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Effect of Graft Attachment Status and Intraocular Pressure on DSAEK Outcomes in the Cornea Preservation Time Study

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Abstract

Purpose: To examine the association of donor, recipient, and operative factors on graft dislocation after Descemet stripping automated endothelial keratoplasty (DSAEK) in the Cornea Preservation Time Study (CPTS) as well as the effects of graft dislocation and elevated IOP on graft success and endothelial cell density (ECD) 3 years postoperatively.

Design: Cohort study within a multi-center, double-masked, randomized clinical trial.

Methods: 1,090 individuals (1,330 study eyes), median age 70 years, undergoing DSAEK for Fuchs endothelial corneal dystrophy (94% of eyes) or pseudophakic or aphakic corneal edema (6% of eyes). Recipient eyes receiving donor corneal tissue randomized by preservation time (PT) of 0-7 days (N=675) or 8-14 days (N=655) were monitored for early or late graft failure through 3 years. Donor, recipient, operative, and postoperative parameters were recorded including graft dislocation (GD), partial detachment, and pre- and post-operative IOP. Pre- and postoperative central donor ECD were determined by a central image analysis reading center. Proportional hazards, mixed effects, and logistic regression models estimated risk ratios and {99% confidence intervals}.

Results: Three independent predictive factors for GD were identified: a history of donor diabetes (odds ratio {OR}: 2.29 {1.30, 4.02}), increased pre-lamellar dissection central corneal thickness (OR: 1.13 {1.01, 1.27} per 25μ increase), and operative complications (OR: 2.97 {1.24, 7.11}). Among 104 (8%) eyes with GD, 30 (28.9%) developed primary donor or early failure and 5

(4.8%) developed late failure vs. 15 (1.2%; p<0.001) and 29 (2.4%; p=0.04), respectively, of 1226 eyes without GD. 24 (2%) of 1330 study eyes had early acutely elevated postoperative IOP that was associated with a higher risk of graft failure through 3 years (hazard ratio: 3.42 {1.01, 11.53}), but not with a lower mean 3-year ECD (mean difference 61 {−479, 601} cells/mm^2, P=0.77). History of elevated postoperative IOP beyond 1 month was not significantly associated with 3-year graft success or ECD.

Conclusions: Donor diabetes, increased donor corneal thickness, and intraoperative complications were associated with an increased risk of GD. Early acutely elevated postoperative IOP and GD significantly increased the risk for graft failure following DSAEK.

Introduction

The Cornea Preservation Time Study (CPTS), designed to evaluate the association of preservation time (PT) with graft success and cell loss following Descemet stripping automated endothelial keratoplasty (DSAEK),[1] has yielded data that are being used to identify these and many other associations with endothelial keratoplasty outcomes. In regard to PT, the observed difference in survival of donor corneas with a PT of 7 days or less compared to those with a PT of 8 to 14 days was primarily due to a higher incidence of primary donor and early graft failures in the 8-14 day PT group.[2] Further analysis revealed that the incidence of failure was the highest in the 12-14 day PT subgroup, but analyses were not performed to determine the underlying reasons for this observation.

In a separate publication, we reported the donor, recipient and operative factors that are associated with graft success three years after DSAEK.[3] While donor factors such as age and graft factors such as preoperative endothelial cell density (ECD) and graft diameter were not found to have a significant impact on graft success, other factors, such as indication for surgery [Fuchs endothelial corneal dystrophy (FECD) versus pseudophakic/aphakic corneal edema (PACE)] did have a significant impact.[3,4] When factors associated with an increased risk for primary donor or early graft failure other than PT were evaluated, a history of donor diabetes and the occurrence of operative complications were identified as significant, although the mechanism underlying donor diabetes' impact on graft failure remains speculative.[3] In order to gain a greater understanding of the factors that influence the development of primary donor or early graft failure, the three-year graft success rate and ECD following DSAEK in the CPTS, we performed an analysis of early postoperative events including all degrees of graft malattachment (partial detachment, dislocation) as well as intraocular pressure (IOP) throughout the postoperative period.

Methods

The Cornea Preservation Time Study was originally designed as a non-inferiority clinical trial of 3 year graft success using corneal donor tissue preserved for 8-14 days compared to donor tissue preserved for 0-7 days.[1] Institutional review board approval was secured at each participating clinical site and eye bank (e-Table 1), and all participants provided written informed consent. Study oversight was provided by an independent data and safety monitoring committee. The research adhered to the tenets of the Declaration of Helsinki.

The protocol was registered and is publicly available at https://clinicaltrials.gov/ct2/show/NCT01537393.

Details of the CPTS methods and primary results have been published previously.[1,2,5] Standard donor information was gathered and reported by 23 eye banks, all accredited by the Eye Bank Association of America (EBAA). Donor corneas met current EBAA standards for DSAEK[6] and met additional criteria regarding donor age, death to preservation time, and quantity and quality of endothelial cells.[1]

The study prospectively gathered and recorded data on multiple donor, recipient and operative factors, all of which have been previously assessed for their impact on graft success and endothelial cell loss.[3,4] Specifically, we recorded the following data on donors: age, gender, race, and history of diabetes (yes/no) determined from medical records and/or next of kin as in the Cornea Donor Study (CDS).[7,8] For donor corneas we recorded eye (OD or OS), procurement information (time to refrigeration, time to preservation), and tissue preparation details including thickness prior to lamellar dissection by either the eye bank or surgeon, post-lamellar dissection storage solution (fresh or initial solution), observations noted during lamellar dissection, and post-lamellar dissection donor lenticule thickness. Each eye bank obtained up to 3 images prior to shipping for surgeon-prepared lenticules or following lamellar dissection by the eye bank (“pre-operative”) that were sent to a central reading center [Cornea Image Analysis Reading Center (CIARC, Cleveland, Ohio)] for determination of ECD.

Participant inclusion criteria have been previously published.[1] Participants between 30 and 90 years of age who had endothelial dysfunction suitable for DSAEK were included, but were excluded if they were at high risk for graft failure including patients with tube shunts, uncontrolled glaucoma, anterior chamber intraocular lenses and anterior synechiae greater than 3 clock hours.[1,2] If eligible, both eyes of a participant could be enrolled. We recorded the following data on recipients: pre-operative diagnosis (including history of corneal dystrophy), presence of diabetes, and relevant ocular history including medications and prior glaucoma surgery (i.e., trabeculectomy, laser trabeculoplasty). At baseline each clinical site measured intraocular pressure using their standard routine. Operative details and complications were collected prospectively in pre-determined categories including unplanned vitreous loss, posterior capsule rupture, suprachoroidal hemorrhage, significant hyphema, inverted donor tissue, difficult unfolding and positioning without use of a positioning instrument, difficult unfolding and positioning with use of a positioning instrument, difficult air fill and retention in positioning, and donor extrusion with subsequent reinsertion. None of the aspects of the surgical procedures were regulated but most were tracked as previously published including incision size and location, donor cornea diameter, donor cornea insertion method, corneal stab “venting” incisions , peripheral posterior host stromal scraping, air fill duration, other procedures (e.g. cataract surgery), and trainee participation (e.g. tissue preparation, donor cornea insertion and positioning).[1,2,3] Examinations were scheduled at 1 day, 1 week, and 1, 6, 12, 24, and 36 months following surgery for all participants with postoperative care provided according to each investigator’s standard practice.

Through the first month of scheduled visits, and for any unscheduled visits throughout the first 6 months, donor attachment details were recorded. Specifically, donor positioning and location and extent of interface fluid were tracked, as well as the need for air injection and/or the need for external pressure or rolling maneuver with internal repositioning.[9,10] Graft dislocation was defined as either: 1) total detachment of the graft ("total detachment"), as described in previous publications as a graft dislocation;[9,10] or 2) an attached but decentered graft that required a surgically induced total detachment in order to reposition and reattach the graft accompanied by air injection ("graft repositioning"). All eyes with a partial detachment, characterized by the presence of interface fluid which did not require repositioning, regardless of the need for air injection, were collectively analyzed under the category "interface fluid". Since the utilization of various interventions (air injection, internal or external methods to reposition) varied among surgeons for a given malattachment, we chose to examine the relationship between the malattachment and graft failure rather than exploring the effect of interventions. This was a more inclusive approach since many of the malattachments (e.g. interface fluid) were not necessarily followed by an intervention.

Additionally, at the baseline and every post-operative visit, the study gathered information on topical and systemic medications (including corticosteroid usage but not type or dosage), and any study eye procedures since the previous visit (or history of glaucoma surgery at the baseline visit), allowing the collection of detailed information regarding glaucoma management. Intraocular pressure (IOP) measurement was required at all protocol visits, except the 1-day post-operative visit, using the surgeons' routine methods. If IOP was measured on other visits per the surgeons' preferences, it was recorded as well. Acute IOP events included any occurrence of IOP > 40 mm Hg or paracentesis for pupillary block or angle closure in the first postoperative week. Other postoperative abnormal IOP events included any new glaucoma surgery, the addition of glaucoma medication, or any occurrence of IOP > 25 mm Hg one month or more after surgery.

At each visit, the eye was also assessed for graft failure using the previously published OPTS definitions.[1] In brief, grafts were classified as failed if: 1) the study eye was re-grafted for any reason; 2) the recipient cornea was cloudy or equivocally cloudy on the first postoperative day and did not clear within 8 weeks; or 3) the recipient cornea was initially clear postoperatively but became and remained cloudy for 90 days (late failure). A graft that failed during the first 8 postoperative weeks was further classified as a primary donor or early failure, depending on whether failure occurred in the absence or presence of operative complications, respectively.

Details of CIARC procedures have been previously described, including reader training and certification, image quality grading, image calibration, variable frame analysis for ECD determination by two independent readers, and adjudication procedures for ECD determination.[1,5,11] Readers were masked to all information about the donor corneas, including PT. The analyzed images included the preoperative central endothelial images provided by the eye banks and three specular or confocal microscopic images of the central donor corneal endothelium obtained and provided by the investigators at 6 months and 1, 2,

and 3 years after surgery as long as a participant remained in follow-up without graft failure or a regraft.

Statistical Analysis

Selected candidate predictive factors for graft dislocation included eye bank observations, donor history of diabetes, operative complications, pre-lamellar and post-lamellar dissection thickness. The effect of each factor on graft dislocation was evaluated using logistic regression models. A base model included PT, recipient diagnosis, and random surgeon effect. Each factor was first evaluated using the base model. Factors associated with $p < 0.10$ were included in a multivariable backward model selection procedure.[12] To account for multiple comparisons, only factors with $p < 0.01$ were considered statistically significant and retained in the final models. To provide more information, odds ratios adjusted for the factors in the final model were provided for each factor discarded during variable selection.

Data collected from protocol visits as well as unscheduled visits were included in the analyses of factors associated with graft success and ECD at 3 years. Variables of interest included graft dislocation, interface fluid, history of glaucoma at baseline, abnormal IOP at least 1 month after surgery, and perioperative acutely elevated IOP. Cumulative probabilities of graft success at 3 years along with 99% CIs were calculated using the Kaplan-Meier method. Cox proportional hazards regression models adjusted for PT, recipient diagnosis, donor history of diabetes, and operative complications were used to assess the association of these factors with 3 year graft failure, while mixed effects regression models adjusted for PT, preoperative ECD, recipient diagnosis, donor history of diabetes, and operative complications were used to assess the association of these factors with 3 year ECD. All models included surgeon as a random effect to accommodate the potential correlation in graft success among DSAEKs performed by the same surgeon. Analyses for the effect of graft malattachment and acute IOP events on graft failure included all study eyes in the CPTS (N=1330), while analyses for the effect of history of glaucoma and elevated postoperative IOP at least 1 month after surgery were restricted to eyes at risk 1 month following DSAEK (N=1277). 3 year ECD analysis was restricted to eyes with a functioning graft at 3 years and analyzable 3 year and preoperative endothelial images (N=913).

Missing data were treated as a separate category for discrete factors, and a missing indicator was added for continuous factors. Continuous covariates were evaluated as continuous in all models. For the ease of interpretation, continuous factors were categorized for display. All reported p-values were 2-sided. Statistical analyses were conducted using SAS, version 9.4 (SAS Inc).

Results

Graft Attachment

Eight percent (104/1330) of eyes had at least one graft dislocation by our definition during the postoperative period; among these, 18 were surgically induced total detachments in order to recenter the donor lenticule. Of these 104 eyes, 98 eyes had an air injection performed, and 6 eyes did not. Of the 6 eyes that did not have an air injection, 5 were left free-floating

until regrafted, whereas one eye had blunt trauma and was regrafted without prior air injection attempt. One-hundred-fifty-two of the 1226 eyes (12%) without graft dislocation had at least one occurrence of interface fluid following surgery. Forty-one of these eyes (27%) had air injections with 39 having one injection, 1 eye having 2 injections, and 1 eye 3 injections; 17% (7/41) went on to fail by year 3. The remaining 111 of the 152 eyes (73%) without dislocation but having interface fluid following surgery were simply followed for their interface fluid; 5% (5/111) failed by year 3. Overall, a total of 139 eyes out of the total group of 1,330 eyes experienced at least one post-operative air injection for a re-bubble rate of 10.5%.

The associations between predictive factors and graft dislocation are shown in Table 1. After accounting for PT and recipient diagnosis, a history of donor diabetes (OR 2.29, 99% CI {1.30, 4.02}), greater central donor corneal thickness (prior to lamellar dissection) (OR 1.13, {1.01, 1.27} for every 25μ difference), and operative complications (OR 2.97, 99% CI {1.24, 7.11}) were associated with a higher risk of graft dislocation. Donor lenticule thickness was included in the model selection procedure, but was not statistically significant after adjusting for the factors included in the final model (i.e. $p \geq 0.01$). Mean (SD) pre-lamellar dissection donor thickness was 553 ± 64 μ, while post-lamellar dissection donor lenticule thickness was 130 ± 35 μ. Notably there was only a weak correlation between the pre-lamellar dissection donor cornea and post-lamellar dissection donor lenticule thickness (Spearman correlation 0.20, $p<0.001$, e-Figure 1). Potential interaction effects between donor diabetes with pre/post lamellar dissection thickness, as well as PT with pre/post lamellar dissection thickness were evaluated, and not found to be significant (data not shown).

Twenty-nine percent (30/104) of eyes with graft dislocation developed primary donor or early failure and 4.8% (5/104) developed late failure, compared with 1.2% (15/1226; $p<0.001$) and 2.4% (29/1226; $p=0.04$ of eyes without graft dislocation, respectively. After accounting for donor history of diabetes, PT, recipient diagnosis, operative complications and surgeon, eyes with graft dislocation had an increased risk for failure through 3 years compared with eyes without graft dislocation (Hazard ratio 7.9, 99% CI {4.1, 15.3}, Table 2a). When graft attachment was evaluated as 4 subgroups the 3 year cumulative probability of graft success was 65.6% (99% CI {50.3%, 77.1%}) for eyes with total detachment, 66.7% (99% CI {31.1%, 86.9%}) for eyes requiring graft repositioning, 91.2% (99% CI {81.6%, 95.9%}) for eyes with partial detachment (interface fluid) in the absence of either total detachment or repositioning and 96.8% (99% CI {95.0%, 98.0%}) for eyes without total detachment, repositioning or interface fluid (Table 2b).

After accounting for preoperative ECD, donor diabetes, PT, recipient diagnosis, operative complications, and surgeon and recipient (random effects), graft dislocation was associated with a lower mean (± SD) 3 year postoperative ECD of 1127 (± 546) cells/mm^2 (59% endothelial cell loss) compared with 1719 ± 614 cells/mm^2 (37% endothelial cell loss) for eyes without graft dislocation ($p<0.001$) (Table 3a). Based on a three subgroup analysis (graft dislocation or not; if not, interface fluid or not), results remained similar (Table 3b).

Intraocular pressure (IOP)

Among the 1330 study eyes, 9% (117) had a history of glaucoma, 6% (86) were on glaucoma medications, 1% (18) had a history of glaucoma surgery, and 1% (13) had a history of both glaucoma surgery and medications. Twenty-three percent of eyes (295) with a functioning graft 1 month after surgery experienced an abnormal IOP event at least one month following DSAEK (217 placed on new glaucoma medication without glaucoma surgery, 67 had IOP > 25 mmHg without additional glaucoma medication or surgery and 11 underwent glaucoma surgery). The combination effect of history of glaucoma and elevated IOP more than 1 month after surgery did not have a significant effect on either graft outcome or endothelial cell loss (p=0.28 for graft success; p=0.02 for ECD) (Tables 4 **and** 5).

Two percent of eyes (24) experienced early acutely elevated IOP (> 40 mm Hg) within the first week postoperatively. Of those 24 eyes, 25% (6/24) were classified as failures through 3 years. The 3 year graft success rate for those 24 eyes {75.0% (43.8%, 90.5%)} was significantly lower than in eyes without early acutely elevated IOP (94.1% (92.1%, 95.6%); HR: 3.42 (1.01, 11.53), P= 0.008 (Table 4).

Of those 913 eyes that had functioning grafts at 3 years with analyzable preoperative and 3 year postoperative endothelial images, the mean (SD) ECD of 1630 ± 575 cells/mm^2 in the 9 eyes with early acutely elevated postoperative IOP was not significantly different than the ECD of 1691 ± 625 cells/mm^2 in the 904 eyes without early acutely elevated postoperative IOP (difference in mean ECD was 61 cells/mm^2 (99% CI {−479, 601}; p=0.77) (Table 5).

Discussion

Postoperative dislocation of the donor lenticule is one of the most common complications of DSAEK surgery, with a reported dislocation rate of approximately 1.0%−14.5%.[2,13–16] Donor characteristics that have not been shown to increase the risk for graft dislocation include donor age, death to surgery time, donor lenticule thickness, and post-processing ECD.[14,17] Additionally, recipient characteristics including preoperative corneal thickness, preoperative diagnosis, history of glaucoma or prior glaucoma surgery,[10] and concurrent cataract surgery have not been associated with an increased incidence of graft dislocation.[17] However, other recipient factors such as older age,[17] aphakia,[18,19] presence of an anterior chamber intraocular lens,[18] postoperative hypotony in eyes with prior glaucoma surgery,[15] previous vitrectomy,[20] and concurrent IOL exchange[18] have been associated with graft dislocation. To our knowledge, this is the first report to suggest that tissue from donors with diabetes and greater central donor corneal thickness prior to lamellar dissection are associated with an increased risk of graft dislocation.

Dislocations have been defined in various methods in the literature. Some refer to dislocation as fluid in the interface of an otherwise well-positioned graft which may include complete dislocation into the anterior chamber.[9,10,13] Others define dislocation as those that require another injection of an air bubble to ensure adhesion (vs. only requiring observation) including grafts floating freely.[16] For example, Hood et al[17] defined graft dislocation as the “non-adherence of the donor graft to the recipient requiring surgical intervention with a rebubble technique either in the operating room or in an outpatient procedure room either on

the same day or on a subsequent day". Eighteen percent of their transplanted DSAEK lenticules qualified as dislocated using this definition. Finally, in an American Academy of Ophthalmology Ophthalmic Technology Assessment, Lee et al broadly defined graft dislocation to include fluid in the interface of an otherwise well-positioned graft as well as complete dislocation into the anterior chamber, reporting rates of 0 to 82% with an average rate of 14.5%.[13] We have reported an 8% graft dislocation rate using a more narrow definition, that is, including only eyes that had total detachment of the graft (a complete separation of the DSAEK lenticule from the host stroma),[9,10] or a graft that was attached but decentered and required internal or external manipulation with a surgically induced total detachment plus air injection to reposition. If we include the additional 11% of eyes in the CPTS with incomplete (partial) separation of the DSAEK lenticule from the host stroma (only 27% of which requiring air injection), 19% of the DSAEK procedures in the CPTS had some form of graft malattachment.

The injection of air into the anterior chamber to promote graft adherence is a frequent treatment for graft detachment and dislocation, while repeated air injections into the anterior chamber may increase the risk of endothelial failure as prolonged air exposure has been shown to be toxic to the corneal endothelium.[21–23] In our study, 139 eyes (10.5%) required at least one air injection postoperatively. We were interested in exploring the effect of repeated air injections on graft failure; however, we could not assess this variable in other relatively uncomplicated eyes (without total detachment) with only 2 eyes requiring such multiple interventions. Others[24] have reported that donor endothelial failure is more common after surgical intervention for donor dislocation. We have shown that graft dislocation influences graft success with about an 8-fold increased risk for graft failure. In fact, there appears to be a dose-response effect for degree of detachment on graft success: grafts that were totally detached conferred an 11-fold increased risk of graft failure, grafts that were attached but required repositioning conferred about a 6-fold increased risk, and partially detached grafts had ~3-fold increased risk of graft failure compared to donors that were not totally or partially detached, or decentered requiring additional surgical intervention. Our findings are similar to those of Hood et al[17] who reported that DSAEK lenticule dislocation was associated with a higher rate of repeat transplantation. We also found that graft dislocation, but not grafts that were partially detached with interface fluid, detrimentally impacted ECD in clear grafts 3 years after surgery. This may adversely affect graft survival at longer durations of follow-up. However, the limitation of our findings and others is that it is difficult to distinguish whether the dislocation is a marker of donor corneal endothelial dysfunction or if it is the intervention for the dislocation (i.e., air injection) that increases the risk of endothelial failure. One way to distinguish is with direct measures of endothelial function (e.g. mitochondrial respiration and glycolysis activity[25]), but current eye banking practices employ only the slit lamp examination and specular microscopy and do not have such measures.

Our findings are consistent with prior reports from the CPTS of tissue from donors with diabetes being associated with worse DSAEK outcomes than those from donors without diabetes. Notably, we reported a significant relationship between diabetes in the donor and graft failure after DSAEK, with tissue from donors with diabetes exhibiting a 2.35-fold increased risk for primary donor and early graft failures.[3] Additionally, diabetes in the donor

was associated with lower ECD at 3 years after DSAEK in the CPTS.[4] We are now the first to report an increased risk of dislocation of donor corneas from diabetics, which likely explains the significantly increased risk of primary donor and early graft failures. While the cause(s) of the increased dislocation risk remain(s) unknown, there is evidence to support poor outcomes resulting from detrimental effects of diabetes on the biochemical,[26,27] morphologic[28–31] and functional properties of the corneal endotheium,[28,29,32,33] including abnormalities in the mitochondria[25] and Descemet membrane strength.[34] It is therefore likely that the negative effect of diabetes in the donor on DSAEK graft success that we recently reported in a separate publication[3] is due to impaired adherence and subsequent dislocation of the graft reported in this analysis. Diabetes in our corneal donors was determined from medical records and interviews of associated health care personnel and/or next of kin, if available.[1,8] Future studies are suggested to better characterize diabetes in the donor based on duration, severity[35] and HbA1c testing[36] to identify donors with diabetes whose corneas would be more prone to graft dislocation and failure following endothelial keratoplasty surgery.

While the thickness of the donor lenticule was not associated with the incidence of graft dislocation in this report or in another published study[37], we are the first to report that increasing donor corneal thickness prior to lamellar dissection is associated with graft dislocation. We note the lack of correlation between pre- and post-lamellar donor lenticule thickness, which indicates that the thicker donor corneas did not result in thicker donor lenticules (ie, adjustments were made to the depth of the microkeratome dissection). Although the donor lenticule thickness was not associated with graft dislocation, the increased donor corneal thickness may have served as a marker for reduced endothelial function, which may have predisposed to donor dislocation. With the evaluation of the donor corneal endothelium performed by eye banks being limited to morphologic assessment, without any functional characterization, the cause(s) of the observed association of graft dislocation with donor corneal thickness and a history of donor diabetes remain speculative at this point. In contrast, the association between the third factor found to be associated with an increased risk of graft dislocation, operative complications, may be presumed to be secondary to direct, traumatic corneal endothelial cell loss, leading to the previously described association between operative complications and primary donor and early graft failure.[3]

While acute, significant elevation of IOP in the first postoperative week is uncommon after DSAEK, elevated IOP at least one month after surgery is relatively common. The incidence of elevated IOP (> 25 mm Hg) after DSAEK has been reported to be highest in eyes with medically controlled glaucoma (41.3%), followed by eyes with previous glaucoma surgery (23.8%) and eyes without a history of glaucoma (20.0%).[10] However, the incidence of postoperative complications, including graft dislocation, was not significantly higher in eyes with a history of glaucoma surgery before DSAEK in the largest series published to date.[10] Similarly, the CPTS did not find an increased incidence of graft dislocation in eyes with prior glaucoma surgery, although only 2% of eyes in the CPTS had a history of prior glaucoma surgery, and none of the eyes had prior tube shunt implantation. Even though about one-quarter of study eyes experienced an abnormal postoperative IOP event at least one month following DSAEK, we did not find that a history of glaucoma meaningfully

impacted overall graft success or ECD in this study. Similar to our previous findings of a lack of association between preoperative glaucoma and either graft success[3] or ECD[4] at 3 years, the lack of an association between postoperative glaucoma and either graft success or ECD could be related to the duration of follow-up. It is quite possible that longer follow-up would have demonstrated such an association. However, acutely elevated IOP in the early postoperative period did impact graft success. Overall in the CPTS, 24 of the 1330 study eyes (2%) had an early acute IOP event that was associated with more than a 3fold higher risk of failure. It is well documented that sudden IOP elevation in angle closure glaucoma reduces ECD.[38,39] However, in the surviving clear grafts at 3 years in the CPTS we did not note an impact on ECD. We suspect that acute IOP elevation leads to some endothelial damage, resulting in increased risk for graft failure; the lack of effect on ECD is likely due to the failures being selected out in the ECD analysis, as only eyes with clear grafts at three years were included.

The CPTS, as the largest multicenter study of DSAEK to date, continues to provide new information regarding factors associated with graft success and endothelial cell loss. Similar to our other papers describing the impact of preoperative, donor, recipient and operative factors on graft success[3] and ECD[4], this study also affords us the opportunity to examine the effect of these same factors on graft attachment, graft success and endothelial cell loss. We found that corneas from donors with diabetes, those that were thicker prior to lamellar dissection, and intraoperative complications convey a higher risk of graft dislocation, which, along with early postoperative acute IOP events, resulted in an increased incidence of graft failure. Further studies on the use of donors with diabetes and establishing more specific criteria for maximum donor thickness prior to dissection to minimize graft dislocations are warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Donor and donor cornea factors including diabetes, increased central corneal thickness, and intraoperative complications were associated with an increased risk of graft dislocation following DSAEK.
- Early acutely elevated postoperative IOP and graft dislocation significantly increased the risk for graft failure following DSAEK.

Table 1.

Effect of Donor, Recipient, and Operative Factors on Graft Dislocation

Risk factors	N=1330	Graft Dislocation n (%)	Base Model[a] OR (99% CI)	P-value	Multivariable Model[b] OR (99% CI)	P-value
Factors included in the final multivariable model						
Preservation Time Subgroup				0.005		0.05
0-7 days	675	39 (6)	1.00		1.00	
8-14 days	655	65 (10)	1.81 (1.05, 3.14)		1.55 (0.87, 2.78)	
Recipient Diagnosis				0.58		0.62
PACE (without FECD)	75	5(7)	0.76 (0.21, 2.75)		0.77 (0.20, 2.94)	
FECD	1255	99 (8)	1.00		1.00	
Donor history of diabetes				<0.001		<0.001
No	973	57 (6)	1.00		1.00	
Yes	357	47 (13)	2.35 (1.35, 4.08)		2.29 (1.30, 4.02)	
Operative Complication[c]				<0.001		0.001
No	1256	89 (7)	1.00		1.00	
Yes	74	15 (20)	3.36(1.45, 7.78)		2.97 (1.24, 7.11)	
Pre-Lamellar Dissection Donor Corneal Thickness (μ)[d]				0.001		0.004
<550	658	39 (6)	1.15 (1.03, 1.28) per 25μ		1.13 (1.01, 1.27)	
>=550	629	61 (10)	increase		per 25μ increase	
Factors not included in the final multivariable model						
Post-Lamellar Dissection Donor Lenticule Thickness (μ)[e]				0.01		0.19
< 100	216	14(6)	1.21 (0.99, 1.49)		1.12 (0.89, 1.40)	
100 - <125	403	30 (7)	per 25μ increase		per 25μ increase	

Risk factors	N=1330	Graft Dislocation n (%)	Base Model[a] OR (99% CI)	P-value	Multivariable Model[b] OR (99% CI)	P-value
125 - <150	339	22 (6)				
≥150	305	31 (10)				
Any Eye Bank Observations				0.15		0.22
No	795	59 (7)	1.00		1.00	
Yes	192	23 (12)	1.72 (0.82, 3.61)		1.56 (0.73, 3.34)	
Surgeon prepared tissue	343	22 (6)	0.94 (0.36, 2.47)		0.78 (0.25, 2.48)	

PACE = Pseudophakic/aphakic corneal edema; FECD = Fuchs endothelial corneal dystrophy; DSAEK = Descemet stripping automated endothelial keratoplasty; OR= Odds ratio

a. Base models adjusted for preservation time, recipient diagnosis, and random surgeon effect

b. Multivariable model adjusted for preservation time, recipient diagnosis, and random surgeon effect. Donor history of diabetes, operative complications, and pre-lamellar dissection donor corneal thickness were retained in the final model via backward selection.

c. Operative complications include vitreous loss (unplanned), posterior capsule rupture, suprachoroidal hemorrhage, significant hyphema, inverted donor tissue, difficult unfolding and positioning without use of positioning hook, difficult unfolding and positioning with use of positioning hook, difficult air fill and retention in positioning, reinsertion of donor after extrusion, and other write-ins

d. Pre-lamellar dissection donor corneal thickness is missing for 43 eyes. Eye bank determined by optical coherence tomography (586 eyes), ultrasonic pachymetry (337 eyes), specular microscopy (57 eyes), optical (7 eyes). Surgeon determined by ultrasonic pachymetry (299 eyes), non-ultrasonic method (1 eye)

e. Post-lamellar dissection donor lenticule thickness is missing for 67 eyes. Eye bank determined by optical coherence tomography (703 eyes), ultrasonic pachymetry (216 eyes), specular microscopy (58 eyes), optical (10 eyes). Surgeon determined by ultrasonic pachymetry (276 eyes)

Table 2a.

Effect of Graft Dislocation (2 groups) on 3 Year Graft Success

	N=1330 n (%)	Failures		3-year Cumulative Graft Success (99% CI)	3-year Hazard Ratio (99% CI)	P value[a]
		Primary donor/Early n (%)	Late n (%)			
Graft dislocation						<0.001
Yes (defined as total detachment or graft repositioning)	104 (8)	30 (28.9)	5 (4.8)	65.8% (52.1%, 76.4%)	7.9 (4.1, 15.3)	
No	1226 (92)	15 (1.2)	29 (2.4)	96.1% (94.3%, 97.4%)	1.0	

[a.] Model adjusted for PT, recipient diagnosis, donor history of diabetes, operative complications, and surgeon effects

Table 2b.

Effect of Graft Dislocation (4 groups) on 3 Year Graft Success

			Failures				
		N=1330 n (%)	Primary donor/Early n (%)	Late n (%)	3-year Cumulative Graft Success (99% CI)	3-year Hazard Ratio (99% CI)	P value[a]
Graft dislocation	**Graft attachment status**						
Yes	At least 1 occurrence of Total detachment	86 (6)	24 (27.9)	5 (5.8)	65.6% (50.3%, 77.1%)	11.0 (5.3, 22.9)	<0.001
	At least 1 occurrence of Graft repositioning (with no TD)	18 (1)	6 (33.3)	0 (0.0)	66.7% (31.1%, 86.9%)	6.2 (1.6, 23.5)	
No	At least 1 occurrence of Interface fluid (with no TD or GR)	152 (11)	9 (5.9)	3 (2.0)	91.2% (81.6%, 95.9%)	3.2 (1.3, 7.9)	
	None	1074 (81)	6 (0.6)	26 (2.4)	96.8% (95.0%, 98.0%)	1.0	

TD = total detachment; GR = graft repositioning

[a]Model adjusted for PT, recipient diagnosis, donor history of diabetes, operative complications, and surgeon effects

Table 3a.

Effect of Graft Dislocation (2 groups) on 3 Year ECD - among eyes with successful graft

	N=913	Mean (SD) (cells/mm^2)	P value
Graft dislocation			<0.001
Yes (defined as total detachment or graft repositioning)	45 (5%)	1127 (546)	
No	868 (95%)	1719 (614)	

ECD = endothelial cell density; CIARC = Cornea Image Analysis Reading Center

[a.] Of 1330 study eyes, 913 had functioning grafts at 3 years with acceptable endothelial images

[b.] Model adjusted for CIARC-determined preoperative ECD, preservation time, diagnosis, donor history of diabetes, operative complications, and random surgeon and recipient effects.

Table 3b.

Effect of Graft Dislocation (3 groups) on 3 Year ECD - among eyes with successful graft

		N=913	Mean (SD) (cells/mm^2)	P value
Graft dislocation	**Graft attachment status**			<0.001
Yes	At least 1 occurrence of Graft dislocation (defined as total detachment or graft repositioning)	45 (5%)	1127 (546)	
No	At least 1 occurrence of Interface fluid (with no GD)	103 (11%)	1764 (599)	
	None	765 (84%)	1713 (617)	

ECD = endothelial cell density; CIARC = Cornea Image Analysis Reading Center

a. Of 1330 study eyes, 913 had functioning grafts at 3 years with acceptable endothelial images

b. Model adjusted for CIARC-determined preoperative ECD, preservation time, diagnosis, donor history of diabetes, operative complications, and random surgeon and recipient effects.

Table 4.

Effect of IOP on 3 Year Graft Success

	N	3-yr Graft Success (99% CI)	Hazard Ratio (99% CI)	P value
History of glaucoma/ Postoperative Abnormal IOP at least 1 month following DSAEK	**N=1277**			**0.28**
No/No	927	97.9% (96.1%, 98.9%)	1.00	
Yes/No	55	98.1% (78.2%, 99.9%)	0.77 (0.05, 11.66)	
No/Yes	239	95.8% (90.2%, 98.2%)	1.81 (0.60, 5.47)	
Yes/Yes	56	91.8% (73.3%, 97.7%)	2.59 (0.50, 13.41)	
Early Acute IOP Event	**N=1330**			**0.008**
No	1306	94.1% (92.1%, 95.6%)	1.00	
Yes	24	75.0% (43.8%, 90.5%)	3.42 (1.01, 11.53)	

IOP = intraocular pressure; DSAEK = Descemet stripping automated endothelial keratoplasty

a. Base model adjusted for PT, recipient diagnosis, donor history of diabetes, operative complications, and surgeon effects

b. History of glaucoma defined as had glaucoma surgery, and/or on glaucoma medications

c. Postoperative abnormal IOP defined as had new glaucoma surgery, or put on new glaucoma meds without new glaucoma surgery, or had IOP > 25 m Hg without any new glaucoma surgery or medications. (Eyes failed or censored within 1 month following DSAEK were eliminated). New glaucoma surgery performed included: tube shunt only (5 eyes), trabeculectomy only (2 eyes), laser trabeculoplasty only (3 eyes), and all 3 procedures (1 eye) in 11 participants.

d. Early acute IOP defined as any occurrence of IOP>40 or paracentesis for pupillary block or angle closure in the first week post-operatively

Table 5.

Effect of IOP on 3 Year ECD - among eyes with successful graft

	N=913	Mean (SD) (cells/mm^2)	P-value
History of glaucoma/ Postoperative abnormal IOP at least 1 month following DSAEK			**0.02**
No/No	687	1689 (615)	
Yes/No	41	1589 (676)	
No/Yes	155	1733 (638)	
Yes/Yes	30	1651 (692)	
Early acute IOP event			**0.48**
No	904	1691 (625)	
Yes	9	1630 (575)	

IOP = intraocular pressure; ECD = endothelial cell density; DSAEK = Descemet stripping automated endothelial keratoplasty

[a] Of 1330 study eyes, 913 had functioning grafts at 3 years with acceptable endothelial images

[b] Model adjusted for CIARC determined preoperative ECD, PT, recipient diagnosis, donor history of diabetes, operative complications, and random surgeon and recipient effects

[c] History of glaucoma defined as had glaucoma surgery, and/or on glaucoma medications

[d] Postoperative abnormal IOP defined as had new glaucoma surgery, or put on new glaucoma meds without new glaucoma surgery, or had IOP >25 without any new glaucoma surgery or medications. (Eyes failed or censored within 1 month following DSAEK were eliminated). New glaucoma surgery performed included: laser trabeculoplasty (3 eyes) in 3 participants.

[e] Early acute IOP defined as any occurrence of IOP>40 or paracentesis for pupillary block or angle closure in the first week post-operatively