IN VIVO CORNEAL CONFOCAL MICROSCOPY AND ENDOTHELIAL SURGERY

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Disclosure: No potential conflict of interest.

Citation: EMJ Ophth. 2013;1:23-26.

ABSTRACT

Lamellar endothelial surgery has gained increasing popularity in the last decade. This surgery is generally considered less invasive and allows faster recovery. However, differently from standard perforating keratoplasty, donor and recipient tissues are placed one over the other, and an interface is created between these two. The purpose of this review is to summarise findings of interface as observed with *in vivo* confocal microscopy.

Keywords: Endothelial keratoplasty, *in vivo* confocal microscopy, interface.

INTRODUCTION

Endothelial keratoplasty encompasses a wide range of surgical procedures addressing the corneal endothelium and posterior stroma. These techniques include Descemet Stripping Endothelial Keratoplasty (DSEK/DSAEK) and Descemet Membrane Endothelial Keratoplasty (DMEK). Finally, non-DSAEK (nDSAEK) refers to a procedure where the recipient endothelium is left in place and the donor lenticule is placed above it. They have gained extensive popularity, since the end of the twentieth century, as invasivity is lower, recovery faster, and final visual acuity better than standard perforating keratoplasty. However, as with any novel technique, new challenges arose, and cases were described where vision varied thoroughly, though no evident pathology could be detected at the slit-lamp.

In vivo confocal microscopy (IVCM) allows us to examine corneal histology *in vivo*, almost non-invasively, and can be repeated over time. Despite some unresolved technical issues, such as the inability to exactly locate the same corneal area over time, IVCM is routinely performed in a number of corneal diseases, most commonly in infections. Moreover, it can easily detect the donor-recipient interface following DSAEK, making it possible to grade reflectivity.

DISCUSSION

The interface area is critical in lamellar endothelial surgery, as the presence of metallic or organic debris, folds or oedema is inevitable, it could potentially influence the outcome of the graft, and finally, visual acuity. Interestingly, slit-lamp examination - the mainstay of clinical exam - and even optical coherence tomography (OCT) imaging do not have enough resolution to analyse subtle modifications in the interface area adequately. In fact, a recent study by Dirisamer et al.[1] found that a high reflectivity at the donor-recipient interface is associated in 75% of cases with poor visual outcome following DSAEK/DSEK.

Kobayashi et al.[2] described the donor-recipient interface haze following DSAEK surgery and proposed a grading scale for interface reflectivity. They also noticed a number of particles, which were reduced over time. They proposed that the number of particles may not correlate with final visual acuity. This has been confirmed by subsequent reports.[3,4] Similarly, interface haze was progressively and significantly reduced over 6 months. Other authors confirmed a progressive reduction of interface reflectivity after DSAEK.[5]

Prasher et al.[6] examined the interface reflectivity 6 months after DSAEK surgery and found it

Table 1. Data retrieved from relevant studies addressing interface grading, particle number and their correlation with time and visual acuity.

A - Dirisamer et el., 2013[1]
B- Kobayashi et al., 2008[2]
C- Ferrari et al., 2012[4]
D- Prasher et al., 2009[6]
E- Kobayashi et al., 2009[7]
F- Espana et al., 2010[10]
G- Baratz et al., 2012[13]
H- Kobayashi et al., 2013[14]

Key: n.c.=no correlation

	Surgery	Confocal micro-scope	Interface grade	VA/ Particle number	VA/subepi interface grade	VA/ donor interface grade	Time/ particle number	Time/inter-face haze	Time/ subepi haze
A	DMEK	Confoscan 4	Yes/No	-----	-----	-----	------	absent interface	-----
B	DSAEK	HRT2-RCM	Reference images	-----	-----	-----	p=0.0005	p=0.0047	p=0.0112
C	DSAEK	HRT2-RCM	Reference images	p=0.15	-----	p<0.001	p=0.06	p<0.001	-----
D	DSAEK	Tandem scanning	Confocal back scatter units	-----	n.c.	n.c.	-----	-----	-----
E	nDSAEK	HRT2-RCM	Reference images	-----	-----	-----	p=0.013	p<0.001	p<0.001
F	DSEK	Confoscan 4	Reference images	p=0.25	p=0.0004	p=0.67	-----	-----	-----
G	DSEK	Confoscan 4	Scatter units	-----	n.c.	n.c.	-----	improves with recipient age: p=0.01 (12 mo); 0.02 (24 mo)	-----
H	DMEK	HRT2-RCM	Reference images	-----	-----	-----	p=0.49	p=1	p=1

significantly higher in the anterior stroma than at the interface. Interestingly, slit-lamp examination failed to detect any interface, confirming that IVCM is a more sensitive exam. Unlike other studies however, these authors did not find any correlation between the mean reflectivity and best corrected visual acuity.

Results similar to those obtained after DSAEK surgery were replicated for nDSAEK.[7] With regards to the origin of particles, this may be the same of post-LASIK particles, metal or plastic from the microkeratome, and cellular debris.[8,9] Unlike particles observed after DSAEK, after nDSAEK particles were bigger (>30 microns) and were interpreted as necrotic host endothelial cells. In summary, both studies[2,7] confirmed persistence of donor-recipient and subepithelial haze following surgery, which are not easily observed nor quantifiable by slit-lamp examination.

Evidently, if and to what extent these morphological alterations affect visual outcome is a key factor. In these regards, Espana et al.[10] performed scanning confocal microscopy post-DSAEK and found that subepithelial haze, but not interface haze, correlated with best corrected visual acuity. In accordance with others,[2,7] they found that the interface particle number had no influence on visual outcome. Based upon these observations, the authors suggest that performing DSAEK early, before activation of

keratocytes and development of oedema-associated stromal fibrosis, may significantly improve visual outcomes.

Seery et al.[11] performed IVCM on pseudophakic eyes following DSAEK and found that the donor lenticule contributes to the wavefront errors observed after surgery. Thicker grafts were associated with high order aberrations and more graft folds. However, interface reflectivity was not considered in his study.

We[4] have studied 18 eyes of 16 patients between 1 and 24 months after DSAEK. We found that interface reflectivity, but not the number of particles, was correlated with time passed from surgery and with best corrected visual acuity. In summary, a good donor-recipient interface quality is related with a better post-surgical visual acuity. Interestingly, interface reflectivity improved over time, as reported by others in a DSEK animal model.[12] In our study, we did not consider the anterior stroma reflectivity. Our findings are in contrast with those reported by Espana et al.,[10] where no correlation was detected between visual acuity and interface reflectivity. It should be considered, however, that despite the similar age of the patients enrolled, IVCM was performed with different instruments. Differently from Espana et al., who used ConfoScan 4, we used Heidelberg Retina Tomograph II (HRT II). It is known that the latter has a much higher axial resolution (approximately 4 μm) as opposed to the former (about 10 μm). Moreover, the observation time was different (1-24 months vs. 6-22 months). In line with previous reports,[2,3,10] we confirmed that the interface particle number does not affect the final visual outcome.

Baratz et al.[13] recently used ConfoScan 4 to examine subepithelial and donor-recipient haze and correlated those with other measures such as light scatter and patient age. They proposed that after DSEK, visual function is more affected by anterior stromal haze than interface haze. They also found that improvement is more frequent in younger patients, suggesting that chronic corneal oedema may induce persistent pathological changes.

Finally, Kobayashi et al.[14] investigated subepithelial and donor-recipient haze in a small series of DMEK patients. They found that, although the former persisted during the follow-up period, the latter was barely noticeable, unlike what was observed after DSAEK. Since post-DMEK visual acuity was significantly better, it can be hypothesised that the low reflectivity may be involved. Results from relevant studies reviewed in this article are summarised in Table 1.

CONCLUSION

In summary, the development and diffusion of posterior lamellar surgery has represented a significant improvement in the treatment of patients affected with endothelial diseases. At the same time, however, it has become clear that visual outcome may vary significantly in grafts that appear normal at the slit-lamp examination. Metal particles and cellular debris can be found after surgery and may persist over time. Anterior and posterior interface hazes develop and can be detected and measured with IVCM.

What appears clear so far is that the presence of particles at the interface, regardless of their nature (plastic, metal, biologic), does not affect final visual acuity. Although there is still discussion on their impact on final visual acuity, two areas are critical after endothelial surgery: (i) the donor–recipient interface, which shows increased reflectivity, and (ii) the anterior stromal area, where haze seems to persist long after surgery. These are morphological changes induced by long-standing corneal oedema and are likely more related with previous disease than with surgery. This should be considered in clinical practice, possibly tailoring anti-fibrotic and/or anti-inflammatory therapy before surgery is performed. Moreover, the timing of surgery should be carefully pondered, as in younger patients the subepithelial haze improves more than in older ones, possibly as a consequence of shorter disease duration.

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