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Correlation of Corneal Parameters and Visual Acuity Outcomes after Descemet Stripping Endothelial Keratoplasty

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Abstract

Purpose: To assess a potential relationship between visual acuity and corneal haze and thickness after Descemet Stripping Endothelial Keratoplasty (DSEK).

Methods: Retrospective review of patients who underwent DSEK surgery with at least 3 months of post-operative follow up. Best-spectacle corrected visual acuity (BSCVA) and ultrasonic pachymetry were measured, and a Pentacam scan was performed for each study eye. Pentacam images were analyzed to determine the surface, host stromal, interface, and graft light scattering levels, which were used as markers of corneal haze. The central donor graft and overall central thicknesses were also measured from the Pentacam. Pearson correlation coefficients were calculated for each of the parameters and post-operative BSCVA to identify any potential associations. A multivariate analysis was performed using a linear regression model predicting visual acuity for each of the significant parameters from the univariate analysis adjusting for patient age and pre-operative acuity.

Results: Results are reported for 41 eyes of 36 patients. Pearson correlation coefficients showed a statistically significant positive correlation between post-operative BSCVA and age (r=0.36, P=0.020), interface-stromal scattering (r=0.44, P=0.004), and interface-graft scattering (r=0.36, P=0.022). No correlation was found between BSCVA and surface scattering (r=0.04, P=0.78), host stromal scattering (r=-0.15, P=0.35), mean interface scattering (r=0.18, P=0.25), or graft scattering (r=-0.14, P=0.38). A trend towards a positive correlation between BSCVA and central donor graft thickness was noted on the exploratory scatter plot but this was not statistically significant (r=0.27, P=0.085). A linear regression analysis controlling for age and pre-operative acuity was performed for the above parameters and the correlation between BSCVA and the difference between interface and host stromal scattering remained statistically significant (β=0.00375, P=0.0195).

Conclusion: Eyes with better BSCVA after DSEK tend to have lower differences between interface and stromal light scattering. However, no relationship was found between BSCVA and the other measures of corneal light scattering or corneal thickness. Additional prospective studies using techniques such as *in vivo* confocal microscopy to supplement the present methods could be performed to validate the relative impact of regional differences in corneal haze on visual acuity outcomes after DSEK.

Keywords: Best spectacle corrected visual acuity; Descemet stripping endothelial keratoplasty; Corneal haze; Graft thickness

Introduction

Selective replacement of the dysfunctional endothelial layer of the cornea with Descemet stripping endothelial keratoplasty (DSEK) offers several advantages over traditional full-thickness corneal grafts, including more predictable and stable refractive error, reduced surgically-induced astigmatism, improved corneal integrity, and faster visual rehabilitation. However, visual acuity outcomes in patients following DSEK can be quite variable with a smaller than desired percentage of patients achieving a best corrected visual acuity of 20/20 [1-7].

Previous studies in patients with lamellar endothelial keratoplasty have demonstrated a reduction in visual acuity secondary to increased corneal light scattering [8-10]. It has been hypothesized that optical aberrations and haze at the graft-host interface or corneal surface may account for the reduced postoperative best-corrected visual acuity in patients following DSEK [7]. However, surface and interface haze (clinical or sub-clinical) may not be apparent on slit-lamp examination. Even when present, the degree of haze can be difficult to grade objectively and reproducibly, making inter-patient or intra-patient comparisons across time extremely difficult. The development or validation of a technique which would permit the identification and quantification of interface haze would resolve these issues. Such a technique would also improve the ability of clinicians to detect and quantify the effects of modified surgical techniques or treatment regimens aimed at reducing corneal surface and interface haze, thereby improving visual outcomes.

Previous studies have used a scatterometer or other devices that are not widely available in clinics. For this study we used a the Pentacam anterior segment imaging system (Oculus, Inc., Dutenhofen, Germany) which has become increasingly utilized in the management of various corneal conditions and may be more available in clinical practice. We

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determined corneal light scattering from Pentacam Scheimpflug images as a marker of haze. We then explored a possible relationship between corneal light scattering and visual acuity after DSEK. We also evaluated a possible association between donor graft and total corneal thickness and post-operative visual acuity.

Methods

Subjects

An observational study of patients from the clinical practices of two cornea specialists (ASJ and WJS) was performed. Patients who had undergone primary DSEK (pseudophakic prior to the DSEK) or combined DSEK and cataract extraction between January 1, 2006 and January 30, 2009 were identified using billing database records. Charts were reviewed and eyes with vision limiting ocular co-morbidities (such as optic neuropathies, severe glaucoma, macular degeneration or other retinal disease), active corneal graft rejection, graft failure, or history of prior corneal surgery were excluded. Eligible patients were contacted and recruited to participate in the study. The study was approved by the Institutional Review Board of Johns Hopkins Medicine and informed consent was obtained from all participants.

Surgical technique

The patients included in the study underwent uncomplicated DSEK surgery using a previously described technique [11,12].

Outcome measures

In addition to a standard ophthalmic slit-lamp and dilated examination, each patient underwent an assessment of best spectacle corrected visual acuity (BSCVA) with a Snellen eye chart. The Snellen acuities were converted to logMAR to facilitate averaging and statistical analyses. Ultrasonic pachymetry (DGH Instruments, Exton, PA) and a Pentacam scan of the operative eye were performed. Historical, demographic, and clinical data were also gathered from the chart including pre-operative diagnosis, gender, race, pre-operative BSCVA and pachymetry.

Four parameters of corneal light scattering were measured directly from the Pentacam Scheimpflug images: (1) surface (2) host stromal (3) interface (4) graft. Images were first opened with the Pentacam Oculus software. Two representative images of each eye (in perpendicular planes to ensure that all four quadrants of the cornea were evaluated) were randomly identified and converted to jpg image format (Figure 1 left). The images were then analyzed using the grayscale densitometry tool in ImageJ (U.S. National Institutes of Health, http://rsb.info.nih.gov/ij/download.html) as follows. The host-graft interface was outlined in the central 2 mm of the cornea (the area most likely to affect visual acuity) and the grayscale value quantified (Figure 1 right).

Similar sized outlines were used to analyze the grayscale values of the surface, host stroma, graft stroma and the room air in the same screenshot. The air densitometry value was subtracted from each of numbers obtained for surface, host stromal, interface, and graft, and the values for the two perpendicular planes were averaged. Two additional parameters of corneal scattering were calculated by subtracting the raw densitometry values of the host stroma or graft from the interface readings to give the interface-stroma scattering (S_i-S_{st}) and interface-graft scattering (S_i-S_g) and then averaging the values for the perpendicular planes. This was done to better assess the change in scattering through the different layers of the cornea at the interface in addition to the absolute amount of scattering of the interface.

The central donor graft thickness and overall central corneal thickness were also measured manually from the Scheimpflug images using the Oculus software measuring tool. Measurements from two independent observers were averaged and used for the analysis.

Study statistics

Statistical analyses were performed using SAS statistical software version 9 (SAS Institute Inc., Cary, NC). An exploratory analysis to survey trends was first done graphically with scatter plots produced using the R graphing program version 2.15.1 (www.r-project.org), and the Lowess function in R was used to generate regression lines indicating the relationship between variables. Pearson correlation coefficients were then calculated for post-operative BSCVA and each of the following parameters: pre-operative BSCVA; age; pre- and post-operative ultrasonic pachymetry; donor and overall graft thickness as measured on the Pentacam; and the surface, host stromal (Sst), interface (S_i) and graft (S_g) light scattering; (S_i-S_{st}) and (S_i-S_g). The two factors that appeared to be positively correlated with post-operative BSCVA (i.e., (S_i-S_{st}) and (S_i-S_g)) were then reanalyzed using a linear regression model that adjusted for patient age and pre-operative acuity. A P-value of ≤0.05 was considered significant.

Results

Subjects

Forty-one eyes of 36 patients (24 women and 12 men) were included in the analysis except where noted if historical data was missing. The preoperative diagnosis was Fuchs' corneal dystrophy in 37 eyes and

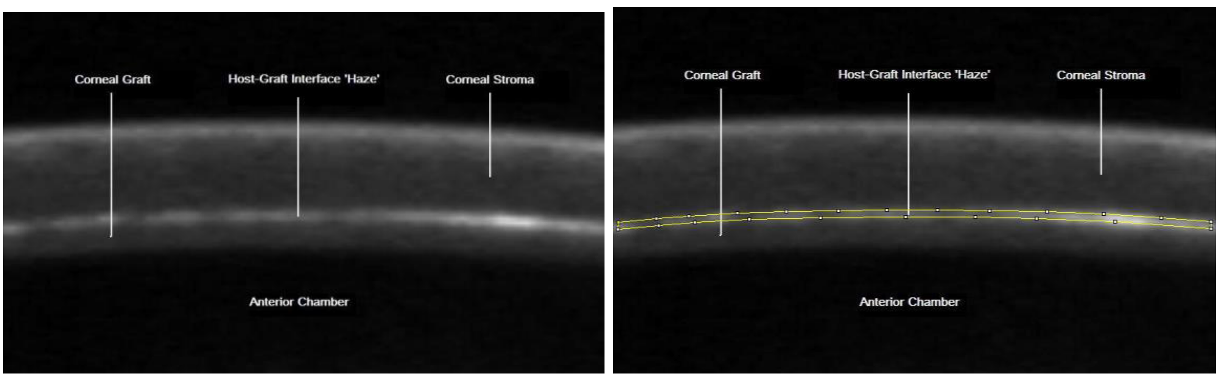

Figure 1: Left: Sample image from Pentacam with zones of the cornea marked. Right: Sample image with interface outlined.

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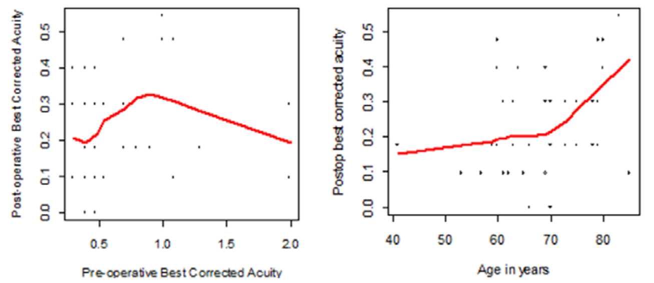

Figure 2: Left: Scatter plot of Post-operative vs. Pre-operative Visual Acuity using logMAR equivalents. Right: Scatter plot of Post-operative Visual Acuity (logMAR) vs. Age (years).

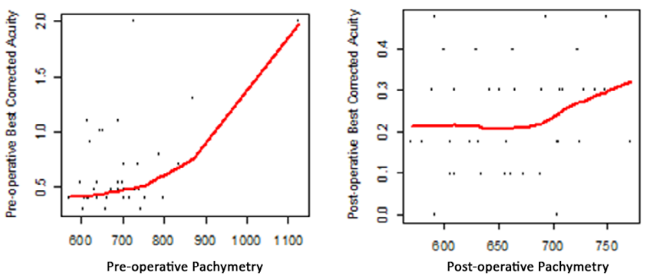

Figure 3: Left: Scatter plot for Pre-operative BSCVA (logMAR) vs. Pre-operative pachymetry (micrometers). Right: Scatter plot of Post-operative BSCVA (logMAR) vs. Post-operative pachymetry (micrometers).

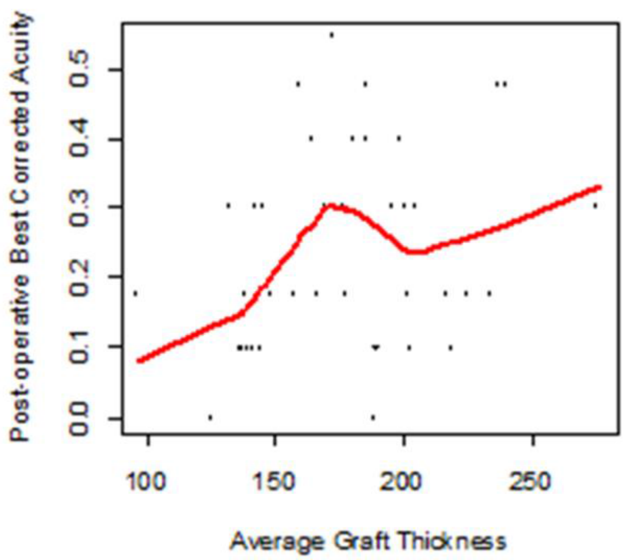

Figure 4: Scatter plot of Post-operative BSCVA (logMAR) vs. average central donor graft thickness (micrometers) measured on Pentacam images.

pseudophakic bullous keratopathy in 4 eyes. The mean age at the time of the study visit was 69 ± 9 years (range 41-85 years), and the average post-operative follow up was 10.2 ± 7.9 months (range 3-33 months). Twenty eyes underwent DSEK surgery alone and 21 eyes underwent combined DSEK/phacoemulsification/intraocular lens placement. All eyes were pseudophakic post-operatively with a posterior chamber intraocular lens and no posterior capsular opacification.

Visual acuity

BSCVA improved after surgery in 37/41 eyes. Mean pre-operative visual acuity was 20/80 ranging from 20/40 to count fingers with a logMAR equivalent mean of 0.6 ± 0.4 and range 0.3-2.0 in 39/41 eyes. Mean post-operative BSCVA was 20/30 (range 20/20 to 20/70) with a logMAR equivalent of 0.2 ± 0.1 (range 0.0-0.5). No correlation was found, however, between pre-operative and post-operative acuity (r=0.13, P=0.44) (Figure 2 left). A statistically significant correlation was found between post-operative BSCVA and patient age (r=0.36, P=0.02) with younger patients having better acuities (Figure 2 right). No relationship was found between post-operative BSCVA and time since surgery.

Pachymetry

The mean preoperative pachymetry in 39/41 eyes was 704 ± 98 (range 573-1126) which correlated with pre-operative acuity (r=0.53, P=0.0005) such that eyes with higher central corneal thickness had worse vision (Figure 3 left). The mean post-operative pachymetry in 38/41 eyes was 663 ± 54 (range 570-772), which did not correlate with post-operative BSCVA (r=0.16, P=0.34) (Figure 3 right).

Pentacam corneal and graft thickness

Pentacam measurements of overall central corneal thickness were highly correlated with the ultrasonic measurements of central corneal thickness post-operatively (r=0.82, P<0.0001). As with ultrasound pachymetry, Pentacam corneal thickness measurements also did not correlate with post-operative BSCVA (r=0.26, P=0.098). A slight trend towards a positive correlation between BSCVA and average central donor graft thickness was noted on the exploratory scatter plot but this was not found to be statistically significant (r=0.27, P=0.085) (Figure 4).

Corneal light scattering

All six measures of corneal light scattering were individually analyzed to assess for a relationship with post-operative BSCVA. The scatter plots showed a possible relationship between worsening visual acuity and increasing values of (S_i-S_{st}) and (S_i-S_g). Eyes with very high values of (S_i-S_{st}) (Figure 5 left) or (S_i-S_g) (Figure 5 right) tended to have worse visual acuity. The univariate analysis confirmed that the statistical relationship was significant for these two parameters (Table 1).

A multivariate analysis adjusting for age and pre-operative BSCVA was performed with a linear regression model for these 2 parameters (Table 2). The correlation between (S_i-S_{st}) remained statistically significant.

Discussion

The techniques of endothelial keratoplasty have evolved and improved significantly from posterior lamellar keratoplasty (PLK) to deep lamellar endothelial keratoplasty (DLEK) to the currently most popular DSEK technique. While visual outcomes have improved with these procedures, a smaller than desired number of patients achieve 20/20 visual acuity despite a clinically clear graft and minimal astigmatism on examination [5]. The development of various anterior segment imaging devices has greatly enhanced the ability to understand post-operative changes in the cornea which could affect corneal optics and post-operative acuity. This study explored the relationship between corneal thickness and corneal light scattering at various levels in the post-DSEK cornea and post-operative BSCVA.

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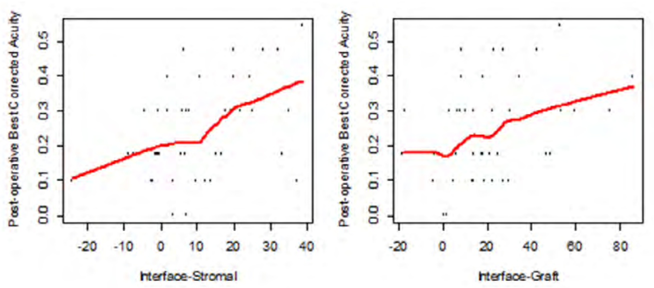

Figure 5: Left: Scatter plot of Post-operative BSCVA (logMAR) vs. the difference between measured interface and stromal scattering (S_i-S_{st}). Right: Scatter plot of the Post-operative BSCVA (logMAR) vs. the difference between the measured interface and graft scattering (S_i-S_g).

Mean surface scattering (S_{surf})	r=0.04	P=0.78
Mean host stromal scattering	r=-0.15	P=0.35
Mean interface scattering (S_i)	r=0.18	P=0.25
Mean graft scattering (S_g)	r=-0.14	P=0.38
(S_i-S_{st})	r=0.44	P=0.004*
(S_i-S_g)	r=0.36	P=0.022*

Table 1: Pearson correlation coefficients for light scattering parameters and post-operative BSCVA, *P < 0.05.

	β-Coefficient	P-value
(S_i-S_{st})	0.00375	0.0195*
(S_i-S_g)	0.00172	0.0908

Table 2: Linear regression model adjusted for age and pre-operative BSCVA, *P<0.05.

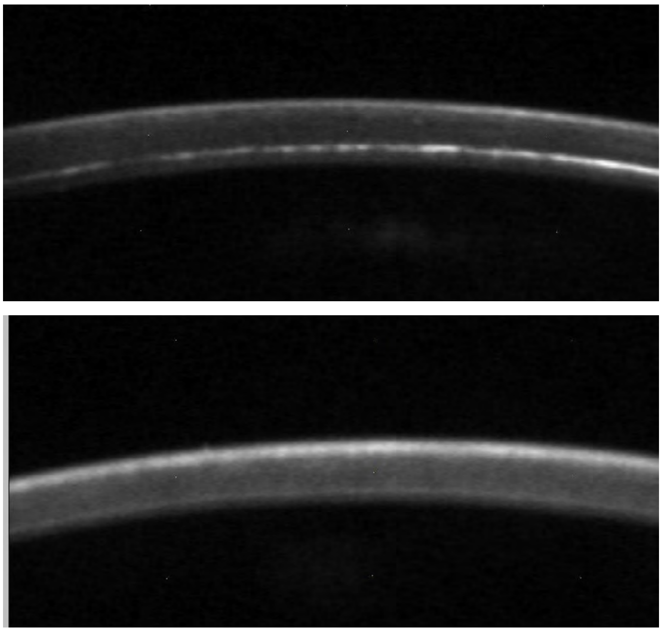

Figure 6: Top: Sample Pentacam image from a patient with 20/50 BSCVA and high level of graft-host interface scattering. Bottom: Pentacam image from a patient with 20/25 BSCVA and a barely perceptible graft-host interface.

The data showed no statistically significant relationship between corneal thickness parameters and BSCVA. A previous large case series with a multivariate analysis found that recipient age, preexisting retinal disease, or amblyopia were most predictive of post-operative visual acuity outcomes in patients after DSEK [6]. It also found no relationship between the overall central corneal thickness and visual outcome post-DSEK [6], although *in situ* donor graft thickness and its contribution to the overall corneal thickness or relationship with visual outcome were not assessed. However, another large case series found a small but statistically significant correlation between thicker corneas and worse visual outcomes [7]. We found no statistically significant relationship between post-operative visual acuity and overall corneal thickness measured either with ultrasonic pachymetry or from Pentacam images. The data (Figure 3) indicate a trend toward worse post-operative BSCVA for very high pachymetry values (>700 µm). It is possible that visual acuity is correlated with corneal thickness, but only at very high levels where the additional tissue added has a more significant impact on corneal optics. Further studies would be needed with more data at the higher range of thickness to validate such a relationship.

We further evaluated the relative contribution of donor graft thickness to BSCVA. One small case series did suggest that variable donor graft thickness, as measured by very high frequency ultrasound, contributes to post-operative refractive shift [13]. However, this was not correlated to best-corrected visual acuity. Holz et al. also documented a correlation between decreasing graft thickness and decreasing post-operative hyperopic shift in the refractive error over increasing post-operative time period [14]. We found no statistically significant relationship between the central donor graft thickness and post-operative acuity, although the scatter plot was suggestive of an inverse trend. Recent studies have sought a significant relationship between graft thickness and visual acuity. Neff et al. noted that when they divided thirty-three eyes into thin and thick graft groups based on their median postoperative graft thickness of 131 µm, thin grafts were significantly associated with better postoperative BSCVA than thick grafts [15]. Furthermore, Nuijts et al. observed a strong relationship between thin grafts and better vision gain in patients without previous vision-limiting comorbidities such as retinal disease or amblyopia [16].

We found no relationship between the directly measured light scattering from the surface, host stroma, interface, and graft and visual acuity outcomes. Using anterior segment optical coherence tomography, one study demonstrated that the graft-host interface became progressively less transparent during post-operative follow-up in one patient, although no correlation to visual acuity was made [14]. Others have documented a gradual improvement in vision in some patients between 3- and 6-month follow-up visits, and conjectured that the change was associated with stromal remodeling at the graft-host interface [6]. In fact when subjectively viewing the Scheimpflug images, patients with a relatively imperceptible interface tended to have better visual acuities than patients with significant interface haze (Figure 6). However, our quantitative analysis did not support this subjective observation.

Each of the measured parameters was correlated with each other suggesting that the scattering for each layer of the cornea is consistent with other segments of the cornea (Table 3). It is interesting then, that we found a statistically significant relationship between the *difference* in measured interface and stromal scattering and visual acuity. This suggests that the absolute scattering levels may not be as important in affecting visual acuity as their change across the cornea.

Furthermore, a previous study has shown that light scatter in the cornea is an age-related phenomenon [9] and that age is the best pre-operative predictor of post-operative visual acuity. It is possible that the age of each patient in the study impacts the measurements of the scattering determined from Pentacam images. Thus, we adjusted our

Mean surface scattering (S_{surf})	r=0.41	P=0.008*
Mean host stromal scattering (S_{st})	r=0.68	P<0.0001*
Mean graft stromal Scattering (S_g)	r=0.48	P=0.0015*
(S_i-S_{st})	r=0.46	P=0.0028*
(S_i-S_g)	r=0.80	P<0.0001*

Table 3: Pearson correlation coefficients for mean interface light scattering and other scattering parameters, *P < 0.05.

data for age and pre-operative acuity, and the relationship between the difference in interface and host stromal scattering levels and BSCVA was maintained. It is possible that the wide spread in ages of our study patients and the potential inherent age-related variability in corneal scattering prevented us from detecting a relationship between visual acuity and the directly measured scattering in our study.

It was also interesting that we found no relationship between surface scattering and BSCVA. Chronic corneal edema can result in subepithelial changes including fibrosis. We have had a few patients (not included in this study) who also had subepithelial scarring evident on slit-lamp examination. These patients were successfully treated with phototherapeutic keratectomy (PTK) with improvement in vision [17]. Another recent Pentacam analysis of DSEK eyes found a relationship was between higher order anterior surface topographic corneal irregularities and post-operative vision [18]. Our study was not designed to account for this possibility in our patients, and thus it could explain the lack of a significant correlation between some of our scattering parameters and BSCVA.

In summary, our work confirms that changes in the post-DSEK cornea have complex effects on corneal optics and post-operative acuity. Our study demonstrates that large changes in light scattering across the cornea at the level of the interface adversely affect visual acuity. Reducing the interface light scattering may also reduce the difference between interface and host stromal scattering and thereby improve outcomes. Further studies of corneal optics after endothelial keratoplasty will likely identify additional clinically modifiable parameters that will in turn lead to improved surgical outcomes.

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