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Prelamellar Dissection Donor Corneal Thickness Is Associated With Descemet Stripping Automated Endothelial Keratoplasty Operative Complications in the Cornea Preservation Time Study

Kevin W. Ross, MS, MPH^{*}, Christopher G. Stoeger, MBA, CEBT[†], George O. D. Rosenwasser, MD, CEBT[‡], Robert C. O'Brien, PhD[§], Loretta B. Szczotka-Flynn, OD, PhD[¶], Allison R. Ayala, MS[§], Maureen G. Maguire, PhD[¶], Beth Ann Benetz, MA[¶], Patricia Dahl, CEBT^{**}, Donna C. Drury, MBA, CEBT^{††}, Steven P. Dunn, MD^{‡‡}, Sameera M. Farazdaghi, MPH^{§§}, Caroline K. Hoover, MBA, CEBT^{¶¶}, Marian S. Macsai, MD^{¶¶}, Shahzad I. Mian, MD^{***}, Michael L. Nordlund, MD, PhD^{†††}, Jeffrey G. Penta, MBA, CEBT^{‡‡‡}, Mark C. Soper, CEBT^{§§§}, Mark A. Terry, MD^{¶¶¶}, David D. Verdier, MD^{¶¶¶}, Doyce V. Williams, CEBT, MA^{****}, Jonathan H. Lass, MD[¶] Cornea Preservation Time Study Group

^{*}Eversight (formerly Midwest Eye-Banks), Ann Arbor, MI

[†]Lions VisionGift, Portland, OR

[‡]Central Pennsylvania Eye Institute, Hershey, PA

[§]Jaeb Center for Health Research, Tampa, FL. Dr. O'Brien is now with the University of Mississippi Medical Center, Jackson, MS

[¶]Case Western Reserve University, Department of Ophthalmology and Visual Sciences and University Hospitals Eye Institute, Cleveland, OH

^{¶¶}Center for Preventive Ophthalmology and Biostatistics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA

^{**}Eye-Bank for Sight Restoration, New York, NY

Correspondence: Jonathan H. Lass, MD, University Hospitals Cleveland Medical Center, 11100 Euclid Avenue, Cleveland, OH 44106 (jonathan.lass@uhhospitals.org).

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††Transplant Services, University of Texas, Southwestern, Dallas, TX

‡‡Michigan Cornea Consultants, P.C., Southfield, MI

§§CorneaGen (formerly Tissue Banks International, and KeraLink International), Baltimore, MD

¶¶CorneaGen (formerly SightLife), Seattle, WA

|||Northshore University Health System, Glenview, IL

***Kellogg Eye Center, University of Michigan, Ann Arbor, MI

†††Cincinnati Eye Institute, Cincinnati, OH

‡‡‡San Diego Eye Bank, San Diego, CA

§§§VisionFirst (formerly Indiana Lions Eye Bank), Indianapolis, IN

¶¶¶Devers Eye Institute, Portland, OR

||||Verdier Eye Center, Grand Rapids, MI

****Alabama Eye Bank, Birmingham, AL.

Abstract

Purpose: To identify donor and recipient factors, including eye bank tissue observations, predictive of operative complications in the Cornea Preservation Time Study.

Methods: One thousand three hundred thirty study eyes undergoing Descemet stripping automated endothelial keratoplasty for Fuchs dystrophy or pseudophakic/aphakic corneal edema were randomized to receive a donor cornea with preservation time (PT) of 0 to 7 days (N = 675) or 8 to 14 days (N = 655). Donor factors included demographics, prelamellar corneal and postlamellar lenticule dissection thickness, central endothelial cell density, and tissue processing time. Recipient factors included demographics, intraocular pressure, and glaucoma medications or surgery (trabeculectomy, laser trabeculoplasty). Eye bank observations included donor tissue folds, pleomorphism/polymegethism, and endothelial cell abnormalities. Possible tissue-related operative complications were recorded including difficult donor lenticule unfolding and positioning. Multivariable logistic regression with backward selection was used to identify statistically significant ($P < 0.01$) associations between factors and operative complications.

Results: The only factor predictive of operative complications [58 (4.4%) of 1330 surgeries] was prelamellar dissection donor corneal thickness ($P = 0.002$). For every 50 μm of donor corneal thickness prior to lamellar dissection, operative complication odds increased by 40% (odds ratio [99% confidence interval (CI)]: 1.40 [1.06–1.83]) adjusting for PT and whether the epithelium was on or off. The estimated mean prelamellar dissection donor corneal thickness for PT 0 to 7 days was 537 μm (99% CI: 516 μm –558 μm) compared with 567 μm (99% CI: 546 μm –588 μm) for PT 8 to 14 days ($P < 0.001$).

Conclusions: Thicker donor tissue (prelamellar dissection) is associated with operative complications and should be considered in tissue selection for Descemet stripping automated endothelial keratoplasty lenticule preparation.

Keywords

corneal endothelium; eye banking; Descemet stripping automated endothelial keratoplasty

Since the Eye Bank Association of America (EBAA) began certifying eye bank technicians, the technician's role within the eye bank has expanded from only acquisition of donor history and donor tissue recovery to include obtaining donor blood for serologic testing, screening for transmissible diseases from the donor, donor tissue evaluation by slit-lamp biomicroscopy,¹ donor tissue processing with excision of the donor cornea with scleral rim and placement in a hypothermic storage solution, and finally to donor tissue distribution.^{2,3} Subsequently, specular microscopy was added to assess donor endothelial cell density (ECD) and morphology.⁴ With the tremendous growth of Descemet stripping automated endothelial keratoplasty (DSAEK) over the past 10 years,⁵ more advanced processing has been added to the lamellar dissection of the donor cornea, necessitating the measurement of the corneal thickness and the assessment of the donor tissue both before and after lamellar dissection using ultrasonic pachymetry and, more recently, optical coherence tomography.^{3,6} More recently, the skill of Descemet/endothelium stripping and assessment of stripped donor tissue for Descemet membrane endothelial keratoplasty (DMEK) has been added to the trained eye bank technician skill set.⁷ Finally, the preparation of the lenticule for DSAEK and DMEK now also involves stamping the tissue for orientation and preloading into a delivery system.⁸⁻¹¹ Because the responsibility for donor evaluation and processing has expanded for the eye bank technician, standards became necessary for the donor and the donor's corneal tissue for suitability for penetrating keratoplasty (PKP), DSAEK, and DMEK.² Using these minimum criteria, jointly agreed to by the medical director and eye bank, the results of these procedures have been well described for PKP, DSAEK, and DMEK.¹²

The Cornea Preservation Time Study (CPTS) was a randomized multicenter clinical trial assessing the association of preservation time (PT) with 3-year DSAEK graft success and endothelial cell loss.¹³ The CPTS¹⁴ and other keratoplasty studies¹² have shown great success in over 90% of cases for primary endothelial failure conditions. This success has come while overcoming significant donor tissue preparation including more recently the practice of cutting (DSAEK) or peeling (DMEK) the endothelium with the Descemet membrane away from the stromal supporting structure, and then maintaining the functional health of delicate endothelial cells during planned uncomplicated surgery. However, the likelihood of graft success was significantly lower (79.5% vs. 94.6%) if the surgeon reported the occurrence of a defined group of complications at the time of surgery (see Supplemental Table 1, Supplemental Digital Content 1, <http://links.lww.com/ICO/A831>).¹⁵

The Cornea Donor Study has previously examined the association of donor¹⁶ and recipient factors,¹⁷ as well as observations by the eye bank during donor evaluation and preparation, on graft failure after PKP, but not for operative complications. In this study, we examine donor and recipient factors, including eye bank observations of donor tissue, and evaluate their association with operative complications for DSAEK, the most common procedure performed for endothelial dysfunction conditions in the United States, replacing PKP.⁵ The

significance of such an association is clear—factors known or knowable by the eye bank or surgeon can point the way to improved selection and preparation of donor tissues for this procedure.

METHODS

Details of the CPTS protocol have been previously reported.¹³ The protocol was approved by institutional review boards governing each investigational site, and individual participants gave written informed consent to participate in the study. 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>.

Participants were enrolled at 40 clinical sites, and donor corneas were provided by 23 eye banks across the United States. Eyes undergoing DSAEK were randomly assigned to receive a donor cornea with PT of 0 to 7 days or 8 to 14 days; for participants with both eyes eligible, the first eye was assigned randomly to a PT group and the second eye was assigned to the other PT group. The 1330 eyes completing surgery with a CPTS-assigned cornea were considered the “study eyes.” Assigned corneas were from donors 12 to 75 years old (median age 61 years) with an eye bank-measured central ECD at the time of screening of at least 2300 cells/mm². Surgeons elected to either receive the lenticule after lamellar dissection by the eye bank or have the tissue shipped for the dissection by the surgeon at the time of the DSAEK.

Supplemental Table 2 (see Supplemental Digital Content 2, <http://links.lww.com/ICO/A832>) shows the list of all eye bank observations prospectively obtained at the time of screening and prelamellar and postlamellar dissection of the donor cornea. Candidate factors were selected from the list of all eye bank observations reflecting possible endothelial health that could be associated with complications at the time of surgery. Candidate donor and recipient factors were selected in accordance with the other CPTS articles on predictive factors.^{14,40,41} Methods for screening and preoperative ECD determination and determination of corneal thickness (Table 1 footnotes [§] and ^{**}) have been previously described.^{13,18} The prelamellar dissection donor corneal thickness was determined either by an eye bank technician or the surgeon after a decision was made to make the measurement with the epithelium intact or after it had been removed mechanically. Surgeons reported predetermined categories of operative complications, primarily difficult donor unfolding and positioning. (see Supplemental Table 1, Supplemental Digital Content 1, <http://links.lww.com/ICO/A831>).¹³ Complications that did not fall into these predetermined categories were recorded in a write-in field. From among all reported operative complications, the Writing Committee (composed of surgeons and eye bankers) selected categories for analysis that were judged to be possibly tissue-related either by concern with donor tissue appearance or difficulty encountered with tissue insertion and/or positioning.

Statistical Analysis

Associations between donor and recipient factors and relevant eye bank observations with operative complications were evaluated in multivariable logistic models. All candidate factors that were considered are listed in Table 1.

The base model for evaluating candidate predictive factors included PT. Each factor was evaluated first by adding the factor to the base model individually, with the exception of 1) the status of the epithelium at the time of prelamellar dissection (on or off) and 2) prelamellar dissection donor corneal thickness measurement; these 2 variables were only considered together for the model. To informally control the probability of false-positive findings due to multiple comparisons, candidate factors were selected for inclusion in a final multivariable logistic regression model using a backward model selection procedure with $P < 0.05$ as the criterion for inclusion in the full model and $P < 0.01$ as the criterion for remaining in the model. Random effects for surgeon and eye bank were also explored; because only one of the 240 bilateral cases experienced operative complications in both eyes, a random recipient effect was not considered. For the analyses with operative complications as the outcome, all donor corneas that were processed for DSAEK and grafted were included in the analyses. For the analysis with prelamellar dissection donor corneal thickness as the outcome, only those donor corneas with known prelamellar dissection donor corneal thickness were included in the analysis. Only eyes with complete data were analyzed for the primary analysis. A sensitivity analysis with missing values treated as a separate category for discrete factors and associated with a missing indicator for continuous factors was also conducted.

The effect of categorical factors on operative complications was reported as the estimate odds ratio (OR) from the reference category with 99% confidence interval [OR (99% CI)]. For ease of interpretation of continuous factors, the estimated OR and the corresponding 99% CI [OR (99% CI)] associated with a clinically relevant difference in the continuous factor were reported.

As an additional related analysis, we looked at the association between PT and prelamellar dissection donor corneal thickness in a linear mixed model adjusting for epithelial status on/off, folds in Descemet membrane with and without snail tracks (linear areas of endothelial dropout), and stromal folds/stress lines as fixed effects and eye bank as the random effect with prelamellar dissection donor corneal thickness as the continuous outcome. No variable selection/elimination was conducted for this analysis. Only cases where prelamellar dissection donor corneal thickness was available were included in this analysis.

All reported P values are 2-sided. The data were analyzed using SAS version 9.4 (SAS Institute, Cary, NC) and R version 3.4.17.

RESULTS

Tissue-related operative complications occurred in 58 (4.4%) of 1330 surgeries (see Supplemental Table 1, Supplemental Digital Content 1, <http://links.lww.com/ICO/A831>). The ORs for each candidate factor are shown in Table 1. Only prelamellar dissection donor

corneal thickness was statistically significant ($P=0.002$) and thus was included in the final logistic regression model along with epithelial status and PT, both of which were retained in the model, regardless of statistical significance. Microkeratome head thickness was entered into the model (because it may relate to prelamellar dissection donor corneal thickness, epithelial status, and PT), but it was not statistically significant ($P=0.71$) and was removed. Random effects for surgeon and eye bank did not significantly affect any model and were dropped. In the final model, for every 50 μm thicker a donor cornea was before dissection, the odds of an operative complication increased by 40% [OR (99% CI): 1.40 (1.06–1.83)].

The estimated probability from the final logistic regression model of an operative complication for prelamellar dissection donor corneal thickness $<600\ \mu\text{m}$ was 0.03 (99% CI: 0.02–0.05) [ie, 3% chance (2% chance to 5% chance) vs. 0.09 (99% CI: 0.05–0.15)] [ie, 9% chance (5% chance to 15% chance)] for prelamellar dissection donor corneal thickness $\geq 600\ \mu\text{m}$, where 600 μm represents the 80th percentile of prelamellar dissection donor corneal thickness in the CPTS.

The adjusted mean estimates for prelamellar dissection donor corneal thickness by PT and other factors are shown in Table 2. In the linear mixed model containing epithelial status on/off, folds in the Descemet membrane with and without snail tracks, and stromal folds/stress lines, the estimated mean thickness for PT 0 to 7 days was 537 μm (99% CI: 516 to 558 μm) versus 567 μm (99% CI: 546 to 588 μm) for PT 8 to 14 days ($P<0.001$).

DISCUSSION

As the DSAEK technique evolved and eye banks assumed a greater role in donor tissue preparation, the greatest attention in the literature was on postlamellar dissection lenticule thickness and its relation to visual results.^{19–42} Eye bank technicians and surgeons showed refined skill in preparing DSAEK lenticules to a preferred lenticule thickness across a wide range of prelamellar dissection donor tissue thicknesses. Published lenticule thickness initially was as high as 200 to 250 μm ²³ and now as thin at ultrathin and nanothin down to 26 to 50 μm .⁴² None of these studies, however, examined the association of the prelamellar donor tissue thickness with complications at the time of surgery or in the immediate postoperative period. Hood et al⁴³ examined a number of donor tissue characteristics of 355 eyes undergoing DSAEK including prelamellar dissection donor tissue thickness with a mean \pm SD of 557.8 \pm 46.9 μm and found no relation to graft dislocation; they did not report the relation of this donor characteristic to operative complications.

The CPTS, in a large prospective, multicenter trial of 1330 eyes, has now shown that thicker prelamellar dissection donor tissue is not only associated with a higher graft dislocation rate⁴⁴ but also associated with a higher operative complication rate. The risk was 3 times higher for tissues greater than 600 μm compared with tissues less than or equal to 600 μm . Notably, there was no association of operative complications or graft dislocation⁴⁴ with the postlamellar dissection lenticule thickness in the CPTS. The CPTS in turn has shown that the occurrence of operative complications leads to a higher graft failure rate¹⁵ and higher endothelial cell loss⁴⁵ after DSAEK. Thus, the finding that prelamellar dissection donor corneal thickness is a factor in operative complications suggests that further

assessment of the possible impact of the use of thicker donor tissue to achieve the requested lenticule thicknesses under 150 μm or thinner with various lamellar dissection techniques is warranted. Many eye banks do not consider donor corneal thickness until planning the microkeratome head selection immediately before processing using optical coherence tomography or even during processing with ultrasonic pachymetry. Logistical challenges could be substantial if tissue placed for DSAEK was suddenly determined to be unsuitable for the intended use at the time of processing. This fact could prompt changes so that screening donor corneal thickness happens before offering tissue for surgery.

Why should thicker prelamellar dissection donors result in higher operative complications? Could the thicker tissue serve as a marker for reduced endothelial function before dissection and thus alter tissue characteristics during insertion and positioning? Or could the additional measure of increasing microkeratome head thickness for tissue preparation with these thicker tissues to achieve acceptable lenticule thickness result in endothelial damage? Or both? The eye banks were able to achieve the requested lenticule thickness by the surgeon no matter what the prelamellar dissection thickness was, as evidenced by the weak correlation between prelamellar and postlamellar thickness (Spearman correlation 0.20).⁴⁴ Whatever the cause of the greater thickness in these donor tissues is, the end result is a higher operative complication rate and a higher graft dislocation rate.⁴⁴

The CPTS has already reported that longer PT (8–14 days) failed to meet noninferiority criteria relative to shorter PT (1–7 days) regarding graft success¹⁴; however, this result was driven by the donor tissue preserved 12 to 14 days with no difference in graft success for tissue preserved up to 11 days. This report now suggests that the lower graft success rate in the longer PT group may have been driven at least in part by greater prelamellar dissection thickness associated with longer PT, leading to greater risk of operative complications. Thus, eye bankers, medical directors, and surgeons, encouraged by the CPTS findings for the use of longer preserved donor corneas, should also keep in mind our findings regarding thicker prelamellar dissection donor corneas and consider establishing or adjusting criteria for maximum predissection donor corneal thickness.

Notably, all other donor, recipient, or eye bank observation factors were not associated with operative complications during DSAEK. An absence of such associations supports the continued use of broad donor selection criteria as determined by our eye bank medical directors and surgeons, the execution of the high standards for donor/tissue evaluation and tissue processing by our eye banks certified according to the Medical Standards of the EBAA,² and speaks to the effective collaboration between our CPTS eye banks and corneal surgeons in securing, preserving, and preparing corneal donor tissue for DSAEK.

The strengths of this study were 3-fold. The CPTS prospectively collected a predetermined number of potential donor and recipient factors and eye bank observations at time of donor evaluation and processing and their association with a predetermined number of operative complications. Our findings are broadly representative because they were obtained from 23 EBAA-accredited eye banks and 70 experienced, masked DSAEK surgeons. Finally, the results were derived from a large sample size. Limitations included missing data on prelamellar dissection thickness/epithelial status and postlamellar dissection thickness for

43 (3%) and 67 (5%) donor corneas, respectively, all of which were surgeon-dissected. However, the results did not change when missing data were treated as a separate category for discrete factors, and a missing indicator was created for continuous factors. Furthermore, we were not able to account for possible differences in surgeon-dissected versus eye bank-dissected donor tissues because 66% of surgeon-dissected tissues had the epithelium removed and 72% of eye bank-dissected tissues did not, essentially confounding the 2 variables. The measurement of prelamellar dissection thickness was also not standardized among the eye banks (measurement instrument, reproducibility); however, the CPTS study organizers did not want to disrupt usual operations for each eye bank, and thus, our findings reflect the process for most of the eye banks in the United States. Finally, although the sample size was large, the low number of operative complications (N = 58) limited the statistical power to detect factors associated with greater risk, particularly factors with relatively low numbers within categories, such as donor cause of death.

In conclusion, prelamellar dissection donor corneal thickness arises as a factor to be considered and managed for DSAEK. Continuing collaborative work is needed for surgeons, medical directors, and eye banks to assess and sustain the health of the donor corneal endothelium because they relate to both prelamellar and postlamellar dissection thickness, operative complications, graft attachment, and ultimately successful graft outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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TABLE 1. Association of Factors With Tissue-Related Operative Complications in the CPTS (N = 1330 Eyes)

Donor factors	Logistic Regression Model*		
	N = 1330	OR (99% CI)	P Value
Preservation time (d)			
0–7	675	1 [ref]	0.88
8–14	655	0.96 (0.48–1.92)	
Epithelial status ^{†,‡,§}			0.92
Off	500	0.97 (0.46–2.04)	
On	787	1 [ref]	
Prelamellar donor corneal dissection thickness (µm) ^{†,‡,§}		1.40 (1.06–1.83) per 50 µm	0.002
Screening ECD (cells/mm ²) [¶]		0.74 (0.39–1.38) per 500 cells/mm ²	0.21
Preoperative ECD (cells/mm ²) [¶]		1.25 (0.82–1.90) per 500 cells/mm ²	0.17
Donor age (yr)		1.02 (0.78–1.35) per decade	0.83
Donor sex			0.74
Female	486	0.91 (0.44–1.88)	
Male	844	1 [ref]	
Donor race/ethnicity			0.64
Black/AA	77	1.56 (0.45–5.44)	
Other	53	0.88 (0.13–5.85)	
White	1200	1 [ref]	
Diabetic donor			0.18
Yes	357	1.46 (0.70–3.03)	
No	973	1 [ref]	
Donor cause of death			0.68
Cancer	250	0.59 (0.12–2.88)	
Cardiovascular disease	523	0.85 (0.20–3.55)	
Cerebrovascular accident	165	0.70 (0.13–3.66)	
Pulmonary/respiratory	155	0.74 (0.14–3.91)	
Accident	170	0.38 (0.06–2.43)	

Logistic Regression Model*			
	N = 1330	OR (99% CI)	P Value
Other	67	1 [ref]	
Dissection to surgery time (h)/#		1.02 (0.99–1.04)	0.10
Postlamellar lenticule thickness (µm)**		1.06 (0.64–1.73) per 50 µm	0.77
Death to refrigeration time (h)			0.52
<2	315	1.58 (0.35–7.04)	
2 to <3	346	1.55 (0.35–6.81)	
3 to <4	257	2.44 (0.56–10.55)	
4	261	1.61 (0.35–7.44)	
Not refrigerated	151	1 [ref]	
Refrigeration to preservation time (h)			0.41
<5	300	1.14 (0.24–5.46)	
5 to <8	346	2.13 (0.50–9.00)	
8 to <12	302	2.06 (0.48–8.88)	
12	231	1.66 (0.35–7.81)	
Not refrigerated	151	1 [ref]	
Death to preservation time (h)		1.03 (0.96–1.11)	0.29
Storage solution			0.41
Life 4°C	51	0.43 (0.03–5.91)	
Optisol-GS	1279	1 [ref]	
Change in solution \ddagger			0.19
Original	360	1.84 (0.62–5.42)	
Fresh	627	2.00 (0.74–5.37)	
Surgeon-dissected tissue	343	1 [ref]	
Recipient factors			
Recipient diagnosis			0.87
PACE (without FECD)	75	0.91 (0.19–4.31)	
FECD	1255	1 [ref]	
Recipient age (yrs)		1.14 (0.77–1.68) per decade	0.40
Recipient sex			0.11
Female	801	0.65 (0.32–1.29)	

		Logistic Regression Model*		
		N = 1330	OR (99% CI)	P Value
Male		529	1 [ref]	
Recipient race/ethnicity				0.72
Black/AA		47	1.54 (0.32–7.50)	
Other		76	1.26 (0.32–4.98)	
White		1207	1 [ref]	
Glaucoma medications at enrollment				0.72
Yes		99	1.18 (0.34–4.08)	
No		1231	1 [ref]	
Previous glaucoma surgery				0.57
Yes		31	1.53 (0.23–10.38)	
No		1299	1 [ref]	
Diabetic recipient				0.59
Yes		242	0.82 (0.32–2.13)	
No		1088	1 [ref]	
Current cigarette smoker				0.97
Yes		90	1.02 (0.26–4.00)	
No		1240	1 [ref]	
Baseline IOP (mm Hg)				0.66
Eye bank observations			1.02 (0.91–1.14) per 1 mm Hg	
Folds in Descemet membrane/Snail tracks				0.26
None/no		136	1 [ref]	
None/yes		150	1.21 (0.17–8.88)	
Mild/no		266	2.29 (0.43–12.20)	
Mild/yes		604	2.16 (0.44–10.51)	
Moderate/no		35	5.76 (0.75–44.05)	
Moderate/yes		139	2.00 (0.32–12.71)	
Stromal folds or stress lines				0.63
Yes		33	1.44 (0.21–9.74)	
No		1297	1 [ref]	
Pleomorphism/polymegethism				0.15

	N = 1330	Logistic Regression Model [*]	
		OR (99% CI)	P Value
Yes	338	0.60 (0.24–1.49)	
No	992	1 [ref]	
Cell damage/trauma or dystrophy			0.33
Yes	133	1.47 (0.53–4.03)	
No	1197	1 [ref]	
Air bubbles			0.88
Yes	75	0.91 (0.19–4.33)	
No	1255	1 [ref]	

^{*}Model-based ORs adjusted for the PT group.

[†]Epithelial status denotes whether the epithelium was mechanically removed (“Off”) prior to thickness measurement and lamellar dissection, or was not removed (“On”). For those corneas where the epithelium was mechanically removed and off, thickness was measured after the epithelium was removed and before lamellar dissection.

[‡]Prelamellar donor corneal dissection thickness and epithelial status are entered in the model together.

[§]There are 43 eyes for which epithelial status on/off and prelamellar donor corneal dissection thickness are missing. Eye bank determined using optical coherence tomography (586 eyes), ultrasonic pachymetry (337 eyes), specular microscopy (57 eyes), and optical (7 eyes). Surgeon determined using ultrasonic pachymetry (299 eyes) and other nonultrasonic methods (1 eye).

^{||}Determined by the eye bank at time of donor cornea screening.

[¶]Determined by CIARC postlamellar dissection or before shipping to the surgeon if the surgeon was dissecting the tissue; there are 44 eyes for which preoperative ECD is missing.

[#]There are 18 eyes for which dissection to surgery hours is missing.

^{**}There are 67 eyes for which postlamellar lenticule thickness is missing. Eye bank determined using optical coherence tomography (703 eyes), ultrasonic pachymetry (216 eyes), specular microscopy (58 eyes), and optical (10 eyes). Surgeon determined using ultrasonic pachymetry (276 eyes).

^{††}Corneas dissected by the eye bank were either kept in the original solution the entire time until surgery or they were placed in fresh solution before surgery. CIARC, cornea image analysis reading center; FECD, Fuchs endothelial corneal dystrophy; IOP, intraocular pressure; PACE, pseudophakic/aphakic corneal edema.

TABLE 2.

Mean Prelamellar Dissection Donor Corneal Thickness by Selected Factors in the CPTS (N = 1287 Eyes With Known Thickness)

	N = 1287	Multivariable Model*	
		Mean Thickness (99% CI) (μm)	P Value
Epithelial status [†]			0.56
Off	500	554 (532–576)	
On	787	550 (529–571)	
Preservation time, d			<0.001
0–7	675	537 (516–558)	
8–14	655	567 (546–588)	
Folds in Descemet membrane/snail tracks			<0.001
None/no	136	526 (503–549)	
None/yes	150	541 (518–563)	
Mild/no	266	549 (527–571)	
Mild/yes	604	553 (532–574)	
Moderate/no	35	583 (552–615)	
Moderate/yes	139	580 (556–603)	
Stromal folds or stress lines			0.02
Yes	33	576 (544–608)	
No	1297	551 (531–572)	

* No variable selection/elimination was conducted for this analysis.

[†] Epithelial status denotes whether the epithelium was mechanically removed (“Off”) prior to thickness measurement and lamellar dissection, or was not removed (“On”). For those corneas where the epithelium was mechanically removed and off, thickness was measured after the epithelium was removed and before lamellar dissection.