Search for indicators of an upcoming allograft rejection after DMEK

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To identify parameters that may *announce* or even predict an upcoming allograft rejection after DMEK using routine ophthalmic diagnostic devices.

Ethical review	Approved WMO
Status	Pending
Health condition type	Eye disorders
Study type	Observational non invasive

Summary

ID

NL-OMON44300

Source
ToetsingOnline

Brief title
Allograft rejection after DMEK

Condition

- Eye disorders

Synonym
Fuchs endothelial dystrophy and bullous keratopathy / corneal disease

Research involving
Human

Sponsors and support

Primary sponsor: Melles Hoornvlieskliniek Rotterdam
Source(s) of monetary or material Support: Melles Hoornvlieskliniek Rotterdam (MHR)

Intervention

Keyword: Allograft rejection, Confocal microscopy, Endothelium, Laser flare photometry

Outcome measures

Primary outcome

Changes in corneal layers as observed by confocal microscopy (e.g. increase in the number of activated keratocytes) that are typical before and/or during allograft rejection, significant changes in endothelial cell morphology and density, changes in intraocular inflammation levels by laser flare photometry.

Secondary outcome

- Endothelial cell density, as assessed by specular microscopy.

- Pachymetry of the cornea measured using a Pentacam and/or an Anterior Segment Optical Coherence Tomography apparatus (AS-OCT).

- Visual acuity, measured by the optometrist using a Snellen chart

- Number of complications.

Study description

Background summary

The cornea is the most anterior transparent part of the eye and consists of five layers which include: epithelium, Bowman*s layer, stroma, Descemet membrane, and endothelium. The cornea transmits light to the lens and retina and therefore, abnormalities in the cornea such as observed e.g. with Fuchs endothelial dystrophy (FED) or bullous keratopathy (BK) can significantly reduce vision. In these diseases, mainly the endothelial cells, which main function is to keep the cornea thin and transparent, are affected. This results in corneal swelling and loss of transparency, which greatly impairs the transmission of light. The abnormal corneal layers may be replaced by healthy tissue from a deceased donor, i.e. a corneal transplant.
There are several types of corneal transplantation, such as penetrating keratoplasty (PK), in which all corneal layers (including the healthy lamellae) are replaced by that of a donor, and lamellar keratoplasty, in which ideally only the affected parts of the cornea are replaced. For FED, a lamellar technique called DMEK in which only the diseased DM and endothelium are replaced was developed by NIIOS about 10 years ago. Compared to PK,

suture-related complications are eliminated, ocular infections and recovery time are considerably reduced whereas visual outcome is improved. In addition, the risk of graft rejection is reduced: from 5-15% after PK, to about 2.5% after DMEK. Although the chance of a clinically manifested graft rejection after DMEK is low, it is still a serious complication because when not recognized in time, it may lead to graft failure requiring repeat surgery. The second surgery in turn might further increase the risk of graft rejection of the second transplant.

However, some DMEK patients do not experience any clinical signs and symptoms and report no subjective complaints during the rejection episode, which increases the risk of irreversible damage to the DMEK-graft when the rejection episode is not diagnosed and treated in time. Therefore, the prediction, early detection, and timely treatment of graft rejection are of the utmost importance to maintain graft survival and functionality. If not detected and treated on time, an upcoming allograft rejection may irreversibly damage the graft which eventually requires repeat transplantation.

For some DMEK patients with an allograft rejection, we could retrospectively identify signs of an upcoming rejection by either routine Scheimpflug imaging of the cornea or by routine specular microscopy imaging of the endothelial cell layer. However, not all DMEK patients with a clinically manifested rejection episode showed clear signs of these alterations. Either the alterations were too subtle to be detected with the aforementioned imaging techniques or they might have been present in other corneal layers or in the aqueous humour. In either case, addition of two other routine ophthalmic examination techniques for the detection of an upcoming allograft rejection might provide valuable information: confocal microscopy and laser flare photometry. Confocal microscopy is a non-invasive, in vivo imaging technique. This is a reliable clinical diagnostic tool which we standardly use in our clinic to assess patients that show signs of endothelial cell alterations as detected by specular microscopy. It provides detailed images of endothelial cell morphology and also shows if other corneal layers such as the stroma, are affected. It may also detect changes in the endothelium which may not be visible by specular microscopy. Laser flare photometry, on the other hand, is used to non-invasively measure intraocular inflammation levels.

In this prospective study, we would like to extend the use of confocal microscopy and laser flare photometry to identify parameters associated with an upcoming or sub-clinical graft rejection episode. Early detection of these parameters would allow prompt intervention with medications to possibly avoid irreversible graft damage or (ideally) prevent clinical manifestation of the allograft rejection.

These two diagnostic tools may allow the detection of intraocular inflammatory signs that can not be visualized on slit-lamp or specular microscopy examination. Thus, an upcoming allograft rejection or eyes that may be at risk to develop an allograft rejection may be earlier recognized. This may then allow us in the future to monitor the inflammation status, as well as the response to treatment more precisely.

Therefore, in this observational study we intend to employ both tools next to

our standard ophthalmic examinations after DMEK. The investigators intend to perform a prospective observational study with a cohort of patients that undergo DMEK in order to identify early signs of an upcoming allograft rejection that may not be detected with conventional devices used for evaluating post DMEK eyes.
Importantly, not only DMEK patients may benefit from the results of this study, but also patients that received other keratoplasty techniques such as PK and Descemet (automated) stripping endothelial keratoplasty where the chance of graft rejection is considerably higher than after DMEK. Preventing graft failure and thus not requiring a new transplant would indirectly also alleviate the problem of corneal donor tissue shortage and it would lower cost burden on our healthcare system (corneal transplantation is the most common type of human-transplant surgery with over 1400 corneas transplants done annually in The Netherlands only).

Study objective

To identify parameters that may *announce* or even predict an upcoming allograft rejection after DMEK using routine ophthalmic diagnostic devices.

Study design

Observational study.

250 patients with Fuchs endothelial dystrophy, bullous keratopathy or failed previous corneal transplants scheduled for DMEK transplantation will be included.
In this observational study, we will prospectively perform study related measurements at regular follow-up visits. Patients that received DMEK at our institute are normally followed seven times during the first year (before surgery, 1 day, 1 week and at 1, 3, 6, 9, 12 months), and optionally four times in the second and third year (e.g. at 18, 24, 30 and 36 months postoperative). Confocal microscopy will be used to scan the parts of the cornea to analyze its cellular structures including (activated) keratocytes, immune cells and nerves, and laser flare photometry will be use to evaluate intraocular inflammation levels.
These examinations will be added to our routine standard specular microscopy that is used to determine the central endothelial cell density and other standard ocular examinations using Scheimpflug imaging (Pentacam HR, Oculus, Wetzlar, Germany), anterior segment optical coherence tomography (Slit-Lamp OCT, Heidelberg Engineering GmbH, Heidelberg, Germany), slit-lamp photography (Topcon Medical Europe BV) and ophthalmic examinations (slit-lamp examination, visual acuity evaluation, eye pressure measurement, etc.).
*

Study burden and risks

During every follow-up visit, patent will have to undergo two additional examinations (using confocal microscopy and laser flare photometry). The total duration of the additional examinations is about 30-45 minutes.

The risk for participating in this study is the same as for patients that are not included in the study since the DMEK procedure itself is not altered. Burden is limited to the additional time and costs needed for these additional measurements. Assessments will be scheduled at the time of regular visits. Study related measurements include confocal microscopy and laser flare photometry next to the standard ophthalmic measurements. Extra measurements will take about 30-45 minutes.
The only recognized potential health burden is that during the confocal microscopy examination the surface layer of cornea (epithelium) may be rubbed off, which usually heals within several days without any remaining damage. This risk is the same as with other ophthalmic contact procedures, like the standard intraocular pressure measurements performed by applanation.

We believe that health benefits from study participation outweigh risks and burdens to a research subject.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- Patients with Fuchs endothelial dystrophy, bullous keratopathy or failed previous corneal transplant
- Patient scheduled for DMEK surgery
- 18 years and older

Exclusion criteria

- Patients with ocular surface disease and delayed epithelial healing.
- Patients with an additional corneal inflammation or other inflammatory disease.
- Patient with concomitant ocular disease not related to the corneal disorder, or any type of circumstances that may be expected to adversely affect the efficacy of the surgery.
- Severe diabetes.
- Patients that may not be able to keep the position for 15 min.
- Not able to understand the language used in the clinic (Dutch).
- Inability to give informed consent for any reason

Study design

Design

Study type: Observational non invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	02-10-2017

Enrollment:	250
Type:	Anticipated

Ethics review

Approved WMO Date:	30-10-2017
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL62237.101.17