Cambridge University Hospitals NHS Foundation Trust

Study Protocol

Long Title

Micro thin Descemet's stripping automated endothelial keratoplasty (Micro thin-DSAEK) versus Descemets membrane endothelial keratoplasty (DMEK): A randomized controlled clinical trial of corneal transplant outcomes and visual function

Short Title

Micro thin DSAEK vs DMEK

R&D Reference Number: A093988 IRAS Number: 201097
NIHR CRN Number: 32383
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Research Team

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Sponsor: Cambridge University Hospitals NHS Foundation Trust

Trial Summary

Trial Title	Micro thin Descemet's stripping automated endothelial keratoplasty (Micro thin-DSAEK) versus Descemets membrane endothelial keratoplasty (DMEK): A randomized controlled clinical trial of corneal transplant outcomes and visual function
Internal ref. no. (or short title)	Microthin DSAEK Vs DMEK
Clinical Phase	Not applicable
Trial Design	RCT
Trial Participants	All patients referred to Addenbrooke's corneal service with endothelial dysfunction requiring corneal transplantation, and with no significant ocular comorbidities.
Planned Sample Size	56 eyes of 56 patients randomised into two arms (28 eyes in each arm)
Treatment	A Single Surgical intervention- corneal endothelial keratoplasty

	(Microthin DSAEK or DMEK)	
Follow up duration	12 months	
Planned Trial Period	Aug 2016 – April 2020	
	Objectives	**Outcome Measures**
Primary	Functional (Visual) Improvement	Improvement in LogMAR visual Acuity
Secondary	1. Post-operative evaluation of transplant function 2. Intraoperative and postoperative complications 3. Patient satisfaction	1. Transplant survival 2. Post-operative complications including: a. Transplant detachment b. primary transplant failure c. Transplant rejection d. Loss of Endothelial cell density 3. Patient satisfaction questionnaire
Investigational Medicinal Product(s)	Microthin DSAEK surgery or DMEK surgery	
Formulation, Dose, Route of Administration	N/A	

Background and Literature review

Corneal disorders resulting in corneal opacification is a significant cause of blindness in the UK and remains the second most common cause of blindness in the developing world. Recent innovations in corneal transplant techniques (Endothelial keratoplasty) have shown significant benefit to patients in relation to visual function, rapid post-operative recovery, minimal hospital stay and fewer complications. Endothelial transplants are prepared from human cadaveric donor corneas either using a mechanized microkeratome (Microthin DSAEK) or by manual dissection (DMEK) with variations in surgical technique. Both these techniques are currently available and practised at Addenbrooke's eye unit for patients requiring corneal endothelial keratoplasty. A brief description of these two procedures is provided below:

Microthin DSAEK

In Microthin DSAEK the endothelial transplant is prepared from the cadaveric human donor cornea using a mechanised microkeratome with transplant thickness varying between 70-130 microns. The DSAEK endothelial transplant consists of a monolayer of endothelial cells on the descemets membrane with posterior stromal layer. The conventional DSAEK procedure in comparison yields transplant thickness averaging 170microns with a wide variance between 70-250microns with less than optimum visual results. By regulating the corneal donor thickness using a stromal dehydration technique we have shown a reliable way to create an endothelial transplant thickness of 100microns with minimal variance, termed microthin DSAEK[1]. This technique will be compared to DMEK in this trial.

DMEK

In this procedure the endothelial transplant is prepared by manual peeling of the descemets membrane, which consists of a monolayer of endothelial cells without the posterior corneal stroma measuring 15-20 microns in thickness.

Both transplants (MT-DSAEK and DMEK) are delivered to the eye using a sterile disposable surgical injecting instrument. And the attachment of the transplant to the host cornea is assisted with an air bubble in the anterior chamber.

There is evidence in the literature on the widespread use of both these techniques and several studies comparing **conventional** DSAEK with DMEK[2,3]. However, there has not been an attempt in literature to compare **Microthin** DSAEK with DMEK. Also, these trials have been retrospective and not randomised. Our study proposes a randomised controlled comparison of outcomes between Microthin DSAEK and DMEK to identify the effect of variations in corneal transplant preparation techniques in the field of corneal endothelial keratoplasty to visual outcomes.

Objectives and Outcome measures

In this proposal, we aim to undertake a randomized controlled clinical trial comparing Microthin DSAEK and DMEK to assess visual improvement, complications, corneal transplant survival up to 12 months and patient satisfaction.

The Primary end point is:

1. *The improvement in vision measured in LogMAR units at 12 months.*

The time points will be pre-operative, at 6months and then at the last visit in 12months. Our hypothesis assumes to detect a 2 line difference in final visual outcomes between the groups.

Secondary end points:

1. *Graft thickness at 6months and at 12months and comparison between the two arms. Hypothesis will be a difference of at least 50microns thickness between the two types of graft.*
2. *Endothelial count at 6m and at 12m visit. Hypothesis is no difference in the two arms.*

3. *Transplant survival at 12months.*
4. *Patient's satisfaction assessed using the questionnaire at 3 time points – Before transplant surgery, at 6months and at last visit in 12months.*
5. *Complications – rate of intra operative and post operative complications*

Trial Procedures

Recruitment: - All patients referred to the corneal service in Addenbrookes hospital with endothelial disease and no significant ocular comorbidities requiring endothelial keratoplasty will be invited to participate in the trial.

Inclusion Criteria:

1. All patients between 50-90 years of age attending/ referred to Addenbrooke's Hospital (Cambridge University Hospitals NHS Trust) corneal tertiary referral service for management of corneal diseases affecting the endothelial function and requiring endothelial lamellar keratoplasty.
2. Patients with visual acuity between 6/9 to Perception of Light will be included in the study.

Exclusion criteria:

Complicated anterior segment of the eye with the following features

1. Deficient iris diaphragm
2. Aphakia
3. Uncontrolled Glaucoma
4. Age related macular degeneration causing poor visual potential
5. Patients unable to posture after procedure for 1-2 hours on their back
6. Patient's inability to position on the slit lamp interfering with post op assessments
7. Dementia

Consenting Will be done in the clinical setting at time of offering surgery. Information on the trial will be provided to patients on preoperative consultation. Patient will be given 4 weeks to decide whether he wants to take part in the trial. Should the patient decide not to take part in the trial, it will not have any impact on their clinical care.

Randomisation: Paper based randomisation technique will be used for enrolling the patients to either arm of the study.

An independent statistician will prepare a randomisation and concealment list by writing a script or code for a statistical package with a recorded randomisation seed to allow reproducibility. A randomisation list for each combination will be produced. This will typically be produced using blocked randomisation. As our study is blinded, a concealment list will be made to produce kit numbers in an agreed format (number of digits, prefixes and suffixes) that are linked in a random fashion to treatment. The randomisation list is then augmented with a specific kit number for each patient

A member of the team (ideally not involved) in the trial will take the randomisation list and concealment list to prepare envelopes, based on, one per patient that gives sufficient detail to assign treatment. The envelopes should be sealed with tamper-proof tape and be completely opaque. The envelopes will be enumerated in the order in which they will be opened. Ink will be used directly onto the envelope rather than pre-printed adhesive labels. A record the date/time and signature of the PI, or delegate, who opens the envelope will be made. Patients will be linked to the main body of the study data according to their hospital numbers.

Serious adverse events – definitions and reporting:

Damaged corneal transplant, primary transplant failure, post-operative endophthalmitis, and any type of serious adverse events will be reported to NHS Blood and Transplant Serious events form. They form the Independent monitor committee for all the graft that are done in UK.

Statistics and data analysis:

Based on power calculation[4-6], we estimate a sample size of 56 would provide sufficient power to the study. Group sample sizes of 28 and 28 achieve atleast 80% power to reject the null hypothesis of equal means when the mean difference of intended primary outcome measure is 0.1 with a standard deviation of 0.1 and with a significance level (alpha) of 0.050 using a two-sided two-sample equal-variance t-test. Only one eye of each patient will be enrolled in the study. An interim data analysis and power calculation will be undertaken at 6 months.

Further statistical analysis[7] will be carried out using parametric and non-parametric tests depending upon the distribution of the results and comparing secondary outcome measures between the two arms of the study. The transplant thickness and relative visual gain would also be assessed using Pearson correlation coefficient. Kaplan-Meier limit analysis would be used to determine the cumulative probability of the transplant survival in the two groups with multi-variate analysis on factors influencing transplant survival.

References

1. Roberts HW, Mukherjee A, Aichner H, Rajan MS. Visual Outcomes and graft Thickness in Microthin DSAEK--One-Year Results. Cornea. 2015 Nov;34(11):1345-50
2. Hamzaoglu EC, Straiko MD, Mayko ZM, Sáles CS, Terry MA. The First 100 Eyes of Standardized Descemet Stripping Automated Endothelial Keratoplasty versus Standardized Descemet Membrane Endothelial Keratoplasty. Ophthalmology. 2015 Nov;122(11):2193-9
3. Droutsas K1, Lazaridis A, Papaconstantinou D, Brouzas D, Moschos MM, Schulze S, Sekundo W. Visual Outcomes after Descemet Membrane Endothelial Keratoplasty versus Descemet Stripping Automated Endothelial Keratoplasty-Comparison of Specific Matched Pairs. Cornea. 2016 Mar 30
4. Julious, S. A. 2010. Sample Sizes for Clinical Trials. Chapman & Hall/CRC.
5. Boca Raton, FL. Chow, S.-C., Shao, J., and Wang, H. 2008. Sample Size Calculations in Clinical Research (Second Edition). Chapman & Hall/CRC.
6. Boca Raton, FL. Machin, D., Campbell, M., Fayers, P., and Pinol, A. 1997. Sample Size Tables for Clinical Studies, 2nd Edition. Blackwell Science. Malden, MA.
7. Zar, Jerrold H. 1984. Biostatistical Analysis (Second Edition). Prentice-Hall. Englewood Cliffs, New Jersey.

Dissemination of findings

Finding will be disseminated by publishing the results in a peer reviewed journal and conference presentations.

STUDY PROTOCOL

1st Referral clinic visit

The following investigations and tests would be undertaken by the relevant staff of the clinical research team

Visual acuity testing performed by staff nurse /HCA

Specular Microscopy (SM) / Pentacam (Pc) / Auto-refraction (AR) / Intraocular Pressure (IOP) check / afferent pupil defect (APD) and Dilatation / Patient Quality of Life (QOL) questionnaire – **Corneal Nurse**

Slit Lamp examination – **Doctor**

If suitable for enrolment, research team will be approached if doctor not part of the research study.

Study and procedure discussed – **research team to include Consultant / Corneal fellow and corneal specialist nurse**

Patient recruited following satisfactory consent to participate and patient listed for their anaesthetic choice LA/GA with information leaflets and 4 weeks cooling off period to make decision to participate in the trial.

Pre-operative assessment

Corneal Nurse will carry out the pre-assessment checks according to the local trust policy.

Day of Surgery

Admission arranged

Pre-operative Ward Round – Surgeons (Rajan and team)

Randomised allocation of patient to undergo either Microthin DSAEK or DMEK

Transplant preparation will be completed as per randomisation

Patient brought into theatre and surgery performed with appropriate anaesthesia.

Post-operative Follow ups

Inpatient Follow up

- 1 hour post op – transplant position check , air bubble reduction – surgeon
- 1 day post op – transplant attachment status, IOP check
- 2nd day post-op – transplant status, IOP check and discharge with post-operative instructions (included)

Outpatients follow up:

- **1 week post op –**
  - vision / IOP – corneal nurse
  - slit lamp examination – research team
- **4weeks post op-**
  - vision / IOP / specular / OCT – corneal nurse
  - slit lamp examination – research team
  - removal of sutures
  - Patient QOL questionnaire
- **10 Weeks post op**
  - vision / IOP / specular / pentacam / auto-refraction / anterior segment OCT and photo– corneal nurse
  - slit lamp examination – research team
- **6 months post op**
  - vision / IOP / specular / pentacam / anterior segment OCT and photo– corneal nurse
  - Refraction - optometrist
  - slit lamp examination – research team
  - Patient QOL questionnaire
- **9 months post op**
  - vision / IOP / specular / pentacam / anterior segment OCT and photo– corneal nurse
  - slit lamp examination – research team
- **12 months post op**
  - vision / IOP / specular / pentacam / anterior segment OCT and photo– corneal nurse
  - Refraction - optometrist
  - slit lamp examination – research team
  - Patient QOL questionnaire

In case of complications:

1. Patient will have tailored follow ups depending upon the type of complication and appropriate management provided and documentation completed.

Tests used in the pre- and post-operative period:

Specular Microscopy (SM): *a non-contact machine that measures the thickness of the cornea using the specular principle of light reflection.*

Pentacam (Pc): *A non-contact machine to measure the corneal astigmatism or shape of both the front surface and back surface of the cornea, using the scheimpflug principle.*

Auto-refraction (AR): *This non-contact machine measures the refractive power of the eye and guides us, whether the patient needs any glasses after surgery to sharpen the vision.*

Intraocular Pressure (IOP) check: *The pressure in the eye will need to be checked using the icare tonometer system which is a rebound technology and is based on the rebound measuring principle, in which a very light-weight probe is used to make a momentary contact with the cornea. The change in the speed and its contact time of the probe is reflected as a function of IOP change.*

Afferent pupil defect (APD): *a test to check the functional capacity of the optic nerve of the eye. This guides us in establishing the prognosis or gain in vision when unhealthy cornea is replaced by donor tissue and cornea function is improved.*

Anterior segment OCT: *Optical coherence tomography (OCT) is a non-invasive, non-contact, in vivo imaging technique based on low-coherence interferometry. The principle of OCT is similar to ultrasound; however, it uses reflection of light from biological tissues. It gives us a 2D cross sectional image of the cornea and helps us look at the position of graft and also look for signs of dislocation, should there be a concern in terms of graft functionality.*