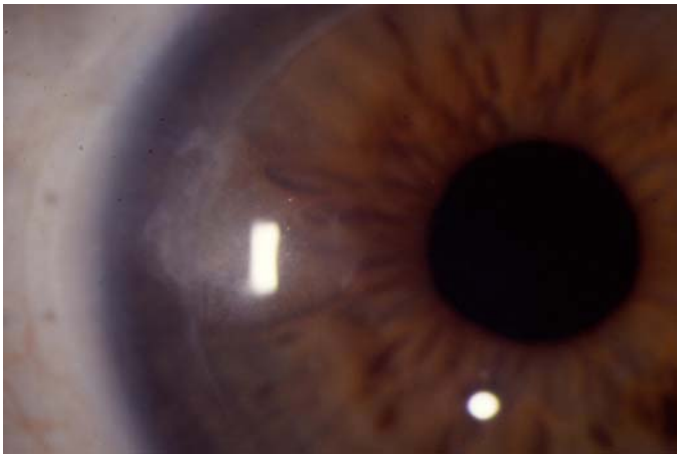

FIGURE 3

Surface scar from herpes simplex infection following deep lamellar endothelial keratoplasty (DLEK) surgery. Note the clarity of the graft central to the surface scar. Visual acuity was 20/30.

Uncontrolled Glaucoma

There were 2 eyes that developed uncontrolled glaucoma, and both eyes were in the same patient. The left eye required a filtering bleb 13 months after DLEK surgery. This eye had a BSCVA of 20/70 and an ECD of 1841 cells/mm^2 at 2 years after the DLEK surgery. The second eye required a filtering bleb 5 months after DLEK surgery. The second eye had a BSCVA of 20/50 and an ECD of 1592 cells/mm^2 at his last completed follow-up visit, 1 year after the DLEK surgery.

Vision Worse Than Preoperatively

Three patients with no retinal disease did not show any improvement from their preoperative vision at any examination postoperatively. The BSCVA on these patients preoperatively was 20/25, 20/30, and 20/40 and the BSCVA at 2 years postoperatively was 20/30, 20/40, and 20/70, respectively. All patients have clear grafts with no unusual interface haze or scarring noted at slit-lamp examination. The first 2 of the 3 patients claim that they subjectively see better postoperatively than they did preoperatively. None of the patients have requested regrafting or conversion to PK surgery.

DISCUSSION

Endothelial keratoplasty represents an entirely new approach to corneal transplant surgery for the treatment of patients suffering from endothelial disease. By using a limbal incision for access to endothelial replacement, the EK procedure completely avoids 2 inherent liability factors of standard full-thickness PK surgery—perforating vertical wounds and surface corneal sutures. The practical clinical questions to be asked with this new surgery are as follows: (1) What is the level and quality of vision that can be expected from EK surgery over time? (2) What percentage of donor endothelial survival can be expected from EK surgery over time? and (3) What are the short- and long-term risks with EK?

In this study, I evaluated my first 116 consecutive eyes that received small-incision DLEK surgery, and the data on the eyes that made it to each postoperative protocol visit are shown in Table 1. The complications reported are from this entire cohort of patients (to prevent underreporting). I chose to do in-depth analysis on the patients that were local and had all of their measurements done here at our institution in a controlled and consistent fashion. To determine the long-term stability of the small-incision DLEK procedure, I looked at the 79 eyes from local patients that had both preoperative visits and 2-year postoperative visits, and this group had greater than 97% of those eyes returning for their interim 6- and 12-month visits as well. The data on these eyes are presented in Tables 2 through 4. The MANOVA testing demonstrated that the 79 local eyes analyzed were truly representative of the overall consecutive group of 116 eyes, and so the data presented should give the reader an honest appraisal of the impact of small-incision DLEK surgery on a typical range of eyes with endothelial dysfunction.

VISUAL RECOVERY

My analysis of small-incision DLEK in this study demonstrates that the usual BSCVA is about 20/42 6 months after surgery, and that this average visual level generally stays about the same throughout the 2-year study period, with only slight improvement to an average visual acuity of 20/39. If eyes without retinal pathology are excluded from the group, then the average visual acuity is better, at 20/39 at 6 months with some improvement over time to a visual acuity of 20/36 at 2 years. To determine the difference in visual outcome between eyes in Table 2 and Table 3, a Student *t* test was performed comparing those patients with retinal comorbidity and those without, examining BSCVA at each time gate. No difference in preoperative vision was found (P = .117, power = .995), indicating that there was not a selection bias. At every postoperative visit, as expected, the vision of the eyes without retinal disease was significantly better: 6-month BSCVA, P = .0001 (95% CI, ˉ.3 to .3); 1-year BSCVA, P = .003 (95% CI, ˉ.25 to ˉ.05); 2-year BSCVA, P = .0001 (95% CI, ˉ.5 to ˉ.22). What is interesting, however, is that the number of eyes that are able to see 20/40 or better increases with each subsequent examination. Fully 57% of eyes (44 of 78) see 20/40 or better at 6 months, and at 2 years 71% (56 of

79) of this same group sees that well. Eliminating the confounding variable of retinal disease, the percentages increase to 60% (40 of 67 eyes) at 6 months and 79% (53 of 67eyes) at 2 years of eyes which have 20/40 or better visual acuity. Therefore, based on these data, it would appear that patients receiving small-incision DLEK surgery (with no confounding retinal pathology) can expect to attain between 20/30 and 20/40 visual acuity on average, and they have a 79% chance of attaining 20/40 or better BSCVA by 2 years. A comparison of these DLEK results to the literature reports of vision after PK surgery is found in Table 8. Small-incision DLEK surgery appears to compare well to literature reports with the percentage of eyes with good vision to be on par with PK in most reports,[10,11,48] better than some reports,[11,43,45,46] and not as frequent as seen in the 2 outlier reports by Price and associates[48] and Serdarevic and coworkers.[18,49] It should be pointed out, however, that the visual results in my series are derived strictly from spectacle correction, and the visual results after many PK studies includes visual correction with the aid of gas permeable contact lenses or after secondary surgeries, such as relaxing incisions and/or excimer laser refractive surgery.[19] There can be dramatic visual loss after PK surgery from a variety of causes, with reports of percentages of 29% to 37% of PK eyes resulting in visual acuity of 20/200 or worse.[43,44] In this series of DLEK eyes, only 1% of eyes had 20/200 or worse visual acuity postoperatively, and in the subgroup without retinal disease, no patient ended up with 20/200 or worse visual acuity at 2 years.

TABLE 8. DEEP LAMELLAR ENDOTHELIAL KERATOPLASTY (DLEK) VISUAL ACUITY: COMPARISON WITH SCIENTIFIC LITERATURE*

STUDY	AVERAGE POSTOPERATIVE FOLLOW-UP INTERVALS	PERCENTAGE OF PATIENTS WITH ACUITY OF 20/40 OR BETTER	RESULTS COMPARED TO CURRENT STUDY
Current study	2 years	71% (56 of 79)	
Barkana et al[14]	18 months	27% (13 of 48)	*P=.0001*
Claesson et al[46]	2 years	54% (38 of 71)	*P=.003*
Jonas et al[45]	34 ± 25 months	58% (14 of 24)	*P=.012*
Davis et al[10]	25 ± 16 months	70% (33 of 47)	*P=.807*
Reddy et al[11]			
Combined procedure	32 months	48% (12 of 25)	*P=.0001*
Triple procedure	19 months	66% (21 of 32)	*P=.343*
Olson et al[47]	Range, 4 to 12 months†	75%(15 of 20)	*P=.438*
Price et al[16‡]	12 months	74% (116 of 157)	*P=.611*
	24 months	86% (101 of 117)	*P=.0001*
Serdarevic et al[49]	Range, 18 to 24 months†	100% (16 of 16)	*P=.0001*

*All results compared using a chi-square goodness-of-fit test.
†Average follow-up not available.
‡Percentages approximated from graph in publication.

The surface of the edematous cornea becomes smoother with EK surgery as the donor tissue clears the overlying stroma of fluid and any subepithelial edema resolves. I found that the corneal map indices of SRI and SAI were usually quite abnormal preoperatively, averaging 1.61 ± .85 and 1.88 ± 1.5, respectively. Both indices normalized to below 1.0 by 6 months and remained low and normal throughout the 2-year follow-up period. It is reasonable that the return to the normal prolate shape and smoothness of the corneal surface following EK surgery would enhance the quality of the visual outcome for the patient, especially compared to standard PK surgery, where high and irregular astigmatism is common.[7,9,12,14] Poorer levels of vision preoperatively in this study were modestly correlated with elevated levels of SRI (r = .279, P = .021) and SAI (r = .338, P = .005), and elevated levels of these topography indices have frequently been present postoperatively after routine PK surgery.[7] Even after EK surgery, however, the SRI and SAI can be abnormal in some eyes for several reasons. Subepithelial edema resolves after EK; however, the epithelial redundancy that results from chronic preoperative bullous keratopathy can remain, and this can result in irregular surface astigmatism with a clear postoperative cornea. In these cases, Terry and Ousley[100] have found improvement in topography with corneal scraping and removal of the irregular preoperative epithelium, and this secondary surgical maneuver will generally improve the SAI and SRI measurements and the vision. Chronic edema preoperatively can also result in surface fibrous scar formation of Bowman's layer.[101] The degree of this permanent opacity cannot be fully ascertained at the time of surgery due to the presence of edema, and additionally it is difficult to treat after EK. Surface fibrosis can reduce postoperative vision through creation of irregular astigmatism (ie, increased SRI and SAI) and by subtle opacification of the anterior cornea. Although excimer laser phototherapeutic keratectomy might be a possible treatment, this has not been done in this series.

In the 67 eyes without retinal disease (Table 3), although 14% achieved a BSCVA of 20/25 or better by 2 years postoperatively, corneal factors likely prevented the other 86% from achieving this superb level of vision. Some of the eyes had SRI and SAI values up to the outlier levels of 1.33 and 3.30 (respectively), and this surface irregularity was due to either the surface scarring changes noted above, or to problems common in this elderly population, such as dry eye and/or epithelial toxicity from glaucoma medications or other drops. Therefore, even with successful DLEK surgery, other factors not related to the surgery can still prevent the patient from achieving his or her full visual potential. Unique to EK treatment of Fuchs dystrophy and pseudophakic bullous keratopathy is the fact

that we leave the recipient anterior cornea behind. The anterior stroma of the chronically edematous cornea undergoes structural changes that may persist even after detergescence by the donor endothelium of EK.[101] At the Mayo Clinic, Bill Bourne and Keith Baratz are able to measure increased light scatter from the anterior recipient tissue that has been left behind after EK, independent of any interface light scatter (Patel SV et al, Federated Societies Scientific Session, October 15, 2005, Chicago). It may be that the residual recipient tissue after EK surgery creates enough light scatter and loss of contrast sensitivity in EK eyes to limit the final visual outcome. This may be obvious in cases that start out with count fingers vision or worse preoperatively, such as those described by Amayem and colleagues,[93] but may be more subtle in cases of only mild, but chronic, stromal edema. Contrast sensitivity testing after DLEK was not performed in our study and requires further research. Finally, the horizontal interface of the donor and recipient tissues is most likely the most important factor in preventing EK eyes from achieving their highest potential vision.[102] Similar to the cut stromal fibril interface that limits the visual results in therapeutic anterior lamellar keratoplasty,[58] DLEK surgery may suffer from these same optical disadvantages. At the current time, however, I have not found an objective means of measuring the interface irregularities and correlating them with visual outcome by the use of slit-lamp examination, confocal microscopy, or wavefront aberrometry in this series (unpublished data). Further objective characterization of the interface overlying the visual axis in DLEK eyes would be worthwhile.

The newer techniques of EK surgery represent an attempt to improve the optical properties of the corneal interface by making each surface of that interface smoother. In DSEK surgery, Terry and associates[85] have shown with scanning electron microscopy that the stripped surface of the recipient corneal bed in DSEK is "glassy" smooth compared to the recipient bed in DLEK surgery, which has evenly cut stromal fibrils present and appears less smooth. In DSAEK surgery, the donor tissue is prepared with an automated microkeratome, and it is felt by some that the donor tissue side of the stromal interface would be smoother in DSAEK than that prepared manually in DSEK or DLEK surgery.[83,94] No comparative histology of the stromal smoothness of manual vs microkeratome-prepared tissue has been published, but the early visual results following DSAEK, DSEK, and DLEK surgery can be compared. Tables 9 and 10 show the visual results of eyes achieving 20/40 or better visual acuity in this DLEK study compared to those of published series of DSEK and DSAEK surgery. It is striking that the 57% of eyes reaching 20/40 or better visual acuity in this DLEK 6-month study is very close to the 55% and 53% of eyes reaching that same level of visual acuity at 6 months in separate series of DSEK surgery by other surgeons.[82,87,94] The similarity is retained even when eyes with known retinal disease are removed from the groups. Although Price has asserted that the visual recovery is more rapid after his DSEK surgery than after his DLEK surgery,[82,94] the data from this study presented in Table 9 would suggest that by 6 months, any disparity in optical clarity between the manually created recipient bed and the stripped recipient bed is reduced by wound healing. The concept that wound healing over time improves the optical properties of the interface is also supported in this study by the tendency of a higher percentage of eyes that see 20/40 or better at 2 years (78%;52 of 67 eyes) than at 6 months (60%;40 of 67 eyes) after my DLEK surgery (Table 10). A larger number of eyes in DLEK and DSEK groups and greater control of other confounding variables for vision would be necessary, however, to really know if there is ultimate equivalency in visual outcome between the 2 groups.

TABLE 9. DEEP LAMELLAR ENDOTHELIAL KERATOPLASTY (DLEK) VISUAL ACUITY: COMPARISON OF STUDY PATIENTS WITH DSEK AND DSAEK IN LITERATURE*

STUDY	AVERAGE POSTOPERATIVE FOLLOW-UP INTERVALS	% OF PATIENTS WITH ACUITY OF 20/40 OR BETTER	RESULTS COMPARED TO CURRENT STUDY
Current study (DLEK)	6 months	57% (44/78)	
Current study (DLEK)	24 months	71% (56/79)	
Nieuwendaal et al[87] (DSEK)	6 months to 24 months	53% (10/19)	Compared to 6 months: $P = .364$ Compared to 24 months: $P = .002$
Price & Price[94] (DSEK)	6 months	55% (53/98)	Compared to 6 months: $P = .649$
Price & Price[94] (DSAEK)	6 months	69% (64/93)	Compared to 6 months: $P = .027$
Gorovoy[83] (DSAEK)	12 months	81% (13/16)	Compared to 6 months: $P = .0001$ Compared to 24 months: $P = .022$

DSAEK, Descemet's stripping automated endothelial keratoplasty; DSEK, Descemet's stripping endothelial keratoplasty.
*All results compared using chi-square goodness-of-fit test.

In comparing this DLEK group's data to the published DSAEK data, it appears that adding a microkeratome cut donor to a stripped recipient bed (DSAEK) may produce greater optical quality of the interface with resultant better vision than when both the donor and recipient sides of the interface are prepared manually. The 57% (44 of 78 eyes) that achieved 20/40 or better visual acuity in my DLEK series at 6 months was worse than the 69% (64 of 93 eyes) in the Price DSAEK series at 6 months[94] and the 81% (13 of 16 eyes) in the Gorovoy DSAEK series at 1 year[83] (Table 9). This disparity between DLEK and DSAEK was even more apparent when retinal pathology was removed as a confounding variable, with 60% (40 of 67 eyes) in our series achieving 20/40 or better visual acuity, whereas 79% (57 of 72 eyes) in the Price DSAEK series[94] at 6 months and 100% (14 of 14) of the Gorovoy DSAEK series[83] at

1 year that attained this category of vision (Table10). Although by 2 years after surgery 78% (52 of 67 eyes) of our DLEK eyes were 20/40 or better, there is currently no data on long-term visual acuities in DSAEK to know if continued visual improvement is to be expected with that form of EK surgery as well.

TABLE 10. VISUAL ACUITY: COMPARISON OF STUDY PATIENTS WITH NO RETINAL COMORBIDITY TO DSEK AND DSAEK EYES WITH NO COMORBIDITY IN LITERATURE*

STUDY	AVERAGE POSTOPERATIVE FOLLOW-UP INTERVALS	% OF PATIENTS WITH ACUITY OF 20/40 OR BETTER	RESULTS COMPARED TO PRESENT STUDY
Current study (DLEK)	6 months	60% (40/67)	
Current study (DLEK)	24 months	78% (52/67)	
Nieuwendaal et al[87] (DSEK)	6 months to 24 months	62% (10/16)	Compared to 6 months: $P = .801$ Compared to 24 months: $P = .009$
Price & Price[94] (DSEK)	6 months	69% (52/75)	Compared to 6 months: $P = .646$
Price & Price[94] (DSAEK)	6 months	79% (57/72)	Compared to 6 months: $P = .0001$
Gorovoy[93] (DSAEK)	12 months	100% (14/14)	Compare to 6 months: $P = .0001$ Compared to 24 months: $P = .0001$

DSAEK, Descemet's stripping automated endothelial keratoplasty; DSEK, Descemet's stripping endothelial keratoplasty.
*All results compared using chi-square goodness-of-fit test.

DONOR ENDOTHELIAL SURVIVAL

The sine qua non of any successful surgery in the treatment of endothelial disease is the transfer and survival of healthy donor endothelial cells. Penetrating keratoplasty has been the "gold standard" therapy for many years, and the recent techniques of PK have shown good ECD achieved years after PK surgery with clear grafts the rule. The initial average percent of cell loss from preoperative ECD in small series of Optisol preserved corneas has been shown to be about 15% to 35% in the first year after modern PK surgery with a fairly high spread of values.[23-31]

Although better than the 34% average cell loss reported in a large, but older series of PK eyes,[15] the 26% cell loss at 6 months in my small-incision DLEK study is at the high end of cell loss found in most modern PK reports.[23-31] Therefore, it seems fair to say that the initial donor cell loss measured at 6 and 12 months after DLEK surgery is on par with that found with PK surgery, but certainly is not better than PK. A controlled, randomized study of these 2 procedures with a very large number of eyes would likely be needed to determine advantages of endothelial survival in one technique of transplantation vs the other.

The donor ECD following the small-incision DLEK cases of this series is shown in Table 2 and also shown and compared in Table 11 to the ECD reported in the literature for other EK series. In Table 11, the ECD and percentage of donor cell loss in our series at 6, 12, and 24 months postoperatively is compared to similar time points for studies in the literature of other EK surgery. What is most striking about the ECD postoperatively in my series is that while the cell loss remained fairly stable, at 26% cell loss at 6 months to 29% cell loss at 1 year, there was a dramatic cell loss at the 2-year protocol visit, with fully 46% of the cells lost at 2 years after DLEK compared to the preoperative values obtained by the Eye Bank. With the exception of the Terry and Ousley report[91] on large- and small-incision DLEK in 2005, the other EK studies published have an extremely low number of eyes for analysis, making a quantitative comparison difficult. Nonetheless, it is again striking that all of the EK studies report cell loss of between 15% and 26% 6 months after the surgery, and that the Van Dooran study [95] has an identical cell loss in large-incision PLK at 1 and 2 years after surgery as we had with small-incision DLEK in this study, including the 46% cell loss found at 2 years. It is also interesting that in the first publication of DSAEK surgery with endothelial survival data, the endothelial cell loss was quite high with 40% loss at just 7 to 12 months postoperatively.[83] With only 16 eyes reported in the series, it is not possible to determine if this high cell loss is due to the difference in the EK technique, intersurgeon variation, or simply random. The only other published report of DSEK surgery with endothelial data is from Nieuwendaal and associates,[87] who reported using their own precut tissue in organ culture media on 15 eyes with varying follow-up of between 6 and 27 months. They reported a 31% to 38% donor endothelial cell loss in just the first 18 months after their DSEK surgery with a large range of cell loss of between 0% and 64%.

A closer look at the data from Ousley and Terry[92] for their long-term ECD measurements in large-incision DLEK shows that there is only a 7% drop in ECD between the 1-year visit and the 2-year visit in this series of 20 eyes. This is in stark contrast to the large increase in cell loss in this series of small-incision DLEK with a 29% cell loss at 1 year and then an additional 17% cell loss from 1 to 2 years, totally a 46% cell loss at 2 years. The main difference between the large-incision DLEK and the small-incision DLEK is that the tissue is folded prior to insertion for small-incision DLEK but is inserted flat, without folding, in the large-incision DLEK procedure. Although both techniques have similar 6-month endothelial cell loss, the abrupt cell loss at 2 years in small-incision DLEK leads one to consider the folding and added manipulation of the tissue in small-incision DLEK as having a delayed effect on central ECD. It may be that it takes time for the central endothelial cells to redistribute to the midperipheral damaged areas surrounding the

60%/40% fold, and that the true damage to the endothelium from small-incision DLEK is not made manifest until 2 years postoperatively, or even later. Further study is necessary and, obviously, other confounding variables (eg, immune mediated endothelial cell loss, accelerated apoptosis) would need to be controlled.

TABLE 11. ENDOTHELIAL CELL DENSITY (ECD): COMPARISON TO ENDOTHELIAL KERATOPLASTY LITERATURE*

STUDY (SURGERY TYPE AND INCISION SIZE)	N	AVERAGE POST-OPERATIVE FOLLOW-UP INTERVAL	ECD (CELLS/MM^2)	% OF CELL LOSS FROM PRE-OPERATIVE CELL COUNT*	RESULTS COMPARED TO CURRENT STUDY
Current study (small-incision DLEK)	78	6 months	2095 ± 380 (1097-2920)	26%	
Van Dooren et al[95] (large-incision PLK)	10	6 months	2366 ± 357 (1681-2969)	17%	*P* =.0001
Terry & Ousley[91] (large-incision DLEK)	36	6 months	2189 ± 440 (1167-2897)	23%	*P* =.072
Terry & Ousley[91] (small-incision DLEK)	62	6 months	2112 ± 420 (1097-3202)	25%	*P* =.655
Fogla & Padmanabhan[71] (small-incision DLEK)	15	6 months	1732 ± 514 (638-2341)	15%	*P* =.0001
Current study (small-incision DLEK)	77	12 months	2009 ± 393 (612-2679)	29%	
Van Dooren et al[95] (large-incision PLK)	9	12 months	2062 ± 320 (1338-2508)	26%	*P* =.192
Ousley & Terry[92] (large-incision DLEK)	20	12 months	2335 ± 468 (1144-3048)	28%	*P* =.813
Gorovoy[83] (small-incision DSAEK)	16	7-12 months	1714 (987-2994)	40%	*P* =.0001
Current study (small-incision DLEK)	79	24 months	1536 ± 547 (500-2546)	46%	
Ousley & Terry [92] (large-incision DLEK)	20	24 months	2151 ± 457 (730-2871)	36%	*P* =.0001
Van Dooren et al[95] (large-incision PLK)	9	24 months	1538 ± 434 (741-2033)	46%	*P* =.808

DLEK, deep lamellar endothelial keratoplasty; DSAEK, Descemet's stripping automated endothelial keratoplasty; PLK, posterior lamellar keratoplasty.
*Percentage of cell loss compared using a one-sample *t* test.

RISKS AND COMPLICATIONS

The primary complication in this study was the presence of interface fluid on the day after surgery leading to a second, surgical intervention. Interestingly, of the 11 cases where this occurred, only 4 of the grafts were actually dislocated into the anterior chamber, with the rest of the grafts still positioned in the recipient pocket. Although another air bubble was placed and the edges of the recipient bed wound manipulated to ensure posterior position relative to the graft in every case, it may have been possible to simply observe the cases with just interface fluid and wait for spontaneous attachment of the graft. This conservative approach has been utilized by us in my own DSEK/DSAEK cases with success, and recently even more dramatic nonsurgical EK graft reattachment has been reported in the literature.[103] The problem of complete dislocation of the graft is a unique complication of EK surgery, and although it usually occurs within 24 hours after surgery, dislocation has been reported even several days later.[84,85] The incidence of dislocation of the graft has been reported by Terry and Ousley as 5% in their initial 100 cases of DLEK surgery; however, we did not find any cases in that series where the tissue had interface fluid but was not dislocated.[91] Fogla and Padmanabhan[71] did not report any dislocation in their series of 15 DLEK cases. The incidence of dislocation has been reported much higher in the DSEK and the DSAEK procedures. Price and Price[84] reported a 50% dislocation rate in their first 10 cases (5 of 10 eyes), and Gorovoy[83] reported an initial dislocation rate of 25% (4 of 16 eyes) in his first experience with DSAEK. Nieuwendaal and associates[87] reported a 14% dislocation rate (3 of 22 eyes) in their recent report of DSEK surgery using "pre-cut" tissue. Terry and associates[85] performed cadaver eye studies with scanning electron microscopy analysis, which confirmed the exquisitely smooth surface of the stripped recipient surface in DSEK surgery compared to DLEK, and we hypothesized that this surface contributed to the relatively poorer donor adhesion in DSEK or DSAEK surgery compared to DLEK. As a laboratory-based solution, Terry and associates[85] have recommended that the surgeon scrape the peripheral recipient bed in DSEK or DSAEK surgery to "roughen" it so that the mechanical adhesive properties of the DSEK recipient bed would mimic those of the DLEK cut fibril recipient bed. In that same report, Terry and associates[85] reported a graft dislocation rate of just 4% in our first 100 cases of DSEK and DSAEK using this surgical technique modification. Price and Price[84] have advocated the evacuation of interface fluid after donor insertion by directly "sweeping" the corneal surface while air fills the anterior chamber. With this method they reduced their dislocation rate from 50% (5 of 10) to 13% (17 of 126). They then added the maneuver of surface stab incisions to "release" interface fluid and reported a 6% dislocation rate (4 of 64) in DSEK/DSAEK surgery.[84] Most disturbingly, surgeons who have utilized these same techniques in their initial 10 cases of DSEK or DSAEK surgery are experiencing extraordinarily high levels of dislocation of 35% (range, 10%-70%). This dislocation rate remains high at a rate of 26% (range, 4%-64%) for those with greater than 10 cases of experience (Mokhtarzadeh and Weiss, Federated Societies Meeting, November 10, 2006). Results from this survey of "novice" EK surgeons suggest that the dislocation rate of EK surgery is highly dependent not only on the specific technique but also on the care that the surgeon takes with the tissue during folding, insertion, and unfolding. Hopefully the "learning curve" of EK surgery for the individual surgeon will be further foreshortened by continued advances in technique and training.

In this series I evaluated the effect on the BSCVA and ECD over time on tissue with interface fluid but no dislocation (Table 5) and on tissue that had frank dislocation into the anterior chamber (Table 6). The 7 eyes with interface fluid and no dislocation maintained excellent donor ECD over time, and the statistical analysis (as shown in Table 5) did not demonstrate any significant difference in ECD at any time point postoperatively between this subset of 7 eyes and the overall group of 79 eyes analyzed in Table 2. The BSCVA was also quite good early on with these 7 eyes, with 5 of 6 eyes achieving 20/40 or better visual acuity by 6 months, all 7 by 1 year, and then with retinal disease of age-related macular degeneration affecting 2 eyes, only 4 of 6 eyes were 20/40 or better by 2 years. No statistical difference in BSCVA for this group compared to the overall group of 79 eyes was found at any postoperative visit, with the exception of the 2-year visit. The data for the 4 eyes that suffered true dislocation of the graft was somewhat worse for the measurement of ECD. The 6-month ECD was available on only 3 eyes, and this ranged from 1239 to 2235 cells/mm^2. At 1 year it was about the same, but at 2 years, the 2 patients that had data had cell counts of only 574 and 759 cells/mm^2. This dramatic drop-off in the ECD from 1 to 2 years postoperatively is consistent with what we saw in the overall group of 79, but also points to perhaps a more exaggerated cell loss due to the extra manipulations of the donor tissue in the secondary surgery of reattachment with a second air bubble. Although the number of patients with dislocation was too small in this series for meaningful statistical analysis, our findings are consistent with those of Terry and Ousley,[100] who found in a report on dislocations in large- and small-incision DLEK that the grafts that required repositioning had an average ECD of 1534 ± 366 cells/mm^2 at 6 months, which was significantly worse than the ECD of the overall group that did not require repositioning (P = .003). Despite the low cell densities, as long as the graft remains clear as it did in all of these cases with this postoperative complication, the vision remained reasonably good for all eyes out to the 2-year postoperative follow-up time.

The loss of endothelial cells in small-incision DLEK surgery is acceptable in the first year after surgery. However, the dramatic change in ECD from 1 to 2 years with a resultant 46% cell loss from preoperative measurements at 2 years postoperatively is of great concern. If the cell loss continues at this accelerated rate, it is possible that we may see a higher percentage of eyes that require regrafting due to late endothelial failure after EK than what we have come to expect from PK in the therapy patients suffering from similar endothelial failure. An example of delayed and severe endothelial cell loss without precipitating event (eg, allograft rejection episode) is shown in Figure 4.

In one case in this series, I experienced an eccentric trephination of the donor tissue, resulting in a 1-mm-thick edge on one side of the donor disc tissue. This surgeon error prevented the tissue from becoming attached postoperatively, and so the tissue was proclaimed to be an "iatrogenic" primary graft failure and was successfully replaced. The incidence of true primary graft failure in PK surgery is less than 1% (Eye Bank Association of America, Statistical Report, 2005), but the donor tissue loss from the EK procedures is much higher. Terry and Ousley[91] reported a 1% rate (1 in 100) of primary graft failure in their first 100 DLEK cases, and Terry and associates[85] also reported a 1% rate (1 of 100) of primary graft failure in their first 100 DSEK/DSAEK cases. Fogla and Padmanabhan[71] reported no cases of primary graft failure in their small series of 15 DLEK eyes. Price and Price[84] reported a 3% rate (7 of 200) of primary graft failure in their 200 cases of DSEK/DSAEK, with 2 secondary graft failures within 6 months postoperatively. Nieuwendaal and associates[87] reported a 14% rate (3 of 22) of primary graft failure due to nonattachment of donor tissue in their latest series of DSEK surgery. Gorovoy[83] reported one case of primary graft failure in 16 cases (7%) of DSAEK surgery. Most disturbingly, in a survey by Jane Weiss (Eye Bank Association of America annual meeting, June 2006), she found that among "novice surgeons" (those with less than 10 cases of DSEK/DSAEK comprising their surgical EK experience), there was a 25% rate of primary graft failure for the overall group. The high rate of primary graft failure currently associated with EK surgery in the United States is a major issue for Eye Banks involved in the processing, allocation, and distribution of precious and limited donor tissue.

The complication of rejection is expected in any surgery that transplants antigenic donor endothelium. In this series, there were only 3 eyes in 116 (3%) that experienced an episode of graft rejection as defined by increased inflammatory cells in the anterior chamber occurring after resolution of initial postoperative inflammation. All 3 eyes were treated with topical prednisolone acetate 1% every 2 hours initially, and the inflammation subsided, leaving a healthy and clear cornea. The ECD of 2 of the 3 eyes is seen in Table 7 and was similar to the overall group. Two of the 3 eyes were from out-of-state referrals, and therefore longer-term endothelial data is not available.

The rate of rejection in this series is lower than what has been reported for PK. The largest prospective study reporting rejection rates in eyes with endothelial failure exists in the Swedish Corneal Transplant Registry database.[46] In an updated evaluation of 378 eyes with Fuchs dystrophy and 330 eyes with pseudophakic bullous keratopathy that had been treated with PK surgery and had a minimum of 2 years follow-up, Claesson and colleagues have found that there was a 13% rate of rejection event (92 of 708), and of the eyes that had a rejection, 28% (26 of 92) went on to failure. This is a higher rate than what we experienced with our series. Aside from the main stimulus to rejection by the exposure of donor endothelial antigens to the host aqueous environment, factors that contribute to graft rejection following PK surgery include loose or broken corneal sutures[45] as well as the transplantation of the donor anterior stroma that contains host-sensitizing donor dendritic cells.[104] EK procedures, including the small-incision DLEK cases reported here, inherently avoid these secondary known causes of graft rejection and so may hold some advantages over PK in avoiding graft rejection. It should be noted, however, that at 2 years postoperatively, 56 of 81 eyes (70%) in this study were still on at least some steroid drops, and this was not the rule for cases reported in the Swedish Graft Registry, where the custom is to remove all steroids shortly after 6 months postoperatively.[46] Until the confounding variable of topical steroids can be controlled in a randomized study, the theoretical advantages of EK in reducing the complication of rejection compared to PK is an appealing proposition, but unproven.

In this series of 116 eyes, I had only one eye that presented with an anterior chamber lens in place. The lens had been in place for

decades, and the cornea had only recently decompensated. I elected to leave the lens in place and performed the DLEK surgery. This scenario creates greater difficulty for insertion and unfolding of the donor tissue; however, with successful surgery, this patient went on to recover excellent vision and to maintain an excellent ECD even out to 2 years. This case brings to the forefront one of the key differences between the postoperative management of DLEK vs DSEK or DSAEK surgery. In DLEK surgery, I remove nearly the entire air bubble at the end of surgery, yet in DSEK or DSAEK, most experienced surgeons[82-85] feel that an air bubble of at least 8-mm diameter is necessary to maintain the graft in position. In the situation of an anterior chamber lens in place (or in aphakia, anorexia, or large-sector iridectomy), there is an open communication between the posterior chamber and the anterior chamber. If an air bubble is left in place at the end of EK surgery, as soon as the patient sits up, it usually migrates into the posterior chamber, and the EK graft loses its support for attachment. Because of this air bubble migration, I choose to perform DLEK surgery (rather than DSEK or DSAEK surgery) in any case where the decision is made to leave the anterior chamber lens in place (rather than doing a lens exchange with a replacement posterior chamber lens) and in any case where there is an open communication between the anterior chamber and the posterior chamber. Until data are presented on the safety and dislocation rate of doing DSEK or DSAEK surgery in these complex cases, DLEK surgery would seem a prudent course to follow.

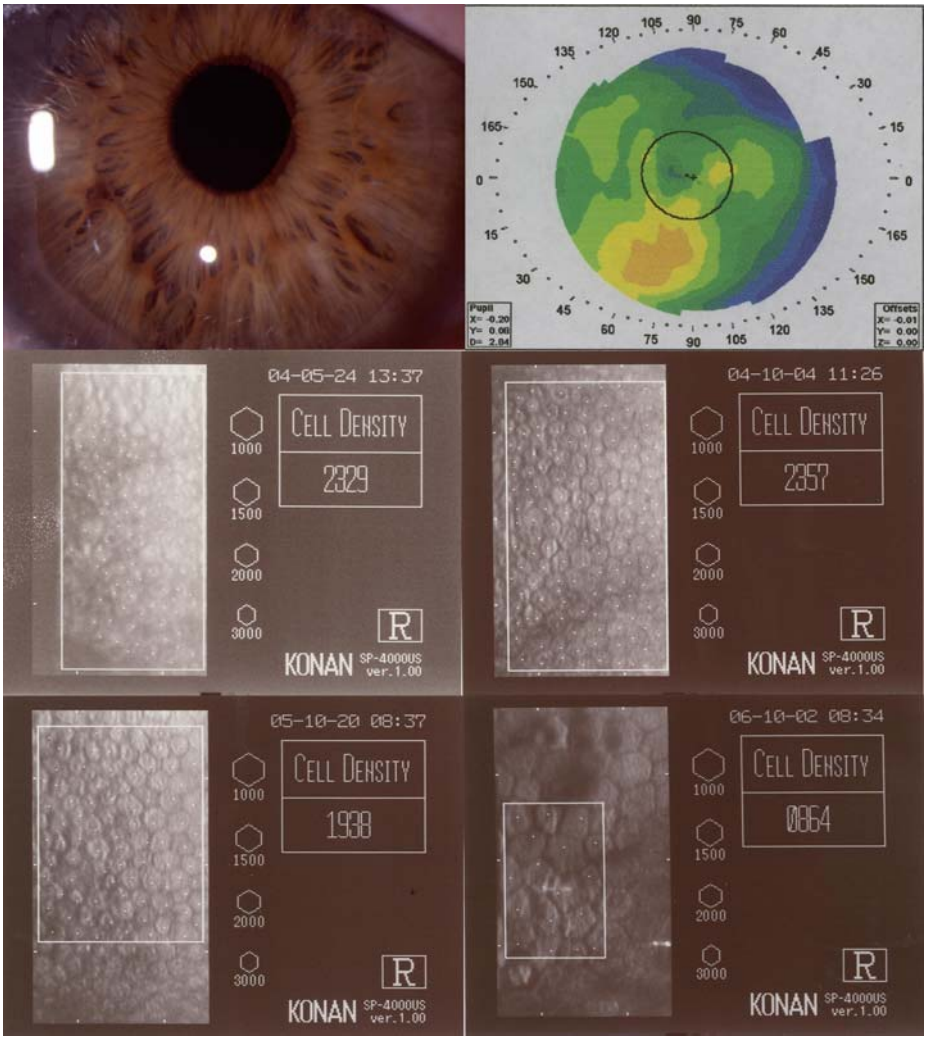

FIGURE 4

Small-incision deep lamellar endothelial keratoplasty (DLEK): Eye 35 in series. *Top row:* Left, Crystal clear DLEK cornea 3 years after surgery. Right, Normal corneal topography with 0.35 diopters of cylinder 3 years after surgery. *Center row:* Left, Endothelial cell density at 6 months postoperatively = 2329 cells/mm^2. Right, Endothelial cell density at 12 months postoperatively = 2357 cells/mm^2. *Bottom row:* Left, Endothelial cell density at 24 months postoperatively = 1938 cells/mm^2. Right, Endothelial cell density at 36 months postoperatively = 864 cells/mm^2.

There were 2 cases that had the first DLEK graft removed, and it was replaced with a second DLEK graft prepared with a microkeratome. In the first case, the hope was that the smoother surface of the microkeratome-prepared donor tissue would yield

better optics and vision for the patient. The fact that it did not improve the vision indicates that other factors, such as recipient interface stromal irregularity or residual anterior stromal tissue haze, may contribute to poorer visual performance than expected after EK surgery. The second case of "EK donor tissue exchange" was done for late endothelial failure after DLEK surgery and was successful. Both of these cases demonstrate that re-operation even years after DLEK surgery is technically possible when indicated.

There were 2 cases in this series that underwent a PK replacement of their DLEK graft. The first case was yet another attempt to improve the vision of the patient who was dissatisfied with his original DLEK surgery as well as his replacement DLEK surgery. In the second case, a PK replacement was done to save the eye after severe trauma to a DLEK eye resulting in a badly ruptured globe. Both cases demonstrate that doing DLEK or any EK surgery does not preclude the possibility of performing a standard PK surgery at any time in the future. This has been an important safety net in the development of this new procedure and will continue to offer safety advantages for the surgeon and the patient.

I was fortunate that I did not experience any cases of infectious keratitis in this series, with the exception of an eye that had an episode of herpes simplex keratitis in the late postoperative period. Infections of the interface in EK surgery would be difficult to treat with their location in the deep stroma, and there is only one anecdotal report of bacterial keratitis that required PK surgery to cure the eye and prevent endophthalmitis (John T, ARVO Meeting, 2004, Abstract). It is also remarkable that there have been no cases of sterile deep lamellar keratitis in my series, such as that described as a complication after LASIK surgery. This complication of lamellar surgery can be difficult to treat and vision-threatening, but it was not seen in my series or any other reported series to date.

The 2 eyes in my series that required filtering procedures after our small-incision DLEK surgery were from the same patient. The patient had glaucoma preoperatively with his IOP controlled on 2 medications prior to his DLEK surgery. In each eye, the IOP became uncontrolled with the chronic topical steroid drops to prevent rejections, and despite maximal medical therapy, the eyes went on to filtration surgery. This case emphasizes the need for patients with chronic glaucoma to be cautious about undergoing DLEK surgery if they are already on maximal medical therapy, as the need for chronic steroids postoperatively puts them at higher risk of requiring a filtration surgery after DLEK. In addition, it seems reasonable to recommend that EK surgery be done from a temporal position routinely, so as to avoid damaging the superior conjunctival limbal tissue, which may be needed later for filtration surgery.

In 3 eyes in my series, Snellen BSCVA postoperatively was worse than preoperative BSCVA and there was no documented retinal disease before or after the DLEK surgery. Interestingly, 2 of the 3 patients state that their visual acuity and their quality of vision are better than before the surgery. This subjective sense of visual improvement (despite Snellen testing to the contrary) appears to be due to the removal of the diseased Descemet's membrane with its associated guttata. The fact that these first 2 patients felt their vision was improved also illustrates that the Snellen visual acuity is inadequate in our assessment of visual decrement in patients with Fuchs dystrophy. More sophisticated testing of contrast sensitivity and other measures that were not done in this study should be done in a prospective fashion to better understand this phenomenon of subjective visual improvement in the face of worse Snellen BSCVA.

These cases also bring up the question of when is the best time to operate on patients with Fuchs dystrophy. Should the surgery be done early, when visual loss is only mild, or should the surgery of EK be done when the visual loss is more severe, consistent with our threshold for PK surgery? The association of better visual outcomes for patients with better preoperative vision has been described by Terry[6] for DLEK surgery, and also by Price and Price[94] for DSEK and DSAEK surgery. This would argue for doing EK surgery before the chronic edema causes permanent structural changes in either the recipient stromal tissues or the subepithelial basement membrane and Bowman's layer tissue. On the other hand, if the average visual acuity in patients after EK surgery is between 20/30 and 20/40, with only 12% achieving 20/25 or better BSCVA 2 years after surgery, it is difficult to justify operating on an eye that is 20/25 preoperatively. In light of this conundrum, the limitations of visual recovery after EK surgery should be thoroughly explained to the patient and a consensus reached on the most prudent course of action for the individual patient's visual circumstance.

THE FUTURE OF ENDOTHELIAL KERATOPLASTY

The horizontal, donor-recipient interface created by EK procedures is likely the main limiting factor toward achievement of full visual potential following transplantation. Whereas the evolution from DLEK to DSEK to DSAEK has likely improved one side of that interface (the recipient side), it is apparent that, regardless of the methods or technology of stromal dissection utilized,[76-79] the donor side of the interface will never be as optically smooth as the recipient bed that has been stripped along the natural tissue plane between Descemet's membrane and the overlying stroma.[85] The obvious solution to this interface problem is to eliminate the donor stromal tissue as the carrier for endothelial transplants.

Pure donor Descemet's membrane transplantation is technically difficult due to the fragile nature of the tissue. Shimmura and associates[105] have recently experimented in rabbit and cadaver eyes with using an artificial carrier for the donor tissue. In their technique, they separate the donor Descemet's membrane with hydrodissection and then wrap the fragile tissue around a hydroxyethyl methacrylate polymer, which has been coated with viscoelastic to protect the endothelium. By using this stronger carrier for tissue transfer, and then removing it after donor insertion, they have provided a practical means of tissue transport with retention of the same familiar surgical maneuvers utilized in DSEK or DSAEK surgery. A more direct approach has been taken by Tappin[90] with his technique of transferring the donor Descemet's membrane directly onto a specialized spatula and then transplanting the flat membrane through a larger incision. This technique, similar to large-incision DLEK, avoids folding the tissue and damage to the endothelium from that maneuver. Melles and associates[89] have also taken a direct approach by allowing the Descemet's membrane to roll up into a scroll shape, aspirating the scroll into an injection cartridge, and then injecting and unraveling the donor tissue within the recipient anterior chamber. All of these techniques show promise, but all of them also suffer from the difficulty and uncertainty of removing the healthy Descemet's membrane from the donor cornea without tearing it or causing severe endothelial trauma. Obviously, more work

needs to be done to show the rate of donor tissue loss at the time of surgery as well as the longer-term (at least 2 years) endothelial survival of these forms of DMEK surgery.

Extensive investigation has been done over the past 30 years in developing pure endothelial transplantation, with important work done by the groups of McCulley,[106] Maurice,[107] Wood,[108] Bohnke,[109] Alvarado,[110] and a host of others.[111,112] Their work has established that human endothelial cells can be cultured in vitro and amplified to produce viable monolayers. Various techniques of donor endothelial transfer have been investigated, including direct injection, use of carriers such as recipient stroma, denuded Descemet's membrane, hydrogel lenses, and amniotic membrane.[111-114] This continuing work holds the promise of our ability to one day remove recipient peripheral endothelial cells, induce mitosis with amplification of the ECD in the laboratory, and then return the densely populated monolayer of cells to the same recipient using advanced EK surgical strategies. The recent laboratory work of Tatsuya Mimura[115] in Japan echoes the work of others over the past decades. He has successfully treated bullous keratopathy of the rabbit cornea with the xenograft transplantation of human precursor cells into the anterior chamber and subsequent eye-down positioning. If we can extrapolate this animal model to the clinical realm, then EK as we know it may be completely transformed.

CONCLUSIONS

Endothelial keratoplasty is an exciting new form of surgery that provides selective endothelial transplantation. This surgery allows restoration of the normal corneal topography, with very little change from the preoperative corneal curvature. This in turn provides more accurate IOL calculations for combined cataract and transplantation procedures, as well as avoiding the surprises of high astigmatism and high refractive errors that are so common after standard PK surgery. The visual recovery rate after EK appears to be faster than most PK eyes, and this is accomplished with an inherently safer operation and stronger globe for the short and the long term. All of these advantages of EK, however, are mitigated by a concern with the level of donor endothelial cell loss over the first 2 years and by a donor-recipient interface that restrains many patients from achieving their full visual potential. Longer-term, prospective data on endothelial survival after EK is desirable, and work toward improvement of the interface is currently under way. Whereas the surgical techniques of EK are still in accelerated development, it appears that EK is moving forward quickly to become the preferred, if not the ideal, method of corneal transplantation for the treatment of endothelial dysfunction.

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