AARHUS UNIVERSITY

A comparison of visual function and side-effects after UT-DSAEK or DMEK for Fuchs' endothelial dystrophy

PhD dissertation

Morten Brok Molbech Madsen

Health
Aarhus University
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Preface

The present thesis is the culmination of research conducted at the Department of Ophthalmology, Aarhus University Hospital, between July 2020 and June 2023.

I wish to thank my main supervisor Professor *Jesper Hjortdal* who introduced me to ophthalmic research and sparked my curiosity in the field. I also wish to thank my supervisor *Anders Ivarsen* for always thorough and careful feedback and suggestions. Their vast knowledge in the field of ophthalmology has been inspiring throughout the entire process. I am grateful for their continuous engagement and admirable responsiveness whenever guidance was needed.

I would like to express my appreciation to all my colleagues in the cornea team, cataract team and the surgical ward at the Department of Ophthalmology at Aarhus University Hospital for supporting and facilitating the project. A special thanks to optometrists *Christian, Henrik,* and *Christina* for constructive criticism and advice in the process. Thanks to my skilled colleagues in the Danish Cornea Bank at Aarhus University Hospital for their assistance and contributions to the project.

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Finally, a sincere thanks to my family and friends for their support throughout the journey. Thanks to *Mads* and *Charlotte* for numerous discussions about the intricacies of the eye. I am grateful to *Jens Christensen* for his linguistic advice during the process. A special thanks to my wife, *Trine*, for her endless support and understanding.

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List of publications

Paper I — Madsen MBM, Ivarsen A, Hjortdal J. Visual function after ultrathin Descemet's stripping automated endothelial keratoplasty or Descemet's membrane endothelial keratoplasty combined with cataract surgery: a randomized controlled clinical trial. *The British journal of ophthalmology.* Jun 8, 2023; doi: 10.1136/bjo-2023-323304, *Online ahead of print.*
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Paper II — Madsen MBM, Ivarsen A, Hjortdal J. Macular thickness after ultrathin Descemet stripping automated endothelial keratoplasty and Descemet membrane endothelial keratoplasty combined with cataract surgery: A randomized controlled clinical trial. *Cornea.* Feb 27, 2023; doi: 10.1097/ICO.0000000000003256, *Online ahead of print.*
(Published)

Paper III — Madsen MBM, Ivarsen A, Telinius N, Hjortdal J. Intraocular pressure-related side-effects after endothelial keratoplasty.
(Submitted for publication)

List of abbreviations

BCVA	Best corrected visual acuity
CCT	Central corneal thickness
CME	Cystoid macular edema
CRT	Central retinal thickness
DMEK	Descemet's membrane endothelial keratoplasty
DSAEK	Descemet's stripping automated endothelial keratoplasty
ECD	Endothelial cell density
ETDRS	Early treatment diabetic retinopathy study letters
FED	Fuchs' endothelial dystrophy
FrACT	Freiburg Acuity and Contrast Test
IOL	Intraocular lens
IOP	Intraocular pressure
LOCS III	Lens Opacities Classification System III
LogMAR	Logarithmic minimum angle of resolution
NSAID	Non-steroidal anti-inflammatory drugs
OCT	Optical coherence tomography
PBK	Pseudophakic bullous keratopathy
RNFL	Retinal nerve fiber layer
SF_6	Sulphur hexafluoride
Triple-EK	Endothelial keratoplasty combined with phacoemulsification and IOL implantation
UT-DSAEK	Ultrathin Descemet's stripping automated endothelial keratoplasty

Introduction

Endothelial keratoplasty

Penetrating keratoplasty became popular in the 1960s and remained the procedure of choice for endothelial dysfunction for many years. In 1998, Melles et al.[1] described a new technique for selective posterior keratoplasty. This technique was gradually refined,[2-4] and when Gorovoy[5] in 2006 proposed graft dissection using a microkeratome, Descemet's stripping automated endothelial keratoplasty (**DSAEK**) was a reality.[6] Later in 2006, Melles et al. described Descemet's membrane endothelial keratoplasty (**DMEK**).[7] The new endothelial keratoplasties resulted in improved visual acuity, faster recovery and less surgically induced astigmatism than penetrating keratoplasty.[8,9] Additionally, they also had a lower risk of rejection.[10]

The DSAEK and DMEK procedures are schematically presented in **Figure 1**. Both DSAEK and DMEK grafts consist of endothelium and Descemet's membrane, but DSAEK grafts also consist of a variable amount of stroma. Since DSAEK and DMEK were invented, they have been thoroughly compared. In several studies, DMEK has proven superior when it comes to visual acuity and patient satisfaction.[11-13] Still, the DSAEK technique has been popular, since DMEK has been considered surgically more challenging.[14,15] Therefore, there has been an ongoing interest to improve the DSAEK technique.

In the pursuit of improving DSAEK grafts, it was observed that graft thickness affected the visual outcome of the procedure. This discovery led to the term ultrathin DSAEK (**UT-DSAEK**) that typically is defined as DSAEK grafts with a thickness of less than 100 µm.[16-18] Afterwards, the clinical relevance of this was debated.[19] However, UT-DSAEK grafts have proven to be significantly better than the conventional DSAEK grafts with better visual acuity and faster recovery.[20] Once again, this has raised the question of which type of graft, UT-DSAEK or DMEK, that provides the best surgical outcome. In 2019, Chamberlain et al.[21] published a randomized clinical trial, which compared UT-DSAEK and DMEK. This study found a superior visual acuity after DMEK throughout the first 12 postoperative months. They used a cohort of patients with both Fuchs' endothelial dystrophy (**FED**) and pseudophakic bullous keratoplasty (**PBK**) which could complicate the interpretation of their results. Later, Dunker et al.[22] did another randomized trial with a homogenous cohort of patients with PBK to circumvent the interpretation problems from the previous study. In contrast to the study by Chamberlain et al., Dunker

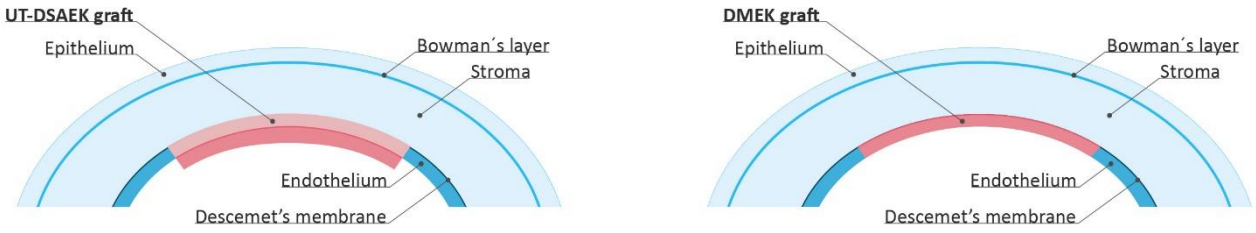

Figure 1: Schematic presentation of ultrathin Descemet's stripping automated endothelial keratoplasty (UT-DSAEK) to the left and Descemet's membrane endothelial keratoplasty (DMEK) to the right.

et al. found a comparable visual acuity after UT-DSAEK and DMEK. Recently, Matsou et al.[23] published their comparison of UT-DSAEK and DMEK, that also found a superior visual acuity after DMEK. They used a cohort only comprised of patients with FED. However, their study included both phakic and pseudophakic patients. All were treated with endothelial keratoplasty, but phakic patients were additionally treated with phacoemulsification and intraocular lens (**IOL**) implantation (**triple-EK**). Therefore, a randomized trial comparing UT-DSAEK and DMEK with all procedures performed as triple-EK is yet to be conducted.

Endothelial dysfunction

The main causes of endothelial dysfunction are FED and PBK, while other causes, such as uveitis and glaucoma surgery, also contribute to bullous keratopathy. In Europe and the US, endothelial keratoplasty is frequently performed due to FED.

FED is characterized by the accumulation of extracellular material on Descemet's membrane that forms so-called guttae. This is accompanied by an increased loss of endothelial cells that leads to endothelial dysfunction and disturbances in corneal deturgescence. The development of FED is believed to be influenced by different factors such as genetic predisposition, lifestyle, and environmental influences.[24] In contrast, PBK is believed to result from a substantial endothelial cell loss from surgical trauma with subsequent endothelial dysfunction.[25] The loss of endothelial cells in FED generally starts at the center with viable cells remaining in the periphery whereas PBK represents a more diffuse depletion of cells.[24,25] Both guttae and disturbed corneal deturgescence lead to a reduced optical quality of the cornea. Since corneal endothelial cells do not naturally regenerate in vivo,[26] the restoration of endothelial function necessitates treatment.

Cystoid macular edema

The formation of intraretinal cysts after uneventful cataract surgery was initially described in the middle of the last century by Irvine[27] and Gass et al.[28] The condition is hence termed Irvine-Gass syndrome but is more often referred to as cystoid macular edema (**CME**). Since the initial description, the condition has also been described after other ocular surgical procedures. CME is characterized by increased central retinal thickness (**CRT**) due to fluid accumulation in the outer plexiform or inner nuclear retinal layers.[29] The condition is believed to arise primarily due to trauma to the uveal tissue during the surgical procedure. This causes a release of prostaglandins that leads to postoperative inflammation and increased permeability of the blood-retina barrier.[30]

CME is the most common vision-affecting adverse event after cataract surgery with an estimated incidence between 1%-2% for clinically significant visual impairment.[31] Furthermore, the condition results in substantially higher economical costs after cataract surgery.[32] Most often, it is self-limiting, but severe cases with detrimental, permanent effect on visual acuity occur.[33] Both systemic and ocular disorders such as diabetes, uveitis and retinal vein occlusion increase the risk for CME in relation to cataract surgery.[31] In agreement with the proposed pathophysiological mechanism, surgical trauma to

the iris has proven to increase the risk[34]; an interesting observation considering the frequent use of iridotomy or iridectomy to avoid pupillary block in relation to endothelial keratoplasty. CME has repeatedly been described after endothelial keratoplasty.[35-37] However, direct comparisons of DSAEK and DMEK are scarce. Myerscough et al.[38] performed a retrospective study on CME and found a higher risk of CME after DMEK compared with DSAEK. Still, the evidence on how retinal changes affect visual acuity after endothelial keratoplasty is limited.

Intraocular pressure related side-effects

The result of corneal grafting greatly depends upon topical steroid treatment that reduces the chance of donor tissue rejection. However, topical steroid treatment increases IOP and can lead to glaucoma.[39] In agreement with this, steroid-induced intraocular pressure (**IOP**) elevation is frequent after endothelial keratoplasty.[40-42] The procedure itself can also lead to increased IOP due to the injection of gas into the anterior chamber to ensure graft adhesion.

Different techniques are used to secure graft adhesion when endothelial keratoplasty is performed. To mention a few, some centers use a 100% anterior chamber gas tamponade for two hours followed by a gas reduction; some only expose patients to this for about 10 minutes[43]; and others terminate the surgical procedure with an 80-95% anterior chamber gas fill accompanied by an inferior iridectomy.[44] The use of anterior chamber gas tamponade presents a risk of pupillary block, that can substantially increase the IOP. Furthermore, the need for rebubbling will expose the patient to additional instances of increased IOP as the procedure is repeated.

Although the pathophysiology is not fully understood, increased IOP is the main contributing factor to retinal ganglion cell loss.[45] Using optical coherence tomography (**OCT**), this loss is quantifiable as retinal nerve fiber layer (**RNFL**) thinning.[46] Due to the frequent occurrence of increased IOP in patients treated with endothelial keratoplasty, the RNFL thickness may be affected in these patients. However, despite the apparent association, little is known about how IOP elevations from endothelial keratoplasty affect the RNFL thickness.

Iris alterations

Urrets-Zavalia syndrome is characterized as a permanently dilated pupil after intraocular surgery. The syndrome was initially described after penetrating keratoplasty and was associated with posterior synechiae and iris atrophy.[47] Also, cases presenting with the syndrome have been reported after endothelial keratoplasty.[48,49] The diagnostic criteria of the syndrome are still poorly defined[50] and the incidence is therefore difficult to estimate. Nonetheless, the syndrome is believed to be rare, and some have even doubted its existence.[51] The syndrome is presumably caused by increased IOP which makes the iris to be compressed against the lens. This compression is thought to cause obstruction of iris vessels that leads to ischemia, and hence atrophy.[52] Furthermore, a partial form of the syndrome, characterized by a less-than-normal response to light and accommodation, has been proposed.[53]

As patients treated with endothelial keratoplasty are exposed to increased IOP from the air or gas used to secure graft adhesion, a partial form of the syndrome may be observable in these patients. Arnalich-Montiel et al.[43] investigated pupillary abnormalities in patients treated with DMEK. In their study, they described a less responsive pupil after surgery. However, they attributed this effect to posterior synechiae that seem to be prevalent after endothelial keratoplasty. Mori et al.[54] investigated iris abnormalities after DMEK and found alterations in 17 out of 32 eyes. Nine of these eyes had pupillary shape changes that were caused by posterior synechiae. Furthermore, Shimizu et al.[55] found posterior synechiae in 20 out of 23 eyes treated with DMEK. Whether reduced iris function results from posterior synechiae or a partial form of iris atrophy is still unknown, and a study on iris function after endothelial keratoplasty remains to be performed.

Aims

The present thesis aimed to study the following:

1) Visual function after UT-DSAEK or DMEK with simultaneous phacoemulsification and IOL implantation in patients operated for FED and cataract. Furthermore, to compare visual function in patients with cataract only undergoing uneventful cataract surgery.

2) The effect of CME on best corrected visual acuity (**BCVA**) in patients treated with UT-DSAEK or DMEK with simultaneous phacoemulsification and IOL implantation and in patients only suffering from cataract and treated with uneventful cataract surgery.

3) Changes in RNFL thickness and iris function after UT-DSAEK or DMEK with simultaneous phacoemulsification and IOL implantation. Furthermore, to compare this with the changes in patients undergoing uneventful cataract surgery.

Hypotheses

We hypothesized that:

1) BCVA and contrast sensitivity were comparable 12 months after UT-DSAEK, DMEK and cataract surgery.

2) CRT was comparable 12 months after UT-DSAEK, DMEK and cataract surgery, and the changes in CRT and BCVA were uncorrelated.

3) RNFL thickness and pupil function were comparable 12 months after UT-DSAEK, DMEK and cataract surgery.

Materials and methods

Study design

A randomized, single-center, parallel-group design was used for this study. Patients with FED and cataract were equally allocated (1:1) to either UT-DSAEK or DMEK with simultaneous phacoemulsification and IOL implantation. These groups were accompanied by a non-randomized control group. Patients in the control group only suffered from cataract and were treated with uneventful phacoemulsification and IOL implantation.

Participant inclusion

Patients referred to the Department of Ophthalmology, Aarhus University Hospital, Aarhus, Denmark, between June 2020 and January 2022 with FED and/or cataract and aged between 50 and 81 were recruited for the study. Exclusion criteria were corneal vascularization, uveitis, glaucoma, exudative age-related macular degeneration or non-exudative age-related macular degeneration with geographic atrophy, retinal vein occlusion, epiretinal membrane, prior ocular surgery or trauma, and vision-affecting systemic disorders. Based on referrals from general ophthalmologists, potentially suitable patients were invited to participate in the study. Only one eye was included from each patient.

The study took place at the Department of Ophthalmology, Aarhus University Hospital, Aarhus, Denmark, between June 2020 and January 2023. This is a tertiary health care center for Western Denmark with corneal grafting recognized as a highly specialized function. The Western Denmark area includes the Central Jutland Region, the North Jutland Region and the Region of Southern Denmark with a total population of approximately 3.1 million people.[56] The study was registered at http://clinicaltrials.gov (Identifiers ID: NCT04417959) before the enrolment was initiated. The research conducted in this study followed the principles outlined in the Declaration of Helsinki and was approved by The Central Jutland Regional Committee on Health Research Ethics. Patients were carefully informed about the procedures and the nature of the study, and all provided a written informed consent before enrolment.

Corneal banking

The tissue used for this study was provided by the Danish Cornea Bank at Aarhus University Hospital, Aarhus, Denmark. Procurement, examination, and preparation of tissue were undertaken by trained staff in the cornea bank.

Enucleation of the donor eyes was undertaken within 48 hours after the event of death. Upon arrival at the cornea bank, the tissue was biomicroscopically examined by the staff. A manual cell count was performed to ensure that the tissue exceeded the required density of 2000 cells/mm^2. After that, a 16-mm corneoscleral button was excised and tissue was stored in 50-60 mL organ culture medium (Tissue-C, Alchimia, Ponte San Nicoló, Italy) at 30°C.

After organ culture, the endothelial cell density (**ECD**) was recounted and corneas with a density of 2000 cells/mm^2 or more were processed for UT-DSAEK or DMEK in the cornea bank. Preparation of tissue for UT-DSAEK grafts was initiated by dehydrating the tissue in an organ culture transport medium containing dextran (Carry-C, Alchimia, Ponte San Nicolò, Italy) for 24-48 hours. Tissue dissection was performed by means of a microkeratome (OU LC head-Art. Chamber, Moria, Anthony, France) and console (Evolution 3E, Moria, Anthony, France). The cutting head was selected to obtain a graft thickness as close as possible to 80 µm. Graft thickness was checked using OCT (CASIA SS-1000, TOMEY, Nagoya, Japan) and the tissue was returned to the organ culture transport medium and shipped to the surgical ward.

To prepare DMEK grafts, the donor tissue was incised along the trabecular meshwork by means of a Sinskey Hook. Trypan blue (MONOBLUE NafX, BVI, Toulouse, France) was used for tissue staining. Peeling was undertaken using blunt forceps with the tissue submerged in a saline solution. The graft diameter was adjusted to 8 mm by trephination and an asymmetrical triangular cut was made at the edge to indicate tissue orientation. The graft was then folded with the endothelium in and preloaded into a Tan Endoglide (DMEK EndoGlide, Coronet, Ripon, United Kingdom) at the cornea bank. The graft was transferred to the organ culture medium without dextran and shipped to the surgical ward.

Surgical interventions

For patients in the control group, anesthesia was induced by oxybuprocaine eye drops (Novesine, 0.4%, OmniVision, Puchheim, Germany). Additionally, intracameral lidocaine (Xylocain, 10 mg/mL, Aspen Pharma, Dublin, Ireland) was employed before phacoemulsification and IOL implantation was performed. The surgery was ended with the administration of intracameral cefuroxime 0.1 mL (Aprokam 50 mg/mL, Théa, Clearmont-Ferrand, France) and a dorzolamide eye drop (Dorzolamid, 20 mg/mL, STADA Nordic, Denmark).

For endothelial keratoplasty, anesthesia was induced using peribulbar injection of a mixture of lidocaine and bupivacaine (3 mL 2% Lidokain-Adrenalin SAD Amgros I/S, Copenhagen, Denmark, and 2 mL 0.5% MarcainAdrenalin, Aspen Nordic, Ballerup, Denmark). All procedures were initiated by phacoemulsification and IOL implantation. After cataract surgery, an anterior chamber maintainer was inserted, and a reverse Sinskey hook was subsequently used for descemetorhexis and stripping of Descemet's membrane.

UT-DSAEK grafts were punched in an 8-mm diameter and were inserted into the anterior chamber via a 4-mm tunnel created at the 12 o'clock position. This was performed as a pull-through technique using Busin glide and forceps.

DMEK grafts preloaded in the Tan Endoglide (DMEK Endoglide, Coronet, Ripon, United Kingdom) were inserted through a 2.65-mm incision using Tan Endoglide forceps. As for the UT-DSAEK grafts, the incision was placed at 12 o'clock and a pull-through technique was used. Unfolding and positioning of the graft was facilitated by a small gas bubble. The graft positioning and orientation were evaluated in each case by means of intraoperative OCT (HS Hi-R NEO 900A NIR, Haag-Streit, Koeniz, Switzerland).

Thereafter, 0.1 mL intracameral cefuroxime (Aprokam 50 mg/ml, Théa, Clearmont-Ferrand, France) was administered and the anterior chamber was filled with a 20% sulfur hexafluoride (SF_6) gas mixture. At the end of the procedure, 1 mg subconjunctival dexamethasone (Dexamethasone 4 mg/mL phosphate Hameln, Hameln pharma gmbh, Hameln, Germany) was administered. For 2 hours, the patient was left supine. The amount of gas was then reduced to between 33%-50% of the anterior chamber volume. No perioperative iridotomy or intraoperative iridectomy was performed. Patients were given 500 mg of oral acetazolamide after reducing the gas and before going to sleep at the day of surgery. All procedures were performed by one of two experienced surgeons.

Postoperative management

After UT-DSAEK and DMEK, patients were treated with diclofenac eyedrops (Voltaren Ophtha, 1mg/mL, GSK Consumer Healthcare, Brøndby, Denmark) 3 times daily for 3 weeks. In addition, an eyedrop containing tobramycin and dexamethasone (Tobramycin 3 mg/mL and Oridecin, dexamethasone 1 mg/mL, Orifarm Generics, Odense, Denmark) was prescribed 6 times daily during the first week after surgery and then reduced to 4 times daily. The dosage was further reduced by one drop a day every other month until the end of treatment.

After cataract surgery, patients in the control group were treated only with diclofenac eyedrops (Voltabak 1 mg/mL, Théa Nordic, Hørsholm, Denmark) 3 times daily for 3 weeks after surgery and dexamethasone eyedrops (Maxidex 1 mg/mL, Novartis, Copenhagen, Denmark) 3 times daily for 2 weeks.

In case of steroid-induced IOP elevation (defined as IOP > 21 mmHg), the dexamethasone treatment was substituted with fluorometholone (Flucon, 1 mg/mL, Novartis Pharma S.A.S., Rueil-Malmaison, France). Timolol eyedrops (Optimol 5 mg/mL, Santen, Tampere, Finland) were additionally administered twice daily to patients presenting with an IOP ≥ 27 mmHg.

Outcome measures and clinical examinations

The primary outcome of the study was BCVA at 12 months. The secondary outcomes were contrast sensitivity, ECD, central macular thickness, RNFL thickness, and pupillary function. All study outcomes were measured preoperatively as well as 3, 6, and 12 months after surgery, where a full clinical examination was performed. Furthermore, IOP was assessed 2 hours after surgery, at the first postoperative day. All outcome measures were assessed by one investigator (Morten Madsen).

At every visit, anterior segment OCT was performed (CASIA2, Tomey Corporation, Nagoya, Japan) to determine the central corneal thickness. Furthermore, autorefraction was performed (TONOREF II, NIDEK Co., Ltd., Gamagori, Japan) before evaluating the visual function. The overall timeline for patients is depicted in **Figure 2.**

Figure 2: Schematic presentation of timeline for patient visits.

Visual function testing

The visual function of patients was tested using an electronic LED monitor (Polaphor light system, Block Optics Ltd., Dortmund, Germany) with a luminance of 260 cd/m^2. Optotypes were presented at a 4-meter distance. The utilized clinic was equipped with blackout curtains and LED lights in the ceiling. This was used to keep the illuminance within the clinic at a level between 250-270 lx (LX-1108 light meter, Lutron Electronic Enterprise Co., Ltd., Datong, Taiwan) during examinations.

Visual acuity

The BCVA testing was performed in agreement with a previously described method for visual acuity testing using an early treatment diabetic retinopathy study letter (**ETDRS**) chart.[57] In brief, ETDRS letters were presented to the patient who was asked to read one letter at a time from left to right. Patients were allowed to change their answer before moving on to the next letter. For each row, the total number of correctly identified letters was noted. When less than three letters were correctly identified, the test was terminated, and the cumulative number of correct letters was used for analysis.

Contrast sensitivity

The Freiburg Acuity and Contrast Test (**FrACT**) was used to determine contrast sensitivity of patients. FrACT is a forced-choice test using an eight-position alternating Landolt C with an angular size equivalent to 1.1 logMAR. The test uses a best parametric estimation by sequential testing algorithm to determine the contrast sensitivity threshold. The test was presented to the patients at the LED monitor with an in-built program to run the FrACT. For each presented optotype, the patient was asked to indicate the orientation of the Landolt C opening. The answer was entered into the system by the examining physician, and the contrast sensitivity threshold was provided by the system in Weber contrast units after the test. The reciprocal of this value was logarithmic transformed (**logCS**) and used for analysis in agreement with the FrACT manual.[58]

Specular microscopy

The ECD was determined using non-contact specular microscopy (NIDEK CEM-530, NIDEK Co., Ltd., Gamagori, Japan). Three consecutive images were obtained at every visit and transferred to the optional NIDEK software package (NAVIS-EX, NIDEK Co., Ltd., Gamagori, Japan). A manual cell count was performed for each obtained image using the center point function of the software and the average of the three estimates was used for analysis.

Retinal optical coherence tomography scans

OCT evaluation of posterior ocular segments was performed with a spectral-domain OCT imaging system (Spectralis OCT, Heidelberg Engineering, Heidelberg, Germany). For measurement of both the CRT and the RNFL thickness, three consecutive images were obtained at each visit. The image quality scores were evaluated (Heidelberg Eye Explorer Version 1.10.4.0) and the image with the highest score was in each case used for analysis. Furthermore, the image with the best quality score at the preoperative examination was defined as a reference scan for all follow-up examinations.

CRT was defined as the central 1 mm subfield. OCT scans were at each examination evaluated and checked for CME. This was defined as intraretinal cysts or an increase in CRT > 10%.

The RNFL thickness was measured in a diameter of 3.5 mm around the optic disc. From the scan, an averaged global RNFL thickness was provided as well as the RNFL thickness in 6 specific sectors. From the 12 o'clock position, these were a superior temporal sector (45°), a temporal sector (90°), an inferior temporal sector (45°), an inferior nasal sector (45°), a nasal sector (90°), and a superior nasal sector (45°). **Figure 3** depicts an RNFL thickness scan with the different sectors schematically presented.

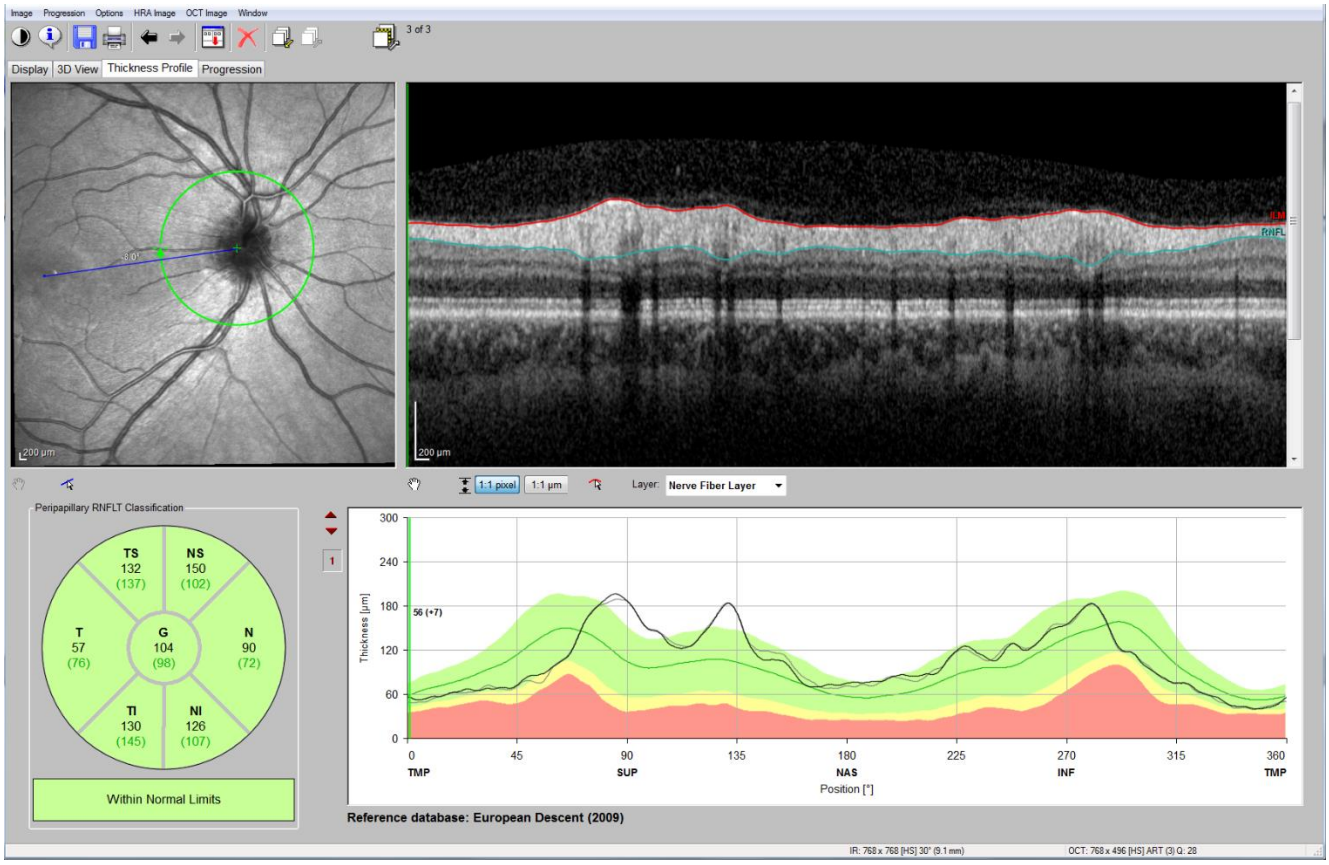

Figure 3: (Paper III) Optical coherence tomography (OCT) scan of the peripapillary retinal nerve fiber layer (RNFL) thickness. The individual sectors of the scan are demonstrated in the lower left corner.

Pentacam measurements

Anterior corneal astigmatism was evaluated using Scheimpflug tomography (Pentacam, HR, Oculus Optikgeräte GmbH, Wetzlar, Germany). Measurements were performed under standardized low-light conditions. At every visit, two measurements were performed, and the quality score provided by the software was evaluated. The best obtained image was used for further analysis; if images had equal quality, the first obtained measurement was used. If problems were detected in both measurements, a third was allowed to be acquired. If a problem also was detected with the third measurement, the one with the best quality score was used for further analysis.

Slit-lamp examination and IOP measurement

At every visit, patients underwent slit-lamp examination with evaluation of iris transillumination defects and posterior synechiae. IOP was measured using Goldmann applanation tonometry (AT 900, Haag-Streit, Koeniz, Switzerland). Moreover, using a previously described standardized method,[59,60] a Lens opacities classification system III (**LOCS III**) cataract grading was performed at the preoperative examination.

Pupillometry

The pupillometry was performed in a completely darkened clinic. During measurements, patients were exposed to a predefined stimulus profile from the pupillometer (DP-2000, Neuroptics, Irvine, CA, USA). The profile consisted of 1 s of complete darkness followed by 5 s of 2.5 log(lx). All patients were initially exposed to 5 s of 2.5 log(lx) to get familiar with the stimulus profile. Thereafter, they were left for 5 minutes of dark adaptation before the measurements were performed. Using the pupillometer, the scotopic and photopic pupil diameters as well as the average constriction velocity (**CV**) and maximum constriction velocity were determined (**MCV**). **Figure 4** depicts a pupillary diameter curve during exposure to the stimulus profile.

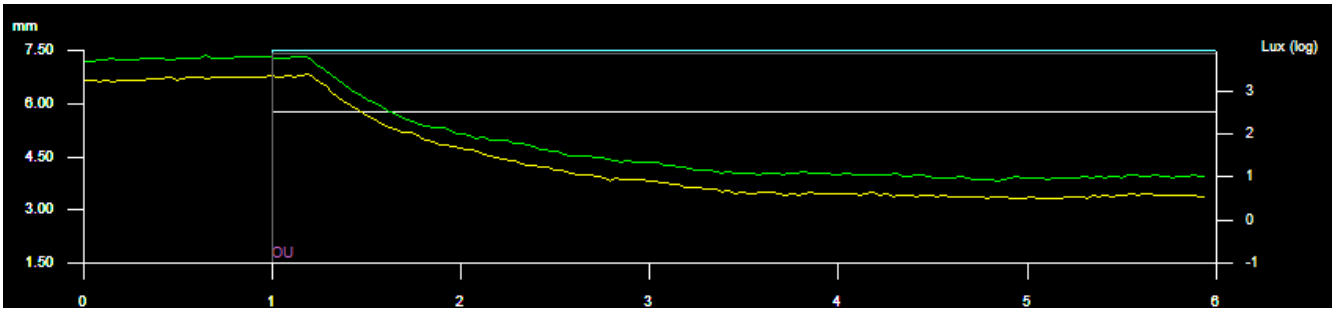

Figure 4: (Paper III) Schematic presentation of the pupillary diameter curve of the right (green curve) and left eye (yellow curve).

Randomization

Patients with FED and cataract included for endothelial keratoplasty were equally randomized to either UT-DSAEK or DMEK in blocks of 2, 4, 6, 8, or 10 patients at a time. The randomization was undertaken approximately once every month after agreement on participation using random computer-generated numbers (Microsoft Excel 2019 for Windows). Through this process, a number between 0 and 1 was assigned to each patient; the half with the highest assigned numbers was allocated to UT-DSAEK; the other half to DMEK.

The sequence generation and intervention allocation were performed by a staff member without any relation to the project and who only was provided with record IDs of the recently included patients. Afterwards, a list of record IDs with assigned interventions was returned to the examining physician who implemented the treatment by informing the cornea bank and the surgical ward.

Blinding

Patients randomized to UT-DSAEK or DMEK were blinded to the performed intervention. As the postoperative treatment, restrictions and cautions were the same for UT-DSAEK and DMEK, the patients were given the same preoperative information. This was provided by the examining physician and the nurses from the ophthalmologic department who were unaware of the intervention that would later be performed. At the follow-up examinations, the examining physician was not blinded to the performed intervention. Patients of the control group who were only referred for cataract surgery were not blinded.

Power calculation and statistics

To demonstrate a BCVA difference of 6 ETDRS letters, the study power calculation indicated that 31 patients were needed in each study group to obtain a two-sided $\alpha = 0.05$ and a power = 85%. The data used for the power calculation originated from the study by Chamberlain et al.[21] This study found a mean BCVA difference of 0.12 logMAR. The standard deviation was 0.18 logMAR after UT-DSAEK and 0.12 logMAR after DMEK. Since patients were recruited from a large geographic area and many visits were planned, a substantial drop-out rate from attrition or non-compliance was expected. Therefore, it was attempted to include 40 patients in each study group.

Analyses were performed in STATA 17.0 (StataCorp., College Station, TX, USA). For comparison of repeated measures, a mixed linear effects model was used. Estimates were adjusted for age, sex, and baseline values. Post hoc ANOVA or t-tests were used for individual comparisons. The normality assumptions were checked using histograms and QQ-plots, and data were logarithmically transformed for analyses as appropriate. Assumptions of equal variation were checked using standard deviation comparison tests. In case of heteroscedasticity, approximate estimates were determined instead of exact ones. Baseline variables were compared using t-test for continuous variables and the χ^2-test for dichotomous outcomes. Correlations between variables were assessed using linear regression models. Diagnostic residual plots were used for model validation and scatter plots for correlation assessment. Analyses were undertaken according to the *intention-to-treat* principle for randomized groups followed by sensitivity analyses as relevant. P-values < 0.05 was considered statistically significant.

Methodological changes

The protocol specified that patients who needed regrafting were to receive the same treatment as their initial allocation. However, when a case of primary failure occurred after inclusion of the last patient, we reevaluated the available literature. As the study by Matsou et al.[23] had found a better visual acuity after DMEK compared with UT-DSAEK and as our own data showed the same tendency, it was decided that the regrafting should be performed as DMEK regardless of allocation.

Results

Participant inclusion and flow

Between June 2020 and January 2022, 72 patients were included for endothelial keratoplasty and randomized. Furthermore, 40 patients were included in the control group. The inclusion was terminated according to plan.

Table 1 (Paper I, II, and III, modified). Baseline characteristics, mean ± SD (95% confidence interval)

	UT-DSAEK (n = 35)	DMEK (n = 36)
Recipient characteristics		
Female, %	62.9 (44.9; 78.5)	72.2 (54.8; 85.8)
Age, years	69.2 ± 6.1 (67.1; 71.3)	68.5 ± 6.2 (66.4; 70.6)
BCVA, ETDRS	69.0 ± 4.9 (67.3; 70.7)	67.4 ± 7.7 (64.8; 70.0)
CS, LogCS	1.02 ± 0.17 (0.96; 1.07)	1.05 ± 0.19 (0.99; 1.12)
CCT, µm	616 ± 56 (597; 635)	606 ± 52 (589; 624)
Anterior corneal astigmatism, D*	-0.78 (-0.98; -0.63)	-0.80 (-1.04; -0.61)
CRT, µm	276 ± 24 (268; 284)	279 ± 20 (273; 286)
IOP, mmHg	15.1 ± 3.0 (14.0; 16.1)	16.0 ± 3.2 (14.9; 17.0)
Global RNFLT, µm	93.3 ± 11.5 (89.3; 97.2)	92.3 ± 9.9 (88.9; 95.6)
LOCS III grading		
NO	2.8 ± 0.7 (2.6; 3.1)	3.0 ± 0.8 (2.7; 3.2)
NC	2.6 ± 1.0 (2.2; 2.9)	2.7 ± 0.9 (2.4; 3.0)
C	1.5 ± 0.7 (1.3; 1.8)	1.6 ± 0.9 (1.3; 1.9)
P	0.7 ± 0.7 (0.5; 0.9)	1.0 ± 1.0 (0.7; 1.3)
Pupillometry		
Scotopic diameter, mm	5.48 ± 0.90 (5.17; 5.79)	5.48 ± 0.83 (5.20; 5.76)
Photopic diameter, mm	2.30 ± 0.37 (2.17; 2.43)	2.38 ± 0.37 (2.26; 2.51)
MCV, mm/s	4.95 ± 0.85 (4.66; 5.25)	4.96 ± 0.80 (4.69; 5.23)
CV, mm/s	0.84 ± 0.21 (0.77; 0.91)	0.86 ± 0.23 (0.78; 0.93)
Donor characteristics		
Female, %	48.6 (31.4; 66.0)	36.1 (20.8; 53.8)
Age, years	73.4 ± 12.1 (69.3; 77.6)	71.3 ± 10.0 (67.9; 74.7)
Time to enucleation, hours*	16.6 ± 1.6 (14.1; 19.5)	16.6 ± 1.7 (13.9; 19.8)
Tissue preservation time, days	33.0 ± 9.1 (29.9; 36.1)	31.4 ± 8.3 (28.6; 34.2)
ECD, cells/mm^2	2482 ± 342 (2364; 2599)	2696 ± 245 (2613; 2779)
Post-cut graft thickness, µm	81 ± 16 (75; 86)	-

UT-DSAEK, ultrathin Descemet's stripping automated endothelial keratoplasty; DMEK, Descemet's membrane endothelial keratoplasty; BCVA, best corrected visual acuity; ETDRS, early treatment diabetic retinopathy study letters; CS, contrast sensitivity; CCT, central corneal thickness; D, diopters; CRT, central retinal thickness; IOP, intraocular pressure; RNFLT, retinal nerve fiber layer thickness; LOCS III, lens opacities classification system III; NO, nuclear opalescence; NC, nuclear color; C, cortical cataract; P, posterior subcapsular cataract; MCV, maximum constriction velocity; CV, average constriction velocity; ECD, endothelial cell density.
*Median values.

In the UT-DSAEK group, one patient died before the surgical intervention was undertaken and was excluded from the study. Additionally, one patient was unable to attend the examination 6 months after surgery. One episode of primary failure was observed after UT-DSAEK and DMEK, respectively. These patients were both regrafted with DMEK but analyzed based on the original allocation. Furthermore, one patient in the UT-DSAEK group had an episode of sterile endophthalmitis, and one had a capsular rupture with a later IOL exchange. Both were included in the final analyses in agreement with the *intention-to-treat* principle with sensitivity analyses undertaken as appropriate. Therefore, 35 patients treated with UT-DSAEK and 36 treated with DMEK were included in the analyses.

Three of the patients in the control group had capsular rupture during the procedure and were excluded from the study. Furthermore, one patient was lost to follow-up after the 3-month examination but was included in the final analyses. As such, 37 patients treated with cataract surgery were included in the analyses. **Tables 1 and 2** show the baseline characteristics of the three study groups, and **Figure 5** shows a flow diagram of patient inclusion and follow-up.

Table 2 (Paper I, II, and III, modified). Baseline characteristics, mean (95% confidence interval)

	EK (n = 71)	Control (n = 37)	P value
Female, %	67.6 (55.5; 78.2)	73.0 (55.9; 86.2)	0.57
Age, years	68.9 (67.4; 70.3)	71.7 (69.7; 73.7)	0.02
BCVA, ETDRS letters	68.2 (66.7; 69.7)	72.3 (70.5; 74.1)	0.001
CS, LogCS	1.03 (0.99; 1.08)	1.26 (1.22; 1.31)	< 0.001
CCT, µm	611 (598; 624)	551 (541; 560)	< 0.001
Anterior corneal astigmatism, D*	-0.79 (-0.94; -0.67)	-0.67 (-0.86; -0.52)	0.14
CRT, µm	278 (272; 283)	280 (274; 285)	0.57
IOP, mmHg	15.5 (14.8; 16.3)	15.9 (14.9; 16.8)	0.58
Global RNFLT, µm	92.7 (90.2; 95.3)	90.7 (87.6; 93.8)	0.33
ECD, cells/mm^2	-	2461 (2324; 2598)	-
LOCS III Grading			
NO	2.9 (2.7; 3.1)	3.6 (3.3; 3.8)	<0.001
NC	2.7 (2.4; 2.9)	3.5 (3.2; 3.9)	<0.001
C	1.6 (1.4; 1.7)	1.6 (1.2; 1.9)	0.95
P	0.8 (0.6; 1.1)	1.6 (1.2; 2.0)	<0.001
Pupillometry			
Scotopic diameter, mm	5.48 (5.28; 5.68)	5.19 (4.89; 5.50)	0.11
Photopic diameter, mm	2.34 (2.25; 2.43)	2.21 (2.09; 2.33)	0.08
MCV, mm/s	4.96 (4.76; 5.15)	4.94 (4.66; 5.23)	0.94
CV, mm/s	0.85 (0.80; 0.90)	0.87 (0.81; 0.94)	0.54

EK, endothelial keratoplasty; BCVA, best corrected visual acuity; ETDRS, early treatment diabetic retinopathy study; CS, contrast sensitivity; CCT, central corneal thickness; D, diopters; CRT, central retinal thickness; IOP, intraocular pressure; RNFLT, retinal nerve fiber layer thickness; LOCS III, lens opacities classification system III; NO, nuclear opalescence; NC, nuclear color; C, cortical cataract; P, posterior subcapsular cataract; MCV, maximum constriction velocity; CV, average constriction velocity; ECD, endothelial cell density.
*Median values.

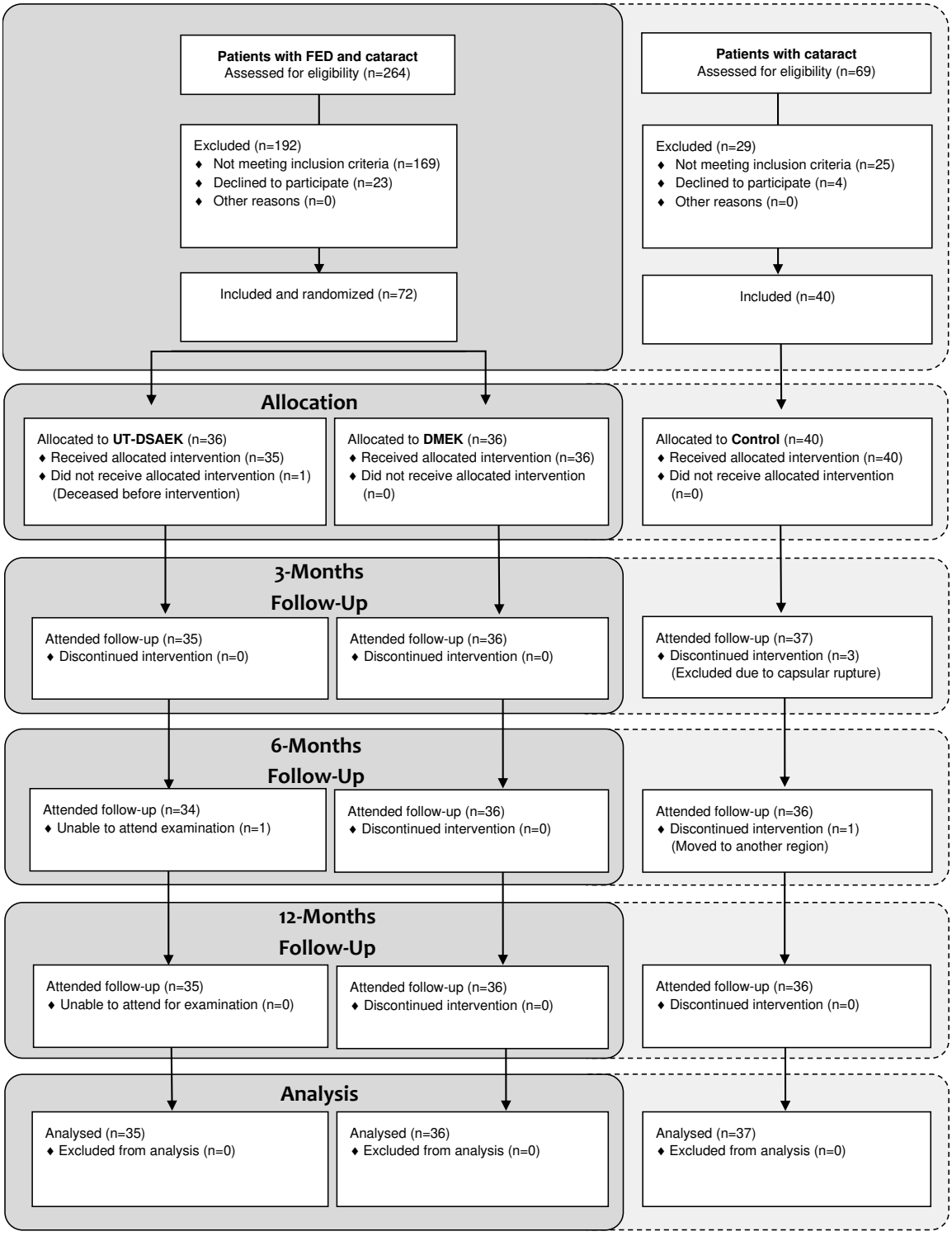

Figure 5: (Paper I) CONSORT diagram of patient inclusion and loss to follow-up. UT-DSAEK, Ultrathin Descemet's stripping automated endothelial keratoplasty; DMEK, Descemet's membrane endothelial keratoplasty.

Visual function

The results of the visual function are shown in **Table 3**. Furthermore, the development in BCVA is shown in **Figure 6** and the progression in contrast sensitivity is shown in **Figure 7**. The mean number of correctly identified ETDRS letters was significantly lower for patients treated with UT-DSAEK than for patients treated with DMEK at 3 (P = 0.001), 6 (P < 0.001), and 12 months (P < 0.001) after surgery. The mean number of correct letters was, however, significantly lower for patients treated with DMEK than for patients in the control group 12 months after surgery (P < 0.001). The BCVA progression significantly differed among the study groups (P < 0.001).

The mean contrast sensitivity in patients treated with UT-DSAEK was significantly lower than in patients treated with DMEK at 3 months after surgery (P = 0.03); however, no difference was found after 6 (P = 0.09) and 12 months (P = 0.08). The mean contrast sensitivity was significantly lower for patients treated with DMEK than for patients in the control group 12 months after surgery (P = 0.01). The contrast sensitivity progression was comparable among the study groups (P = 0.07).

Table 3 (Paper I). Visual function, ECD and astigmatism, mean (95% confidence interval)

	UT-DSAEK (n = 35)	DMEK (n = 36)	Control (n = 37)	P value§
BCVA (ETDRS letters)				
3 months	76.7 (73.6; 79.7)	82.6 (80.7; 84.5)	89.8 (88.5; 91.2)	< 0.001
6 months	76.9 (74.1; 79.7)*	84.0 (81.8; 86.1)	89.2 (87.6; 90.8)*	< 0.001
12 months	80.4 (78.2; 82.7)	86.0 (84.2; 87.8)	90.2 (88.7; 91.7)*	< 0.001
CS (LogCS)				
3 months	1.29 (1.22; 1.36)	1.40 (1.34; 1.46)	1.49 (1.45; 1.52)	< 0.001
6 months	1.32 (1.24; 1.39)*	1.40 (1.33; 1.47)	1.47 (1.43; 1.52)*	< 0.001
12 months	1.35 (1.28; 1.42)	1.44 (1.39; 1.49)	1.50 (1.46; 1.54)*	< 0.001
ECD (Cells/mm^2)				
3 months	1048 (886; 1211)	1541 (1360; 1723)	2104 (1941; 2266)	< 0.001
6 months	1024 (873; 1176)*	1475 (1294; 1657)	2081 (1919; 2242)*	< 0.001
12 months	1010 (874; 1147)	1401 (1227; 1574)	2094 (1936; 2251)*	< 0.001
Anterior corneal astigmatism (D) ‡				
3 months	-0.82 (-1.04; -0.66)	-0.94 (-1.21; -0.72)	-0.69 (-0.87; -0.55)	0.24†
6 months	-0.89 (-1.15; -0.70)*	-0.84 (-1.08; -0.66)	-0.65 (-0.83; -0.51)*	0.11†
12 months	-0.77 (-1.03; -0.58)	-0.87 (-1.09; -0.70)	-0.65 (-0.83; -0.50)*	0.18†

UT-DSAEK, ultrathin Descemet's stripping automated endothelial keratoplasty; DMEK, Descemet's membrane endothelial keratoplasty; BCVA, best corrected visual acuity; ETDRS, early treatment diabetic retinopathy study; CS, contrast sensitivity; ECD, endothelial cell density; D, diopters.

* One value missing.

† One-sided p-value

‡ Median values.

§ P values of post-hoc ANOVA calculated based on multivariate linear mixed effects model.

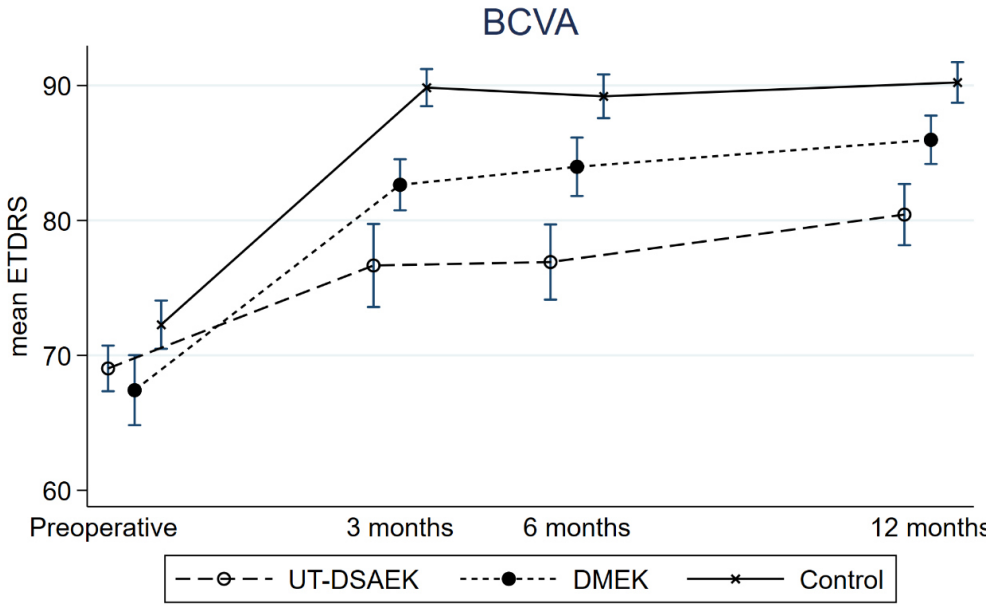

Figure 6: (Paper I) BCVA of UT-DSAEK, DMEK and the control group at baseline and 3, 6, and 12 months after surgery. UT-DSAEK, ultrathin Descemet's stripping automated endothelial keratoplasty; DMEK, Descemet's membrane endothelial keratoplasty.

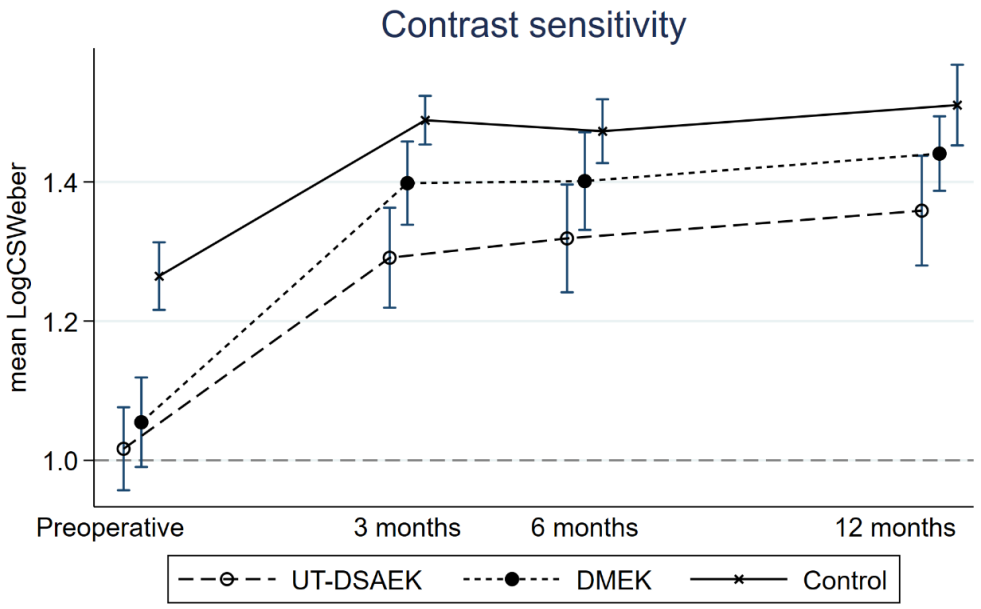

Figure 7: (Paper I) Contrast sensitivity of UT-DSAEK, DMEK and the control group at baseline and 3, 6, and 12 months after surgery. UT-DSAEK, ultrathin Descemet's stripping automated endothelial keratoplasty; DMEK, Descemet's membrane endothelial keratoplasty.

Endothelial cell density

Results on ECD are shown in **Table 3**. Patients treated with UT-DSAEK had significantly lower ECD than patients treated with DMEK at 3 ($P < 0.01$), 6 ($P < 0.01$), and 12 months after surgery ($P = 0.03$). The change in ECD over time was significantly different among study groups ($P < 0.001$).

Central retinal thickness

Results on CRT are shown in **Table 4**. The CRT was comparable between UT-DSAEK and DMEK at 3 ($P = 0.360$) and 6 months after surgery ($P = 0.443$). No intraretinal cysts were observed through the first 6 postoperative months; however, a 10% CRT increase was found in one patient in the DMEK and control group, respectively. The changes in BCVA and CRT showed no significant correlation at 3 ($r^2 = 0.0004$, $P = 0.84$) and 6 months after surgery ($r^2 = 0.0079$, $P = 0.37$). The correlations between changes in BCVA and CRT after 3 and 6 months are shown in **Figure 8**.

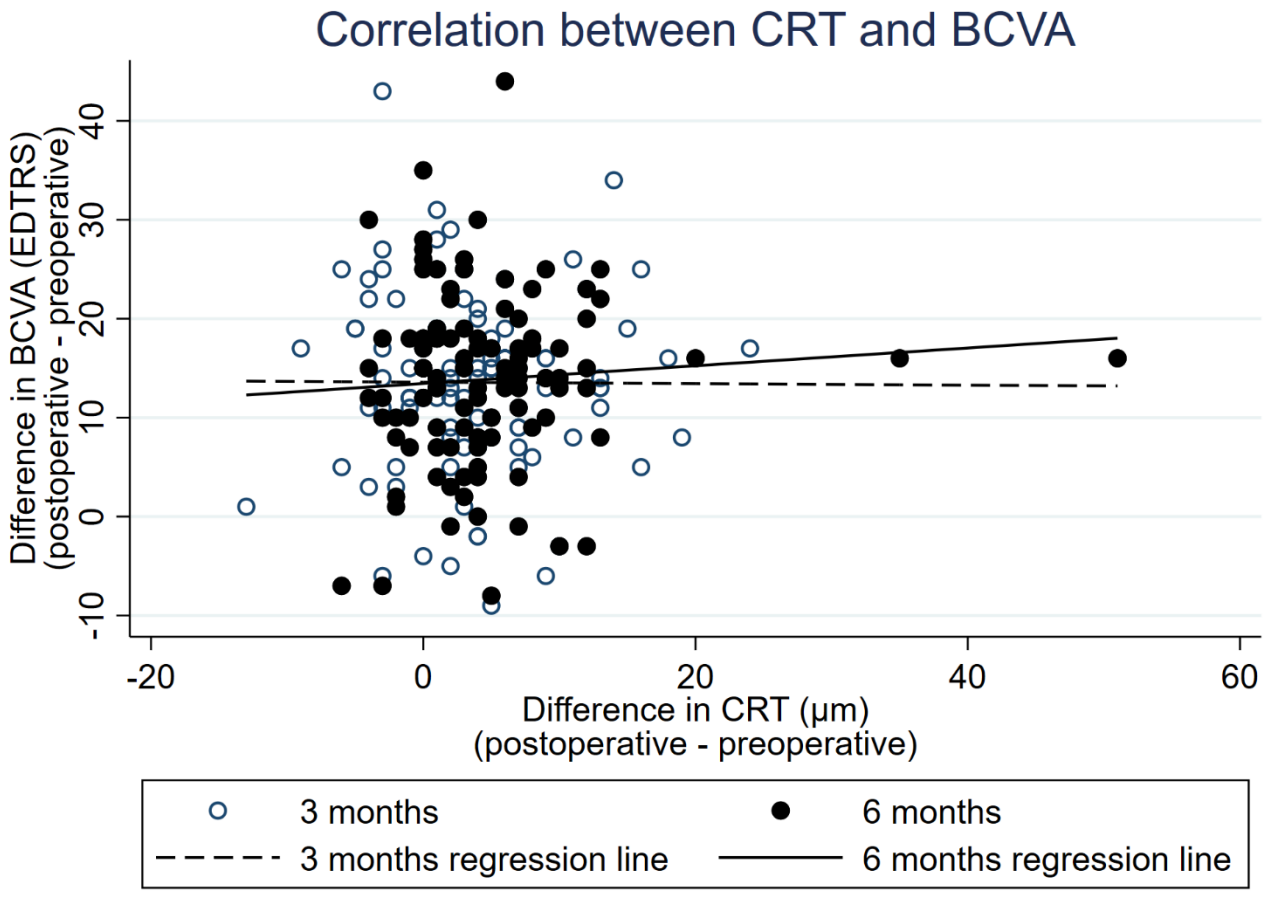

Figure 8: (Paper II) Scatter plot of the difference in BCVA and CRT from baseline for all groups after 3 and 6 months, respectively. ETDRS, early treatment diabetic retinopathy study letters.

Table 4 (Paper II, modified) – CRT and CCT, mean (95% confidence interval)				
	UT-DSAEK (n = 35)	DMEK (n = 36)	Control (n = 37)	P value
CRT (µm)				
Preoperative	276 (268; 284)	279 (273; 286)	280 (274; 285)	
3 months	279 (271; 287)	283 (276; 290)	284 (279; 289)	0.48
6 months	280 (271; 288)*	284 (277; 290)	286 (280; 292)*	0.52
CCT (µm)				
Preoperative	616 (597; 635)	606 (589; 624)	551 (541; 560)	
3 months	581 (566; 596)	518 (505; 530)	551 (541; 561)	<0.001**
6 months	576 (561; 591)*	514 (500; 527)	551 (541; 560)*	<0.001**

CRT, central retinal thickness; CCT, central corneal thickness.
* One missing value
** P < 0.01.

Intraocular pressure

Results on IOP during the first postoperative year are shown in **Table 5**. Patients treated with UT-DSAEK or DMEK had a comparable IOP at 3 (P = 0.96), 6 (P = 0.72), and 12 months after surgery (P = 0.25). Patients in the control group had significantly lower IOP than patients treated with endothelial keratoplasty after 3 (P < 0.001) and 6 (P < 0.001) months. Nonetheless, patients in the control group had a significantly higher IOP after 12 months (P < 0.01).

In the immediate postoperative period, patients treated with UT-DSAEK or DMEK had a comparable IOP 2 hours after surgery before (P = 0.07) and after (P = 0.65) reduction of the anterior chamber gas tamponade as well as at the first postoperative day (P = 0.69).

Retinal nerve fiber layer thickness

Results on RNFL thickness are shown in **Table 5**. The RNFL thickness was significantly higher for patients treated with UT-DSAEK or DMEK compared with patients in the control group for the global (P < 0.01), temporal (P = 0.04) and nasal sectors (P = 0.01) at 12 months after surgery. The RNFL thickness was comparable for all sectors between patients treated with UT-DSAEK and patients treated with DMEK at 3, 6, and 12 months after surgery (P ≥ 0.10 for all comparisons). For patients treated with UT-DSAEK or DMEK, the RNFL thickness increased significantly from baseline to 3, 6, and 12 months after surgery, respectively (P < 0.028 for all comparisons). For patients in the control group, the RNFL thickness increased significantly from baseline to 3 and 6 months after surgery (P < 0.008 for both comparisons). The RNFL thickness at baseline and 12 months after surgery was, however, similar (P = 0.494).

Results on RNFL thickness based on rebubbling status and postoperative IOP increase after the first postoperative week are shown in **Table 6**. RNFL thickness was comparable between patients who were treated with rebubbling and patients who were not (P ≥ 0.16 for all comparisons) as well as between patients who had steroid-induced increased IOP and those who did not (P ≥ 0.09 for all comparisons).

Table 5 (Paper III). Comparisons of intraocular pressure and retinal nerve fibre layer thickness, mean (95% confidence interval)					
	UT-DSAEK (n = 35)	DMEK (n = 36)	Control (n = 37)	P value‡ (UT-DSAEK vs DMEK)	P value‡ (EK vs control)
IOP, mmHg					
Baseline	15.1 (14.0; 16.1)	16.0 (14.9; 17.0)	15.9 (14.9; 16.8)		
3 months	17.4 (15.5; 19.3)	17.9 (15.5; 20.4)	13.3 (12.3; 14.3)	0.96	< 0.001
6 months	16.2 (14.7; 17.7) †	17.1 (15.5; 18.7)	13.1 (12.1; 14.2) †	0.72	< 0.001
12 months	11.6 (10.6; 12.6)	11.6 (10.6; 12.6)	13.6 (12.5; 14.7) †	0.25	< 0.01
RNFLT					
Global, µm					
Baseline	93.3 (89.3; 97.2)	92.3 (88.9; 95.6)	90.7 (87.6; 93.8)		
3 months	95.8 (91.8; 99.8)	94.5 (91.1; 97.9)	92.8 (89.4; 96.1)	0.75	0.70
6 months	95.3 (91.4; 99.1) †	94.2 (90.5; 97.9)	92.8 (89.3; 96.3) †	0.35	0.96
12 months	96.8 (92.4; 101.1)	94.8 (91.0; 98.7)	90.9 (87.7; 94.2) †	0.45	< 0.01
Pupillometry					
Scotopic pupil diameter (mm)					
Baseline	5.48 (5.17; 5.79)	5.48 (5.20; 5.76)	5.19 (4.89; 5.50)		
3 months	5.38 (5.09; 5.67)	5.30 (5.02; 5.58)	5.07 (4.80; 5.35)	0.41	0.77
12 months	5.37 (5.07; 5.66)	5.31 (5.04; 5.59)	5.17 (4.87; 5.46) †	0.51	0.34
Photopic pupil diameter (mm)					
Baseline	2.30 (2.17; 2.43)	2.38 (2.26; 2.51)	2.21 (2.09; 2.33)		
3 months	2.39 (2.26; 2.52)	2.54 (2.38; 2.71)	2.22 (2.09; 2.34)	0.36	< 0.01
12 months	2.25 (2.13; 2.38)	2.39 (2.23; 2.55)	2.21 (2.07; 2.35) †	0.40	0.95
MCV (mm/s)					
Baseline	4.95 (4.66; 5.25)	4.96 (4.69; 5.23)	4.94 (4.66; 5.23)		
3 months	5.09 (4.81; 5.37)	4.58 (4.29; 4.88)	5.16 (4.84; 5.47)	< 0.01	0.02
12 months	5.10 (4.79; 5.41)	4.94 (4.68; 5.20)	4.95 (4.61; 5.29) †	0.35	0.83
CV (mm/s)					
Baseline	0.84 (0.77; 0.91)	0.86 (0.78; 0.93)	0.87 (0.81; 0.94)		
3 months	0.83 (0.75; 0.90)	0.78 (0.71; 0.85)	0.83 (0.76; 0.90)	0.19	0.51
12 months	0.86 (0.80; 0.93)	0.83 (0.73; 0.92)	0.84 (0.76; 0.93) †	0.31	0.95

UT-DSAEK, ultrathin Descemet's stripping automated endothelial keratoplasty; DMEK, Descemet's membrane endothelial keratoplasty; EK, endothelial keratoplasty (UT-DSAEK and DMEK combined); IOP, intraocular pressure; RNFT, retinal nerve fiber layer thickness; MCV, maximum pupil constriction velocity; CV, average pupil constriction velocity.

Data are presented as mean (95% confidence interval)

† One value missing, ‡ P values of the post-hoc t-test were calculated based on multivariate linear mixed effects model.

Table 6 (Paper III, modified). Comparisons of RNFLT and pupil function based on rebubbling and IOP, mean (95% confidence interval)						
	Rebubbling (n = 13)	No rebubbling (n = 58)	P value‡	Increased postoperative IOP* (n = 12)	No increased postoperative IOP (n = 59)	P value‡
RNFLT						
Global, µm						
Baseline	88.8 (84.3; 93.4)	93.6 (90.7; 96.5)		93.5 (88.0; 99.0)	92.6 (89.7; 95.5)	
3 months	91.5 (87.3; 95.8)	96.0 (93.0; 99.0)	0.78	95.8 (90.4; 101.2)	95.0 (92.1; 98.0)	0.95
6 months	91.5 (86.6; 96.3)	95.5 (92.4; 98.5) †	0.80	96.1 (90.9; 101.3)	94.4 (91.4; 97.4) †	0.66
12 months	91.0 (86.4; 95.6)	96.9 (93.6; 100.2)	0.27	95.1 (90.1; 100.0)	95.9 (92.6; 99.2)	0.14
	Rebubbling (n = 13)	No rebubbling (n = 58)	P value‡	Tamponade IOP > 40 mmHg** (n = 32)	Tamponade IOP ≤ 40 mmHg** (n = 39)	P value‡
Pupillometry						
Scotopic pupil diameter (mm)						
Baseline	5.63 (5.19; 6.07)	5.45 (5.21; 5.68)		5.49 (5.15; 5.82)	5.47 (5.21; 5.73)	
3 months	5.21 (4.83; 5.59)	5.37 (5.14; 5.59)	0.03	5.42 (5.09; 5.75)	5.27 (5.03; 5.52)	0.25
12 months	5.27 (4.89; 5.66)	5.35 (5.13; 5.58)	0.04	5.38 (5.04; 5.71)	5.31 (5.07; 5.55)	0.60
Photopic pupil diameter (mm)						
Baseline	2.40 (2.18; 2.63)	2.32 (2.23; 2.42)		2.35 (2.21; 2.48)	2.33 (2.21; 2.46)	
3 months	2.76 (2.38; 3.15)	2.40 (2.31; 2.50)	0.11	2.55 (2.39; 2.72)	2.40 (2.26; 2.53)	0.12
12 months	2.57 (2.21; 2.93)	2.27 (2.17; 2.36)	0.16	2.36 (2.21; 2.51)	2.29 (2.15; 2.43)	0.61
MCV (mm/s)						
Baseline	5.11 (4.55; 5.67)	4.92 (4.71; 5.13)		4.96 (4.61; 5.31)	4.95 (4.73; 5.17)	
3 months	4.46 (3.68; 5.24)	4.92 (4.72; 5.11)	0.23	4.90 (4.55; 5.26)	4.78 (4.53; 5.03)	0.42
12 months	4.83 (4.25; 5.40)	5.06 (4.85; 5.28)	0.40	5.06 (4.74; 5.38)	4.98 (4.72; 5.25)	0.54
CV (mm/s)						
Baseline	0.80 (0.68; 0.92)	0.86 (0.80; 0.92)		0.83 (0.75; 0.91)	0.86 (0.79; 0.93)	
3 months	0.73 (0.60; 0.86)	0.82 (0.76; 0.88)	0.30	0.80 (0.71; 0.88)	0.81 (0.74; 0.88)	0.92
12 months	0.87 (0.65; 1.10)	0.84 (0.79; 0.89)	0.63	0.86 (0.76; 0.96)	0.83 (0.77; 0.89)	0.38

RNFLT, retinal nerve fiber layer thickness; IOP, intraocular pressure; MCV, maximum pupil constriction velocity; CV, average pupil constriction velocity.
Data are presented as mean (95% confidence interval)
* Defined as IOP > 25 mmHg or an IOP increase ≥ 10 mmHg at 3, 6, or 12 months after surgery.
** Intraocular pressure during anterior chamber gas tamponade
† One value missing
‡ P values of the post-hoc t-test were calculated based on baseline adjusted multivariate linear mixed effects model.

Iris changes

Transillumination defects were found in two (6%) patients treated with UT-DSAEK and five (14%) patients treated with DMEK. Posterior synechiae were found in two (6%) patients treated with UT-DSAEK and five (14%) patients treated with DMEK. The presence of transillumination defects did not necessarily imply the existence of posterior synechiae in these patients.

Results on the iris function are shown in **Table 5**. Three months after surgery, the maximum pupillary constriction velocity was significantly higher ($P = 0.02$), and the photopic pupil diameter was significantly smaller ($P < 0.01$) for patients in the control group than patients treated with UT-DSAEK or DMEK. Furthermore, a significantly higher maximum pupillary constriction velocity was found in patients treated with UT-DSAEK compared with patients treated with DMEK 3 months after surgery ($P < 0.01$). However, no significant differences were found among the groups after excluding patients with posterior synechiae ($P > 0.06$ for all comparisons). Furthermore, no significant differences were found among groups after 12 months.

Patients with posterior synechiae had a significantly smaller scotopic pupil diameter after 3 ($P = 0.014$) and 12 months ($P < 0.01$) and a larger photopic pupil diameter after 3 months ($P = 0.03$) than patients without posterior synechiae. Maximum and average constriction velocities were comparable for patients with and without posterior synechiae after 3 and 12 months ($P > 0.16$ for all comparisons).

Results on iris function based on rebubbling status and tamponade pressure are shown in **Table 6.** Patients treated with rebubbling had a significantly smaller scotopic pupil diameter than patients not treated with rebubbling. However, this difference was not significant after excluding patients with posterior synechiae.

Adverse events

The numbers of adverse events for patients treated with endothelial keratoplasty are shown in **Table 7**. Five (14%) patients treated with UT-DSAEK and eight (22%) treated with DMEK were rebubbled. Six patients treated with UT-DSAEK and eight treated with DMEK had increased IOP (defined as > 25 mmHg). The IOP only remained increased in one patient treated with DMEK after terminating the topical steroid treatment. Three patients treated with UT-DSAEK and one treated with DMEK had an episode of graft rejection. All episodes responded well to intensified topical steroid treatment.

Table 7 (Paper I). Adverse events 12 months after surgery

	UT-DSAEK (n = 35)	DMEK (n = 36)
Rebubbling	5	8
Primary failure	1	1
Rejection	3	1
Increased IOP	6	8
Pupillary block	0	1
PCO	4	0
Re-grafted	1	1
Total	20	20

UT-DSAEK, ultrathin Descemet's stripping automated endothelial keratoplasty; DMEK, Descemet's membrane endothelial keratoplasty; IOP, intraocular pressure; PCO, posterior capsular opacification.
Data are presented as absolute numbers.

Methodological reflections

Design related issues

For this study, we chose a randomized, parallel group design with an additional non-randomized control group. As opposed to patients included for endothelial keratoplasty, patients in the control group had healthy corneas without guttae. Since all groups had phacoemulsification and IOL implantation performed, this enabled a comparison of patients with grafted and healthy corneas. The non-randomized nature of these comparisons is, however, prone to confounding. This difference must be kept in mind when interpreting the study results.

We decided to compare grafted patients with patients treated with uneventful cataract surgery. Patients in the control group who experienced capsular rupture were therefore excluded from the analysis. Capsular rupture during cataract surgery is a rare complication. In a large study on 55,567 surgeries, the estimated incidence was around 2%.[61] Additionally, capsular rupture accompanied by vitreous loss may affect visual acuity[62] and the risk of CME[63]; hence CRT. In a study with our sample size, a case of capsular rupture could therefore largely affect the study results depending upon its occurrence. In contrast, patients treated with combined endothelial keratoplasty and cataract surgery were not excluded in case of capsular rupture. The affected optical quality of the cornea in patients with endothelial keratoplasty may complicate phacoemulsification and IOL implantation. The incidence of capsular rupture may therefore be higher during triple-EK than cataract surgery alone. Furthermore, exclusion of patients after randomization introduces confounding to estimates since the advantage of randomization is lost. The analyses were therefore undertaken according to the *intention-to-treat* principle.

Blinding

A difference in the level of expectation could affect the comparison of patients treated with endothelial keratoplasty and the control group. The psychophysical tests used to determine visual acuity and contrast sensitivity are particularly prone to this.[64] Patients with FED were blinded to the performed intervention in contrast to patients in the control group who were not. As cataract surgery is a standard procedure, it is the general perception that this results in an excellent visual outcome. In contrast, patients with FED, who knew they were going to be grafted and who were informed about the expected outcome beforehand, may have had minor expectations. This might have affected our results. Additionally, the follow-up examinations were performed by a non-blinded physician. This could potentially also induce bias through varying degrees of encouragement from the physician during the psychophysical tests. Finally, due to the nature of the study, the surgeons performing the interventions were obviously non-blinded.

Time-aspects of the study

In this study, we used a follow-up duration of 12 months which should be suitable to answer our hypotheses. As a rule of thumb, clinically significant improvement in visual acuity can be seen until 12 months after corneal surgery. In agreement with this, a recent comparison of UT-DSAEK and DMEK found no significant change in BCVA from 12 to 24 months.[65] As such, the timeframe of the present study seems to be suitable when it comes to BCVA.

Our study also aimed to describe the impact of CRT on BCVA. Usually, the largest increase in CRT is observed 4-6 weeks after surgery.[29] Therefore, it could be argued that our study may not provide a reliable CME incidence. Still, another study found that an increase in CRT can be observed as late as 6 months after cataract surgery.[66] As the CRT was measured at 3 and 6 months after surgery, we should be able to investigate whether CRT affects BCVA at these events.

The RNFL thinning after episodes of increased IOP may occur over months; however, most of this effect is observed during the initial period.[67,68] As the patients treated with endothelial keratoplasty were treated with topical dexamethasone for 33 weeks, our study should be suitable to describe potential glaucomatous changes.

Visual acuity testing

In this study, we determined the BCVA using the ETDRS chart. This chart has high reliability and has been proposed as the primary chart for visual acuity testing.[57,69] The chart uses logarithmic decreasing letter sizes that accounts for the skewed nature of visual acuity. In addition, when BCVA is reported as the cumulative number of correctly identified letters, the score will intuitively increase with improved visual acuity as opposed to results reported in logMAR. Reporting the results in number of letters can cause slight confusion as the angle of resolution is not specified. Throughout this study, however, we used the conventional method in agreement with Beck et al.[70] that allows easy conversion of the BCVA into logMAR.

The Freiburg Acuity and Contrast Test

To estimate the contrast sensitivity, we used the FrACT. Many different tests are used to measure contrast sensitivity which complicates direct comparisons between study results. For the comparison of UT-DSAEK and DMEK, other approaches have already been used.[71-73]

A detailed examination of contrast sensitivity requires testing of multiple spatial frequencies forming a contrast sensitivity function curve. This approach is, however, demanding and can lead to patient attrition. FrACT only determines contrast sensitivity for a single optotype. Furthermore, the test is run in an electronic program that uses a best parametric estimation by a sequential testing method. These test characteristics reduce the needed number of presented optotypes thereby shortening examination time and minimizing patient attrition.[74]

As the test only uses one optotype, the results only reflect contrast sensitivity for low- and midrange spatial frequencies. Nonetheless, these may be the most important for patients when it comes to managing tasks in their everyday lives.[75,76]

Specular microscopy

Several instruments are available for ECD estimation. For FDA clinical trials, the Konan non-contact specular microscope has been a recommended instrument as well as confocal microscopy.[77] For patient convenience, however, the NIDEK CEM-530 used for this study is a fast, non-contact option. This specular microscope captures a 0.1 mm^2 image of a desired corneal zone. Previous studies have demonstrated high repeatability of the NIDEK CEM-530 even though automated analysis of the instrument might overestimate the ECD.[78] Manual cell counts, in contrast, have repeatedly proven to increase validity.[79-81] Therefore, we manually determined the ECD using the optional NIDEK software package NAVIS-EX.

Cataract grading

We chose to use the LOCS III for cataract grading. With this system, cataract is scored based on standardized images of four different cataract qualities. As such, scores between 0.1 and 6.9 are given for nuclear color and opalescence and between 0.1 and 5.9 for cortical cataract and posterior subcapsular opacities. The scoring is to some extent a subjective assessment. Therefore, cataract grading was performed before the randomization of patients included for endothelial keratoplasty to avoid bias. To increase the precision of the scoring, we used the standardized settings in agreement with those prescribed for photographic acquisition[59,82] for all scorings to increase the precision. Although slit-lamp grading might not be interchangeable to photographic grading, it has been proven to be reliable.[60]

Glaucomatous damage

Glaucoma patients are traditionally examined with perimetry that directly evaluates the functional status. The results of perimetry are, however, affected by the removal of opacities from cataract surgery[83] and likely from corneal grafting as in the present study. In addition, only patients without glaucoma and hence without perimetry experience were included. As such, the perimetry learning effect would have influenced the examinations over time.[84] As perimetry also is time-consuming and prone to attrition, we chose OCT-determined RNFL thickness as an objective surrogate measure to assess glaucomatous damage.

Pupillometry

For assessment of the iris function, we used the DP-2000 pupillometer which measures the pupil diameter and constriction velocities over a predefined period. The effect of accommodation on pupil size is well-known.[85,86] A standardized light stimulus, therefore, was elicited through diffusing screens that prevented accommodation. Furthermore, patients were placed in a completely darkened clinic for 5 minutes before the examination as light adaptation also affects pupil size.[87] The effect of mental activity on pupil size is also well-established[88]; however, this seems to be relatively short-termed with fluctuations in diameter lasting few seconds.[87] Another advantage of functional pupillometry is the continuous measurement of the scotopic pupil diameter which decreases the influence of fluctuations in the pupil diameter[87]; a phenomenon known as pupil unrest or hippus.[89] The DP-2000 pupillometer measures the pupil diameter as the entrance pupil through the cornea. Therefore, corneal refractive changes might, in theory, affect measurements which we did not account for. On the other hand, this effect is minimal after cataract surgery and endothelial keratoplasty.

Discussion

This study found that patients treated with UT-DSAEK had a significantly inferior BCVA than patients treated with DMEK 12 months after surgery, whereas contrast sensitivity was comparable. Patients treated with cataract surgery had a significantly better BCVA and contrast sensitivity than patients treated with DMEK 12 months after surgery. This study found no difference in CRT among the study groups 3 and 6 months after surgery. Furthermore, no association between change in CRT and BCVA was found. Compared with patients in the control group, the RNFL thickness and iris function in patients treated with endothelial keratoplasty were comparable and seemed unaffected by the increased IOP from the anterior chamber gas tamponade and steroid-induced elevated IOP. Cases with posterior synechiae were, however, observed in patients treated with endothelial keratoplasty. The posterior synechiae tended to affect the iris function.

Visual function

Until now, only the study by Dunker et al.[22] found a comparable visual acuity after UT-DSAEK and DMEK. In the studies by Chamberlain et al.[21] and Matsou et al.[23], UT-DSAEK resulted in an inferior visual acuity compared with DMEK as in the present study. Contrast sensitivity after UT-DSAEK and DMEK has previously been investigated by Dunker et al.[71] who used the CSV-1000 chart to test contrast sensitivity at different spatial frequencies. In agreement with the results of the present study, they found no significant difference between UT-DSAEK and DMEK for a combined estimate of the spatial frequencies. Torras-Sanvicens et al.[72] also found a comparable contrast sensitivity in their fellow-eye comparison of UT-DSAEK and DMEK. Only Mencucci et al.[73] found a significantly inferior contrast sensitivity after UT-DSAEK compared with DMEK. However, all these were minor studies and might have insufficient statistical power to effectively compare contrast sensitivity. As such, the evidence suggests that UT-DSAEK results in an inferior visual acuity compared with DMEK, while the measured contrast sensitivity is comparable.

The difference in visual acuity between UT-DSAEK and DMEK could be related to higher-order aberrations that have been associated with reduced visual acuity after endothelial keratoplasty.[90,91] This has also been found in recent comparisons of UT-DSAEK and DMEK. Duggan et al.[92] as well as Dunker et al.[71] found increased higher-order aberrations at the posterior corneal surface after UT-DSAEK compared with DMEK. Furthermore, both studies found a correlation between visual acuity and posterior corneal higher-order aberrations 6 and 12 months after surgery. Higher-order aberrations also affect contrast sensitivity.[93,94] However, as Dunker et al. found a comparable contrast sensitivity despite a difference in higher-order aberrations, these may play a minor role in contrast sensitivity after endothelial keratoplasty.

Corneal scatter as estimated by densitometry is another relevant factor to consider in relation to visual function. Hirabayashi et al.[95] found no difference in densitometry after UT-DSAEK and DMEK and concluded that densitometry could not explain the difference found in visual acuity. However, with increased corneal scatter, one would expect an inferior contrast sensitivity as a reduced amount of light

reaches the retina. Unfortunately, Hirabayashi et al. did not report contrast sensitivity after UT-DSAEK and DMEK.

Differences between UT-DSAEK and DMEK have often been attributed to the different interfaces that result from these techniques.[96,97] The comparable densitometry found by Hirabayashi et al.[95] does, however, support that the stroma-stroma interface found after UT-DSAEK does not affect the densitometry more than the interface found after DMEK. In fact, they found that the anterior part of the cornea affected the densitometry the most, which has also been found in other studies.[98] The amount of straylight estimated by the C-Quant from Oculus was also found to be comparable between UT-DSAEK and DMEK in the study by Dunker et al.[71], who found an association between straylight and BCVA 6 and 12 months after surgery. Still, the irregularity of the stroma-stroma interface of UT-DSAEK grafts may affect the visual outcomes. This effect is believed to be caused by the formation of corneal haze and fibrosis as stated by Ferrari et al.[99] They demonstrated a correlation between interface reflectivity and visual acuity using laser confocal microscopy. In conclusion, the stroma-stroma interface likely affects visual acuity, but the existing evidence is scarce.

The better visual function of patients in the control group compared with patients undergoing endothelial keratoplasty could be related to stromal changes in patients with FED. Long-term edema, as seen in patients with FED, has been associated with loss of stromal glycosaminoglycans.[100] This loss may affect the arrangement of collagen fibrils that is of utmost importance for corneal transparency. Reduced corneal transparency, in turn, may be observed as increased densitometry. In agreement with this, the duration of stromal edema as well as the recipient corneal thickness has been associated with visual acuity after endothelial keratoplasty in patients with FED.[101,102] Patients treated with DMEK in the present study had a lower CCT 6 months after surgery than patients treated with cataract surgery. As such, the loss of stromal glycosaminoglycans could explain a lower visual acuity in patients treated with EK compared with patients treated with cataract surgery in our study as well. Furthermore, higher-order aberrations and interface straylight may explain the difference in visual function in patients treated with endothelial keratoplasty and patients treated with cataract surgery in the present study.

In summary, the present study confirms that UT-DSAEK results in inferior BCVA compared with DMEK. This may be explained by differences in corneal higher-order aberrations. In addition, the contrast sensitivity is comparable after UT-DSAEK and DMEK. Patients without FED who are treated with cataract surgery obtain better visual acuity and contrast sensitivity than patients treated with endothelial keratoplasty.

Endothelial cell density

This study found a significantly lower ECD 12 months after UT-DSAEK compared with DMEK. Furthermore, 12 months after surgery, the ECD was lower in patients treated with DMEK than in patients treated with cataract surgery.

Previous randomized studies on UT-DSAEK and DMEK have found comparable ECD 12 months after surgery.[21-23] However, the peripheral ECD affects postoperative endothelial cell loss,[103,104] presumably due to migration of endothelial cells to areas with a lower ECD.[105] Therefore, the inclusion of patients with FED or PBK in these studies complicates a direct comparison of these and the present study. A comparison between studies is further complicated as our study only included phakic patients treated with triple-EK in contrast to previous studies. Although a comparable endothelial cell loss has been found 12 months after pseudophakic- and triple-EK,[106] other studies have found a larger endothelial cell loss after triple-EK.[107] As such, the lower ECD found in the present study may partly be explained by the fact that all patients underwent triple-EK.

As also stated in Paper I, the organ culture used for tissue dehydration could be another explanation for the significantly lower ECD after UT-DSAEK. The organ culture transport medium contains dextran which has proven to be toxic to endothelial cells.[108] Dunker et al.[22] also used a dextran-containing transport medium for tissue dehydration. In agreement with our study, they found a significantly lower ECD 3 months after surgery. Nonetheless, this difference gradually disappeared and a comparable ECD was found between UT-DSAEK and DMEK 12 months after surgery. From their data, this appeared to result from a decreasing ECD in their DMEK group. This was also noted by Chamberlain et al.[21] who stated that patients treated with DMEK had a more rapid decrease in ECD. However, Chamberlain et al. found no significant difference between groups through the first 12 postoperative months. Whether they used a dextran containing medium for tissue dehydration is not reported. A lower ECD after DSAEK than DMEK have occasionally been found, but none of these studies specified the organ culture used for tissue dehydration.[13,72]

The rebubbling rate of the present study might also partly explain the lower ECD after UT-DSAEK. Hayashi et al.[109] found an association between reduced ECD and rebubbling. In the present study, we found a rebubbling rate of 14% after UT-DSAEK compared to 3-4% in previous randomized trials.[21-23] However, as Hayashi et al. also stated, the direction of causality between ECD and rebubbling is unknown. Other studies have also failed to demonstrate an association between these outcomes.[110] As a previous study found no association between ECD and increased IOP from gas tamponade,[111] the insignificant effect of rebubbling is further emphasized. Ultimately, patients treated with UT-DSAEK still had a lower rebubbling rate than patients treated with DMEK despite a lower ECD. This further indicates that rebubbling only has a limited effect on ECD.

Retinal changes

CME can be defined as intraretinal cysts in the outer plexiform or inner nuclear retinal layers. The condition is defined as clinically significant if it is accompanied by compromised visual acuity. No patients demonstrated intraretinal cysts during the first 6 months after surgery in the present study. However, two cases demonstrated a CRT increase > 10%: one in the DMEK group and one in the control group. Both cases were subclinical, as they were unnoticed by the patients. We found no significant

differences in CRT among the three study groups 3 and 6 months after surgery. In addition, no correlation was found between BCVA and CRT 3 and 6 months after surgery.

Previous studies found an incidence of CME between 2.4%-12.7% after DSAEK[38,112] and 0.7%-15.6% after DMEK[34,36] which is markedly different from our results. However, we may have underestimated the incidence of subclinical CME since no examination was performed 4-6 weeks after surgery. This is further emphasized by the fact that seven patients had transillumination defects and seven had posterior synechiae without developing CME. A previous study found a strong correlation between iris damage, such as depigmentation or transillumination defects, and an increased risk of CME following DMEK surgery.[34] In agreement with this, Kocaba et al.[113] who routinely performed iridectomy found a CME incidence of 18% after triple-DMEK 6 months after surgery. The reported incidence of CME may as such be affected by the frequent use of iridotomy or iridectomy to avoid pupillary block in relation to endothelial keratoplasty.

The high incidence of clinically significant CME found in previous studies has also fostered an interest in improved CME prophylaxis. Hoerster et al.[114] studied the effect of topical steroids five times daily and an hourly regimen during the first postoperative week. Their study found nine cases of CME when patients were given topical steroids five times daily whereas none developed CME after the hourly regimen. In contrast, a large study on postoperative anti-inflammatory treatment after cataract surgery found no significant effect on postoperative inflammation and CRT when adding steroids to a non-steroidal anti-inflammatory drug (**NSAID**) treatment regimen.[115,116] Hoerster et al. did not mention postoperative NSAID treatment in their study. As the patients in the present study were treated with NSAID and topical steroids without clinically significant CME, this may serve as an applicable alternative to an intensified topical steroid regimen.

Myerscough et al.[38] reported the incidence of clinically significant CME for 2,233 endothelial keratoplasties. Their study showed that 2.4% of patients treated with DSAEK and 5.6% treated with DMEK developed CME. These incidences are in the lower end of what has been reported for both DSAEK and DMEK. In the context of our study these incidences would mean that only a couple of CME cases would be found in either of our study groups. Therefore, the missing CME cases could be a random coincidence. The lower risk of clinically significant CME after DSAEK than after DMEK found by Myerscough et al. is not directly comparable to our investigation of postoperative CRT. Nonetheless, in our study, no difference in CRT between UT-DSAEK and DMEK was found. As such, a conclusion on CME and CRT after DSAEK and DMEK is difficult to draw as the results are diverse and the evidence is limited.

Our results suggest that CRT is equally affected after endothelial keratoplasty and cataract surgery. However, patients treated with cataract surgery had higher LOCS III scores at baseline than patients treated with endothelial keratoplasty. Nuclear opalescence and nuclear color of the LOCS III cataract grading system have been correlated with increased phacoemulsification energy and time.[117,118] These factors, in turn, are assumed to increase postoperative inflammation and the risk of CME.[119] As such, this could also have affected our results.

In the present study, patients treated with endothelial keratoplasty were exposed to increased IOP from the 100% anterior chamber gas tamponade for 2 hours as well as long-term IOP fluctuations in the postoperative period. However, the RNFL thickness was lower in patients treated with cataract surgery than in patients treated with endothelial keratoplasty 12 months after surgery. As such, the IOP fluctuations seem to have had a clinically insignificant effect on the RNFL thickness. IOP increases commonly occur during the first year after endothelial keratoplasty which have been ascribed to the topical steroid treatment.[40,120] In agreement with this, the present study found that patients treated with endothelial keratoplasty had a higher IOP than patients in the control group 3 and 6 months after surgery. As standard, patients treated with endothelial keratoplasty were prescribed topical dexamethasone for 8 months after surgery. As the IOP decreased after dexamethasone treatment was terminated, this may also have been the causative agent in our study.

The clinically insignificant effect is further supported, as the RNFL thickness was comparable between patients, regardless of whether they developed increased IOP later than the first postoperative week or not. Furthermore, patients treated with endothelial keratoplasty had a comparable RNFL thickness regardless of whether they were rebubbled or not. As such, the increased IOP from the anterior chamber gas tamponade seems not to have affected the RNFL thickness.

In the interpretation of our results, one must keep in mind that patients with glaucoma were excluded from the study. IOP is the main risk factor of glaucoma, but the pathophysiology is still incompletely understood. The glaucomatous effect of increased IOP, however, is believed to be related to the anatomical structure of the lamina cribrosa and peripapillary sclera. Individuals with anatomical structures predisposing to glaucoma may as such have been excluded from our study. In addition, the risk of increased IOP after endothelial keratoplasty is higher in patients with preoperative glaucoma.[121,122] Therefore, our results may not be applicable to these patients and the effect of the high IOP related to the endothelial keratoplasty could have a detrimental effect in these susceptible patients.

Overall, the approach used for UT-DSAEK and DMEK seems to be safe when it comes to RNFL alterations. Both UT-DSAEK and DMEK demonstrated a comparable RNFL thickness 12 months after surgery.

The media clarity impacts OCT measurements as lower signal strength leads to an underestimation of retinal thickness. The importance of the OCT signal strength has been demonstrated for both CRT[123] and RNFL thickness.[124,125] In our study, this becomes problematic as both FED and cataract cause reduced signal strength and as these factors are unequally distributed in our groups.

The baseline characteristics of our study participants revealed significantly higher LOCS III scores for patients in the control group. After phacoemulsification and IOL implantation the media clarity, hence the OCT signal strength, may have improved more in the control group than in patients treated with endothelial keratoplasty. On the other hand, patients in the control group had healthy corneas in contrast to patients treated with endothelial keratoplasty who had FED.

Furthermore, the optical opacities are at different distances to the retina, which also might be important to the effect of these. Whatever the cause is, the improved media clarity from the performed procedures has improved the OCT signal strength. Therefore, the estimates of both CRT and RNFL thickness must have been more precise after surgery than at baseline. However, it remains unknown which of the procedures have had the highest impact on media clarity and the results must be carefully interpreted. Nevertheless, this may not have affected our comparison of UT-DSAEK and DMEK, as these groups were randomized and presumably had similar baseline characteristics.

Iris function

This study found a comparable pupillary function 12 months after UT-DSAEK and DMEK. The pupillary function was also comparable 12 months after cataract surgery and endothelial keratoplasty combined with phacoemulsification and IOL implantation.

The fixed dilated pupil of Urrets-Zavalia syndrome represents a severe loss of iris function. Atrophy from iris ischemia is a proposed mechanism for the syndrome,[53] as well as this has been linked to posterior synechiae.[47] These changes are believed to arise from increased IOP during ocular surgery.[51] Already in the 1970s, Gasset et al.[53] proposed, that a partial state of the condition could exist. As patients treated with endothelial keratoplasty are exposed to high IOP, especially during the anterior chamber gas tamponade, such a partial state may be found in these patients. Three months after surgery, the photopic pupil diameter was smaller and the maximum constriction velocity was higher for patients only treated with cataract surgery than patients treated with endothelial keratoplasty. However, after excluding patients with posterior synechiae, none of these findings were significant, indicating that the iris function may be intact after exposure to increased IOP. This notion is further supported, as the iris function was comparable regardless of whether patients had had an anterior chamber gas tamponade pressure above 40 mmHg or not. On the other hand, none of the patients only treated with cataract surgery demonstrated posterior synechiae. As such, endothelial keratoplasty affects the iris although the impact on iris function from atrophy seems negligible.

Patients with posterior synechiae had a smaller scotopic pupil diameter and a larger photopic pupil diameter than patients without posterior synechiae. However, the maximum and average constriction velocities were comparable. This is in agreement with Gasset et al.,[53] who described the partial state with altered pupil size and reaction to light. The Urrets-Zavalia syndrome seems to be associated to posterior synechiae, but these may represent different conditions. The results of the present study do not support that a partial state of Urrets-Zavalia syndrome exists.

Adverse events

This study found a comparable number of adverse events between UT-DSAEK and DMEK. Of interest, we found three rejection episodes after UT-DSAEK and one after DMEK. All presented after dexamethasone treatment had been discontinued and were reversible on intensified dexamethasone treatment. In previous randomized studies,[21-23] only one rejection episode after UT-DSAEK and none after DMEK have been reported during the first postoperative year. As discussed in Paper I, this might be explained by the shorter duration of topical dexamethasone treatment in our study compared with others, but it could also be a random coincidence. In Paper III, we found the increased IOP from steroid treatment to be clinically insignificant. It may therefore be safe to extend the dexamethasone treatment period to reduce the number of rejections. Nonetheless, there seems to be an overall tendency to a higher rejection risk after UT-DSAEK than after DMEK, which has also been found in earlier comparisons of DSAEK and DMEK.[126] This increased rejection risk could be related to the amount of stoma that is transplanted with this technique.[127]

In the studies by Chamberlain et al.[21] and Dunker et al.,[22] 24% of patients treated with DMEK were rebubbled which is comparable to the 22% that were rebubbled in the present study. However, only 4% of patients treated with UT-DSAEK were rebubbled in their study in contrast to 14% in ours. Many attempts have been made to decrease the number of rebubblings after endothelial keratoplasty. As the gas bubble supports graft adhesion, the size of the bubble is probably of importance. In the present study, the procedures were terminated with a 30-50% gas fill in contrast to approximately 80% in the studies by Chamberlain et al. and Dunker et al. An 80% gas fill requires an iridotomy or iridectomy to avoid pupillary block. This iatrogenic iris trauma may cause increased postoperative inflammation and, hence increased risk of CME. The lower rebubbling rate from this approach could cause an increased incidence of CME.

The presence of gas in the anterior chamber does not only support the graft; the physical properties of water are also affected. Through hydrogen bonds, the bipolar nature of water gives it adhesive properties that make it stick to other substances. At the same time, water molecules have strong cohesive properties that allow droplets to form. With the introduction of gas to the anterior chamber, the cohesive force of water surface tension becomes present. This force acts tangentially to the water surface. However, in the setting with a gas bubble in the anterior chamber, this force will ultimately be directed towards the center of the bubble according to Young-Laplace's law.[128] In the lungs, this inward directed force may even cause small airways to collapse as this contributes to airway compression.[129] The stiffness of the anterior chamber obviously prevents it from collapsing, but the force may have a pivotal effect on the graft adhesion. This effect might be exaggerated with ocular movement. Moreover, during a positional change, such as transitioning from the supine position to standing upright, the meniscus of the water can move over the inferior edge of the graft. In this scenario, the surface tension may cause the graft to lift off.

In the studies by Chamberlain et al.[21] and Dunker et al.,[22] the rebubbling rate has been found to be lower after UT-DSAEK than after DMEK. In contrast, Matsou et al.[23] found the rebubbling rate to be

equal between groups. However, in their study, SF_6 was only used for anterior chamber tamponade in patients treated with DMEK. As SF_6 is known to increase graft attachment[130] this may have affected their rebubbling rates.

Limitations

The results of the present study have some limitations which must be considered. One episode of primary graft failure was observed after UT-DSAEK and DMEK, respectively. As these patients were both regrafted with DMEK, our results could have been affected by this. However, as analyses were undertaken according to the *intention-to-treat* principle this would have diminished any difference between groups and increased the risk of a type-II error.

Patients with capsular rupture were excluded from the control group but not from groups treated with endothelial keratoplasty, which might have introduced selection bias to our study. Capsular rupture is associated with suboptimal visual acuity[62] and the selection bias is unbalanced. As such, this could explain some of the differences found in BCVA between the control group and the UT-DSAEK and DMEK groups. Other comparisons may also have been affected by this. Therefore, it must be kept in mind that patients treated with endothelial keratoplasty continuously were compared against patients with healthy corneas treated with uneventful cataract surgery.

As mentioned before, the control group was non-randomized. Differences in baseline characteristics therefore could have unforeseen consequences and introduce confounding to our results. Furthermore, in the present study, patients were excluded in case of concomitant eye diseases and the results might not be transferable to certain patient subgroups. This might be the case for our results on CRT, which might not apply to patients with conditions such as uveitis or diabetes.

The Department of Ophthalmology at Aarhus University Hospital is the only center in the Western Denmark area accredited to perform keratoplasties, and patients with combined FED and cataract were recruited from the entire region. In contrast, patients only suffering from cataract were primarily recruited from private clinics in the area adjacent to Aarhus. The longer distance from home to the department for FED patients and the high number of consultations, could have affected these patients in their decision to participate. For instance, selection bias could have occurred if elderly or disabled patients were more likely to decline participation.

Conclusions and perspectives

The main findings of the present study are as follows:

1) We can reject the hypothesis that BCVA 12 months after UT-DSAEK and DMEK is comparable. DMEK had a significantly better BCVA at 12 months than UT-DSAEK. However, no significant difference in contrast sensitivity was found 12 months after UT-DSAEK and DMEK, and the hypothesis that the contrast sensitivity is similar after UT-DSAEK and DMEK cannot be rejected. Patients treated with uneventful cataract surgery had better BCVA and contrast sensitivity at 12 months compared with patients treated with DMEK. The hypothesis that BCVA and contrast sensitivity are comparable 12 months after uneventful cataract surgery and endothelial dystrophy can be rejected.

2) CRT was comparable 12 months after UT-DSAEK, DMEK and cataract surgery, and the change in CRT and BCVA was uncorrelated. Based on these findings, the hypothesis that CRT was comparable 3 and 6 months after UT-DSAEK, DMEK and uneventful cataract surgery cannot be rejected. Furthermore, the hypothesis that the change in CRT and BCVA are correlated cannot be rejected either.

3) RNFL thickness and pupil function were comparable 12 months after UT-DSAEK, DMEK and cataract surgery. As such, the hypothesis that the RNFL thickness and iris function at 12 months are comparable among the study groups cannot be rejected.

Endothelial keratoplasty is the current standard for the treatment of endothelial dysfunction. Despite the improvement with the UT-DSAEK grafts, DMEK still seems to provide better visual acuity. As such, UT-DSAEK grafts do not seem to represent a significant advancement in the treatment of endothelial dysfunction; however, new options are emerging.

In 2012, Shah et al.[131] reported a case of spontaneous visual recovery after an episode of graft detachment. In their case report, they described that endothelial cells were detectable over the bared corneal center using specular microscopy. This led to studies that investigated the effect of Descemet's membrane removal alone; a procedure known as Descemet's stripping only or Descemet's stripping without keratoplasty. With this technique, usually an area with a diameter of 4 mm is stripped in contrast to the diameter of about 8 mm that is used in endothelial keratoplasty. The technique relies on the migration of endothelial cells from the periphery to the area where Descemet's membrane is removed. The slightly smaller diameter reduced the required number of migrating endothelial cells. Since the technique relies on viable endothelial cells in the periphery, it only applies to patients with FED that hold such a reserve of endothelial cells in contrast to patients with PBK.

The initial success rate of the Descemet's stripping only technique seemed to be limited.[132] However, through studies by Okumura et al.[133] the application of Rho kinase inhibitors proved to improve the proliferation, migration and adhesion of corneal endothelial cells. In studies where the Descemet's stripping only was combined with Rho kinase inhibitors the success rate was higher.[134]

Rho kinase inhibitors have also been used for ex vivo expansion of corneal endothelial cells. Kinoshita et al.[135] cultured human endothelial cells that were later injected into the anterior chamber in a study on 11 participants with bullous keratopathy. After injection participants were left supine, facing downward for three hours. They reported that all 11 participants obtained an ECD above 900 cells/mm^2 24 weeks after the procedure; a promising result. An advantage of this technique is that it does not depend on a peripheral reserve of viable endothelial cells.

An artificial hydrophilic device made of an acrylic material, known as the EndoArt, could also be an alternative to the traditional keratoplasties. The EndoArt is an implant with a diameter of 6 mm and a thickness of 50 µm that intends to block the leaky barrier of the endothelium. The corneal deturgescence is then believed to be reestablished due to evaporation from the corneal epithelium.[136] Although this new device is artificial and has the potential to overcome the donor tissue shortage seen worldwide,[137] the reported visual outcomes still seem to be inferior to DMEK.[136]

As such, promising new approaches are on the horizon, potentially paving the way for a new standard in the treatment of endothelial dysfunction. However, only time will tell if these approaches prove successful.

English summary

The present thesis aimed to compare visual acuity, contrast sensitivity and side-effects in patients treated with ultrathin Descemet's stripping automated endothelial keratoplasty (UT-DSAEK) and Descemet's membrane endothelial keratoplasty (DMEK). Furthermore, the thesis aimed to compare these outcomes in patients treated with endothelial keratoplasty and uneventful cataract surgery.

The thesis is based on three papers with data originating from the same cohort of patients. The study was conducted as a randomized controlled clinical trial with an additional non-randomized control group. Patients suffering from cataract and Fuchs' endothelial dystrophy were included and allocated to either UT-DSAEK or DMEK combined with phacoemulsification and lens implantation. The control group consisted of patients only suffering from cataract who were treated with phacoemulsification and lens implantation.

Paper I investigated visual function in the three study groups. In this paper, patients treated with UT-DSAEK had an inferior visual acuity compared with patients treated with DMEK 12 months after surgery. However, contrast sensitivity was comparable 12 months after UT-DSAEK and DMEK. 12 months after surgery patients treated with UT-DSAEK had a significantly lower endothelial cell density compared with patients treated with DMEK. Furthermore, patients treated with DMEK had inferior visual acuity and contrast sensitivity compared with patients treated with cataract surgery 12 months after surgery.

Paper II investigated the central retinal thickness in patients treated with UT-DSAEK, DMEK or cataract surgery. No difference in retinal thickness was found among the study groups 3 and 6 months after surgery. No cases with clinically significant cystoid macular edema nor intraretinal cysts on OCT were observed 3 and 6 months after surgery. No correlation was found between the change in retinal thickness and visual acuity.

Paper III investigated the retinal nerve fiber layer thickness and the iris function in patients treated with UT-DSAEK, DMEK and cataract surgery. After 12 months, the retinal nerve fiber layer thickness appeared to be equally affected in patients treated with UT-DSAEK and DMEK as well as in patients treated with endothelial keratoplasty or cataract surgery. Furthermore, the iris function was comparable after 12 months in patients treated with UT-DSAEK and DMEK as well as in patients treated with endothelial keratoplasty or cataract surgery.

Dansk resumé

Denne afhandling havde til formål at sammenligne synsstyrke, kontrastsensitivitet og bivirkninger hos patienter behandlet med ultrathin Descemet's stripping automated endothelial keratoplasty (UT-DSAEK) og Descemet's membrane endothelial keratoplasty (DMEK). Afhandlingen havde yderligere til formål at sammenligne disse udfaldsmål hos patienter behandlet med endotelkeratoplastik og ukompliceret kataraktoperation.

Afhandlingen består af tre artikler, som baserer sig på data fra samme patientkohorte. Studiet blev udført som et randomiseret, kontrolleret, klinisk studie suppleret med en ikke-randomiseret kontrolgruppe. Studiet inkluderede patienter med Fuchs' endoteldystrofi og katarakt, som blev allokeret til behandling med enten UT-DSAEK eller DMEK kombineret med phakoemulsifikation og linseimplantation. Patienter uden andre øjensygdomme end katarakt blev inkluderet i studiets kontrolgruppe og behandlet med phakoemulsifikation og linseimplantation.

Artikel I undersøgte synsfunktionen i de tre studiegrupper. Patienter behandlet med UT-DSAEK viste sig i denne artikel at have lavere synsstyrke 12 måneder efter operation sammenlignet med patienter behandlet med DMEK. Dog var kontrastsensitiviteten sammenlignelig 12 måneder efter UT-DSAEK og DMEK. Patienter behandlet med UT-DSAEK havde færre endotelceller end patienter behandlet med DMEK 12 måneder efter operation. Yderligere havde patienter behandlet med DMEK lavere synsstyrke og kontrastsensitivitet 12 måneder efter operation end patienter kun behandlet med kataraktoperation.

Artikel II undersøgte den centrale, retinale tykkelse ved patienter behandlet med UT-DSAEK, DMEK og kataraktoperation. Dette studie fandt ingen forskel i den retinale tykkelse 3 og 6 måneder efter operation blandt de tre studiegrupper. Yderligere blev der ikke observeret tilfælde af klinisk signifikant cystoidt makulært ødem, ligesom ingen patienter havde intraretinale cyster i forbindelse med OCT-skanningerne foretaget 3 og 6 måneder efter operation. Studiet fandt ingen sammenhæng mellem ændring i den retinale tykkelse og synsstyrken.

Artikel III undersøgte det retinale nervefiberlags tykkelse samt irisfunktion ved patienter behandlet med UT-DSAEK, DMEK og kataraktoperation. Påvirkningen af det retinale nervefiberlags tykkelse var sammenlignelig mellem patienter behandlet med UT-DSAEK og DMEK såvel som mellem patienter behandlet med endotelkeratoplastik og kataraktoperation. Ydermere var irisfunktionen efter 12 måneder sammenlignelig mellem patienter behandlet med UT-DSAEK og DMEK såvel som mellem patienter behandlet med endotelkeratoplastik og kataraktoperation.

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Paper I

Visual function after ultrathin Descemet's stripping automated endothelial keratoplasty or Descemet's membrane endothelial keratoplasty combined with cataract surgery: a randomised controlled clinical trial.

Visual function after ultrathin Descemet's stripping automated endothelial keratoplasty or Descemet's membrane endothelial keratoplasty combined with cataract surgery: a randomised controlled clinical trial

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ABSTRACT

Aims To compare best-corrected visual acuity (BCVA), contrast sensitivity and endothelial cell density (ECD) after ultrathin Descemet's stripping automated endothelial keratoplasty (UT-DSAEK) and Descemet's membrane endothelial keratoplasty (DMEK).

Methods A randomised, single-blinded, single-centre design was used. 72 patients with Fuchs' endothelial dystrophy and cataract were randomised to UT-DSAEK or DMEK combined with phacoemulsification and lens implantation. 27 patients with cataract were included in a control group and treated with phacoemulsification and lens implantation. The primary outcome was BCVA at 12 months.

Results Compared with UT-DSAEK, DMEK resulted in better BCVA with mean differences of 6.1 early treatment diabetic retinopathy study (ETDRS) (p=0.001) after 3 months, 7.4 ETDRS (p<0.001) after 6 months and 5.7 ETDRS (p<0.001) after 12 months. The control group obtained significantly better BCVA with a mean difference of 5.2 ETDRS (p<0.001) compared with DMEK 12 months postoperatively. Compared with UT-DSAEK, contrast sensitivity was significantly better 3 months after DMEK with a mean difference of 0.10 LogCS (p=0.03). However, our study found no effect after 12 months (p=0.08). ECD was significantly lower after UT-DSAEK compared with DMEK with mean differences of 332 cells/mm^2 (p<0.01) after 3 months, 296 cells/mm^2 (p<0.01) after 6 months and 227 cells/mm^2 (p=0.03) after 12 months.

Conclusions Compared with UT-DSAEK, DMEK resulted in better BCVA 3, 6 and 12 months postoperatively. Twelve months postoperatively, DMEK had a higher ECD than UT-DSAEK; however, no difference in contrast sensitivity was found.

Trial registration number NCT04417959

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Previous comparisons of visual acuity after ultrathin Descemet's stripping automated endothelial keratoplasty (UT-DSAEK) and Descemet's membrane endothelial keratoplasty (DMEK) have reached differing conclusions and results on contrast sensitivity have rarely been reported. Furthermore, previous studies have included pseudophakic endothelial keratoplasties, and occasionally mixed cohorts with pseudophakic bullous keratopathy and Fuchs' endothelial dystrophy (FED) have been used.

WHAT THIS STUDY ADDS

⇒ A comparison of UT-DSAEK and DMEK combined with phacoemulsification and lens implantation in a well-defined cohort of patients with FED and cataract. It is confirmed that DMEK outperforms UT-DSAEK when it comes to visual acuity, contrast sensitivity and endothelial cell density. Cataract patients without corneal morbidities treated with cataract surgery obtain significantly better visual acuity compared with FED patients treated with DMEK combined with cataract surgery.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study supports the belief that DMEK is the better choice for the treatment of endothelial dysfunction. Still, larger series investigating safety and adverse events after the interventions are needed.

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INTRODUCTION

With studies demonstrating better visual acuity with thinner Descemet's stripping automated endothelial keratoplasty (DSAEK) grafts[1–3] and the advent of the ultrathin DSAEK (UT-DSAEK), the interest for the future application of the DSAEK and Descemet's membrane endothelial keratoplasty (DMEK) techniques has increased.

Only few randomised studies so far have compared visual acuity after UT-DSAEK and DMEK with differing results. Chamberlain *et al*[4] and Matsou *et al*[5] both demonstrated a better visual acuity 12 months after DMEK; however, both pseudophakic and triple endothelial keratoplasties were performed. This fostered a comparison by Dunker *et al*[6] in a homogenous pseudophakic cohort where no difference was found. Still, no comparison of UT-DSAEK and DMEK combined with cataract surgery has been performed.

Additionally, contrast sensitivity is essential for visual quality evaluation.[7 8] Until now, only one randomised trial has studied this after UT-DSAEK and DMEK. However, no significant difference was found.[9] Therefore, we aimed to investigate best-corrected visual acuity (BCVA), contrast sensitivity

and endothelial cell density (ECD) after UT-DSAEK or DMEK combined with cataract surgery for the treatment of Fuchs' endothelial dystrophy (FED). As prior studies,[4 6] we defined UT-DSAEK as DSAEK with a graft thickness <100 µm.

MATERIALS AND METHODS

Trial design and blinding

A randomised, controlled design was used. Patients with FED and cataract were included and equally randomised (1:1) to UT-DSAEK or DMEK combined with cataract surgery. An additional group of patients only suffering from cataract was included as a control group and treated with phacoemulsification and lens implantation. Only one eye was included per participant.

Participants included for endothelial keratoplasty were blinded to the performed intervention (DMEK or UT-DSAEK), whereas participants in the control group were not blinded. The study methods have been described elsewhere.[10] Written informed consent was provided by all included study participants. The study was adhered to the tenets of the Declaration of Helsinki and was approved by The Central Denmark Region Committee on Health Research Ethics. The study registration is available at http://clinicaltrials.gov.

Participants

Patients referred to the Department of Ophthalmology, Aarhus, Denmark between June 2020 and January 2022 were evaluated for inclusion. Patients aged between 50 and 81 years with FED and/or cataract were eligible for inclusion. Patients with other ocular comorbidities such as corneal vascularisation, glaucoma, uveitis, exudative age-related macular degeneration, geographic retinal atrophy, possible vision affecting systemic diseases and prior ocular surgery or trauma were excluded.

Eye banking technique

Corneal grafts were prepared in the Danish Cornea Bank, Aarhus, Denmark. Tissue storage and preparation have been described elsewhere.[11] Tissue procurement was completed within 48 hours after death. Biomicroscopic evaluations were performed by eye bank technicians before excision of 16 mm corneoscleral buttons.

Donor tissue was stored at 30°C in 50 mL to 65 mL organ culture (Tissue-C, Alchimia, Ponte San Nicoló, Italy). The ECD was determined by means of a manual cell count and had to exceed 2000 cells/mm^2 to be suitable for endothelial keratoplasty. Tissue for UT-DSAEK grafts was initially dehydrated in a dextran-containing organ culture transport medium (Carry-C, Alchimia, Ponte San Nicolò, Italy) for 24–48 hours. Donor tissue dissection was performed using a microkeratome (OU LC head-Art. Chamber, Moria, Anthony, France) and console (Evolution 3E, Moria, Anthony, France). Aiming at an 80 µm graft thickness, a cutting head was in each case chosen accordingly. Postdissection graft thickness was determined using optical coherence tomography (OCT) scans (CASIA SS-1000, TOMEY, Nagoya, Japan). UT-DSAEK grafts were transported to the operating theatre submerged in transport medium.

For DMEK grafts, Descemet's membrane of the donor cornea was initially opened along the trabecular meshwork using a Sinskey Hook. Tissue was stained with Trypan blue (MONO-BLUE NafX, BVI, Toulouse, France) and submersed in a saline solution before Descemet's membrane was peeled using blunt forceps. Grafts were trephined to an 8 mm diameter before a triangular mark was cut to indicate orientation. Grafts were preloaded into a Tan Endoglide (DMEK EndoGlide, Coronet, Ripon, United Kingdom) with the endothelium inwards folded and transported to the operating theatre in organ culture.

Surgical technique and postoperative management

All included patients underwent cataract surgery with phacoemulsification and intraocular lens (AcrySof IQ SA60WF, Alcon, Geneva, Switzerland) implantation. Patients in the control group were anaesthetised using diclofenac (Voltaren Ophtha, 1 mg/mL, GSK Consumer Healthcare, Brøndby, Denmark) and oxybuprocaine eyedrops (Novesine, 0.4%, OmniVision, Puchheim, Germany).

Intracameral lidocaine was administered as well (Xylocain, 10 mg/mL, Aspen Pharma, Dublin, Ireland). At the end of surgery, intracameral cefuroxime 0.1 mL (Aprokam 50 mg/mL, Théa, Clearmont-Ferrand, France) and a dorzolamide eyedrop (Dorzolamid, 20 mg/mL, STADA Nordic, Denmark) were administered.

For endothelial keratoplasty, a solution comprised of bupivacaine 2 mL (0.5% MarcainAdrenalin, Aspen Nordic, Ballerup, Denmark) and lidocaine 3 mL (2% Lidokain-Adrenalin SAD Amgros I/S, Copenhagen, Denmark) was used for peribulbar anaesthesia. An anterior chamber maintainer was used for the procedure. Using a reverse Sinskey hook, descemetorhexis was performed and the Descemet's membrane was stripped. UT-DSAEK grafts were trephined to an 8 mm diameter using a Hessburg-Barron punch. At the 12 o'clock position, a 4 mm tunnel was made. The graft was implanted using a pull-through technique by means of a Busin glide and forceps. The DMEK graft was introduced to the anterior chamber through a 2.65 mm incision at the 12 o'clock position using a pull-trough technique by means of forceps and Tan Endoglide. Iridectomies were not performed.

For all endothelial keratoplasties, correct graft positioning was ensured using intraoperative OCT (HS Hi-R NEO 900A NIR, Haag-Streit, Koeniz, Switzerland). In each case, intracameral cefuroxime 0.1 mL (Aprokam 50 mg/mL, Théa, Clearmont-Ferrand, France) and subconjunctival dexamethasone 1 mg (Dexamethasone phosphate Hameln 4 mg/mL, Hameln pharma gmbh, Hameln, Germany) were administered. Graft positioning was secured using full anterior chamber gas tamponade (20% SF_6) and the patient was left supine for 2 hours. Thereafter, the gas was reduced to occupy between one-third and half of the anterior chamber. Oral acetazolamide 500 mg was administered after the procedure and in the evening. All interventions were performed by one of two experienced surgeons (AI and JH). Postoperatively, graft adhesion was evaluated with slit-lamp examination and anterior segment OCT (CASIA2, Tomey Corporation, Nagoya, Japan). If less than two-thirds of the graft was attached, rebubbling was performed.

Postoperatively, patients were prescribed a combination of dexamethasone and tobramycin (Oridecin, dexamethasone 1 mg/mL and tobramycin 3 mg/mL, Orifarm Generics, Odense, Denmark) six times daily for the first postoperative week. This was gradually tapered every 8 weeks to 4, 3, 2 and 1 drop daily until the treatment was ended after 7.5 months. For the first 3 postoperative weeks, diclofenac eyedrops (Voltaren Ophtha, 1 mg/mL, GSK Consumer Healthcare, Brøndby, Denmark) were administered ter in die The control group was postoperatively treated with dexamethasone (Maxidex, 1 mg/mL, Novartis, Copenhagen, Denmark) and diclofenac eyedrops (Voltabak, 1 mg/mL, Théa Nordic, Hørsholm, Denmark) ter in die for 2 and 3 weeks, respectively.

Outcome measures

The primary study outcome was BCVA 12 months after surgery. BCVA at 3 and 6 months; contrast sensitivity at 3, 6 and 12 months and ECD at 3, 6 and 12 months were secondary outcomes.

Clinical examinations

Full clinical examination was performed by a non-blinded physician (MM) preoperatively and 3, 6 and 12 months postoperatively. Patients were examined using specular microscopy (NIDEK CEM-530, NIDEK Co, Gamagori, Japan). At each examination, three consecutive central corneal images were obtained. The ECD was manually determined using the centre point function of the optional NIDEK software package (NAVIS-EX, NIDEK, Gamagori, Japan). For analysis, the average of the three obtained estimates was used. Autorefraction (TONOREF II, NIDEK, Gamagori, Japan) was then performed before CCT was determined using anterior segment OCT scans (CASIA2, Tomey Corporation, Nagoya, Japan) and the magnitude of anterior corneal astigmatism using high-resolution Scheimpflug tomography images (Pentacam, HR, Oculus Optikgeräte GmbH, Wetzlar, Germany).

For visual function testing, the clinic illuminance was kept between 250 and 270 Lux (LX-1108 light metre, Lutron Electronic Enterprise, Datong, Taiwan) and optotypes were presented on an electronic LED-screen (Polaphor light system, Block Optics Ltd., Dortmund, Germany) at a 4 m distance. BCVA was measured using the early treatment diabetic retinopathy study (ETDRS) chart in agreement with a previously described approach.[12] For clarification, patients were asked to read presented letters from left to right. The test was terminated when less than three letters per line were identified and the cumulative number of correctly identified letters was registered. Contrast sensitivity was determined using the Freiburg Acuity and Contrast Test (FrACT) in agreement with a previously described approach.[13] Briefly, the test presented a Landolt C and used a best parametric estimation by sequential testing (PEST) algorithm for threshold determination. For analysis, logarithmic transformed reciprocal values of the contrast sensitivity in Weber contrast units (LogCS) were used.

Sample size

The power calculation was based on the study by Chamberlain *et al*[4] who found an SD of 0.18 and 0.12 logarithm of the minimum angle of resolution (logMAR) for UT-DSAEK and DMEK, respectively. A two-sided $\alpha=0.05$ and a power of at least 85% were used. Based on this, it was estimated that 31 participants in each group were required to detect a 0.12 logMAR or 6 ETDRS difference.

Randomisation

Participants included for endothelial keratoplasty were allocated to UT-DSAEK or DMEK using block randomisation after baseline data had been collected. Approximately once every month, a person with no other relation to the project allocated an equal number of participants using random computer-generated numbers (Microsoft Excel 2019 for Windows). Values between 0 and 1 were simultaneously assigned to each participant in the block. The highest scoring half was allocated to UT-DSAEK; the other half was allocated to DMEK.

Statistical analysis

Collected data were entered into an electronic research database. Statistical analyses were performed in STATA (Stata version V.17.0, Stata, College Station, USA). For repeated measures, a multivariate linear mixed effects model was used. For comparisons of UT-DSAEK and DMEK, estimates were adjusted for baseline levels. All estimates were age and sex adjusted. T-tests were used for pairwise post hoc comparisons and pairwise comparisons of continuous variables. The χ^2-test was used for dichotomous comparisons. QQ-plots were used to check normality assumptions and analyses were undertaken on a logarithmic scale if relevant. Data distributions were evaluated using SD comparison tests. In agreement with the power calculation, a 5% significance level was used.

Table 1 Baseline characteristics, mean±SD (95% CI)

	UT-DSAEK (n=35)	DMEK (n=36)
Recipient characteristics		
Female, %	62.9 (44.9; 78.5)	72.2 (54.8; 85.8)
Age, years	69.2±6.1 (67.1; 71.3)	68.5±6.2 (66.4; 70.6)
BCVA, ETDRS letters	69.0±4.9 (67.3; 70.7)	67.4±7.7 (64.8; 70.0)
CS, LogCS	1.02±0.17 (0.96; 1.07)	1.05±0.19 (0.99; 1.12)
CCT, µm	616±56 (597; 635)	606±52 (589; 624)
Anterior corneal astigmatism, D*	−0.78±1.91 (-0.98; −0.63)	−0.80±2.20 (-1.04; −0.61)
Donor characteristics		
Female, %	48.6 (31.4; 66.0)	36.1 (20.8; 53.8)
Age, years	73.4±12.1 (69.3; 77.6)	71.3±10.0 (67.9; 74.7)
Time to enucleation, hours*	16.6±1.6 (14.1; 19.5)	16.6±1.7 (13.9; 19.8)
Tissue preservation time, days	33.0±9.1 (29.9; 36.1)	31.4±8.3 (28.6; 34.2)
ECD, cells/mm^2	2482±342 (2364; 2599)	2696±245 (2613; 2779)
Post-cut graft thickness, µm	81±16 (75; 86)	–

*Median values.
BCVA, best-corrected visual acuity; CCT, central corneal thickness; CS, contrast sensitivity; D, diopters; DMEK, Descemet's membrane endothelial keratoplasty; ECD, endothelial cell density; ETDRS, early treatment diabetic retinopathy study; UT-DSAEK, ultrathin Descemet's stripping automated endothelial keratoplasty.

RESULTS

Baseline characteristics

In total, 72 patients were included for UT-DSAEK or DMEK and 40 patients for cataract surgery. The participant follow-up was completed in January 2023. Table 1 shows baseline characteristics for participants included for endothelial keratoplasty. In agreement with the Consolidated Standards of Reporting Trials (CONSORT) guidelines,[14] no statistical tests were performed on the baseline characteristics of the randomised groups.

In the UT-DSAEK group, one participant died prior to the intervention. In addition, one patient in the UT-DSAEK group was unable to attend the 6-month examination. After DMEK, no participants were lost to follow-up. In the UT-DSAEK group, one patient had capsular rupture during cataract surgery, and one developed a postoperative condition of sterile endophthalmitis. Two cases of primary graft failure, one after UT-DSAEK and one after DMEK, were observed. Both were regrafted with DMEK but remained in their initially allocated groups for analysis following the intention-to-treat principle. A sensitivity analysis was conducted to evaluate the effect of excluding participants with primary failure, capsular rupture and endophthalmitis but no results were significantly changed. In the control group, one patient relocated and was lost to follow-up 6 and 12 months postoperatively but was included in the final analysis. Three participants in the control group were excluded from the final analyses due to capsular rupture. As such 35, 36 and 37 participants were included for the final analyses for the UT-DSAEK, DMEK and

control group, respectively. Figure 1 shows a CONSORT flow diagram. Table 2 shows baseline characteristics of the control group compared with participants included for endothelial keratoplasty. The control group had a mean ECD of 2461 cells/mm^2 (95% CI 2324 to 2598) at baseline.

Visual acuity

DMEK resulted in a significantly better visual acuity compared with UT-DSAEK with a mean difference of 6.1 ETDRS (95% CI 2.6 to 9.7, p=0.001) after 3 months, 7.4 ETDRS (95% CI 4.1 to 10.7, p<0.001) after 6 months and 5.7 ETDRS (95% CI 3.0 to 8.5, p<0.001) after 12 months. After 12 months, the control group had a significantly higher mean BCVA of 5.2 ETDRS (95% CI 2.9 to 7.4, p<0.001) compared with DMEK. During the study period, the progression in BCVA mean curves was significantly different among the three study groups (p<0.001). Table 3 shows results on visual acuity, and figure 2 depicts BCVA mean curves.

Contrast sensitivity

Contrast sensitivity was significantly better 3 months after DMEK compared with UT-DSAEK with a mean difference of 0.10 LogCS (95% CI 0.01 to 0.19, p=0.03). We found a non-significant mean difference of 0.08 LogCS (95% CI −0.01 to 0.18, p=0.09) after 6 months and a mean difference of 0.07 LogCS (95% CI −0.01 to 0.16, p=0.08) after 12 months. After 12 months, the control group demonstrated a significantly better contrast sensitivity of 0.09 LogCS (95% CI 0.02 to 0.15, p=0.01) compared with DMEK and 0.17 LogCS (95% CI 0.10 to 0.24, p<0.001) compared with UT-DSAEK. The progression of the contrast sensitivity mean curves during the study period was comparable among the three study groups (p=0.07). Nonetheless, contrast sensitivity mean curve levels were significantly different between study groups (p<0.001). Table 3 shows results on contrast sensitivity and figure 3 depicts contrast sensitivity mean curves.

Endothelial cell density

ECD was significantly lower after UT-DSAEK than after DMEK with mean differences of 332 cells/mm^2 (95% CI 108 to 555, p<0.01) after 3 months, 296 cells/mm^2 (95% CI 81 to 510, p<0.01) after 6 months, and 227 cells/mm^2 (95% CI 22 to 431, p=0.03) after 12 months. During the postoperative period, the progression in ECD mean curves was significantly different among the three study groups (p<0.001). Table 3 shows results on postoperative ECD, and figure 4 depicts ECD mean curves.

Adverse events

Rebubbling was performed in 5 (14%) patients after UT-DSAEK and 8 (22%) after DMEK. Six patients (17%) had increased intraocular pressure (defined as >25 mm Hg) after UT-DSAEK and 8 (22%) after DMEK. In one patient of the DMEK group, the intraocular pressure remained increased after termination of steroid treatment. During the first 12 postoperative months, three (9%) rejection episodes were observed after UT-DSAEK and one (3%) after DMEK. All episodes were reversible on intensified steroid treatment. Four (11%) patients developed posterior capsular opacification within 6 months after UT-DSAEK and had Nd:YAG capsulotomy performed. No other patients showed signs of posterior capsular opacification. In total, 20 adverse events were registered after UT-DSAEK and 20 after DMEK. Table 4 shows the cumulative number of adverse events.

DISCUSSION

In our study, DMEK resulted in a significantly better BCVA compared with UT-DSAEK throughout the first postoperative year. This agrees with the studies by Chamberlain *et al*[4] and Matsou *et al*.[5] Additionally, we demonstrated a significant difference in BCVA mean curve progression through the first year among our study groups (p<0.001). As such, only the study by Dunker *et al*[6] have found comparable BCVA after the interventions.

In the studies by Chamberlain *et al* and Matsou *et al* both pseudophakic and triple EK were performed. Previous studies have shown better visual acuity after triple DMEK compared with pseudophakic DMEK,[15 16] which complicates the interpretation of their results. The present study does, however, support these and confirms that DMEK outperforms UT-DSAEK, when it comes to visual acuity.

Results on contrast sensitivity after UT-DSAEK and DMEK have rarely been reported. Our study found a significantly better contrast sensitivity 3 months after DMEK compared with UT-DSAEK. This agrees with the results reported by Dunker *et al*[9] who also found a significantly better contrast sensitivity 3 months after DMEK compared with UT-DSAEK.

Results on contrast sensitivity are usually difficult to compare among studies due to different approaches to threshold estimation. In our study, we used the FrACT, which is based on a best PEST algorithm for threshold estimation. Using a Landolt C at an angular size of 6/75 Snellen fraction, the test measures contrast sensitivity for low and midrange spatial frequencies. In contrast, the test used by Dunker *et al* estimates thresholds for several spatial frequencies.

Using yet another way of reporting contrast sensitivity, Mencucci *et al*[17] performed a retrospective comparison of UT-DSAEK and DMEK. In their study, DMEK resulted in significantly better contrast sensitivity 12 months after surgery compared with UT-DSAEK at a spatial frequency of six cycles per degree under photopic conditions. No significant differences were found at other spatial frequencies. Therefore, DMEK may provide better contrast sensitivity compared with UT-DSAEK, but only for certain spatial frequencies.

As in the study by Dunker *et al*, mean differences in contrast sensitivity between UT-DSAEK and DMEK were reduced over time in our study. Therefore, UT-DSAEK seems to have a slower recovery of contrast sensitivity. However, contrast sensitivity mean curve progression was not significantly different among our groups (p=0.07).

Our results suggest that the difference in contrast sensitivity between the control group and DMEK is comparable to the reduction seen after refractive corneal surgery[13]; the difference between the control group and UT-DSAEK is more than two times of that.

Our study also provides a comparison of visual function after endothelial keratoplasty and cataract surgery. Compared with the DMEK group, participants in the control group without FED obtained significantly better BCVA and contrast sensitivity 12 months after surgery. Therefore, despite that DMEK mimics the normal corneal anatomy, visual acuity remains suboptimal postoperatively. The reason for this could be stromal changes related to the DMEK procedure or to long-term disturbances in corneal deturgescence in FED patients.

In previous studies, no significant differences in ECD have been found 12 months after UT-DSAEK and DMEK.[4–6] This contrasts with our study where UT-DSAEK resulted in a significantly lower ECD compared with DMEK after 12 months. Between-study

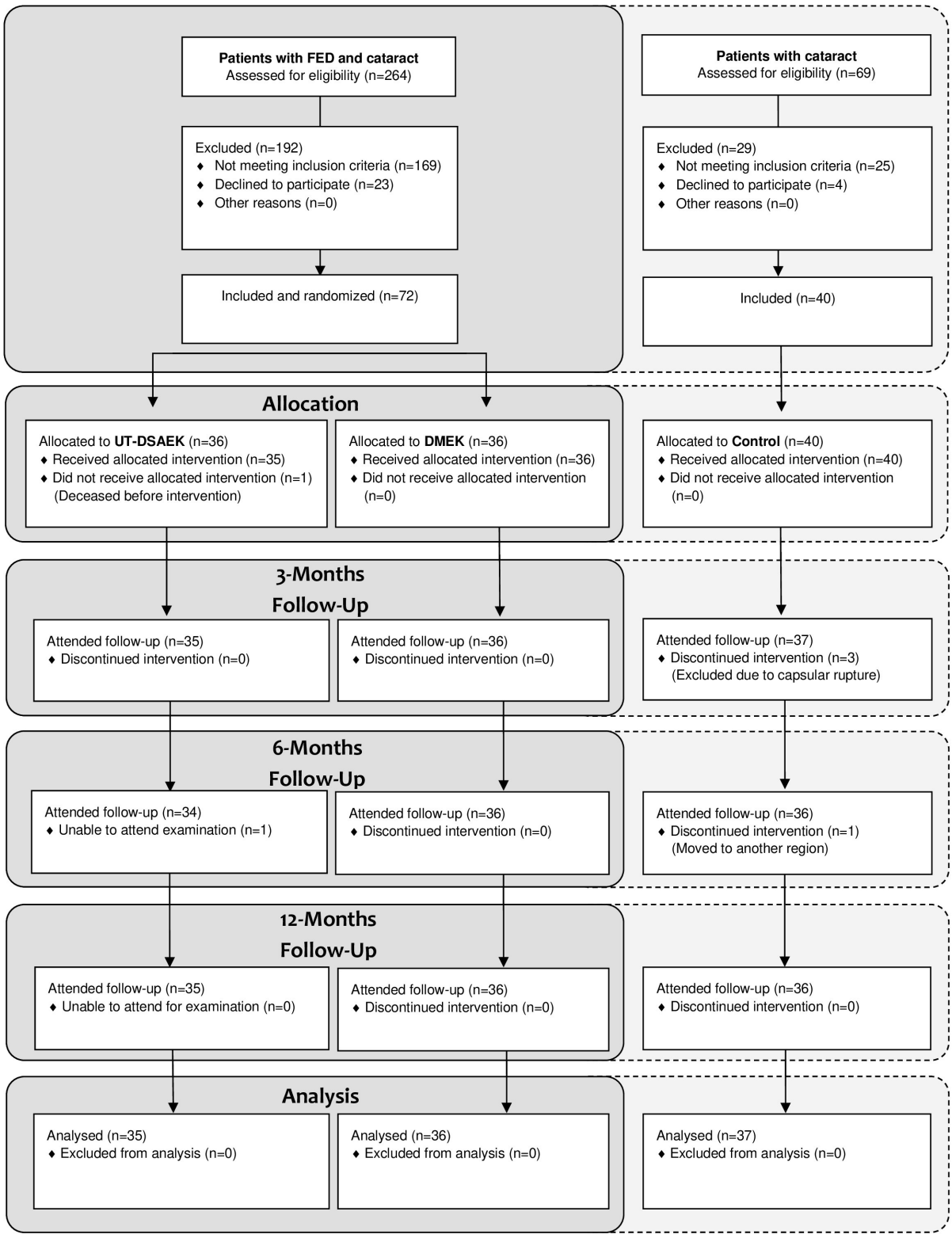

Figure 1 CONSORT diagram showing the inclusion and follow-up throughout the study period. CONSORT, Consolidated Standards of Reporting Trials; DMEK, Descemet's membrane endothelial keratoplasty; FED, Fuchs' endothelial dystrophy; UT-DSAEK, ultrathin Descemet's stripping automated endothelial keratoplasty.

Table 2 Baseline characteristics, mean (95% CI)

	EK (n=71)	Control (n=37)	P value
Female, %	67.6 (55.5; 78.2)	73.0 (55.9; 86.2)	0.57
Age, years	68.9 (67.4; 70.3)	71.7 (69.7; 73.7)	0.02
BCVA, ETDRS letters	68.2 (66.7; 69.7)	72.3 (70.5; 74.1)	0.001
CS, LogCS	1.03 (0.99; 1.08)	1.26 (1.22; 1.31)	< 0.001
CCT, µm	611 (598; 624)	551 (541; 560)	< 0.001
Anterior corneal astigmatism, D*	−0.79 (-0.94; −0.67)	−0.67 (-0.86; −0.52)	0.14

*Median values.
BCVA, best-corrected visual acuity; CCT, central corneal thickness; CS, contrast sensitivity; D, diopters; EK, endothelial keratoplasty; ETDRS, early treatment diabetic retinopathy study.

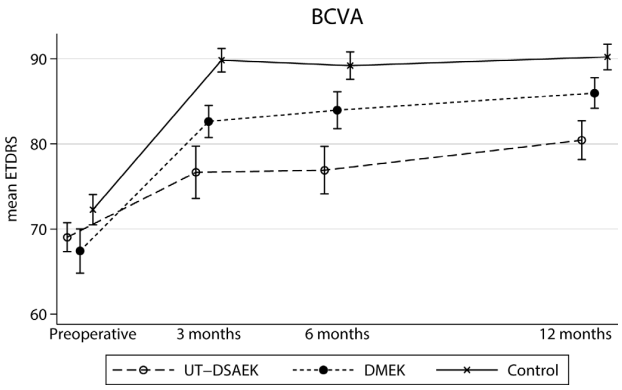

Figure 2 Graph demonstrating mean best-corrected visual acuity preoperatively, as well as 3, 6 and 12 months for UT-DSAEK (hollow circles), DMEK (filled circles) and controls (crosses) measured in early treatment diabetic retinopathy study (ETDRS) letters with 95% CIs. BCVA, best-corrected visual acuity; DMEK, Descemet's membrane endothelial keratoplasty; UT-DSAEK, ultrathin Descemet's stripping automated endothelial keratoplasty.

variation might be related to different approaches and instruments used for ECD estimation. The preloading of DMEK grafts could also partly be an explanation. Furthermore, dextran has proven to be toxic to the corneal endothelium.[18] As only tissue used for UT-DSAEK grafts was exposed to dextran during preparation, this might explain the lower ECD after UT-DSAEK in our study. Dunker *et al* also found a tendency towards a lower ECD after UT-DSAEK compared with DMEK after dextran usage. As ECD must drop below 500 cells/mm^2 to affect corneal deturgescence,[19] we believe that our results on BCVA are unaffected by this difference. Additionally, we observed no cases of cystoid macular oedema; hence, any impact on BCVA may have been negligible. Results on macular thickness have been reported elsewhere.[10]

In our study, no significant difference in the magnitude of anterior corneal astigmatism was found among study groups, which is consistent with the findings by Matsou *et al*[5]

Rebubbling rates vary from 7% to 20% after DSAEK[20 21] and 3% to 13% after UT-DSAEK[5 22] in previous studies. Chamberlain *et al*[4] and Dunker *et al*[6] reported similar rebubbling rates of 24% after DMEK, and 4% after UT-DSAEK. In our study, we found a slightly lower rebubbling rate of 22% after DMEK and a higher rate of 14% after UT-DSAEK. The higher rate after UT-DSAEK could partly be explained by the dextran usage, which might affect the endothelial function through its toxicity. However, neither our study, nor previous studies were statistically powered to compare this outcome and larger series are needed.

In our study, three reversible rejection episodes were found after UT-DSAEK and one after DMEK. In contrast, Chamberlain *et al* and Dunker *et al* did not observe any rejection episodes and Matsou *et al* only observed one after UT-DSAEK. The postoperative steroid regimen may be the explanation for this deference. In the studies by Chamberlain *et al* and Matsou *et al*,

Table 3 Primary and secondary outcome measures, mean (95% CI)

	UT-DSAEK (n=35)	DMEK (n=36)	Control (n=37)	P value*
BCVA (ETDRS letters)				
3 months	76.7 (73.6; 79.7)	82.6 (80.7; 84.5)	89.8 (88.5; 91.2)	<0.001
6 months	76.9 (74.1; 79.7)†	84.0 (81.8; 86.1)	89.2 (87.6; 90.8)†	<0.001
12 months	80.4 (78.2; 82.7)	86.0 (84.2; 87.8)	90.2 (88.7; 91.7)†	<0.001
CS (LogCS)				
3 months	1.29 (1.22; 1.36)	1.40 (1.34; 1.46)	1.49 (1.45; 1.52)	<0.001
6 months	1.32 (1.24; 1.39)†	1.40 (1.33; 1.47)	1.47 (1.43; 1.52)†	<0.001
12 months	1.35 (1.28; 1.42)	1.44 (1.39; 1.49)	1.50 (1.46; 1.54)†	<0.001
ECD (Cells/mm^2)				
3 months	1048 (886; 1211)	1541 (1360; 1723)	2104 (1941; 2266)	<0.001
6 months	1024 (873; 1176)†	1475 (1294; 1657)	2081 (1919; 2242)†	<0.001
12 months	1010 (874; 1147)	1401 (1227; 1574)	2094 (1936; 2251)†	<0.001
Anterior corneal astigmatism (D)‡				
3 months	−0.82 (−1.04; −0.66)	−0.94 (−1.21; −0.72)	−0.69 (−0.87; −0.55)	0.24§
6 months	−0.89 (−1.15; −0.70)†	−0.84 (−1.08; −0.66)	−0.65 (−0.83; −0.51)†	0.11§
12 months	−0.77 (−1.03; −0.58)	−0.87 (−1.09; −0.70)	−0.65 (−0.83; −0.50)†	0.18§

*P values of post-hoc ANOVA calculated based on multivariate linear mixed effects model.
†One value missing.
‡Median values.
§One-sided p value.
BCVA, best-corrected visual acuity; CS, contrast sensitivity; D, diopters; DMEK, Descemet's membrane endothelial keratoplasty; ECD, endothelial cell density; ETDRS, early treatment diabetic retinopathy study; UT-DSAEK, ultrathin Descemet's stripping automated endothelial keratoplasty.

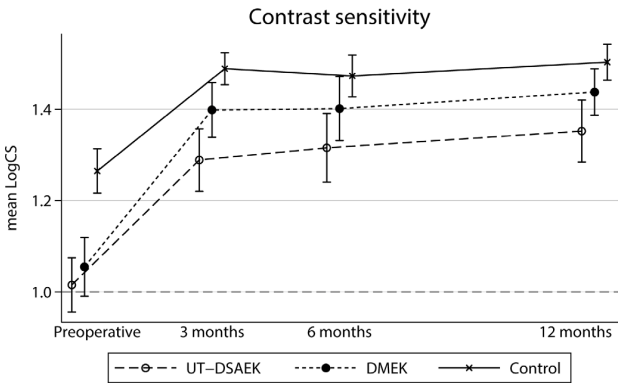

Figure 3 Graph demonstrating mean contrast sensitivity preoperatively, as well as 3, 6, and 12 months for UT-DSAEK (hollow circles), DMEK (filled circles) and controls (crosses) in LogCS with 95% CIs. DMEK, Descemet's membrane endothelial keratoplasty; UT-DSAEK, ultrathin Descemet's stripping automated endothelial keratoplasty.

postoperative steroid treatment was administered for 12 months, whereas treatment was ended after 7.5 months in our study.

As visual acuity testing is a psychophysical test, the examiner performance is of importance to the outcome. The single-blinded design is consequently a limitation of our study. Furthermore, the study was conducted as a single-centre study. This might compromise the external validity of the results since different eye banking and surgical techniques may have an influence on the results. The study sample size, however small, was a strength of our study compared with previous conducted trials. To our knowledge, this is the largest randomised trial to compare UT-DSAEK and DMEK so far. Furthermore, the study group homogeneity with only triple EK procedures having been performed in the randomised groups was a strength of this study.

In conclusion, DMEK resulted in better visual acuity 3, 6 and 12 months after surgery compared with UT-DSAEK. Patients in the control group obtained significantly better visual acuity compared with DMEK 12 months after surgery. Compared with UT-DSAEK, DMEK resulted in better contrast sensitivity 3 months after surgery; however, no difference was found

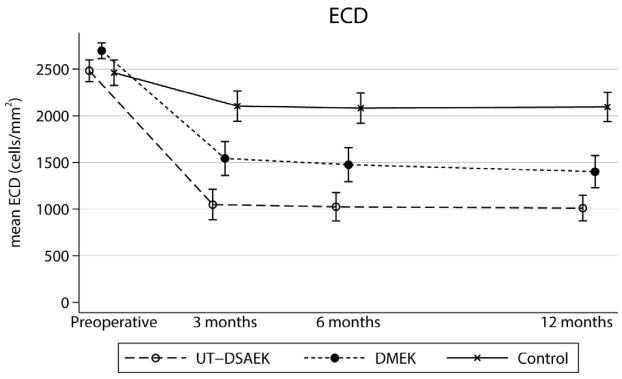

Figure 4 Graph demonstrating mean endothelial cell density (ECD) preoperatively, as well as 3, 6 and 12 months for UT-DSAEK (hollow circles), DMEK (filled circles) and controls (crosses) in cells/mm^2 with 95% CIs. For patients treated with UT-DSAEK or DMEK the mean donor ECD are presented at baseline. DMEK, Descemet's membrane endothelial keratoplasty; UT-DSAEK, ultrathin Descemet's stripping automated endothelial keratoplasty.

Table 4 Cumulative postoperative adverse events at 12 months

	UT-DSAEK (n=35)	DMEK (n=36)
Rebubble	5	8
Primary failure	1	1
Rejection	3	1
Increased IOP	6	8
Pupillary block	0	1
PCO	4	0
Re-grafted	1	1
Total	20	20

Data are presented as absolute numbers.
DMEK, Descemet's membrane endothelial keratoplasty; IOP, intraocular pressure; PCO, posterior capsular opacification; UT-DSAEK, ultrathin Descemet's stripping automated endothelial keratoplasty.

6 and 12 months after surgery. DMEK demonstrated higher ECD compared with UT-DSAEK after 3, 6 and 12 months. The number of adverse events was comparable 12 months after UT-DSAEK and DMEK.

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Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by The Central Denmark Region Committee on Health Research Ethics (Identification 1-10-72-7-20). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

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Paper II

Macular thickness after ultrathin Descemet stripping automated endothelial keratoplasty and Descemet membrane endothelial keratoplasty combined with cataract surgery: A randomized controlled clinical trial.

Macular Thickness After Ultrathin Descemet Stripping Automated Endothelial Keratoplasty and Descemet Membrane Endothelial Keratoplasty Combined With Cataract Surgery: A Randomized Controlled Clinical Trial

Morten Brok Molbech Madsen, MD, Anders Ivarsen, MD, PhD, and Jesper Hjortdal, MD, PhD, DMSci

Purpose: The aim was to investigate alterations in central retinal thickness (CRT) and their implications for visual acuity after ultrathin Descemet stripping automated endothelial keratoplasty (UT-DSAEK) and Descemet membrane endothelial keratoplasty (DMEK) combined with cataract surgery.

Methods: A total of 72 eyes of 72 patients with Fuchs endothelial dystrophy and cataract were included and equally randomized to either UT-DSAEK or DMEK. A control group of 40 eyes of 40 patients with cataract were included for cataract surgery. All participants were examined preoperatively as well as 3 and 6 months postoperatively.

Results: There was no significant difference in CRT between the study groups after surgery ($P = 0.896$). A significant difference in best-corrected visual acuity (BCVA) progression over time was found between the study groups ($P < 0.0001$). Average improvements of 8.03 EDTRS after UT-DSAEK ($P < 0.001$) and 16.77 EDTRS after DMEK ($P < 0.001$) were found 6 months postoperatively. No significant correlation was found between the change in BCVA and CRT from baseline to 3 months postoperatively ($r^2 < 0.0001$, $P = 0.96$) and from baseline to 6 months postoperatively ($r^2 = 0.0053$, $P = 0.46$).

Conclusions: CRT was not altered by UT-DSAEK, DMEK, or cataract surgery 3 and 6 months postoperatively. BCVA significantly improved 3 and 6 months after UT-DSAEK and DMEK, respectively. No significant correlations were found between the change in BCVA and CRT postoperatively. As such CRT alterations were comparable after UT-DSAEK, DMEK, and cataract surgery.

Key Words: UT-DSAEK, DMEK, fuchs endothelial dystrophy, cystoid macular edema

(*Cornea* 2023;00:1–8)

Around the beginning of the millennium, Descemet stripping automated endothelial keratoplasty (DSAEK) was introduced,[1,2] and shortly thereafter Descemet membrane endothelial keratoplasty (DMEK)[3] was invented. DMEK provides some advantages when it comes to visual acuity,[4] but because of graft preparation and surgical difficulties, DSAEK remains a popular choice. This has fostered refinements in the DSAEK technique and improved visual acuity with thinner grafts has been demonstrated.[5] The term ultrathin Descemet stripping automated endothelial keratoplasty (UT-DSAEK) is usually defined by a graft thickness of less than 100 μm.[6] Compared with DSAEK, UT-DSAEK has demonstrated improved visual acuity and faster visual recovery.[7] However, despite a faster visual recovery after UT-DSAEK compared with DSAEK, a recent study demonstrated that DMEK still is superior to UT-DSAEK.[8]

Pseudophakic cystoid macular edema (CME), known as Irvine–Gass syndrome,[9,10] has proven to be a leading cause of visual dysfunction after cataract surgery.[11] The condition is characterized by fluid accumulation in the outer nuclear and inner plexiform retinal layers and subretinal fluid. The pathophysiological mechanism of CME is still incompletely understood. The characteristic changes are believed to arise from disturbances in the retinal microenvironment. Primarily, inflammation is believed to compromise the blood–retina barrier through mediators such as prostaglandins. This leads to increased perifoveal capillary permeability and fluid accumulation.[12] The severity of the condition varies from self-limiting to severe permanent vision loss. In relation to cataract surgery, CME has been shown to cause substantially higher costs by means of diagnosis and treatment.[13] However, CME is not only known after cataract surgery. In recent years, CME after endothelial keratoplasty has been studied with reported rates from 4% to 12.7% after DSAEK[14,15] and 1% to15.8% after DMEK.[16,17] To the best of our knowledge, only one retrospective study by Myerscough et al[18] has compared the CME incidence after DSAEK and DMEK. They found that CME occurred significantly more often after DMEK than after DSAEK, with an odds ratio of 2.42.

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The aim of the current study was to investigate whether differences in visual recovery after UT-DSAEK compared with DMEK, to some extent, could be explained by alterations in the central retinal thickness (CRT). To the best of our knowledge, a comparison of CRT in a randomized controlled trial has not been performed. We hypothesized that the changes in retinal thickness were equal after UT-DSAEK and DMEK.

MATERIALS AND METHODS

Study Design

This single-center study was conducted as a randomized, single-blinded, controlled clinical trial comparing outcomes of UT-DSAEK and DMEK with concomitant phacoemulsification and lens implantation (triple-UT-DSAEK and triple-DMEK). All included patients suffered from both Fuchs endothelial dystrophy and cataract. Patients were only treated on 1 eye and were equally allocated (1:1) to either UT-DSAEK or DMEK. A third group of patients who only suffered from cataract was included as a control group and were treated with phacoemulsification and lens implantation. Control group participants were treated bilaterally if required; however, only 1 eye was included in the study.

Study participants allocated to UT-DSAEK or DMEK were blinded to the performed intervention. Control group participants were only referred for cataract surgery and as such could not be masked to the intervention. Furthermore, the surgeons who performed the procedures and the examining physician were not masked.

Participants

Patients referred to the Department of Ophthalmology, Aarhus University Hospital, Denmark, from June 2020 to January 2022, were assessed for study eligibility. Inclusion criteria were age between 50 and 81 years, Fuchs endothelial dystrophy, and/or cataract. Patients were excluded from the study in case of previous ocular surgery or disease including, but not limited to, uveitis, retinal vein occlusion, epiretinal membrane, glaucoma, ocular trauma, exudative age-related macular degeneration, or nonexudative age-related macular degeneration with geographic atrophy, as well as systemic diseases such as diabetes.

Sample size calculation was based on a previous study of visual acuity after UT-DSAEK or DMEK by Chamberlain et al.[8] The study found a standard deviation of 0.18 logarithm of the minimum angle of resolution (logMAR) for UT-DSAEK and 0.12 logMAR for DMEK. Based on this variation, a sample size of 31 in each group was required to detect a 0.12 logMAR difference (equivalent to 6 early treatment diabetic retinopathy study (ETDRS) letters) with a two-sided α of 0.05 and at least 85% power.

Written informed consent was obtained from all study participants at the time of enrollment. The study was approved by the Central Denmark Region Committee on Health Research Ethics and adhered to the tenets of the Declaration of Helsinki. The study was registered at http://clinicaltrials.gov (Identifiers ID: NCT04417959).

Clinical Examinations

All clinical examinations were performed by 1 physician (MM). Examinations were performed preoperatively as well as 3 and 6 months postoperatively except for the Lens Opacities Classification System III (LOCS III) grading. This was only performed preoperatively. All patients initially underwent autorefraction (TONOREF II, Nidek Co., Ltd., Gamagori, Japan), followed by subjective refraction, and visual acuity testing. Patients were then administered dilating eye drops (Minims phenylephrine hydrochloride 10%, Bausch & Lomb UK Ltd., United Kingdom, and Minims tropicamide 0.5%, Bausch & Lomb UK Ltd., United Kingdom). Thereafter, retinal optical coherence tomography (OCT) scanning (Spectralis OCT, Heidelberg Engineering, Heidelberg, Germany), slit-lamp examination, and LOCS III grading were performed. LOCS III slit-lamp grading was performed in accordance with a previously described standardized approach.[19,20]

Visual Acuity

Best spectacle-corrected visual acuity was determined in agreement with the previously described ETDRS testing protocol.[21] In brief, the ETDRS chart was presented to the patient at 4 meters on an electronic LED screen (Polaphor light system, Block Optics Ltd., Dortmund, Germany) with a luminous intensity of 260 cd/m^2. The illuminance in the clinic (measured between the LED screen and the participant) was set between 250 and 270 Lux provided by LED lights in the ceiling. The patient was asked to read presented lines from left to right. The test was continued until less than 3 letters per line were recognized. The total number of correctly identified letters was noted.

OCT Scans

All participants were examined using optical coherence tomography (Spectralis OCT, Heidelberg Engineering, Heidelberg, Germany). Three consecutive scans were obtained at every visit and the OCT image quality scores were evaluated (Heidelberg Eye Explorer version 1.10.4.0). The scan with the highest quality score was used for further analysis. All consecutive examinations were performed using the follow-up scanning module. Reference scans were in all cases defined at the preoperative visit before randomization. For evaluation of the CRT, the central 1 mm subfield of the ETDRS thickness map was used.

Eye Banking Technique

Donor tissue was provided by the Danish Cornea Bank, Aarhus University Hospital, Aarhus, Denmark. The technique used for storage and preparation has previously been described.[22] In brief, tissue was collected by enucleation no later than 48 hours postmortem. Donor corneas were initially evaluated with biomicroscopy, followed by excision of 16-mm corneoscleral buttons. The corneoscleral buttons were stored at 30°C in 50 to 65 mL of minimum essential medium supplemented with piperacillin, amikacin, and fetal bovine serum. Endothelial cell density was manually counted. Only tissue with an endothelial cell density above 2000 cells/mm^2 was considered suitable for grafting.

Tissue for UT-DSAEK grafts was initially dehydrated in a solution of 8% Dextran 500 for 24 to 48 hours.[23] The donor corneas were then cut using a microkeratome (OU LC head-Art. Chamber, Moria, Anthony, France) and console (Evolution 3E, Moria, Anthony, France). In each case, a cutting head was chosen to obtain a graft thickness of about 80 μm. Precise graft thickness was subsequently measured using optical coherence tomography (CASIA SS-1000, TOMEY, Nagoya, Japan). After cutting, caps were replaced and grafts were transported to the operating theatre in organ culture (Carry-C, Alchimia, Ponte San Nicolò, Italy).

DMEK grafts were peeled in the Cornea Bank. In each case, Descemet's membrane was carefully opened along the trabecular meshwork using a Sinskey hook. Trypan blue (MONOBLUE NafX, BVI, Toulouse, France) was used to stain the tissue, and a pair of blunt forceps was used to peel Descemet's membrane submersed in saline. An 8-mm punch was used to remove unwanted tissue, and an asymmetrical triangular orientation mark was created at the graft edge using forceps and scissors. The DMEK graft was subsequently folded endothelium-in and loaded into a Tan EndoGlide (DMEK EndoGlide, Coronet, Ripon, United Kingdom). The graft was returned to the culture medium and sent to the operating theatre.

Surgical Technique

All participants had cataract surgery performed by means of phacoemulsification and in-the-bag lens implantation. Participants in the control group who were only treated with cataract surgery were anaesthetized using oxybuprocaine (Novesine, 0.4%, OmniVision, Puchheim, Germany) and diclofenac (Voltaren Ophtha, 1 mg/mL, GSK Consumer Health care, Brøndby, Denmark). In addition, intracameral lidocaine was administered (Xylocaine, 10 mg/mL, Aspen Pharma, Dublin, Ireland). A drop of dorzolamide (Dorzolamid, 20 mg/mL, STADA Nordic, Herlev, Denmark) and intracameral cefuroxime 0.1 mL (Aprokam 50 mg/mL, Théa, Clermont-Ferrand, France) were administered postoperatively. For participants included for endothelial keratoplasty, peribulbar anesthesia was used (2 mL of 0.5% Marcaine–adrenaline, Aspen Nordic, Ballerup, Denmark, and 3 mL of 2% lidocaine-adrenalin SAD Amgros I/S, Copenhagen, Denmark). Initially, cataract surgery was performed. An anterior chamber maintainer was inserted, descemetorhexis was performed using a reverse Sinskey hook, and Descemet's membrane was stripped. UT-DSAEK grafts were punched in a diameter of 8 mm and introduced to the anterior chamber through a 4-mm tunnel at the 12-o'clock position using a pull-through technique with Busin glide and forceps. For DMEK, a 2.65-mm main incision was created, and the graft was introduced into the eye with a pull-through technique using the Tan EndoGlide (DMEK EndoGlide, Coronet, Ripon, United Kingdom) and forceps. Correct positioning of the graft was secured using a small gas bubble and correct orientation and positioning of the tissue were ensured by intraoperative OCT (HS Hi-R NEO 900A NIR, Haag-Streit, Koeniz, Switzerland). For all procedures, a 20% sulfur hexafluoride gas solution was used for full anterior chamber gas tamponade. Intracameral cefuroxime 0.1 mL (Aprokam 50 mg/mL, Théa, Clermont-Ferrand, France) and subconjunctival dexamethasone 1 mg (dexamethasone phosphate hameln, Hameln pharma gmbh, Hameln, Germany) were administered, and the patient was left in the supine position. After 2 hours, the gas was reduced and a bubble occupying one third to half of the anterior chamber was left to support graft adhesion. After gas reduction and at bedtime, the patient was administered 500 mg acetazolamide (Diamox, Amdipharm, Helsingborg, Sweden). Preoperative or perioperative iridectomy was not performed. All procedures were performed by 1 of 2 experienced surgeons (AI and JH).

Postoperative Management

Patients treated with UT-DSAEK or DMEK were prescribed a combination of dexamethasone and tobramycin eye drops (Oridecin, Orifarm Generics, Odense, Denmark). This was administered 6 times daily for the first week and then consecutively tapered to 4, 3, 2 and 1 drop daily every 8 weeks until end of treatment. In addition, patients were given diclofenac eye drops (Voltaren Ophtha, GSK Consumer Health care, Brøndby, Denmark) 3 times daily for the first 3 postoperative weeks. Patients in the control group, who only had cataract surgery, were treated with dexamethasone (Maxidex, Novartis, Copenhagen, Denmark) and diclofenac eye drops (Voltabak, Théa Nordic, Hørsholm, Denmark) 3 times daily for 2 and 3 weeks, respectively.

Outcome Measures

BCVA at 12 months was defined as the primary outcome measure of the study. CRT at 3 and 6 months was predefined as a secondary outcome measure. Furthermore, the CME incidence in the form of intraretinal cysts or subretinal fluid and a CRT increase >10% at the 6-month time point was a predefined secondary outcome.

Randomization Procedure

Participants suffering from Fuchs endothelial dystrophy and cataract were randomized equally to either UT-DSAEK or DMEK performed as triple procedures. Group sizes were kept similar throughout the study period using block randomization to compensate for any procedure alterations during the study period. Each block consisted of an even number of participants. Randomization was undertaken approximately once a month by a person without relation to the current study using random computer-generated numbers (Microsoft Excel 2019 for Windows).

Statistical Methods

In agreement with the power calculation, *P* values of less than 0.05 were considered significant. Stata software (Stata version 17.0, Stata Corp.) was used for all analyses. For all tests, normality assumptions were checked using QQ plots. When appropriate, logarithmic transformed data were used for analysis.

The repeated measures of the 3 study groups were compared using a multivariate linear mixed-effects model to test the hypothesis of parallel mean curves between groups.

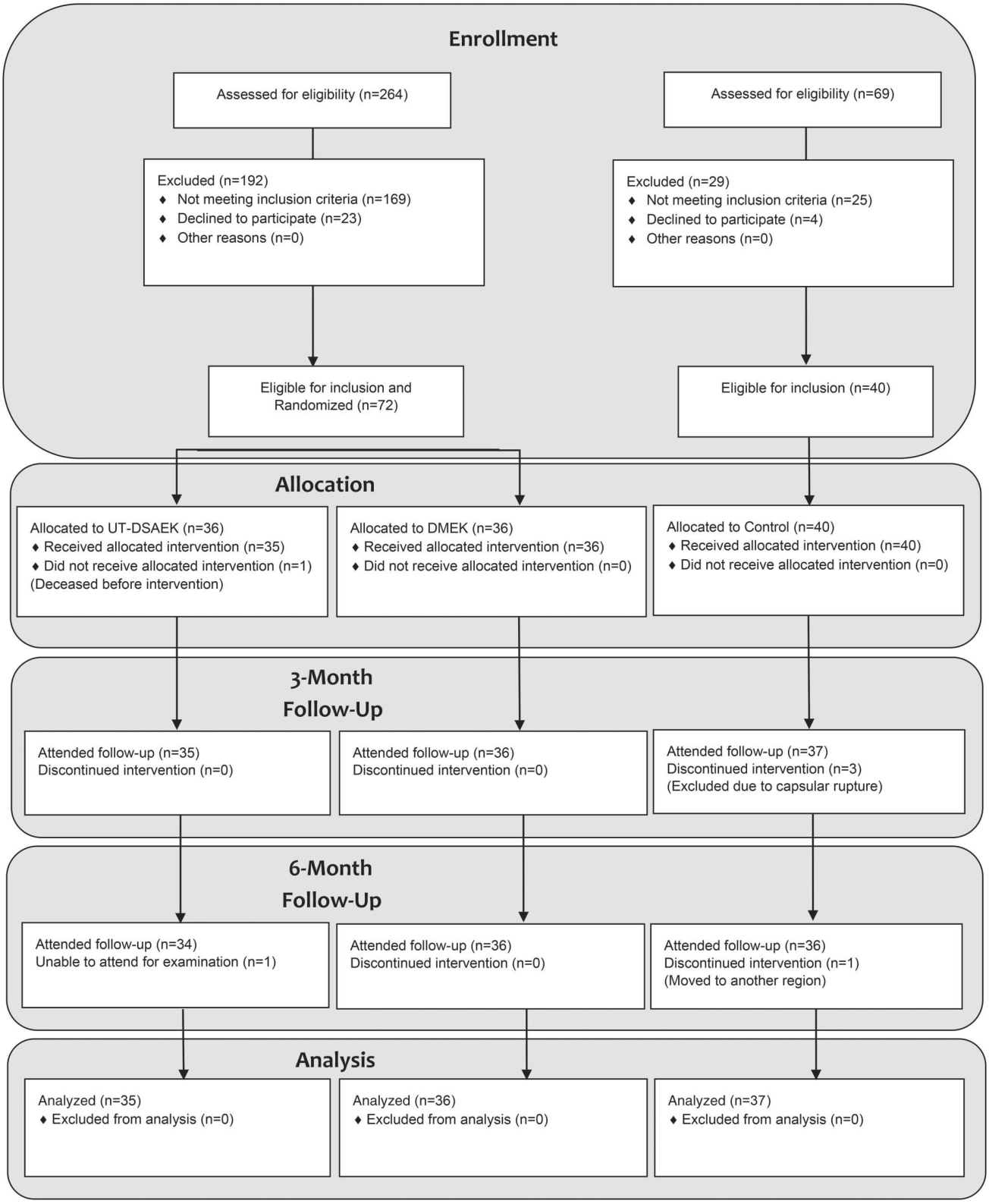

FIGURE 1. Flow diagram showing the inclusion and follow-up of study participants.

TABLE 1. Baseline Characteristics

	UT-DSAEK (n = 35)	DMEK (n = 36)
Female (%), mean (95% CI)	62.9 (44.9; 78.5)	72.2 (54.8; 85.8)
Age (years), mean ± SD (95% CI)	69.2 ± 6.1 (67.1; 71.3)	68.5 ± 6.2 (66.4; 70.6)
BCVA (ETDRS letters), mean ± SD (95% CI)	69.0 ± 4.9 (67.3; 70.7)	67.4 ± 7.7 (64.8; 70.0)
CCT (μm), mean ± SD (95% CI)	615.9 ± 55.9 (596.7; 635.1)	606.4 ± 52.0 (588.8; 624.0)
CRT (μm), mean ± SD (95% CI)	275.9 ± 23.4 (267.8; 283.9)	279.2 ± 19.9 (272.5; 285.9)
LOCS III grading		
NO, mean ± SD (95% CI)	2.8 ± 0.7 (2.6; 3.1)	3.0 ± 0.8 (2.7; 3.2)
NC, mean ± SD (95% CI)	2.6 ± 0.9 (2.2; 2.9)	2.7 ± 0.9 (2.4; 3.0)
C, mean ± SD (95% CI)	1.5 ± 0.7 (1.2; 1.7)	1.6 ± 0.9 (1.3; 1.9)
P, mean ± SD (95% CI)	0.7 ± 0.7 (0.5; 0.9)	1.0 ± 1.0 (0.7; 1.3)

SD, standard deviation; 95% CI, 95% confidence interval; C, cortical cataract; CCT, central corneal thickness; NO, nuclear opalescence; NC, nuclear color; P, posterior subcapsular cataract.

For analysis of independent relations, post hoc t-tests were used. To assess the correlations between variables, linear regression models were used. The models were checked using diagnostic residual plots. Continuous baseline characteristics were compared using t-tests, and dichotomous variables were tested using the χ^2 test. Standard deviations were compared between groups, and in case of unequal variation, approximate estimates were determined instead of exact. All estimates from the multivariate linear mixed-effects model were age and sex adjusted. All mean and median values are presented with 95% confidence intervals (95% CI).

RESULTS

Baseline Characteristics

In total, 72 patients with Fuchs endothelial dystrophy and cataract were enrolled in the study for endothelial keratoplasty. Patients were equally randomized to UT-DSAEK (n = 36) or DMEK (n = 36). One patient allocated to UT-DSAEK died before the intervention. Two patients from the UT-DSAEK group developed sterile endophthalmitis and capsular rupture, respectively. Primary failure occurred in one patient treated with UT-DSAEK and in one treated with DMEK. None of these later developed CME. Both patients were regrafted with DMEK. Following the intention-to-treat principle, randomized patients with endophthalmitis, capsular rupture, or primary failure remained in their allocated groups for the analysis. A following sensitivity analysis excluding the abovementioned subjects did not significantly change the estimates of the intention-to-treat analysis (results not shown). For the control group, 40 patients suffering from cataract were enrolled and treated with cataract surgery. Three patients were excluded because of capsular rupture, and one moved and declined further follow-up. As such, 108 eyes of 108 patients were included in the analysis. Figure 1 shows the flow diagram of the study participant inclusion and follow-up. Table 1 shows baseline characteristics of the UT-DSAEK and DMEK groups. Following the CONSORT guidelines,[24] no statistical tests were used to compare the randomized study groups. Table 2 shows a baseline characteristics comparison between the control group and participants included for endothelial keratoplasty.

Central Retinal Thickness

At 3 months, no patients had experienced an increase in CRT of 10% or more. However, such an increase was found in 1 patient in the DMEK group (1/35) and in one patient in the control group (1/35) at the 6-month time point.

No significant difference in CRT progression over time was found between the 3 study groups ($P = 0.90$) and the hypothesis of parallel CRT mean curves was accepted. There were no significant differences in the levels of study mean curves ($P = 0.60$). No significant differences in CRT were found between the UT-DSAEK and DMEK groups at 3 months ($P = 0.34$) and 6 months ($P = 0.41$) postoperatively. Table 3 and Figure 2 show the progression in CRT over time for the 3 study groups.

Best-Corrected Visual Acuity

The progression of BCVA over time was significantly different between the 3 study groups ($P < 0.001$). Furthermore, the mean BCVA curves were significantly different between the 3 study groups ($P < 0.001$). At the 6 months postoperative

TABLE 2. Baseline Characteristics, Mean (95% Confidence Interval)

	EK (n = 71)	Control (n = 37)	*P*
Female, %	67.6 (55.5; 78.2)	73.0 (55.9; 86.2)	0.33
Age, years	68.9 (67.4; 70.3)	71.7 (69.7; 73.7)	0.023*
BCVA, ETDRS letters	68.2 (66.7; 69.7)	72.3 (70.5; 74.1)	0.001**
CCT, μm	611.1 (598.4; 623.8)	550.7 (541.2; 560.2)	<0.001**
CRT, μm	277.6 (272.5; 282.7)	279.7 (274.5; 285.0)	0.56
LOCS III grading			
NO	2.9 (2.7; 3.1)	3.6 (3.3; 3.8)	<0.001**
NC	2.7 (2.4; 2.9)	3.5 (3.2; 3.9)	<0.001**
C	1.5 (1.3; 1.7)	1.6 (1.2; 1.9)	0.88
P	0.8 (0.6; 1.0)	1.6 (1.2; 2.0)	<0.001**

EK, endothelial keratoplasty; C, cortical cataract; CCT, central corneal thickness; NO, nuclear opalescence; NC, nuclear color; P, posterior subcapsular cataract.
Asterisks indicate $P < 0.05$ and double asterisks $P < 0.01$.

TABLE 3. Outcomes Measures, Mean (95% Confidence Interval)

	UT-DSAEK (n = 35)	DMEK (n = 36)	Control (n = 37)	*P*
CRT (μm)				
Preoperative	275.9 (267.8; 283.9)	279.2 (272.5; 285.9)	279.7 (274.5; 285.0)	
3 mo	278.7 (270.6; 286.8)	283.1 (276.0; 290.1)	283.9 (278.6; 289.3)	0.48
6 mo	279.9 (271.4; 288.3)	283.5 (276.5; 290.5)	285.9 (280.2; 291.6)	0.52
BCVA (ETDRS letters)				
Preoperative	69.0 (67.3; 70.7)	67.4 (64.8; 70.0)	72.3 (70.5; 74.1)	
3 mo	76.7 (73.6; 79.7)	82.6 (80.7; 84.5)	89.8 (88.5; 91.2)	<0.001**
6 mo	76.9 (74.1; 79.7)	84.0 (81.8; 86.1)	89.2 (87.6; 90.8)	<0.001**
CCT (μm)				
Preoperative	615.9 (596.7; 635.1)	606.4 (588.8; 624.0)	550.7 (541.2; 560.2)	
3 mo	581.2 (566.2; 596.2)	517.5 (505.0; 530.0)	550.9 (541.3; 560.6)	<0.001**
6 mo	576.3 (561.5; 591.0)	513.9 (500.4; 527.4)	550.9 (541.2; 560.5)	<0.001**

CCT, central corneal thickness.
Double asterisks indicate $P < 0.01$.

examination, the UT-DSAEK group had on average improved 8.03 ETDRS ($P < 0.001$) and the DMEK group 16.77 ETDRS ($P < 0.001$). Table 3 and Figure 3 show the progression in BCVA over time. The correlations between the change in BCVA and the change in CRT from baseline to 3 months of −0.01 ETDRS/μm ($r^2 < 0.0001$, $P = 0.96$) and from baseline to 6 months of 0.09 ETDRS/μm ($r^2 = 0.0053$, $P = 0.46$) were not significant. The correlations are shown in Figure 4.

DISCUSSION

In general, DMEK is considered not only to provide better visual acuity than DSAEK but also to have a higher complication rate.[4,25] A study by Chamberlain et al[8] found that DMEK remained superior by means of BCVA when compared with the improved UT-DSAEK technique. CME as a postoperative complication is a leading cause of disturbed vision after cataract surgery[26] and with a reported incidence as high as 15.6% after EK[17]; this postoperative condition could be responsible for a slower visual recovery after these procedures. In agreement with the study by Chamberlain et al, this study found a significantly better visual acuity after DMEK than after UT-DSAEK at both 3 and 6 months. However, no significant differences in CRT were found between the 3 groups, and no cases with intraretinal or subretinal fluid were observed. Nonetheless, we did identify 1 case of a >10% CRT increase between the third and sixth postoperative months in the DMEK and control group, respectively. This was not observed in the UT-DSAEK group. The difference in BCVA between DMEK and UT-DSAEK could, however, not be explained by a difference in CRT. As CRT was a predefined secondary outcome measure, our study was not powered to detect significant CRT differences between the study groups. In addition, a CRT examination 6 weeks postoperatively was not performed. This might, further, have affected the ability of the study to detect a difference in CRT between the study groups.

Usually, the incidence of CME and CRT peaks around the sixth postoperative week when cataract surgery is performed.[12] Because no examinations were performed 6 weeks postoperatively in this study, it may have underestimated the CRT difference between the study groups.

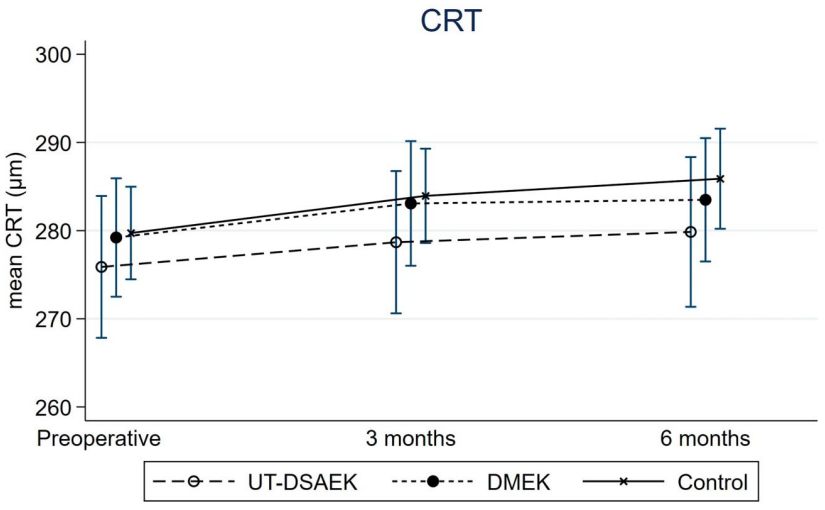

FIGURE 2. Dot plot with 95% confidence intervals over the progression in CRT for UT-DSAEK, DMEK, and the control group. (The full color version of this figure is available at www.corneajrnl.com.)

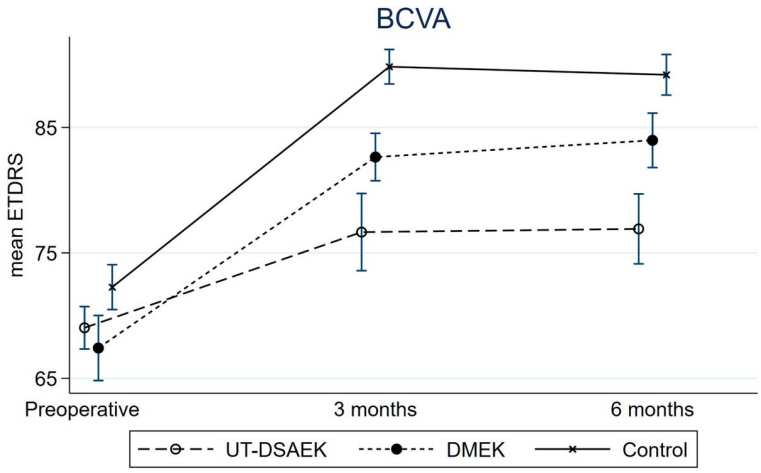

FIGURE 3. Dot plot with 95% confidence intervals over the progression in BCVA in Early Treatment Diabetic Retinopathy Study (ETDRS) letters for UT-DSAEK, DMEK, and the control group. (The full color version of this figure is available at www.corneajrnl.com.)

However, clinically significant CME usually presents after the first postoperative month and spontaneous resolution of the condition usually occurs within the first postoperative year with about two thirds persisting for more than 3 months.[27] This is also reflected in OCT studies where increased CRT usually is seen throughout the first 6 postoperative months after cataract surgery.[28] Hence, we should be able to detect CME affecting visual acuity and alterations in CRT. The timing for the highest CRT and CME incidence might, however, differ between EK and cataract surgery.

A difference in the timing of CME after EK compared with cataract surgery may be explained by the introduction of an allogeneic graft in the former instance. The introduction of allogeneic material has the potential to induce immune reactions and cause ocular inflammation. As such, subclinical inflammation might also be present after EK and might increase the risk of postoperative CME. Because the allogeneic material remains in the eye, the period with subclinical inflammation, and hence, the period in which CME may occur could be prolonged. If CME may occur for a longer period after EK as compared to cataract surgery, we would expect the highest incidence later than the sixth postoperative week. In a study by Kocaba et al,[29] the highest incidence of OCT-verified CME after DMEK was found at the 3-month examination. They studied the results of 80 eyes and reported a postoperative CME incidence of 18.0% six months after triple-DMEK, which is markedly different from our results. A possible cause for this difference could be iridial damage. In their study, they routinely performed iridectomy in relation to the DMEK procedure. This contrasts with this study where no patient had iridectomy performed. It has been postulated that manipulation of uveal tissue during surgery may trigger arachidonic acid release. This, in turn, increases the production of prostaglandins that subsequently increase permeability of perifoveal capillaries with intraretinal fluid accumulation as a consequence.[30] This hypothesis was supported by a previous study by Inoda et al[17] that identified iris damage as a CME risk factor after DMEK. Therefore, the routinely performed iridectomy by Kocaba et al could be an explanation for the difference between the studies. As DMEK is considered surgically more difficult than DSAEK, this technique, assumably, results in a higher degree of iris manipulation. This higher degree of iris manipulation would, according to the theory

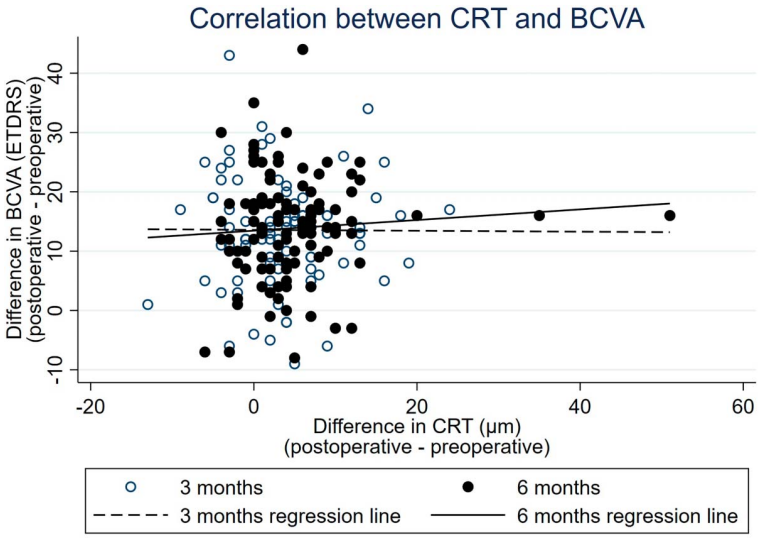

FIGURE 4. Scatterplot of the CRT difference from baseline versus BCVA difference from baseline in Early Treatment Diabetic Retinopathy Study (ETDRS) letters for all groups after 3 and 6 months, respectively. (The full color version of this figure is available at www.corneajrnl.com.)

above, lead to a higher incidence of CME after DMEK compared with DSAEK. This was also stated by Myerscough et al[18] who conducted a retrospective cohort study on the incidence of CME after DSAEK and DMEK in 2233 patients. In contrast to our study, they found a significant odds ratio of 2.42 for developing CME after DMEK compared with DSAEK.

By contrast, when EK was combined with phacoemulsification, as in this study, they did not find an increased odds ratio for developing CME. Nonetheless, it has been speculated whether the cumulative energy used for phacoemulsification correlates with postoperative inflammation and, hence, the risk of CME. Based on this, an increased amount of energy used during phacoemulsification has proven to be correlated with increased scores on the nuclear opalescence and nuclear color scales of the LOCS III cataract grading system.[31,32] Baseline characteristics of this study group revealed higher scores of nuclear opalescence and nuclear color for the control group as compared to the DMEK and UT-DSAEK groups. Therefore, one might have expected the control group to show the largest increase in CRT. On the other hand, reduced corneal transparency in patients with Fuchs endothelial dystrophy may lead to increased use of phacoemulsification energy. However, no difference in CRT was found between the study groups, and the energy used during phacoemulsification in patients with Fuchs endothelial dystrophy could be a topic for future research.

In conclusion, CRT was not significantly different from baseline to 3 and 6 months after DMEK, UT-DSAEK, or cataract surgery, respectively. No significant differences in CRT were found between study groups. BCVA was significantly improved after both DMEK and UT-DSAEK 3 and 6 months postoperatively. Furthermore, BCVA was significantly different between the 3 study groups 3 and 6 months postoperatively. Because no correlation between BCVA and CRT was found, BCVA was not significantly affected by CRT alterations after the interventions. As such, DMEK, UT-DSAEK, and cataract surgery seem to be comparable when it comes to postoperative CRT alterations.

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Paper III

Intraocular pressure-related side-effects after endothelial keratoplasty.

Intraocular pressure-related side-effects after endothelial keratoplasty

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Abstract

Purpose

To investigate circumpapillary retinal nerve fiber layer (**RNFL**) thickness, pupillary function and diameter after endothelial keratoplasty (**EK**) combined with phacoemulsification and lens implantation and in a control group treated with cataract surgery.

Methods

This study was a secondary analysis of data from a randomized, single-masked trial. In that trial, seventy-two patients with Fuchs' endothelial dystrophy and cataract were equally allocated (1:1) to either ultrathin Descemet's stripping automated endothelial keratoplasty or Descemet's membrane endothelial keratoplasty. The control group included forty patients undergoing cataract surgery only. All patients were treated with phacoemulsification and lens implantation.

Results

RNFL was significantly lower in the control group than after EK for the global ($P < 0.01$), nasal ($P = 0.04$), and temporal sectors ($P = 0.01$) 12 months after surgery. RNFL thickness was comparable between patients treated with rebubbling and others ($P \geq 0.16$ for all comparisons) after 12 months. The control group and patients treated with EK demonstrated a comparable scotopic ($P = 0.34$) and photopic pupil diameter ($P = 0.95$) as well as a comparable maximum ($P = 0.83$) and average pupillary constriction velocity ($P = 0.95$) after 12 months. In contrast, patients treated with rebubbling had a significantly smaller scotopic pupil diameter ($P = 0.04$).

Conclusion

Twelve months after surgery, circumpapillary RNFL measurements showed no signs of optic nerve deterioration after any of the procedures. Iris function and pupil diameter were comparable between the control group and patients treated with EK after 12 months.

Keywords

UT-DSAEK, DMEK, Fuchs' endothelial dystrophy, IOP

Introduction

Descemet's stripping automated endothelial keratoplasty (**DSAEK**) and Descemet's membrane endothelial keratoplasty (**DMEK**) are characterized by a replacement of the Descemet's membrane and endothelial cells. Common for these procedures is the air-filled anterior chamber to secure graft adhesion. This is often accompanied by markedly increased intraocular pressure (**IOP**) in the immediate postoperative period. Furthermore, steroid-induced IOP increases and postoperative glaucoma, with retinal nerve fiber layer (**RNFL**) thinning as a key feature, have proven to occur following endothelial keratoplasty (**EK**) (Naveiras et al. 2012; Maier et al. 2013; Maier et al. 2014).

Acutely increased IOP has been associated with impaired iris function and Urrets-Zavalia syndrome. This condition was initially described after penetrating keratoplasty (Urrets Zavalia 1963) but has also been linked to EK (Fournie et al. 2009). Currently, the leading pathophysiological explanation for the condition is ischemia induced iris atrophy caused by an acute postoperative IOP increase (Spierer & Lazar 2014). It has further been postulated that a partial or transient state of the condition could exist (Gasset 1977). Additionally, iris abnormalities can occur after EK (Del Hierro Zarzuelo & Boto de Los Bueis 2016; Arnalich-Montiel et al. 2017).

Despite the occurrence of IOP fluctuations after EK, little is known about their significance. Therefore, we wanted to investigate RNFL thinning, iris function and pupil diameter after EK combined with phacoemulsification and lens implantation (triple EK) and after cataract surgery alone. Furthermore, we wanted to compare these outcomes after ultrathin DSAEK (**UT-DSAEK**), with a graft thickness < 100 µm, and DMEK. We hypothesized that changes in RNFL thickness, iris function and pupil diameter were comparable among our study groups 12 months after surgery.

Methods

Trial design

This was a secondary analysis based on data from a randomized, single-center, single-masked trial designed to investigate best corrected visual acuity (**BCVA**) after UT-DSAEK and DMEK (Madsen et al. 2023a). Participants were chosen from referrals to the Department of Ophthalmology, Aarhus University Hospital, Aarhus, Denmark between June 2020 and January 2022. Included patients were between 50 and 81 years of age and suffered from Fuchs' endothelial dystrophy (**FED**) and/or cataract. Exclusion criteria were other vision-affecting morbidities such as glaucoma, uveitis, retinal vein occlusion, retinal atrophy, previous ocular surgery, trauma, or vision-affecting systemic disorders. Written informed consent was provided by all participants. The study was registered at http://clinicaltrials.gov (Identifiers ID: NCT04417959) adhered to the Declaration of Helsinki and was approved by The Central Denmark Region Committee on Health Research Ethics.

An even number of participants with FED and cataract were allocated (1:1) to UT-DSAEK or DMEK combined with phacoemulsification and IOL implantation using block randomization. This was performed approximately once every month by an impartial technician. Participants were all assigned a random computer-generated number (Microsoft Excel 2019 for Windows). Participants with the highest numbers underwent UT-DSAEK; others, DMEK. Patients with cataract undergoing phacoemulsification and IOL implantation were included as a non-randomized control group.

Eye banking and surgical interventions

Grafts were provided by the Danish Cornea Bank, Aarhus, Denmark. UT-DSAEK grafts were precut by eye bank technicians aiming for a graft thickness of 80 µm. DMEK grafts were pre-peeled and pre-

loaded into a Tan Endoglide (DMEK EndoGlide, Coronet, Ripon, United Kingdom). The eye banking technique has been described elsewhere (Madsen et al. 2023b).

Patients treated with EK were initially administered a drop of atropine (Atropine sulphate 1% w/v, Bausch & Lomb, Laboratoire Chauvin, Aubenas, France) to provide prolonged pupillary dilation. All included patients were treated with phacoemulsification and lens implantation. UT-DSAEK grafts were punched in an 8-mm diameter and pulled into the anterior chamber through a 4-mm scleral tunnel at the 12 o'clock position using forceps and Busin glide. Preloaded DMEK grafts were implanted through a 2.65-mm scleral incision at the 12 o'clock position using a pull-through technique. Graft positioning was ensured using intraoperative OCT (HS Hi-R NEO 900A NIR, Haag-Streit, Koeniz, Switzerland) before intracameral cefuroxime 0.1 mL (Aprokam 50 mg/mL, Théa, Clearmont-Ferrand, France) and subconjunctival dexamethasone 1 mg (Dexamethasone phosphate Hameln 4 mg/mL, Hameln pharma gmbh, Hameln, Germany) were administered. Aiming for a physiological IOP, the anterior chamber was filled 100% with 20% SF_6 (ISPAN* Sulfur Hexafluoride, Alcon, Fort Worth, TX, USA), and the patient was left supine. The IOP was not measured intraoperatively, but subjectively evaluated by palpating the eyeball. No preoperative iridotomy or surgical iridectomy was performed in patients undergoing EK or in the control group.

After two hours, the anterior chamber gas tamponade was reduced at the slit-lamp, leaving a bubble occupying between one-half and one-third of the anterior chamber. Patients were given 500 mg oral acetazolamide (Diamox, Amdipharm, Helsingborg, Sweden) 2 hours after surgery and in the evening on the day of surgery. Graft adhesion was evaluated one week after surgery. Rebubbling was performed, if more than one-third of the graft-host interface was non-adherent.

After UT-DSAEK or DMEK, patients were administered diclofenac eyedrops (Voltaren Ophtha, 1mg/mL, GSK Consumer Healthcare, Brøndby, Denmark) t.i.d. for 3 weeks. Furthermore, a combination of dexamethasone and tobramycin (Oridecin, dexamethasone 1 mg/mL and tobramycin 3 mg/mL, Orifarm Generics, Odense, Denmark) was administered six times daily for 1 week and then tapered to 4, 3, 2 and 1 drop every 8 weeks until end of treatment. For patients with postoperative ocular hypertension, dexamethasone treatment was terminated and fluorometholone (Flucon, 1 mg/mL, Novartis Pharma S.A.S., Rueil-Malmaison, France) was administered instead. Patients demonstrating an IOP ≥ 27 mmHg were additionally prescribed timolol (Optimol 5 mg/mL, Santen, Tampere, Finland) twice daily until IOP normalisation.

The control group received diclofenac eyedrops (Voltabak 1 mg/mL, Théa Nordic, Hørsholm, Denmark) t.i.d. for 3 weeks and dexamethasone eyedrops (Maxidex 1 mg/mL, Novartis, Copenhagen, Denmark) t.i.d. for 2 weeks.

Outcome measures

Circumpapillary RNFL thickness, iris function, pupil diameter and IOP were predefined secondary outcomes of the controlled clinical study and are the focus of this paper. BCVA was the primary outcome of the study and has been reported elsewhere (Manuscript submitted for publication, 2023). Full clinical examination was performed 3, 6, and 12 months after surgery. Additionally, IOP was measured two hours after EK before and after the gas tamponade was reduced and at the first postoperative day. IOP was measured using Goldmann applanation tonometry (AT 900, Haag-Streit, Koeniz, Switzerland). Patients were examined using a slit-lamp at every visit and evaluated for irideal

transillumination defects and posterior synechiae (**PS**) by using retroillumination and anterior segment OCT (CASIA2, Tomey Corporation, Nagoya, Japan).

Circumpapillary RNFL thickness was determined with OCT (Spectralis OCT, Heidelberg Engineering, Heidelberg, Germany). At every visit, three consecutive examinations were performed using the follow-up image acquisition function of the glaucoma module (Heidelberg Eye Explorer Version 1.10.4.0). The scan with the highest quality score at baseline was defined as the reference scan and at follow-up examinations noted for analysis. **Figure 1** shows an RNFL scan. The RNFL scan was performed in a circle with a 3.5-mm diameter with the optic disc in the center. The average RNFL thickness of the circular scan was provided as a global value. Furthermore, six consecutive sectors were provided. In the nasal direction, starting from the 12 o'clock position, these sectors were a 45° superior nasal sector, a 90° nasal sector, a 45° inferior nasal sector, a 45° inferior temporal sector, a 90° temporal sector, and a 45° superior temporal sector.

Iris function was examined using an automated pupillometer (DP-2000, Neuroptics, Irvine, CA, USA) in a completely darkened clinic. Patients were initially bilaterally exposed to 2.5 log(lx) of white light for 5 seconds followed by dark adaptation for 5 minutes. During measurement, patients were bilaterally exposed to a stimulus profile of 1 second without light exposure immediately followed by 5 seconds of 2.5 log(lx) of white light exposure. The scotopic pupil diameter (defined as the largest observed diameter) was determined during the first second. The photopic pupil diameter (defined as the smallest observed diameter) was determined during the 5 seconds of light exposure. Additionally, the average pupillary constriction velocity (**CV**) and maximum pupillary constriction velocity (**MCV**) were determined. **Figure 2** shows the stimulus profile and pupil diameter curves.

Sample size

As data originated from a study primarily designed to investigate BCVA after UT-DSAEK and DMEK, the power calculation was based on a study (Chamberlain et al. 2019) that found a standard deviation of 0.18 and 0.12 logarithm of the minimum angle of resolution after UT-DSAEK and DMEK, respectively. It was determined that 31 patients needed to be included in each study group to detect a 6 ETDRS letter difference with an $\alpha = 0.05$ and a power of 85%.

Statistical analysis

A linear mixed effects model was used for age- and sex-adjusted analysis of repeated measures, with serial measurements treated as paired data. To account for variation in baseline values, these were included as covariates in all estimates. The linear mixed effects model was employed to account for missing data without excluding patients from the analysis. Due to the sample size of the present study, the Kenward-Roger approximation was used to calculate the degrees of freedom. Post hoc t-tests were used for individual comparisons. Normality assumptions were checked using QQ-plots. Data distribution was evaluated with standard deviation comparison tests. Continuous baseline characteristics were analyzed using t-tests and binary baseline characteristics using the χ^2 test. Results are presented as means with 95% confidence intervals (**CI**) unless otherwise stated. All analyses were performed in STATA version 17.0 (StataCorp., College Station, TX, USA). A significance level of 5% was used.

Results

Figure 3 shows a CONSORT diagram. Seventy-two patients with FED and cataract were included for EK, and 40 patients with cataract were included in the control group. **Table 1 and 2** show baseline characteristics. One patient allocated to UT-DSAEK died before the intervention, one had capsular rupture, and one had sterile endophthalmitis. One patient in the UT-DSAEK group was unable to attend the 6-months examination. No patients allocated to DMEK were lost to follow-up. The UT-DSAEK and DMEK groups had one case of primary failure each. Both were regrafted with DMEK but analyzed according to their initial allocation. Three patients of the control group had intraoperative capsular rupture and were excluded from the final analyses that included 35, 36 and 37 participants of the UT-DSAEK, DMEK and control group, respectively.

Intraocular pressure

Two hours after surgery, the IOP was comparable between UT-DSAEK and DMEK before (P = 0.07) and after (P = 0.65) gas tamponade reduction. Furthermore, IOP was comparable between UT-DSAEK and DMEK at the first postoperative day (P = 0.69).

Table 3 shows results on IOP. Two (6%) patients after UT-DSAEK and one (3%) after DMEK developed increased IOP (defined as an IOP > 25 mmHg or an IOP increase from baseline ≥ 10 mmHg) during the first postoperative week. After the first postoperative week, 5 (14%) patients after UT-DSAEK and 7 (19%) after DMEK demonstrated an increased IOP. Only one patient in the DMEK group had increased IOP after steroid treatment was terminated and continued timolol treatment. One patient developed pupillary block due to posterior synechiae seven weeks after the initial intervention.

Patients treated with EK had higher IOP than the control group with mean differences of 4.7 mmHg (95% CI, 3.1; 6.3, P < 0.001) after 3 months, and 3.9 mmHg (95% CI, 2.6; 5.1, P < 0.001) after 6 months. However, after 12 months, patients treated with EK had a lower IOP with a mean difference of 1.6 mmHg (95% CI, 0.6; 2.6, P < 0.01). IOP was comparable between UT-DSAEK and DMEK at all time-points.

Figure 4 shows IOP distribution for patients treated with rebubbling and others. Five (14%) patients were treated with rebubbling after UT-DSAEK and 8 (22%) after DMEK. Patients treated with rebubbling had on average a 0.8 mmHg (95% CI, 0.6; 1.0, P = 0.03) lower IOP at the first postoperative day than patients not treated with rebubbling; IOP was comparable two hours after surgery (P > 0.38 for both comparisons).

RNFL thickness

Table 3 and supplementary tables S1 and S2 show results on RNFL thickness.

Twelve months after surgery, patients treated with EK had a significantly higher RNFL thickness than the control group with mean differences of 2.6 µm (95% CI, 0.8; 4.3, P < 0.01) for the global sector, 2.3 µm (95% CI, 0.2; 4.5, P = 0.04) for the temporal sector, and 3.0 µm (95% CI, 0.7; 5.3, P = 0.01) for the nasal sector. No difference was found for other sectors (P > 0.06 for all comparisons). At all time-points, RNFL thickness was comparable for the global and individual sectors irrespective of the performed EK (P ≥ 0.10 for all comparisons), rebubbling status (P ≥ 0.16 for all comparisons) or increased IOP after the first postoperative week (P ≥ 0.09 for all comparisons). RNFL for the global sector was significantly higher after 3, 6, and 12 months compared with baseline for the UT-DSAEK and DMEK groups (P < 0.028

for all comparisons) and after 3 and 6 months in the control group (P < 0.008 for both comparisons); no difference was found after 12 months (P = 0.494).

Iris changes and function

Table 3 and supplementary table S3 show results on pupil diameter and function. Two (6%) patients after UT-DSAEK and five (14%) patients after DMEK had iris transillumination defects. Likewise, two (6%) patients after UT-DSAEK and five (14%) patients after DMEK had posterior synechiae (**PS**); however, patients with transillumination defects were not necessarily the same as those with PS.

Patients in the control group had a higher MCV (P = 0.02) and a smaller photopic pupil diameter (P < 0.01) than patients treated with EK after 3 months. Patients treated with UT-DSAEK had a higher MCV (P < 0.01) than patients treated with DMEK after 3 months. No differences were found after exclusion of patients with PS (P > 0.06 for all comparisons).

Patients with PS had a smaller scotopic pupil diameter than patients without PS with a mean difference of 0.5 mm (95% CI, 0.1; 0.9, P = 0.014) after 3 months and 0.5 mm (95% CI, 0.2; 0.8, P < 0.01) after 12 months and a larger photopic pupil diameter with a mean difference of 0.6 mm (95% CI, 0.1; 1.2, P = 0.03) after 3 months. After 3 and 12 months, the MCV and CV were comparable between patients with and without PS (P > 0.16 for all comparisons).

Patients treated with rebubbling had a smaller scotopic pupil diameter than patients not treated with rebubbling after 3 (P = 0.03) and 12 months (P = 0.04). No difference was found after excluding patients with PS from the analyses (P > 0.63 for both comparisons).

Anterior chamber gas tamponade pressure

The median IOP two hours after surgery before gas tamponade reduction was 40 mmHg (range: 10; 78) for patients treated with EK. Using this, we defined a group of patients with a gas tamponade IOP > 40 mmHg and a group with an IOP ≤ 40 mmHg.

Patients with a tamponade pressure > 40 mmHg had a significantly lower RNFL thickness for the superior nasal sector compared with others with a mean difference of 6.6 µm (95% CI, 1.5; 11.8, P = 0.01) 12 months after surgery. However, RNLF thickness was comparable for other sectors (P ≥ 0.07 for all comparisons). Three and 12 months postoperatively, pupillary outcomes were comparable irrespective of the tamponade pressure. (P > 0.11 for all comparisons).

Discussion

In this study, IOP was significantly higher 3 and 6 months after EK than after cataract surgery. As steroid-induced IOP increase is a well-known phenomenon (Stein et al. 2021), this most certainly was caused by the dexamethasone treatment administered after EK. This explanation is further supported by the observed IOP decrease after 12 months when topical steroid treatment had been terminated. In the present study Goldmann applanation tonometry was used to measure the IOP, but measurements were not adjusted for CCT. According to the Imbert-Fick law these measurements are affected by the rigidity in the applanated membrane; hence the CCT. However, in the case of FED and EK the rigidity of the cornea may not be correlated to CCT in the same way as in the normal cornea. Clemmensen et al. (2014) found a significantly altered corneal hysteresis and corneal resistance factor between patients with FED and healthy controls; however, comparable in patients with FED regardless of whether they had been treated with DSAEK or not. As patients with prolonged corneal edema may lose stromal

glycosaminoglycans (Kangas et al. 1990), this may explain a change in the biomechanical properties of the cornea in patients with FED. Furthermore, their results suggest that the biomechanical properties of the cornea are insignificantly affected by a DSAEK graft. This makes the effect of the postoperative CCT on IOP unpredictable, and a previous study failed to demonstrate a correlation between these variables (Maier et al. 2017).

In this study, RNFL thickness was comparable between UT-DSAEK and DMEK 12 months after surgery and between patients who demonstrated an increased IOP after the first postoperative week and those who did not. However, patients treated with EK demonstrated a higher RNFL thickness for the global, nasal, and temporal sectors than the control group. In addition to steroid treatment, patients treated with EK had also been exposed to anterior chamber gas tamponade.

These somewhat counterintuitive results may be explained by an increased OCT signal strength. OCT signal strength is correlated with media clarity, which includes cornea opacities or edema and cataract. Low OCT signal strength results in false low RNFL estimates (van Velthoven et al. 2006; Bambo et al. 2014). Whereas all patients in this study preoperatively had cataract, only patients treated with EK had FED. Therefore, the postoperative optical quality improvement, hence better OCT signal strength, could be proportionately larger in these patients as confirmed by their slightly worse baseline visual acuity. It is possible that the OCT machine used in the present study (Heidelberg Spectralis) is less affected by reduced media clarity than other machines since the RNFL measurements changed less after surgery than reported in previous studies. Previous studies of patients with a similar visual acuity gained 5-10 μm global RNFL after cataract surgery but used different machines (Kok et al. 2013).

However, the present study does suggest that RNFL thickness is comparable after cataract surgery and triple EK.

Twelve months after surgery, patients with a gas tamponade pressure > 40 mmHg had a significantly lower RNFL thickness for the superior nasal sector than those with a lower pressure; for other sectors, the RNFL thickness was comparable. Both IOP level and time duration matter in terms of IOP-induced damage. The most well-known transient IOP elevation is probably acute angle closure, where patients develop a sudden IOP increase (>40 mmHg) that lasts for several hours. Although this may lead to optic nerve damage the magnitude is in most cases quite low, probably since most episodes are treated within 12 hours (Aung et al. 2004; Tsai et al. 2007; Moghimi et al. 2019). The damages are primarily located in the superior and inferior quadrants, typical for glaucoma. During acute angle closure, the IOP level most often reaches higher levels than experienced by patients in this cohort (Tsai et al. 2007). In addition, acute angle closure often results in a longer IOP elevation. As an episode of acute angle closure usually exceeds 2 hours, the period with increased IOP after EK may simply be too short to induce retinal nerve fiber damage. As the procedure is terminated with a physiological IOP that afterwards increases due to the gas-bubble-induced pupillary block, the period with increased IOP may even be shorter than 2 hours. If the IOP elevation in our study was harmful, a preferential affection of the superior and inferior quadrants would have been expected, which was not the case. Furthermore, the RNFL thickness was comparable between patients irrespective of rebubbling. This emphasizes the insignificant effect of gas tamponade on RNFL thickness.

The present study was not designed to investigate RNFL alterations; however, similar sample sizes have been used to detect detrimental effects of acute angle closure (Aung et al. 2004; Tsai et al. 2007). Spectral domain OCT has previously proven to have high reproducibility and a small within-

subject standard deviation enabling detection of clinically significant changes in RNFL thickness (Wu et al. 2011), and it is a convenient objective technique with which to assess retinal anatomy. The measurements are however dependent on the signal strength so care must be taken to interpret results when the media clarity of the eye changes, as was the case in this study.

The pathophysiology of Urrets-Zavalia syndrome is largely unknown (Spierer & Lazar 2014). It has been hypothesized that compression of iris vessels from increased IOP could cause iris ischemia (Tuft & Buckley 1995). In the present study, patients treated with cataract surgery demonstrated a significantly smaller photopic pupil diameter and a significantly higher MCV than patients treated with EK 3 months after surgery. As only patients treated with EK were exposed to gas tamponade, this could support the hypothesis of an IOP-induced weakening of the iris sphincter. However, pupillary measures were comparable irrespective of the tamponade pressure. PS have also been described in Urrets-Zavalia syndrome (Urrets Zavalia 1963). In the present study, patients with PS had a smaller scotopic pupil diameter and a larger photopic pupil diameter than patients without PS, which indicates a restrictive effect of PS on iris motion. After exclusion of patients with PS, the control group demonstrated only a non-significant tendency towards a smaller photopic pupil diameter and a higher MCV than patients treated with EK after 3 months. Additionally, without PS, results were comparable irrespective of rebubbling status. Therefore, our results suggest that PS but not increased IOP affects iris function after UT-DSAEK and DMEK compared with cataract surgery.

The pupillary response is influenced by many factors (Mathôt & Van der Stigchel 2015), which complicate its measurement. However, a study conducted at our center showed good reliability and reproducibility of the used pupillometer and stimulus profile (unpublished material).

Acutely increased IOP has previously been associated with graft detachment (Aldave et al. 2019). However, in agreement with a previous study (Schmeckenbächer et al. 2017), we found a comparable IOP before and after anterior chamber gas tamponade irrespective of rebubbling status. Moreover, patients requiring rebubbling had a significantly lower IOP on the first postoperative day than those who did not. This could indicate that graft attachment not only depends on endothelial function but mainly on mechanical support from the gas bubble. Administration of carbonic anhydrase inhibitors to reduce the risk of gas-induced pupillary block does not affect endothelial function (Malikowski et al. 2014), but the lower IOP may lead to suboptimal graft attachment. This agrees with a previous study that found a higher risk of graft detachment after IOP dips (Heinzelmann et al. 2018). Therefore, full anterior chamber gas tamponade appears to be a safe approach to EK. Despite no apparent effect on graft adhesion, a tamponade IOP above 40 mmHg for less than 2 hours appears not to cause substantial ocular damage either. As the gas tamponade techniques in EK are quite diverse, this may affect the external validity of our results.

In conclusion, increased IOP from anterior chamber gas tamponade and long-term steroid treatment had an insignificant effect on RNFL thickness 12 months after surgery. Pupillary function and diameter were comparable between the control group and patients treated with EK, and between UT-DSAEK and DMEK after 12 months.

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Conflicts of interest

The authors have no conflicts of interest to declare.

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Table 1. Baseline Characteristics, mean (95% confidence interval)		
	UT-DSAEK (n = 35)	DMEK (n = 36)
Participant characteristics		
Female, %	62.9 (44.9; 78.5)	72.2 (54.8; 85.8)
Age, years	69.2 (67.1; 71.3)	68.5 (66.4; 70.6)
BCVA, ETDRS letters	69.0 (67.3; 70.7)	67.4 (64.8; 70.0)
CCT, µm	615.9 (596.7; 635.1)	606.4 (588.8; 624.0)
IOP, mmHg	15.1 (14.0; 16.1)	16.0 (14.9; 17.0)
RNFL measurements		
Global, µm	93.3 (89.3; 97.2)	92.3 (88.9; 95.6)
Temporal, µm	62.0 (58.5; 65.5)	65.7 (61.2; 70.2)
Superior temporal, µm	119.1 (113.1; 125.2)	121.3 (115.5; 127.1)
Superior nasal, µm	98.8 (86.5; 111.1)	98.6 (90.9; 106.4)
Nasal, µm	79.0 (72.2; 85.8)	75.4 (69.6; 81.2)
Inferior nasal, µm	117.9 (104.8; 131.0)	106.8 (95.9; 117.7)
Inferior temporal, µm	128.1 (122.4; 133.8)	128.9 (122.4; 135.4)
Pupillometry		
Scotopic diameter, mm	5.48 (5.17; 5.79)	5.48 (5.20; 5.76)
Photopic diameter, mm	2.30 (2.17; 2.43)	2.38 (2.26; 2.51)
MCV, mm/s	4.95 (4.66; 5.25)	4.96 (4.69; 5.23)
CV, mm/s	0.84 (0.77; 0.91)	0.86 (0.78; 0.93)
Donor characteristics		
Female, %	48.6 (31.4; 66.0)	36.1 (20.8; 53.8)
Age, years	73.4 (69.3; 77.6)	71.3 (67.9; 74.7)
Time to enucleation, hours†	16.6 (14.1; 19.5)	16.6 (13.9; 19.8)
Tissue preservation time, days	33.0 (29.9; 36.1)	31.4 (28.6; 34.2)
ECD, cells/mm^2	2482 (2364; 2599)	2696 (2613; 2779)
Post-cut graft thickness, µm	80.7 (75.3; 86.2)	-

UT-DSAEK, ultrathin Descemet's stripping automated endothelial keratoplasty; DMEK, Descemet's membrane endothelial keratoplasty; BCVA, best corrected visual acuity; ETDRS, early treatment diabetic retinopathy study; CS, contrast sensitivity; CCT, central corneal thickness; IOP, intraocular pressure; RNFL, retinal nerve fibre layer; MCV, maximum pupil contraction velocity; CV, average pupil contration velocity.
† Median values.

Table 2. Baseline Characteristics, mean (95% confidence interval)			
	EK (n = 71)	Control (n = 37)	P value
Participant characteristics			
Female, %	67.6 (55.5; 78.2)	73.0 (55.9; 86.2)	0.57
Age, years	68.9 (67.4; 70.3)	71.7 (69.7; 73.7)	0.02
BCVA, ETDRS letters	68.2 (66.7; 69.7)	72.3 (70.5; 74.1)	0.001
CCT, µm	611 (598; 624)	551 (541; 560)	< 0.001
IOP, mmHg	15.5 (14.8; 16.3)	15.9 (14.9; 16.8)	0.58
RNFLT			
Global, µm	92.7 (90.2; 95.3)	90.7 (87.6; 93.8)	0.33
Temporal, µm	63.9 (61.1; 66.7)	64.0 (60.3; 67.7)	0.96
Superior temporal, µm	120.3 (116.2; 124.4)	120.1 (113.8; 126.4)	0.97
Superior nasal, µm	98.7 (91.7; 105.8)	95.8 (88.3; 103.3)	0.57
Nasal, µm	77.2 (72.8; 81.5)	73.6 (67.9; 79.3)	0.33
Inferior nasal, µm	112.3 (103.9; 120.6)	107.1 (96.8; 117.5)	0.46
Inferior temporal, µm	128.5 (124.3; 132.7)	127.0 (120.6; 133.4)	0.68
Pupillometry			
Scotopic diameter, mm	5.48 (5.28; 5.68)	5.19 (4.89; 5.50)	0.11
Photopic diameter, mm	2.34 (2.25; 2.43)	2.21 (2.09; 2.33)	0.08
MCV, mm/s	4.96 (4.76; 5.15)	4.94 (4.66; 5.23)	0.94
CV, mm/s	0.85 (0.80; 0.90)	0.87 (0.81; 0.94)	0.54

EK, endothelial keratoplasty; BCVA, best corrected visual acuity; ETDRS, early treatment diabetic retinopathy study; CCT, central corneal thickness; IOP, intraocular pressure; RNFLT, retinal nerve fibre layer thickness; MCV, maximum pupil constriction velocity; CV, average pupil constriction velocity.

Table 3. Comparisons of intraocular pressure and retinal nerve fibre layer thickness, mean (95% confidence interval)					
	UT-DSAEK (n = 35)	DMEK (n = 36)	Control (n = 37)	P value‡ (UT-DSAEK vs DMEK)	P value‡ (EK vs control)
IOP, mmHg					
Baseline	15.1 (14.0; 16.1)	16.0 (14.9; 17.0)	15.9 (14.9; 16.8)		
3 months	17.4 (15.5; 19.3)	17.9 (15.5; 20.4)	13.3 (12.3; 14.3)	0.96	< 0.001
6 months	16.2 (14.7; 17.7) †	17.1 (15.5; 18.7)	13.1 (12.1; 14.2) †	0.72	< 0.001
12 months	11.6 (10.6; 12.6)	11.6 (10.6; 12.6)	13.6 (12.5; 14.7) †	0.25	< 0.01
RNFLT					
Global, µm					
Baseline	93.3 (89.3; 97.2)	92.3 (88.9; 95.6)	90.7 (87.6; 93.8)		
3 months	95.8 (91.8; 99.8)	94.5 (91.1; 97.9)	92.8 (89.4; 96.1)	0.75	0.70
6 months	95.3 (91.4; 99.1) †	94.2 (90.5; 97.9)	92.8 (89.3; 96.3) †	0.35	0.96
12 months	96.8 (92.4; 101.1)	94.8 (91.0; 98.7)	90.9 (87.7; 94.2) †	0.45	< 0.01
Pupillometry					
Scotopic pupil diameter (mm)					
Baseline	5.48 (5.17; 5.79)	5.48 (5.20; 5.76)	5.19 (4.89; 5.50)		
3 months	5.38 (5.09; 5.67)	5.30 (5.02; 5.58)	5.07 (4.80; 5.35)	0.41	0.77
12 months	5.37 (5.07; 5.66)	5.31 (5.04; 5.59)	5.17 (4.87; 5.46) †	0.51	0.34
Photopic pupil diameter (mm)					
Baseline	2.30 (2.17; 2.43)	2.38 (2.26; 2.51)	2.21 (2.09; 2.33)		
3 months	2.39 (2.26; 2.52)	2.54 (2.38; 2.71)	2.22 (2.09; 2.34)	0.36	< 0.01
12 months	2.25 (2.13; 2.38)	2.39 (2.23; 2.55)	2.21 (2.07; 2.35) †	0.40	0.95
MCV (mm/s)					
Baseline	4.95 (4.66; 5.25)	4.96 (4.69; 5.23)	4.94 (4.66; 5.23)		
3 months	5.09 (4.81; 5.37)	4.58 (4.29; 4.88)	5.16 (4.84; 5.47)	< 0.01	0.02
12 months	5.10 (4.79; 5.41)	4.94 (4.68; 5.20)	4.95 (4.61; 5.29) †	0.35	0.83
CV (mm/s)					
Baseline	0.84 (0.77; 0.91)	0.86 (0.78; 0.93)	0.87 (0.81; 0.94)		
3 months	0.83 (0.75; 0.90)	0.78 (0.71; 0.85)	0.83 (0.76; 0.90)	0.19	0.51
12 months	0.86 (0.80; 0.93)	0.83 (0.73; 0.92)	0.84 (0.76; 0.93) †	0.31	0.95

UT-DSAEK, ultrathin Descemet's stripping automated endothelial keratoplasty; DMEK, Descemet's membrane endothelial keratoplasty; EK, endothelial keratoplasty (UT-DSAEK and DMEK combined); IOP, intraocular pressure; RNFT, retinal nerve fibre layer thickness; MCV, maximum pupil constriction velocity; CV, average pupil constriction velocity.
Data are presented as mean (95% confidence interval)
† One value missing, ‡ P values of the post-hoc t-test were calculated based on multivariate linear mixed effects model.

Supplementary Table S1. Comparisons of intraocular pressure and retinal nerve fibre layer thickness, mean (95% confidence interval)					
	UT-DSAEK (n = 35)	DMEK (n = 36)	Control (n = 37)	P value‡ (UT-DSAEK vs DMEK)	P value‡ (EK vs control)
RNFLT					
Temporal, µm					
Baseline	62.0 (58.5; 65.5)	65.7 (61.2; 70.2)	64.0 (60.3; 67.7)		
3 months	66.2 (62.1; 70.3)	68.5 (63.9; 73.2)	67.1 (63.2; 71.1)	0.34	0.76
6 months	65.0 (61.2; 68.9) †	67.7 (63.3; 72.1)	69.4 (65.0; 73.8) †	0.39	0.08
12 months	66.4 (62.5; 70.2)	70.7 (65.5; 75.9)	66.5 (62.4; 70.6) †	0.78	0.04
Superior temporal, µm					
Baseline	119.1 (113.1; 125.2)	121.3 (115.5; 127.1)	120.1 (113.8; 126.4)		
3 months	122.3 (115.8; 128.9)	122.5 (116.6; 128.4)	122.7 (116.6; 128.7)	0.13	0.58
6 months	121.4 (115.1; 127.8) †	123.6 (116.7; 130.5)	124.5 (118.4; 130.6) †	0.71	0.51
12 months	122.1 (116.0; 128.1)	121.1 (114.4; 127.9)	121.1 (114.5; 127.8) †	0.10	0.62
Superior nasal, µm					
Baseline	98.8 (86.5; 111.1)	98.6 (90.9; 106.4)	95.8 (88.3; 103.3)		
3 months	100.3 (88.5; 112.0)	100.2 (92.4; 108.0)	98.1 (90.5; 105.7)	0.94	0.58
6 months	96.2 (85.9; 106.5) †	99.9 (92.1; 107.8)	97.4 (90.6; 104.1) †	0.90	0.66
12 months	102.1 (87.8; 116.4)	100.4 (91.6; 109.2)	96.7 (90.0; 103.4) †	0.60	0.31
Nasal, µm					
Baseline	79.0 (72.2; 85.8)	75.4 (69.6; 81.2)	73.6 (67.9; 79.3)		
3 months	80.2 (73.5; 86.9)	77.2 (71.4; 82.9)	74.5 (68.5; 80.4	0.71	0.58
6 months	79.9 (73.6; 86.2) †	76.6 (70.7; 82.5)	72.7 (66.9; 78.5) †	0.21	0.24
12 months	82.5 (75.3; 89.7)	77.3 (71.3; 83.4)	72.8 (66.9; 78.7) †	0.40	0.01
Inferior nasal, µm					
Baseline	117.9 (104.8; 131.0)	106.8 (95.9; 117.7)	107.1 (96.8; 117.5)		
3 months	121.2 (108.2; 134.2)	111.2 (101.2; 121.2)	108.6 (97.9; 119.4)	0.78	0.13
6 months	121.6 (108.4; 134.8) †	109.4 (99.2; 119.5)	105.1 (96.0; 114.3) †	0.57	0.21
12 months	119.8 (106.7; 133.0)	110.3 (100.3; 120.4)	105.3 (96.4; 114.3) †	0.59	0.34
Inferior temporal, µm					
Baseline	128.1 (122.4; 133.8)	128.9 (122.4; 135.4)	127.0 (120.6; 133.4)		
3 months	129.9 (123.7; 136.0)	131.0 (124.5; 137.5)	129.2 (122.0; 136.3)	0.91	0.87
6 months	132.7 (126.9; 138.5) †	131.1 (124.4; 137.8)	130.8 (123.3; 138.4) †	0.14	0.74
12 months	131.9 (126.2; 137.7)	130.7 (124.1; 137.2)	125.9 (117.9; 133.8) †	0.24	0.06

UT-DSAEK, ultrathin Descemet's stripping automated endothelial keratoplasty; DMEK, Descemet's membrane endothelial keratoplasty; EK, endothelial keratoplasty (UT-DSAEK and DMEK combined); IOP, intraocular pressure; RNFT, retinal nerve fibre layer thickness.

Data are presented as mean (95% confidence interval)

† One value missing, ‡ P values of the post-hoc t-test were calculated based on multivariate linear mixed effects model.

Supplementary Table S2. Comparisons of intraocular pressure and retinal nerve fibre layer thickness, mean (95% confidence interval)						
	Rebubbling (n = 13)	No rebubbling (n = 58)	P value‡	Increased postoperative IOP* (n = 12)	No increased postoperative IOP (n = 59)	P value‡
RNFLT						
Global, µm						
Baseline	88.8 (84.3; 93.4)	93.6 (90.7; 96.5)		93.5 (88.0; 99.0)	92.6 (89.7; 95.5)	
3 months	91.5 (87.3; 95.8)	96.0 (93.0; 99.0)	0.78	95.8 (90.4; 101.2)	95.0 (92.1; 98.0)	0.95
6 months	91.5 (86.6; 96.3)	95.5 (92.4; 98.5) †	0.80	96.1 (90.9; 101.3)	94.4 (91.4; 97.4) †	0.66
12 months	91.0 (86.4; 95.6)	96.9 (93.6; 100.2)	0.27	95.1 (90.1; 100.0)	95.9 (92.6; 99.2)	0.14
Temporal, µm						
Baseline	63.1 (55.8; 70.3)	64.1 (60.9; 67.2)		61.2 (52.8; 69.5)	64.4 (61.4; 67.5)	
3 months	66.5 (59.5; 73.6)	67.6 (64.1; 71.0)	0.77	62.8 (54.6; 71.0)	68.3 (65.0; 71.6)	0.03
6 months	65.5 (58.0; 73.1)	66.6 (63.4; 69.8) †	0.77	64.3 (56.5; 72.0)	66.8 (63.7; 70.0) †	0.75
12 months	66.2 (58.8; 73.7)	69.1 (65.5; 72.7)	0.16	65.3 (57.1; 73.6)	69.2 (65.7; 72.8)	0.50
Superior temporal, µm						
Baseline	120.9 (107.3; 134.5)	120.1 (115.9; 124.4)		115.4 (104.4; 126.5)	121.2 (116.7; 125.7)	
3 months	123.5 (109.9; 137.0)	122.2 (117.7; 126.7)	0.59	118.4 (108.0; 128.8)	123.2 (118.4; 128.0)	0.55
6 months	124.2 (109.6; 138.8)	122.2 (117.3; 127.0) †	0.40	119.5 (108.9; 130.1)	123.2 (118.0; 128.4) †	0.29
12 months	123.3 (109.7; 136.9)	121.2 (116.5; 125.9)	0.32	116.5 (106.4; 126.6)	122.6 (117.6; 127.6)	0.81
Superior nasal, µm						
Baseline	107.2 (93.9; 120.4)	96.8 (88.7; 105.0)		94.7 (78.6; 110.7)	99.5 (91.5; 107.5)	
3 months	109.9 (98.8; 121.1)	98.1 (90.1; 106.1)	0.46	95.9 (80.2; 111.6)	101.1 (93.4; 108.9)	0.94
6 months	109.5 (96.0; 123.0)	95.5 (88.5; 102.6) †	0.37	96.0 (80.3; 111.7)	98.6 (91.5; 105.6) †	0.77
12 months	107.3 (94.2; 120.4)	99.9 (90.3; 109.5)	0.23	94.4 (80.3; 108.5)	102.6 (93.2; 112.1)	0.13
Nasal, µm						
Baseline	69.4 (59.8; 79.0)	78.9 (74.0; 83.8)		82.2 (73.1; 91.2)	76.2 (71.2; 81.1)	
3 months	71.2 (61.6; 80.8)	80.4 (75.5; 85.2)	0.91	84.8 (75.9; 93.7)	77.4 (72.5; 82.3)	0.49
6 months	71.2 (61.9; 80.4)	79.9 (75.0; 84.5) †	0.87	83.3 (75.3; 91.2)	77.1 (72.3; 82.0) †	0.71
12 months	71.4 (61.6; 81.2)	81.8 (76.6; 87.0)	0.46	83.9 (76.1; 91.7)	79.1 (73.7; 84.4)	0.57
Inferior nasal, µm						
Baseline	95.1 (81.4; 108.8)	116.1 (106.4; 125.8)		121.5 (102.2; 140.8)	110.4 (100.9; 119.8)	
3 months	98.9 (85.9; 112.0)	120.0 (110.7; 129.2)	0.34	125.4 (106.3; 144.5)	114.2 (105.2; 123.2)	0.84
6 months	97.8 (85.6; 110.0)	119.3 (109.8; 128.8) †	0.27	122.5 (103.9; 141.1)	113.8 (104.5; 123.1) †	0.50
12 months	97.9 (84.5; 111.4)	118.8 (109.5; 128.2)	0.35	119.5 (101.3; 137.7)	114.1 (104.9; 123.3)	0.09
Inferior temporal, µm						
Baseline	121.5 (113.1; 130.0)	130.1 (125.3; 134.9)		130.0 (114.6; 145.4)	128.2 (123.9; 132.5)	
3 months	124.0 (115.2; 132.8)	131.9 (126.9; 136.9)	0.92	131.8 (116.3; 147.4)	130.2 (125.7; 134.7)	0.90
6 months	124.8 (116.0; 133.5)	133.5 (128.5; 138.5)	0.62	134.8 (119.0; 150.6)	131.3 (126.9; 135.7) †	0.18
12 months	124.9 (116.2; 133.7)	132.7 (127.9; 137.6)	0.97	130.1 (115.7; 144.4)	131.5 (127.1; 136.0)	0.11

UT-DSAEK, ultrathin Descemet's stripping automated endothelial keratoplasty; DMEK, Descemet's membrane endothelial keratoplasty; EK, endothelial keratoplasty (UT-DSAEK and DMEK combined); IOP, intraocular pressure; RNFT, retinal nerve fibre layer thickness.

Data are presented as mean (95% confidence interval)

* Defined as IOP > 25 mmHg or an IOP increase ≥ 10 mmHg 3, 6 or 12 months after surgery.

† One value missing

‡ P values of the post-hoc t-test were calculated based on baseline adjusted multivariate linear mixed effects model.

Supplementary Table S3. Comparisons of pupil diameter and constriction, mean (95% confidence interval)						
	Rebubbling (n = 13)	No rebubbling (n = 58)	P value‡	*Tamponade IOP > 40 mmHg (n = 32)	*Tamponade IOP ≤ 40 mmHg (n = 39)	P value‡
Pupillometry						
Scotopic pupil diameter (mm)						
Baseline	5.63 (5.19; 6.07)	5.45 (5.21; 5.68)		5.49 (5.15; 5.82)	5.47 (5.21; 5.73)	
3 months	5.21 (4.83; 5.59)	5.37 (5.14; 5.59)	0.03	5.42 (5.09; 5.75)	5.27 (5.03; 5.52)	0.25
12 months	5.27 (4.89; 5.66)	5.35 (5.13; 5.58)	0.04	5.38 (5.04; 5.71)	5.31 (5.07; 5.55)	0.60
Photopic pupil diameter (mm)						
Baseline	2.40 (2.18; 2.63)	2.32 (2.23; 2.42)		2.35 (2.21; 2.48)	2.33 (2.21; 2.46)	
3 months	2.76 (2.38; 3.15)	2.40 (2.31; 2.50)	0.11	2.55 (2.39; 2.72)	2.40 (2.26; 2.53)	0.12
12 months	2.57 (2.21; 2.93)	2.27 (2.17; 2.36)	0.16	2.36 (2.21; 2.51)	2.29 (2.15; 2.43)	0.61
MCV (mm/s)						
Baseline	5.11 (4.55; 5.67)	4.92 (4.71; 5.13)		4.96 (4.61; 5.31)	4.95 (4.73; 5.17)	
3 months	4.46 (3.68; 5.24)	4.92 (4.72; 5.11)	0.23	4.90 (4.55; 5.26)	4.78 (4.53; 5.03)	0.42
12 months	4.83 (4.25; 5.40)	5.06 (4.85; 5.28)	0.40	5.06 (4.74; 5.38)	4.98 (4.72; 5.25)	0.54
CV (mm/s)						
Baseline	0.80 (0.68; 0.92)	0.86 (0.80; 0.92)		0.83 (0.75; 0.91)	0.86 (0.79; 0.93)	
3 months	0.73 (0.60; 0.86)	0.82 (0.76; 0.88)	0.30	0.80 (0.71; 0.88)	0.81 (0.74; 0.88)	0.92
12 months	0.87 (0.65; 1.10)	0.84 (0.79; 0.89)	0.63	0.86 (0.76; 0.96)	0.83 (0.77; 0.89)	0.38

UT-DSAEK, ultrathin Descemet's stripping automated endothelial keratoplasty; DMEK, Descemet's membrane endothelial keratoplasty; EK, endothelial keratoplasty (UT-DSAEK and DMEK combined); MCV, maximum pupil constriction velocity; CV, average pupil constriction velocity.

Data are presented as mean (95% confidence interval)

* Intraocular pressure during anterior chamber gas tamponade

† One value missing

‡ P values of the post-hoc t-test were calculated based on baseline adjusted multivariate linear mixed effects model.

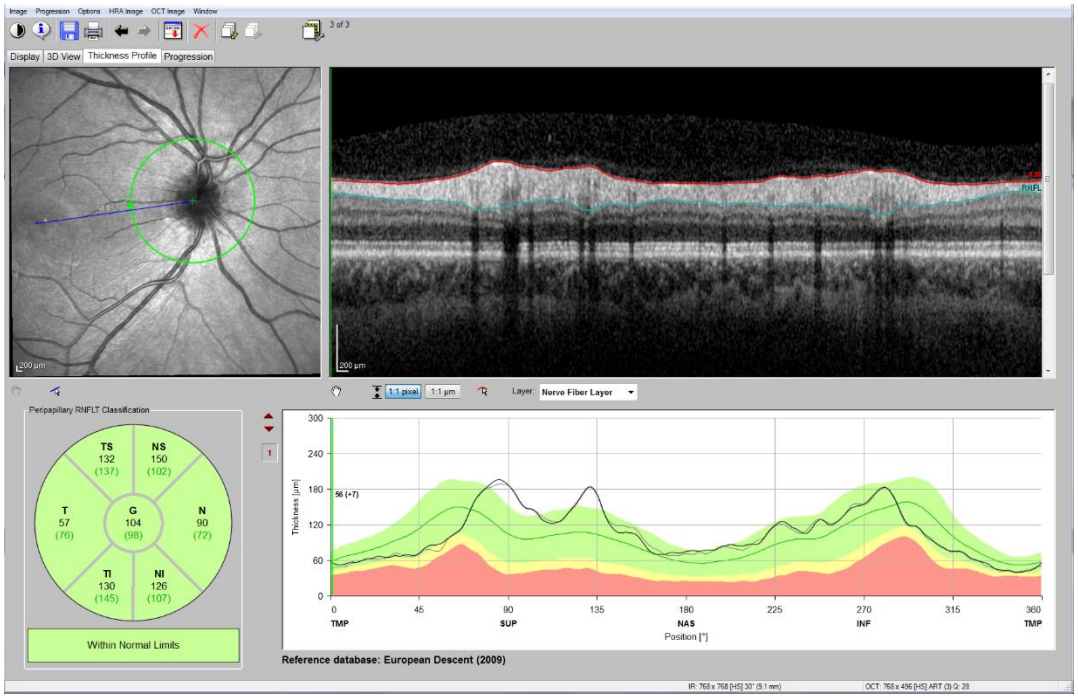

Figure 1: Schematic representation of the stimulus profile and pupillary response. The horizontal white line, corresponding to the right vertical axis, indicates light exposure over time. Pupillary diameter curves, corresponding to the left vertical axis, are shown for the right (green curve) and left (yellow curve) eye over time.

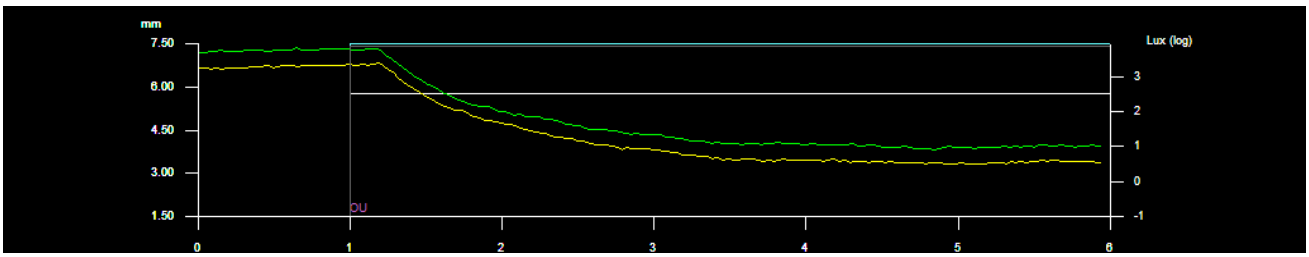

Figure 2: An example of the retinal nerve fiber layer thickness report from the Heidelberg Spectralis OCT used in the present study with a schematic representation of analyzed sectors.

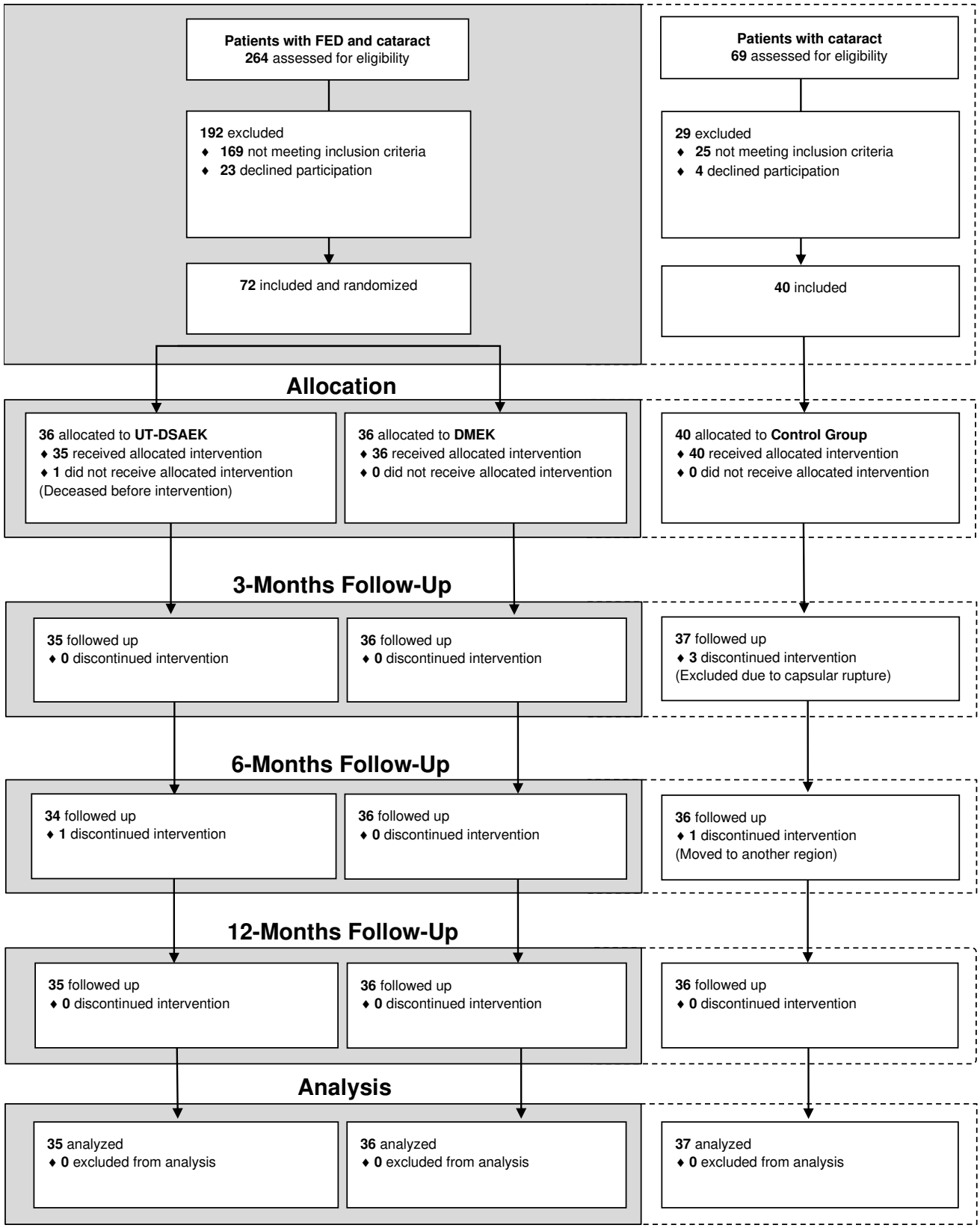

Figure 3: CONSORT diagram showing participant inclusion and follow-up.

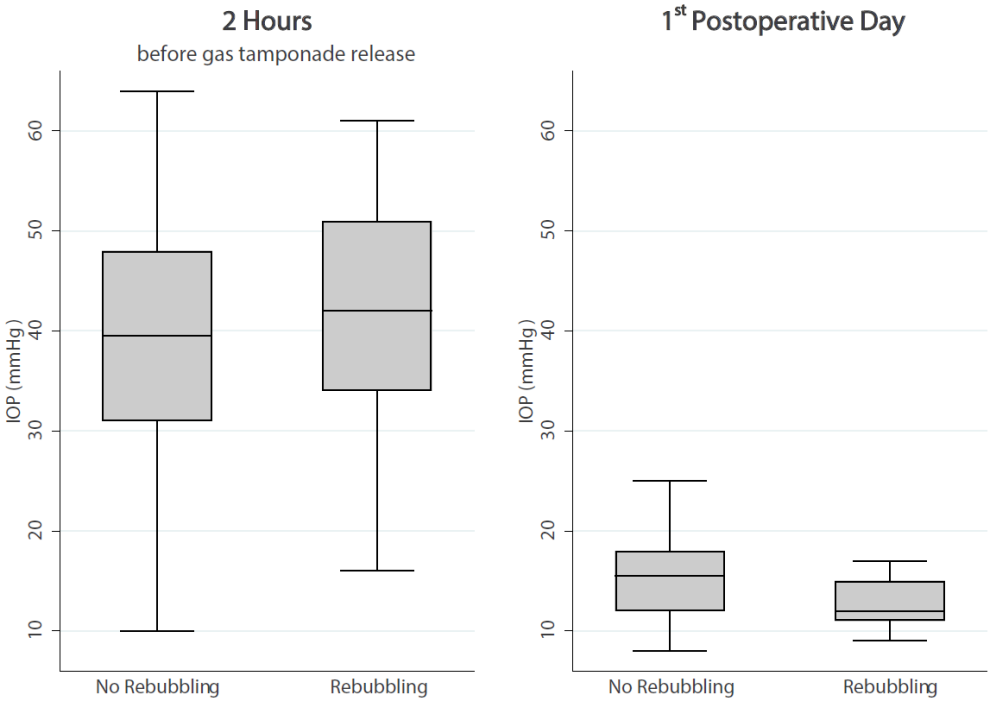

Figure 4: Boxplot showing the distribution of intraocular pressure (**IOP**) 2 hours after endothelial keratoplasty before the reduction of the anterior chamber gas tamponade and at the first postoperative day for patients with and without a requirement for rebubbling.

Declarations of co-authorship

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Declaration of co-authorship concerning article for PhD dissertations

Full name of the PhD student: Morten Brok Molbech Madsen

This declaration concerns the following article/manuscript:

Title:	Visual function after ultrathin Descemet's stripping automated endothelial keratoplasty or Descemet's membrane endothelial keratoplasty combined with cataract surgery: A randomized controlled trial
Authors:	Morten B M Madsen, Anders Ivarsen, Jesper Hjortdal

The article/manuscript is: Published ☒ Accepted ☐ Submitted ☐ In preperation ☐

If published, state full reference: Madsen MBM, Ivarsen A, Hjortdal J. Visual function after ultrathin Descemet's stripping automated endothelial keratoplasty combined with cataract surgery: a randomized controlled trial. Br. J. Ophthalmology. 2023. doi: 10.1136/bjo-2023-323304.

If accepted or submitted, state journal:

Has the article/manuscript previously been used in other PhD or doctoral dissertations?

No ☒ Yes ☐ If yes, give details:

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A. Has essentially done all the work (>90%)
B. Has done most of the work (67-90 %)
C. Has contributed considerably (34-66 %)
D. Has contributed (10-33 %)
E. No or little contribution (<10%)
F. N/A

Category of contribution	Extent (A-F)
The conception or design of the work:	C
Free text description of PhD student's contribution ***(mandatory)*** The study concept and design was made in collaboration between the PhD student and the supervisors. The PhD student planned the measurements and performed the study power calculation.	
The acquisition, analysis, or interpretation of data:	A
Free text description of PhD student's contribution ***(mandatory)*** The PhD student performed data acquisition and registration. The PhD student undertook statistical analysis with subsequent approval by supervisors. The interpretation was done in collaboration with supervisors.	
Drafting the manuscript:	A
Free text description of PhD student's contribution ***(mandatory)*** The PhD student drafted the manuscript with feedback from supervisors.	
Submission process including revisions:	A

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Free text description of PhD student's contribution ***(mandatory)***
The manuscript and subsequent revision was submitted by the PhD student. Revisional changes were approved by supervisors.

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Declaration of co-authorship concerning article for PhD dissertations

Full name of the PhD student: Morten Brok Molbech Madsen

This declaration concerns the following article/manuscript:

Title:	Macular Thickness After Ultrathin Descemet Stripping Automated Endothelial Keratoplasty and Descemet Membrane Endothelial Keratoplasty Combined With Cataract Surgery: A Randomized Controlled Clinical Trial
Authors:	Morten B M Madsen, Anders Ivarsen, Jesper Hjortdal

The article/manuscript is: Published ☒ Accepted ☐ Submitted ☐ In preperation ☐

If published, state full reference: Madsen MBM, Ivarsen A, Hjortdal J. Macular Thickness After Ultrathin Descemet Stripping Automated Endothelial Keratoplasty and Descemet Membrane Endothelial Keratoplasty Combined With Cataract Surgery: A Randomized Controlled Clinical Trial. Cornea. 2023, doi: 10.1097/ICO.0000000000003256.

If accepted or submitted, state journal:

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Drafting the manuscript:	A
Free text description of PhD student's contribution ***(mandatory)*** The PhD student drafted the manuscript with feedback from supervisors.	

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Submission process including revisions:	A
Free text description of PhD student's contribution ***(mandatory)*** The manuscript and subsequent revision was submitted by the PhD student. Revisional changes were approved by supervisors.	

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Declaration of co-authorship concerning article for PhD dissertations

Full name of the PhD student: Morten Brok Molbech Madsen

This declaration concerns the following article/manuscript:

Title:	Intraocular pressure-related side-effects after endothelial keratoplasty
Authors:	Morten B M Madsen, Anders Ivarsen, Niklas Telinius, Jesper Hjortdal

The article/manuscript is: Published ☐ Accepted ☐ Submitted ☒ In preperation ☐

If published, state full reference:

If accepted or submitted, state journal: Acta Ophthalmolica

Has the article/manuscript previously been used in other PhD or doctoral dissertations?

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Your contribution

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Submission process including revisions:	A

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Free text description of PhD student's contribution ***(mandatory)***
The manuscript and subsequent revision was submitted by the PhD student. Revisional changes were approved by supervisors.

Signatures of first- and last author, and main supervisor

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