

**Micro-thin Descemet stripping automated endothelial keratoplasty versus Descemet membrane endothelial keratoplasty: A randomized clinical trial**

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### Abbreviations and Acronyms

BSCVA: best spectacle-corrected visual acuity

BSS: balanced salt solution

CI: confidence interval

CCT: central corneal thickness

CGT: central graft thickness

DMEK: Descemet's membrane endothelial keratoplasty

DSAEK: Descemet stripping automated endothelial keratoplasty

ECC: endothelial cell count

EDTRS: Early Treatment Diabetic Retinopathy Study

EK: endothelial keratoplasty

IOL: intraocular lens

logMAR: logarithm of the minimum angle of resolution

MT-DSAEK: micro-thin Descemet stripping automated endothelial keratoplasty

QoL: quality of life

VFQ14: visual function questionnaire 14

## **Abstract**

**Purpose:** To compare visual outcomes, complications and vision-related quality-of-life (QoL) following micro-thin Descemet stripping automated endothelial keratoplasty (MT-DSAEK) versus Descemet membrane endothelial keratoplasty (DMEK) for the management of corneal endothelial dysfunction in Fuchs dystrophy.

**Design:** Prospective, double-blinded randomized controlled clinical trial

**Methods:** Patients with visually significant endothelial decompensation from Fuchs dystrophy were prospectively randomized to receive MT-DSAEK or DMEK surgery. The primary outcome was best spectacle-corrected visual acuity (BSCVA) at 12 months. Secondary outcomes included refraction, keratometry, endothelial cell count, complications and vision-related QoL at 6 and 12 months post-operatively.

**Results:** A total of 56 eyes of 56 patients were enrolled, 28 in each group. Post-operatively, LogMAR mean BSCVA in the MT-DSAEK group was  $0.17 \pm 0.08$  and  $0.11 \pm 0.09$  at 6 and 12 months compared to  $0.09 \pm 0.13$  and  $0.04 \pm 0.13$  following DMEK ( $p=0.03$ ,  $p=0.002$  respectively) with the DMEK cohort achieving 3.5logMAR letters better BSCVA at 1 year compared to MT-DSAEK. Complication rates were similar with 3.5% re-bubbling rate in both groups, 1 primary graft failure in DMEK and a single endothelial rejection in the MT-DSAEK arm. Vision-related QoL was comparable at 6 and 12 months post-operatively and no eyes demonstrated loss of vision from pre-operative BSCVA.

**Conclusion:** DMEK surgery resulted in significantly better BSCVA at 1, 3, 6 and 12 months post-operatively compared to MT-DSAEK. Patient satisfaction was similar with no differences reported in vision-related QoL scores, as was the complications profile between groups. Thus, our results favor DMEK as the better choice procedure for eyes with Fuchs-related corneal decompensation without ocular comorbidities.

key words: DMEK, thin DSAEK, ultra-thin DSAEK, micro-thin DSAEK, endothelial keratoplasty

## **Introduction**

Corneal endothelial keratoplasty has by far superseded penetrating keratoplasty (PK) as the procedure of choice for endothelial decompensation [1]. It is widely acknowledged and proven that endothelial keratoplasty (EK) results in better visual outcomes, faster recovery time and fewer complications [2, 3]. Descemet stripping automated endothelial keratoplasty (DSAEK) and Descemet membrane endothelial keratoplasty (DMEK) are the two most commonly used EK techniques worldwide, with DMEK being the newer iteration of EK. Each has its own advantages and disadvantages, with a number of studies investigating and comparing visual, anatomical and surgical outcomes between the two methods [4- 7]. DSAEK has an easier learning curve and is favored over DMEK in relation to reduced post-operative complication rate. However the larger and variable thickness of the transplanted lamella in DSAEK grafts seems to contribute to increased higher order aberrations and hyperopic shift, leading to degradation of the visual and refractive quality compared to DMEK [8, 9]. DMEK on the other hand has gained significant ground in corneal endothelial transplantation with faster and superior visual rehabilitation over DSAEK. However, increased graft dislocations, primary graft failures, the need for repeated postoperative interventions, higher rates of operative complications (tissue loss during graft preparation, endothelial trauma during graft positioning and attachment) [10], longer intraoperative time and a steep learning curve in DMEK has contributed to the delayed wide spread adoption of this technique over DSAEK that continues to influence patient's satisfaction and surgeon's preference in EK [11]. In the UK, EK contributed to 49% of all corneal transplant procedures under taken in 2015 of which the uptake of DMEK was only 18.7% compared to 81.3% still undergoing DSAEK as the preferred surgery for endothelial decompensation [12]. Recent years have shown an increasing trend in DMEK uptake with 38.1% of all EK procedures comprising of DMEK in 2019 [12, 13].

The development of thin DSAEK techniques (graft thickness < 130µm) has been reported to provide better visual outcomes compared to conventional DSAEK in recent literature by way

of achieving a thinner stromal interface, more regular posterior corneal surface, fewer higher order aberrations and lower hyperopic shift [14- 16]. Therefore the Micro-thin (MT-DSAEK) or Ultra-thin DSAEK (UT-DSAEK) surgery ( graft thickness <130µm) could possibly provide the solution to achieve good visual quality with low operative complications, thereby balancing the benefits and risks in conventional DSAEK and DMEK procedures. Recently, two prospective randomized controlled clinical trials provided a head-to-head comparison of visual outcomes between thin DSAEK versus DMEK surgery [17, 18]. The results are equivocal with one trial supporting the superiority of DMEK [17] and the other advocating similar visual outcomes between the techniques [18]. Previously, we had published the 12 months outcomes following MT-DSAEK with good visual outcomes of  $\leq$  0.18 logMAR acuity and 2% graft detachment rate, in eyes with no other ocular comorbidity. These results were shown to be better than conventional DSAEK but this was not compared to DMEK surgery [19, 20]. To address this requirement, we conducted a randomized clinical trial to compare the visual outcomes, complication rates and vision-related quality of life (QoL) of patients undergoing micro-thin DSAEK and DMEK surgery.

## **Materials & Methods**

We conducted a prospective, randomized, double-blinded clinical trial, comparing clinical outcomes, complication rates and patient-reported vision related quality-of-life impact between two methods of corneal endothelial replacement surgery; micro-thin DSAEK and DMEK. Although we acknowledge that different terms have been adopted to characterize thin DSAEK grafts, we selected the term “micro-thin DSAEK” following our previous published standardized technique on preparing micro-thin DSAEK grafts, nevertheless implying the same range of graft thickness as ultra-thin or nano thin DSAEK [19]. In this study, our technique of stromal dehydration followed by microkeratome single pass had achieved a thickness of <130µm in 100% of grafts and <100µm in 71%. The primary outcome measure investigated in this trial was visual outcomes at 12 months. Ethical approval was obtained prior to the commencement of the study from the Fulham Research Ethics Committee, Health Research Authority, England. The study was registered in the ISRCTN registry.

All patients presenting or referred to the Corneal transplant services at Addenbrookes Hospital (Cambridge University Hospitals NHS Trust) between October 2016 and October 2018 with symptomatic corneal endothelial dysfunction secondary to Fuchs endothelial dystrophy and no other ocular comorbidity, were prospectively evaluated and recruited to the trial. 56 eyes of 56 participants conformed to the eligibility criteria of the trial.

One eye per patient was randomized to either undergo MT-DSAEK or DMEK based on a paper based randomization process led by the clinical trials unit, with an independent statistician preparing the concealment/randomization list and sealed envelope preparation. We calculated that 28 patients in each arm would give at least 80% power to detect a 0.1 logarithm of the minimum angle of resolution (logMAR) difference (around 1 line difference or 5 letters). The trial was a double blind trial where patients were unaware of the type of endothelial keratoplasty, as were the optometrists, data analysts and technicians taking measurements of Best Spectacle Corrected Visual Acuity (BSCVA), refraction, keratometry, endothelial cell count and central corneal thickness. Only the surgeon (MSR) performing the surgery was aware of the type of EK procedure assigned to the patient.

Sample size was calculated using data from previously reported results supported by the literature. The convention power was taken at 0.8 and a two tailed type I error was assumed for 0.05. Minimum clinically significant difference was estimated at 1 line on EDTRS chart (which is equivalent to 0.1 LogMAR or 5 letters). The two groups were independent. All 56 participants received the treatment intervention.

Written informed consent was obtained from all participants, and the trial conformed to the tenants of the Declaration of Helsinki. All consented patients underwent a comprehensive eye examination. Best Spectacle Corrected Visual Acuity (BSCVA), slit lamp examination, dilated funduscopy and retinal optical Coherence Tomography (OCT), were conducted to assess for any ocular co morbidities. The primary outcome of the trial was BSCVA at 12 months following the intervention. Secondary outcomes included change in spherical equivalent, central corneal thickness, endothelial cell count (ECC), keratometry, intraoperative and postoperative complication rates at 6 and 12 months following surgery. Vision related QoL was assessed using the Visual Function Questionnaire (VFQ-14) at baseline, 6 and 12 months post-surgery. Exclusion criteria were ocular comorbidity other than corneal decompensation that could lead to poor visual prognosis such as retinal or macula disorders, aphakia, abnormal anterior chamber, loss of iris or capsular diaphragm, previous glaucoma

procedures including laser interventions. In addition, patients unable to posture after the procedure for 1-2 hours on their back, patients unable to position on the slit lamp interfering with post-operative assessments and inability to complete self-reported patient questionnaires were also excluded from our study. Patients with dementia and unable to provide informed consent were not included.

### Surgical intervention

A standardized surgical technique was adopted for both MT-DSAEK and DMEK procedures. There were 20/28 patients in the MT-DSAEK group and 24/28 in the DMEK cohort who underwent simultaneous, combined phacoemulsification surgery with intraocular lens (IOL) implantation with endothelial keratoplasty and remaining were all pseudophakic and underwent only the endothelial keratoplasty procedure. All patients received a peribulbar anesthetic block with 5ml of a 1:1 mixture of 2% lignocaine and hyaluronidase 300IU. The phacoemulsification procedure was completed in all cases successfully (Bausch + Lomb's Stellaris) with a posterior chamber IOL in the bag (EyeCee® One Preloaded IOL - Bausch + Lomb, UK) based on biometry measurements. Target refraction was emmetropia for DMEK eyes, while a myopic target (-1.0 Dioptre) was selected to counteract the anticipated hyperopic shift and achieve emmetropia for the MT-DSAEK eyes. This was based on our previously published results on MT-DSAEK where a mean spherical equivalent deviation of +0.85D from prediction was observed [20]. Host descemetorhexis was performed in all patients at an 8.25mm area under ProVisc® (Alcon Laboratories, Inc.) viscoelastic in the case of combined phacoemulsification or BSS infusion via anterior chamber maintainer in standalone EK, using a reverse Sinsky hook and a Descemet stripper. In the case of DMEK surgery, an inferior peripheral iridotomy was also performed via 20G vitrector in all patients. All donor corneas were supplied by British eye banks using organ culture for storage. For patients undergoing MT-DSAEK surgery, an artificial anterior chamber (ALTK system, Moria, Antony, France) connected to balanced salt solution (BSS) infusion was used to mount and prepare the donor cornea. The preparation and thinning was achieved by our custom airflow device (CamFlow, Network Medicals Ltd, United Kingdom) as described by Roberts et al in 2015 [20]. This airflow device delivers air through a 4mm x 10cm sterile tubing and 0.2mm micropore filter (High Flow Filter, Surgistar, United Kingdom) while held at 15mm above the

corneal apex. Stromal thinning was deemed adequate when consecutive ultrasound pachymetry (P2000 Palm Scan, MicroMedical Devices Inc) measurements confirmed a donor corneal thickness at a target range of  $530\mu\text{m} \pm 10\mu\text{m}$ . Subsequently, pressure of the artificial chamber was increased and microkeratome dissection of the thinned graft was performed using a CB2000 automated microkeratome (Moria, St Anthony, France) with a  $350\mu\text{m}$  cutting head. Post-cut thickness was then checked and recorded. Finally, the graft was trephined at 8mm using a manual trephine (Coronet donor punch, Network Medical Products, United Kingdom). The graft was then implanted through a temporal 4.5mm scleral tunnel using the Tan EndoGlide (Coronet, Network Medical Products, United Kingdom).

In the DMEK cohort, the grafts were prepared using the SCUBA (Submerged Cornea Using Backgrounds Away) technique under BSS after staining the endothelium with trypan blue and scoring just inside the trabecular meshwork with a Sinskey hook in a full circle [21]. The Descemet's was then lifted from posterior stroma with forceps and stripped in four quadrants, then trephined at 8mm using the Coronet manual trephine, and the scroll was stained with membrane blue dual for 50 seconds prior to implantation (endothelium- out) via the Geuder Glass Cannula (Geuder AG, Heidelberg, Germany) using a 2.2mm temporal corneal incision.

Following positioning of the grafts, MT-DSAEK patients had complete air fill which was maintained for 10 minutes intraoperatively, then reduced to a bubble of 80% of anterior chamber volume for 1 hour postoperatively, while DMEK patients received sulfur hexafluoride (SF<sub>6</sub>) 20% gas tamponade with 100% fill for 10 minutes intraoperatively, then reduced to a bubble of 80% of anterior chamber volume for 1 hour post-operatively. All incisions were secured with 10-0 nylon sutures. All patients were reviewed at 1 hour post-operatively and after having maintained the supine position. Further reduction of air/gas fill through a paracentesis was decided at that point in order to achieve a 60-70% air fill in the anterior chamber. The patients were subsequently instructed to assume a 65° back recline in supine position at bed times. Subjects in both groups received the same post-operative positioning instructions. Paracentesis corneal sutures were removed at 1 month for both groups and the corneal incision suture at 10 weeks for the DMEK cohort.

Post-operative treatment comprised Dexamethasone 0.1% drops and chloramphenicol 0.5% drops in the operated eye four times a day tapered over 4 weeks and continued on Dexamethasone eye drops through the course of 12 months.



All patients enrolled in the study were examined at baseline and post-operative day 1, week 1, months 3, 6 and 12. BSCVA was assessed at baseline, month 3, 6 and 12 as was intraocular pressure and manifest refraction (performed by trained optometrists blinded to the type of EK performed). The endothelial cell count (Tomey EM 3000, UK specular microscope), central corneal thickness, DSAEK graft thickness (Visante AS OCT, Carl Zeiss Meditec, CA USA), keratometry (Oculus Pentacam) assessments and analysis were undertaken as per protocol described previously [19]. The visual function questionnaires (VFQ-14) were completed at 6 and 12 months. The original VF-14 questionnaire was used. Each question is scored on a scale of 0 (unable to perform an activity at all) to four (able to engage in activity fully). The average score is multiplied by 25 to give an overall score ranging from 0 to 100 points. Zero implies inability to do any of the activities, whereas a score of 100 denotes ability to perform all activities without any difficulty [22]. Intra and post-operative complications were recorded and analyzed. The trials monitoring committee monitored the recruitment process, progress, safety and data collection in this study.

### Statistical Analysis

For the purposes of statistical analysis, the measured Snellen visual acuity was converted to logarithm of the minimum angle of resolution (logMAR) visual acuity. Data are presented as mean  $\pm$  SD. The Shapiro-Wilk test was used to test for normality. Chi-square or Fisher exact tests were used for categorical variables. To compare continuous variables between groups, the independent t test or Mann–Whitney U test were used based on data normality. Comparisons between the pre- and postoperative values in each study group were performed using the paired t-test or Wilcoxon signed rank test. The simple linear regression models were initially used to study the relationships between visual acuity and other study parameters. The potential predictors with a  $p < 0.2$  according to the simple linear regression models were included in the multiple regression models with 1000 bootstrap samples.. Statistical analysis was performed using Stata statistics software version 14.2. The level of significance was considered as  $p < 0.05$  with two tails.

## **Results**

### **Pre-operative characteristics**

Baseline clinical characteristics did not differ significantly between groups in terms of age, gender, pre-operative BSCVA and baseline SE as outlined in table 1. A majority of patients in both groups underwent simultaneous, combined phacoemulsification with IOL implantation at the time of endothelial keratoplasty (71% MT-DSAEK Vs 86% DMEK,  $p=0.19$ ). The underlying cause of endothelial decompensation in all patients was Fuchs endothelial dystrophy. Donor characteristics were similar between groups. In the MT-DSAEK group the mean central DSAEK graft thickness was  $63 \pm 12.9 \mu\text{m}$ .

### **Visual and refractive outcomes**

Eyes in the DMEK group achieved a significantly better BSCVA compared to MT-DSAEK eyes as early as the 4th post-operative week ( $p=0.04$ ). At 6 months, DMEK patients had a mean BSCVA of  $0.09 \pm 0.13$  compared to  $0.17 \pm 0.08$  in the MT-DSAEK ( $p=0.03$ ) and at 12 months the DMEK cohort achieved a mean BSCVA of  $0.04 \pm 0.13$  compared to mean BSCVA of  $0.11 \pm 0.09$  in the MT-DSAEK arm ( $p=0.002$ ). Overall, both groups achieved significant improvement of vision compared to baseline and no loss/ reduction of VA was recorded in either group. Visual acuity outcomes between groups at all timepoints are demonstrated in table 2. Refractive outcomes, as demonstrated in table 3, were similar between groups at 6 and 12 months of follow up, with no significant differences in mean spherical equivalent. Anterior and posterior keratometric astigmatism did not change significantly from baseline to 12 months in either group ( $p=0.44$  MT-DSAEK,  $p=0.35$  DMEK), nor was it different between groups at 6 and 12 months ( $p=0.79$ ,  $p=0.95$  respectively).

### **Endothelial cell count (ECC) and central corneal thickness (CCT)**

Endothelial cell counts did not differ at baseline, month 6 and 12 between groups, as shown in table 3. Both groups demonstrated endothelial cell drop from baseline to 6 months after surgery ( $p<0.0001$  in both groups, Wilcoxon test), with 39% loss for MT-DSAEK and 37.1% for DMEK grafts ( $p=0.36$ ). A further 5.2% average loss for MT-DSAEK and 2.2% for DMEK was observed between 6 and 12 months follow up. The total average loss from baseline to 12

months was 44.2% for MT-DSAEK and 39.3% for DMEK. Central corneal thickness was significantly higher in the MT-DSAEK group at both the 6th and 12th month follow-up visit as compared to DMEK ( $p=0.0028$ ,  $p=0.0048$  respectively) (table 3). The mean central graft thickness (CGT) in the MT-DSAEK arm at 3 and 12 months was recorded as  $82.85\pm 17.84\mu\text{m}$  (95% CI 75.64- 90.05) and  $75.43\pm 18.44\mu\text{m}$  (95% CI 68.28- 82.58) respectively ( $p=0.02$ ).

#### Visual function questionnaire (VFQ-14)

Baseline median and IQR of visual function questionnaire 14 composite scores did not differ significantly between groups (table 4, figure 2). There was a significant improvement in patient reported VFQ14 scores from baseline to 6 and 12 months for both groups ( $p<0.0001$ ). Compared to baseline, MT-DSAEK patients had approximately a 19 point improvement in their mean scores at 6 months while the DMEK arm showed a 24-point improvement. The composite score results remained equal between groups at 6 and 12 months, although more DMEK patients had a score of  $>95$  at 12 months (17/28) compared to MT-DSAEK (13/28), however this was not statistically significant.

#### Complications

Complications and adverse events are presented in table 5. No intra-operative complications were recorded in either group. Re-bubbling rate was equal in both arms, with 1 patient in each one requiring 1<sup>st</sup> day post-operative graft re-attachment with re-bubbling. In both occasions this was managed successfully with no further sequelae. There was one case of graft rejection in the MT-DSAEK group at 9 months which was treated promptly with increased topical steroid drops and resolved gradually while the patient remained under close follow-up. One case of primary graft failure was recorded in the DMEK cohort. The patient subsequently underwent a MT-DSAEK procedure, recovered successfully to achieve 0.2 logMAR BSCVA and therefore not included in the DMEK visual outcome analysis at all subsequent time points following the diagnosis. Steroid-induced ocular hypertension occurred in 8 (29%) subjects of the MT-DSAEK and 6 (21%) of the DMEK arm. These cases were managed with topical IOP lowering eye drops, with 7/28 of the MT-DSAEK and 5/28 of the DMEK arm showing no evidence of glaucomatous optic neuropathy on subsequent visits and visual field testing, with IOP normalizing upon gradual tapering of topical steroids.

However, 1 patient in each group developed persistent rise in IOP with evidence of early visual field defects, hence topical anti-glaucoma treatment was continued and the patients were co-managed with the glaucoma specialist team without surgical or laser intervention. Overall, there were 10 reported complications/adverse events in the MT-DSAEK arm and 8 in DMEK with no significant difference between groups ( $p=0.78$ ).

### Linear regression analysis

The simple and multiple linear regression model using logMAR VA as the dependent variable was analyzed at 6 and 12 months following surgery (table 6). The simple linear regression analysis revealed that at 6 months, posterior corneal astigmatism, total corneal thickness and the type of the EK were significantly associated with visual acuity. At 12 months, total corneal thickness, endothelial cell count and type of EK were significantly associated with visual acuity. We examined the correlations between the explanatory variables before doing the multiple linear regression by plotting the scatter plots to observe the correlations between the variables and calculating the correlation coefficients. In addition, the variance inflation factor (VIF) was used to access the multicollinearity. The results showed that the value of  $VIF=1.12$  for both the multiple regressions, which suggested that there is no multicollinearity. Using the multiple regression model, only the type of EK was significantly associated with visual acuity at 6 and 12 months ( $p=0.035$  and  $p=0.026$  respectively,  $R\text{-squared}= 0.24$ , based on 1000 bootstrap replicates).

### Discussion

In this randomized clinical trial we compared the visual outcomes between MT-DSAEK and DMEK surgery in eyes with Fuchs related endothelial dysfunction and no other ocular comorbidities. Our results corroborate that DMEK outperforms MT-DSAEK, with best corrected visual acuity improving faster and significantly better in the DMEK cohort from as early as the 4<sup>th</sup> post-operative week and at all time points of follow up. At 12 months, DMEK patients could see on average 3.5 logMAR letters more compared to the MT-DSAEK arm ( $0.04 \pm 0.13$  Vs  $0.11 \pm 0.09$ ,  $p=0.002$ ). Our primary endpoint results (BSCVA at 12 months) are in agreement with Chamberlain et al [17] trial, who also reported more rapid visual acuity

improvement in DMEK eyes compared to ultrathin-DSAEK (UT-DSAEK), with 1.5 lines difference in BSCVA at 12 months of follow-up ( $0.16 \pm 0.18$  UT-DSAEK Vs  $0.04 \pm 0.12$  in DMEK,  $p < 0.001$ ). Their thin DSAEK visual outcomes were slightly poorer compared to that reported in our trial, thereby widening the visual acuity differences between the groups. Dunker et al [18] reported no such differences in the visual outcomes between UT-DSAEK and DMEK groups at all time points of follow up with a concluding difference of  $0.15 \pm 0.11$  Vs  $0.08 \pm 0.14$  ( $p = 0.06$ ) at 12 months. Yet a significantly higher number of DMEK eyes were reported to have achieved a Snellen BSCVA of 20/25 or better compared to their thin DSAEK eyes (19/29 [66%] Vs 8/24 [33%],  $p = 0.02$ ), Kurji et al [23], in their prospective comparative case series of nanothin-DSAEK (NT-DSAEK) Vs DMEK, reported that mean BSCVA was significantly better in the DMEK group at 1 month but by 3 months it was comparable between groups, with no significant difference throughout the remainder of the study. A few more studies have also reported lack of significant differences between NT-DSAEK/ UT-DSAEK and DMEK visual outcomes but these are non-RCTs, retrospective series with varying protocols [24- 27]. Thus, the thin DSAEK techniques overall demonstrate significantly better visual results compared to the suboptimal vision (logMAR 0.2-0.3) reported in earlier conventional DSAEK techniques [14, 15]. So, in general, recent literature shows improving visual standards in thin DSAEK techniques not too dissimilar to DMEK, closely trailing behind but not totally matching it. Our RCT results seem to confirm this notion [17].

The VFQ-14 was used to assess the vision related quality, the validity of which has been previously tested in patients undergoing corneal transplantation [22]. Albeit the advantage of DMEK in terms of measured visual acuity at 6 and 12 months, we detected no significant difference in vision-related quality of life (QoL). Both groups reported a substantial improvement in their vision-related QoL from baseline to 6 and 12 months, with mean composite scores  $>90$  in both arms, indicating that all participants enjoyed a significant gain in their QoL as a consequence of EK surgery, irrespective of the type of EK. Our findings are in keeping with those reported by Ang et al [28] who also failed to identify a difference in vision-related QoL outcomes between the UT-DSAEK and DMEK groups in the DETECT trial using the VFQ-39, concluding that both techniques are equally effective in improving QoL. This dissociation or lack of correlation between visual acuity and patient reported outcomes on quality of life has been recognized by other investigators as well [29, 30]. The patient's self-reported ability or disability following EK surgery is an important outcome measure and has

value. The fact that it didn't differ in our study or that published by Ang et al would indicate that DMEK and MT-DSAEK are both equally effective to visually rehabilitate patients with simple Fuchs related corneal decompensation to recover normal daily vision related activities. VFQ-14 is easier to administer and has a high rate of patient compliance, while meeting the criteria of unidimensionality and interval-level measurement [37]. By norm, the QoL score improves along with improvement in BSCVA, but it is possible that VF 14 as an instrument is not sufficiently sensitive to ascertain a difference in QoL within the visual acuity range of 0.1 or 0.2 logMAR as encountered in the MT-DSAEK and DMEK groups in our trial (threshold phenomenon) [31]. We acknowledge that perhaps the evaluation of higher order aberrations between the groups might have added value to our study.

Regarding differences in refractive outcomes, our study revealed that mean spherical equivalent, posterior and anterior corneal astigmatism did not differ significantly between groups at any time point. This is similar to the refractive results published by Dunker et al [18]. Endothelial cell (EC) loss in the MT-DSAEK group at 12 months in our trial was 44.2% compared to 39.3% for the DMEK arm. This loss seemed to stabilize earlier in DMEK eyes with no further significant reduction of mean endothelial cell count after the 6<sup>th</sup> month of follow up. Dickman et al reported a similar 40% ECC loss both in UT-DSAEK and conventional DSAEK at 3 months after surgery with stabilization thereafter [15], while Busin et al [24] described a  $35.6 \pm 20.2\%$  ECC loss at 12 months in their UT-DSAEK cohort with stabilization of cell loss at 1 year post-operatively. Dunker et al [18] reported a 38.7% ECC loss in the UT-DSAEK and 39.3% in the DMEK group at 12 months of follow up. Further follow up would be needed to ascertain the effect of EC loss during the early recovery period on long term graft survival. However, a recent study by Price et al [32] found that DMEK and DSAEK had similar 5-year graft survival rates (both 93%) and endothelial cell loss (48% vs. 47%, respectively;  $P = 0.22$ ). We did not detect a statistically significant discrepancy in complication rates between the 2 groups. Both groups had a low complication profile and our re-bubbling rate was significantly less (3.5% in each group) than that reported in DMEK and DSAEK trials in literature [12, 21, 24, 25]. Chamberlain et al [17] reported that 6/25 (24%) DMEK patients required re-bubbling compared to only 1/25 (3.5%) in the UT-DSAEK arm. Dunker et al [18] recorded a significantly higher total number of complications after DMEK Vs UT-DSAEK (17/29 vs. 6/24,  $p = 0.01$ ) with a 24% (7/29) re-bubbling rate in their DMEK cohort. Of note, this was a multicenter study across 6 surgical centers with surgeons who had performed at least 25 DMEK procedures. In

contrast, our study included a single experienced surgeon who had completed over 100 DMEK and 350 DSAEK procedures and passed the learning curve. Endothelial rejection rate at 1 year was 0% in the DMEK arm and 3.5% (1 patient) in the MT-DSAEK group which was treated successfully with topical corticosteroids and did not necessitate re-grafting. There was a single case of primary graft failure in the DMEK group and none in the MT-DSAEK cohort.

Limitations of this study include the small sample size and inclusion of eyes without other ocular co-morbidities. Additionally, all procedures were performed by a single surgeon, using a standardized technique in eyes with simple corneal decompensation all these factors could account for the lower number of complications compared to other published studies. A similar study involving multiple surgeons or sites at varying stages of the learning curve might not necessarily reproduce the results encountered in our trial [33]. The surgical challenges are far greater in eyes with complex anterior segment pathology such as aphakia, lens-iris abnormalities, previous glaucoma filtering surgery (such as trabeculectomy or glaucoma drainage devices- GDD), vitrectomized eyes, anterior chamber intraocular lenses (AC-IOL) and previously failed cornea grafts. DSAEK has been favored for these cases over DMEK [34] in order to avoid difficulties in graft introduction, attachment and post op dislocation. MT-DSAEK and other thin DSAEK methods could hold an important role in the management of these eyes and a trial investigating the role of thin DSAEK vs DMEK in such complex eyes would be a valuable addition to available literature [35, 36]. Other limitation to this study is the follow-up period, as longer term data could offer more insight on graft survival differences and graft rejection. This is already being addressed as our patients will remain under observation and reported accordingly.

In conclusion, our randomized clinical trial shows that DMEK results in superior visual outcomes to MT-DSAEK at 12 months in eyes with Fuchs corneal decompensation with no other ocular co-morbidities. Although the visual acuity advantages in DMEK was statistically significant, the vision related quality of life outcomes supports the equivocal efficacy of DMEK and MT-DSAEK from the patient's perspective and their daily vision related activities. The study also demonstrated that low complications rates could be achieved with improved surgeon experience in both techniques. Longer term follow up is being planned to report on risk of allograft rejection and graft survival at 2 and 5 years.

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## Tables

Table 1: Baseline patient and donor characteristics

	MT-DSEAK (n=28)	DMEK (n=28)	p
<b><u>Baseline Patient Characteristics</u></b>			
Age			
Mean $\pm$ SD	72 $\pm$ 10.32	73 $\pm$ 7.5	0.64 <sup>^</sup>
Range	54-91	51-85	
Gender			
Male	14 (50%)	9 (32%)	0.17 <sup>~</sup>
Female	14 (50%)	19 (68%)	
Pre-operative logMAR BSCVA			
Mean $\pm$ SD	0.38 $\pm$ 0.23	0.38 $\pm$ 0.15	0.48 <sup>*</sup>
Range	0.1-1.2	0.2-0.6	
Spherical equivalent pre op (mean $\pm$ SD)	-0.65 $\pm$ 5.65	0.89 $\pm$ 2.6	0.29 <sup>*</sup>
Surgery			
Combined Phaco- EK	20 (71%)	24 (86%)	0.19 <sup>~</sup>
Endothelial Keratoplasty alone	8	4	
<b><u>Donor Characteristics</u></b>			
Age of donor ( $\pm$ SD)	68 ( $\pm$ 10)	69 ( $\pm$ 6.8)	0.9 <sup>^</sup>
Endothelial Cell count of the graft			
Mean $\pm$ SD	2632 $\pm$ 160.47	2682 $\pm$ 201.42	0.36 <sup>*</sup>
Range	2400-3000	2300-3150	
Central Graft Thickness post cut (um)			
Mean $\pm$ SD	63 $\pm$ 12.9	NA	
Range	42-95	NA	

Gender			
	46%	57%	0.42~
Male%	54%	43%	
Female%			

^unpaired t test    ~chi-square test    \***Mann-Whitney test**

MT-DSAEK: micro-thin Descemet stripping automated endothelial keratoplasty

DMEK: Descemet's membrane endothelial keratoplasty

logMAR: logarithm of the minimum angle of resolution

BSCVA: best spectacle-corrected visual acuity

Table 2: Primary outcome: post-operative logMAR best corrected visual acuity

BSCVA at timepoints	MT-DSAEK (mean $\pm$ SD) N=28	DMEK (mean $\pm$ SD) N=28	p-value*
4 weeks	0.32 $\pm$ 0.22	0.21 $\pm$ 0.13	0.04
10 weeks	0.21 $\pm$ 0.11	0.15 $\pm$ 0.10	0.03
6 months	0.17 $\pm$ 0.08	0.09 $\pm$ 0.13	0.03
9 months	0.13 $\pm$ 0.08	0.07 $\pm$ 0.13	0.03
12 months	0.11 $\pm$ 0.09	0.04 $\pm$ 0.13 <sup>v</sup>	0.002
*Mann Whitney test MT-DSAEK: micro-thin Descemet stripping automated endothelial keratoplasty DMEK: Descemet's membrane endothelial keratoplasty logMAR: logarithm of the minimum angle of resolution BSCVA: best spectacle-corrected visual acuity <sup>v</sup> Patients included in analysis: n=27, 1 patient excluded from 12 month analysis due to primary graft failure			

Table 3: Refractive outcomes between study groups at 6 and 12 months of follow-up

	MT-DSAEK n=28		DMEK n=28		p value
	(mean ±SD)	95% CI	(mean ±SD)	95% CI	
<b>Spherical equivalent</b>					
<b>6 months</b>	-0.02 ± 1.11	-0.45 to 0.40	-0.45 ± 1.2	-0.91 to 0.01	0.17**
<b>12 months</b>	-0.28 ± 1.02	-0.67 to 0.11	-0.53 ± 1.11 <sup>▽</sup>	-0.98 to -0.08	0.38**
<b>Anterior keratometric astigmatism</b>					
<b>6 months</b>	1.50 ± 0.83	1.18 to 1.83	1.50 ± 0.97	1.12 to 1.88	0.79*
<b>12 months</b>	1.36 ± 0.85	1.03 to 1.69	1.38 ± 0.98 <sup>▽</sup>	0.98 to 1.77	0.95*
<b>Posterior keratometric astigmatism</b>					
<b>6 months</b>	0.29 ± 1.43	-0.26 to 0.84	0.38 ± 0.24	0.29 to 0.45	0.04*
<b>12 months</b>	0.26 ± 1.44	-0.29 to 0.82	0.37 ± 0.26 <sup>▽</sup>	0.26 to 0.48	0.15*
<b>Anterior Q value</b>					
<b>6 months</b>	-0.31 ± 0.18	-0.39 to -0.24	-0.34 ± 0.18	-0.41 to -0.27	0.69**
<b>12 months</b>	-0.29 ± 0.19	-0.36 to -0.21	-0.34 ± 0.22 <sup>▽</sup>	-0.43 to -0.25	0.34*
<b>Posterior Q value</b>					
<b>6 months</b>	-0.99 ± 0.52	-1.19 to -0.79	-0.40 ± 0.20	-0.48 to -0.32	<0.0001**
<b>12 months</b>	-1.02 ± 0.63	-1.27 to -0.78	-0.43 ± 0.26 <sup>▽</sup>	-0.53 to -0.32	<0.0001**
<p>*Mann- Whitney **unpaired t test</p> <p><sup>▽</sup>Patients included in analysis: n=27, 1 patient excluded from 12 month analysis due to primary graft failure</p> <p>MT-DSAEK: micro-thin Descemet stripping automated endothelial keratoplasty</p> <p>DMEK: Descemet's membrane endothelial keratoplasty</p>					

Table 4: Endothelial cell count and central corneal thickness measurements.

	<b>MT-DSAEK n=28</b>		<b>DMEK n=28</b>		<b>p value</b>
<b>Endothelial cell count</b>	<b>mean ±SD</b>	<b>CI 95%</b>	<b>mean ±SD</b>	<b>CI 95%</b>	
<i>Baseline</i>	2632 ± 163.4	2569 to 2696	2682 ± 205.1	2603 to 2762	0.36*
<i>6<sup>th</sup> month</i>	1605 ± 383.6	1457 to 1754	1702 ± 377.2	1550 to 1854	0.28*
<i>12<sup>th</sup> month</i>	1468 ± 385.6	1319 to 1618	1641 ± 385.5 <sup>▽</sup>	1485 to 1796	0.09*
<b>Central corneal thickness</b>	<b>mean ±SD</b>	<b>CI 95%</b>	<b>mean ±SD</b>	<b>CI 95%</b>	
<i>6<sup>th</sup> month</i>	561 ± 55.97	539 to 582	520 ± 40.21	504 to 535	0.0028 <sup>^</sup>
<i>12<sup>th</sup> month</i>	551 ± 57.89	529 to 574	518 ± 40.71 <sup>▽</sup>	499 to 526	0.0048 <sup>^</sup>
<p style="text-align: center;">*Mann Whitney    ^unpaired t test</p> <p style="text-align: center;"><sup>▽</sup> Patients included in analysis: n=27, 1 patient excluded due to primary graft failure</p> <p style="text-align: center;">MT-DSAEK: micro-thin Descemet stripping automated endothelial keratoplasty</p> <p style="text-align: center;">DMEK: Descemet's membrane endothelial keratoplasty</p>					

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