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Causes that influence the detachment rate after Descemet membrane endothelial keratoplasty

T. Röck[1] · M. Bramkamp[2] · K. U. Bartz-Schmidt[1] · D. Röck[1] · E. Yörük[1]

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Abstract
Purpose To investigate Descemet graft (DG) detachment rate after Descemet membrane endothelial keratoplasty (DMEK) in relation to DG position.
Methods A total of 175 consecutive pseudophakic eyes that underwent DMEK (175 eyes for Fuchs endothelial dystrophy) from September 2009 through February 2014 at the Tübingen Eye Hospital DG position were studied retrospectively by surgical video at the end of an operation. A group of 45 eyes showed a decentration of the DG with a stromal gap of ≥1.5 mm over at least 3 clock hours between the descematorhexis edge and the DG. DG detachment was documented at a mean follow-up of 13.9±3.7 months after surgery. DG detachment was defined as a detachment of 20 % or more of the DG surface area. Various donor characteristics and patient characteristics were analyzed.
Results The best spectacle-corrected visual acuity (BCVA) in the group of eyes with central well-positioned DG differed significantly from those of eyes with decentered DG. The preoperative BCVA in the central well-positioned DG group was 0.63±0.40 logMAR, and in the decentered DG group 0.91±0.51 logMAR ($P<0.001$). The postoperative BCVA in the group of eyes with central well-positioned DG was 0.12±0.11 logMAR, and in the group with decentered DG 0.23±0.29 logMAR ($P<0.001$). Endothelial cell density and patient characteristics such as age, gender, and intraocular pressure did not differ significantly between the two groups. The group of eyes with central well-positioned DG showed DG detachment in 12 %; the group with decentered DG findings had DG detachment in 87 % ($P<0.001$) at the 12 month follow up.
Conclusion The present findings demonstrate the importance of central well-positioned DG and the relation of disease severity. Central well-positioned DG may reduce the incidence of DG detachment. Overlapping of the donor DG and the host Descemet membrane seems to be responsible for DG detachment. One possible way to enhance graft adhesion could be a larger descematorhexis, which avoids an overlapping. The second possible way could be not waiting too long for surgery to reduce disease severity.

Keywords Descemet membrane endothelial keratoplasty (DMEK) · Posterior lamellar keratoplasty · Descemet graft detachment · Centrally positioned Descemet graft · Recovery of corneal transparency

Introduction

The corneal endothelial cells (ECs), a monolayer of hexagonal cells organized in the basal membrane, are important for vision by regulating corneal transparency [1]. Central EC density, expressed in cells per mm^2, decreases 0.6 % per year in grown-ups. If EC density falls below the threshold of 300–500 cells/mm^2, an irreversible corneal edema occurs [2]. Advanced EC disorders with corneal edema and impaired visual acuity require treatment. Fuchs endothelial dystrophy is the leading cause of severe EC disorder, leading to vision impairment due to corneal edema and even to bullous keratopathy. EC disorders in our centre are routinely managed with a corneal transplant, replacing the recipient endothelium by donor tissue, known as Descemet membrane endothelial

✉ T. Röck
tobias.roeck@googlemail.com

[1] Centre for Ophthalmology, University of Tübingen, Tübingen, Germany

[2] Department of General Medicine, Ruhr-University Bochum, Bochum, Germany

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keratoplasty (DMEK). DMEK is a well-established alternative to penetrating keratoplasty (PK) treatment of corneal endothelial dysfunction [3–5]. The procedure was described in 2006 by Melles [6, 7], offering several advantages over PK based on its minimal invasiveness and minimal refractive changes with rapid visual recovery [8–10]. DMEK needs a descematorhexis, meaning that ECs and their basal membrane are removed. The donor endothelium restores a normal, balanced stromal hydration, restoring normal corneal clarity and thus a recovery of the visual acuity of the recipient.

Donor DG is inserted into the anterior chamber, and DG is oriented downwards at the endothelial side followed by positioning against host posterior stroma. This maneuver, DG positioning centrally, represents a challenge for the surgeon because DG sometimes can not be ideally positioned centrally. When this happens, there will be a stromal gap between the descematorhexis edge and DG on one side and an overlapping edge of the donor DG and host Descemet membrane (DM) on the other side.

This retrospective study investigates DG detachment rate after DMEK in dependence on DG position.

Materials and methods

Patients

Our study reviewed 175 pseudophakic eyes (138 patients) that underwent DMEK operation at the Tübingen Eye Hospital from September 2009 through February 2014. Written informed consent in accordance with the declaration of Helsinki was obtained from all the subjects prior to study inclusion.

In 175 cases, Fuchs endothelial dystrophy was diagnosed. We preferred using patient complaints as the main indication for surgical treatment. When these complaints indicated that daily activities were significantly affected, we pursued treatment with a DMEK. Patients were evaluated preoperatively, intraoperatively, and perioperatively [13.9±3.9 months (mean ±SD)].

Definition of a decentered DG was stromal gaping between the descematorhexis edge and DG of ≥1.5 mm over at least 3 clock hours. Stromal gaping was documented by surgical video after operation. Figure 1 shows a graphic example of a central well-positioned and decentered DG after surgery. Figure 1a illustrates central well-positioned trypan blue stained 8.5 mm DG and a 9.0 mm diameter descematorhexis after surgery. Figure 1b represents decentered trypan blue stained DG after surgery. Donor DG overlaps host DM by ≥1.0 mm, and stromal gap between descematorhexis edge and DG is ≥1.5 mm over at least 3 clock hours.

DG detachment was documented at a mean follow-up of 13.9±3.7 months after surgery. DG detachment was defined as a detachment of 20 % or more of the DG surface area.

This study was approved by the institutional review board of the University of Tübingen, and adhered to the tenets of the Declaration of Helsinki.

Donor preparation

Donor corneoscleral rim was placed on a sterile circular surface scoring and staining by trypan blue to highlight the scoring mark. Afterwards, it was placed in a corneal viewing chamber containing corneal storage solution (Culture Medium I; Biochrom AG, Berlin, Germany). Circular incision by Hockey knife followed. Complete dissection of the DMEK tissue from the corneoscleral rim was achieved by grasping the peripheral free tissue flap using untoothed curvilinear forceps specially developed for this tash by Yoeruek [11]. Spatula was taken to lift the trephinated 8.5 mm diameter graft off the stromal bed after completing dissection and trephination. DM was placed in culture medium before the surgery. During surgery, the culture medium was carefully drained and DMEK roll was thoroughly rinsed by BSS. For opening tissue and creating a double roll, direct flow on the top of the tissue with BSS was applied. Afterwards, tissue was stained with trypan blue.

Recipient preparation, graft insertion and positioning

Peripheral yttrium–aluminium–garnet (YAG) iridotomy was performed one day before surgery to reduce the risk of air-associated pupillary block. Otherwise, an intraoperative peripheral iridectomy was performed.

Surgical technique involved initial placement of two paracenteses in the 2- and 10-o'clock positions. Removal of recipients' DM requires proper visualization of the anterior chamber using air pressurized at 30 mmHg. Introduction of a reversed Sinskey hook through a paracentesis for a 9.0 mm diameter descematorhexis followed. A 2.75 mm clear corneal tunnel was peformed with a 2.75 mm slit knife at the 12-o'clock position. The dissected donor DM was loaded into a shooter (DMEK shooter Geuder AG, Heidelberg, Germany) in the double-roll form. The injector was turned upwards facing the double roll. Implantation took place in a soft eye. After confirmation of orientation, mainly using Melles rule of rolled edges by endothelium facing outwards, the anterior chamber was obliterated completely via the paracenteses. No air was injected above or below the DM (to aid in the process of unfolding). The eye was kept in the soft state, digital pressure was applied at the equatorial plane, preventing any refolding or recurling. Apposition and centration were achieved because of the shallow anterior chamber, the soft eye status, and the corneal tapping in combination with equatorial digital pressurization. After complete unfolding, air was (continued to be) injected below the DM via a 30-gauge cannula for final

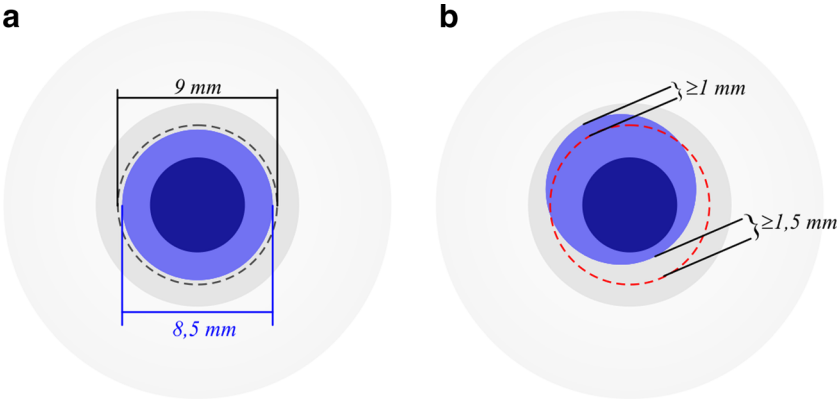

Fig. 1 Graphic example of a central well-positioned and a decentered Descemet graft (DG) after surgery: **a** Central well-positioned trypan blue stained DG with a diameter of 8.5 mm and a 9.0 mm diameter descematorhexis after surgery. **b** Decentered trypan blue stained DG after surgery. Donor DG overlaps the host Descemet membrane by ≥1.0 mm, and the stromal gap between the descematorhexis edge and the DG is ≥1.5 mm over at least 3 clock hours

DM fixation [12]. A single experienced surgeon performed the recipient preparation, graft insertion and positioning of the DM.

Statistical analysis

Statistical analysis of the results was performed using *t*-tests. Differences between groups were assessed by Mann–Whitney *U* test. Statistical analysis was conducted using the Statistical Package for the Social Sciences (SPSS 18.0). Quantitative variables were expressed as mean±standard deviation (SD). $P<0.05$ was considered statistically significant.

Results

The mean±standard deviation (SD) age of patients at time of surgery was 73.4±8.9 years (range, 49 to 91 years). The female:male ratio was 1.8:1. Mean±SD duration of follow-up after DMEK was 13.9±3.7 months (range 7 to 26 months). From a total of 175 DMEK eyes, 15 eyes were excluded from analysis because of endothelium dysfunction, and a secondary DMEK or PK was performed within 3 months after initial DMEK. Of the remaining 160 eyes, 115 revealed a central well-positioned DG, and 45 eyes showed a decentration of the DG by surgical video at the end of an operation.

Figure 2 shows an example of decentered Descemet graft (Fig. 2a) and an example of well-positioned DG (Fig. 2d) after surgery. DG detachment was found in 14 cases (12 %) in the central well-positioned DG group at the 12-month follow-up (Fig. 2b, c). In the decentered group, 39 cases (87 %) ($P<0.001$) were identified after 12 month (Fig. 2e, f).

The central well-positioned DG group presented complete clearance of the corneal quadrants not covering by DG within 1 to 3 months. The decentered DG group showed a progressive corneal clarity of the denuded posterior stromal area which started approximately 3 months after DMEK.

After 1 week, the most important and most frequent complication was partial DG detachment in 37 of the 160 eyes (23 %), requiring a repeated air injection, or rebubbling, to reattach the DG. The rebubbling rate in the central well-positioned DG group was 17 of 115 (15 %), compared to 20 of 45 (44 %) ($P<0.001$) in the decentered DG group.

The prognosis after rebubbling in the central well-positioned DG group was significantly better. Only in five of 17 cases of rebubbling was DG detachment found after 1 year. The decentered DG group showed DG detachment after 1 year in all 20 cases of rebubbling ($P<0.001$).

Mean age in the central well-positioned DG group was 72.9±8.1 years compared to 73.5±9.0 years in the group of eyes with decentered DG ($P=0.4$). The female:male ratio in the group of eyes with central well-positioned DG was 1.9:1, and in the group of eyes with decentered DG the ratio was 1.5:1 ($P=0.5$).

The preoperative best spectacle-corrected visual acuity (BCVA) in the central well-positioned DG group was 0.63±0.40 logMAR and in the decentered DG group was 0.91±0.51 logMAR ($P<0.001$). The postoperative BCVA in the group of eyes with central well-positioned DG was 0.12±0.11 logMAR and in the group with decentered DG was 0.23±0.29 logMAR ($P<0.001$).

Mean preoperative endothelial cell density (ECD) of the grafts in the central well-positioned DG group was 2387±317 cells/mm^2 and in the decentered group 2405±334 cells/mm^2 ($P=0.8$). The postoperative ECD in the group of eyes with central well-positioned DG was 1632±422 cells/mm^2, while it was 1552±398 cells/mm^2 in the group of eyes with decentered DG ($P=0.12$).

Preoperative intraocular pressure (IOP) in the central well-positioned DG group was 14.5±3.1 mmHg. The group of eyes with decentered DG showed 13.9±4.5 mmHg ($P=0.6$).

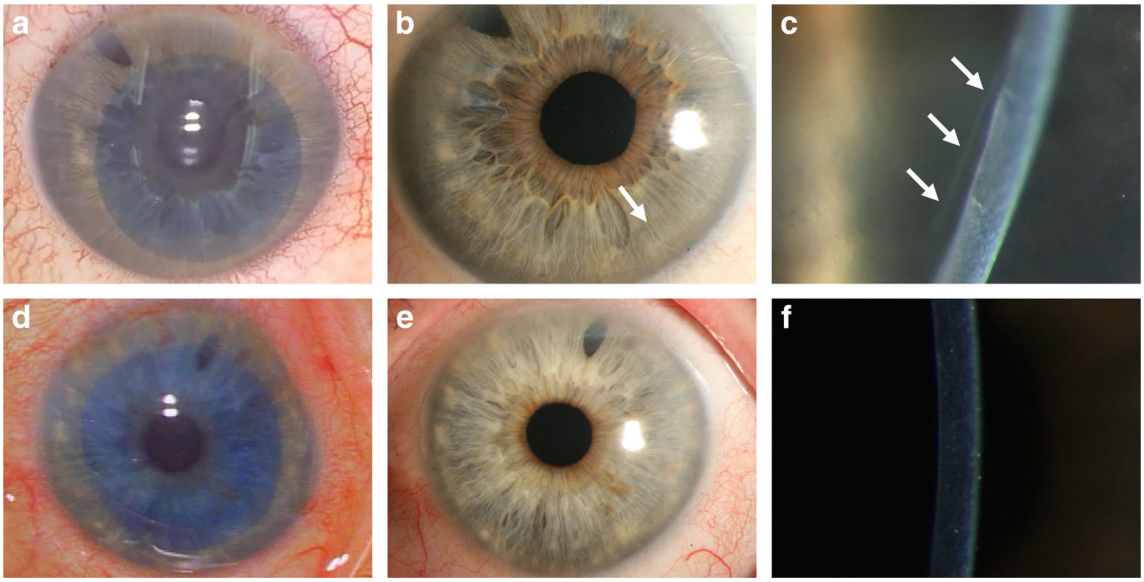

Fig. 2 One example of decentered Descemet graft (**a**) and one example of well-positioned Descemet graft (**d**) after surgery: **a** Color photography of surgical video after completely unfolding of trypan blue stained Descemet graft (DG) with decentered DG. **b** Slit-lamp color photography of cornea after 12 months. The *arrow* marks the DG detachment area. **c** Enlargement of detachment area of **b**. The *arrows* mark the detached DG. **d** Color photography of surgical video after completely unfolding of trypan blue stained descemet graft with well-positioned DG. **e** Slit-lamp color photography of cornea without DG detachment area after 12 months. **f** Enlargement of cornea. The DG is completely attached

Postoperative IOP in the group of eyes with central well-positioned DG was 14.9±4.1 mmHg., and in the group of eyes with decentered DG was 14.3±4.2 mmHg (P=0.7).

Discussion

There is a relatively low risk of complications using DMEK. DG detachment may be the most frequently observed complication after DMEK [13]. Our study showed that central well-positioned DG could reduce the incidence of DG detachment. Additionally, a faster recovery of corneal transparency and a lower rebubbling rate after central well-positioned DG was observed. In accordance with our results, Satué et al. reported no significant differences in BCVA and ECD between groups with higher and lower detachment rate after DMEK [14].

Faster recovery of corneal transparency can be explained by a smaller area which must be re-endothelialized if DG is central well-positioned. If an endothelial repopulation is necessary, a slower corneal clearance will be observed. A re-endothelialization of the recipient posterior stroma, which is denuded of its DM and its ECs, may be explained by different mechanisms: migration of recipients' remaining peripheral rim DM, or from donor endothelium, or both [15–17]. In 1976, Sherrard demonstrated that EC defects were covered by enlargement and migration of adjacent Ecs [18]. A higher EC density at the endothelial periphery was described almost 30 years ago by Schimmelpfennig [19]. There are hints that stem cells may exist at the posterior limbus, the edges of the corneal endothelium [20–22]. He et al. in 2012 reported EC organization at the extreme periphery of the human cornea, in small clusters of two or three layers [23]. Continuous centripetal migration of EC could go from these clusters, and ECs may be continuously pushed towards the centre. Additionally, in the periphery of the human cornea higher polymorphism and elongated radially oriented cell nuclei have been found than in central ECs. These differences suggest that peripheral ECs have a higher cell-mobility potential than in the centre.

DMEK surgery is complex for surgeons, presenting the challenges of stripping the donor graft and afterwards manipulating it. Handling the stripped DM donor tissue continues to present a challenge. Tissue scrolls up on itself, showing the endothelial layer outwards. During insertion, the main challenges are unrolling it in the anterior chamber, determining which side presents the endothelial layer, and actually positioning it centrally without wrinkles. All these maneuvers have to be performed without touching the DG. To prevent damaging endothelial cells, current techniques use balanced salt solution or air to unroll DG in the anterior chamber. Viscoelastic cannot be used, as it may go between the donor and the recipient cornea. Successful DMEK surgery restores the anatomy back to normal, with no evidence of any interface between the donor and recipient tissue, and DMEK then provides faster and complete visual rehabilitation.

DG may partially or completely detach after surgery, requiring a repeated air injection, or rebubbling, to reattach the DG. The rebubbling rate in the group of eyes with central well-positioned DG compared with the group of eyes with decentered DG was significantly lower. In 37 eyes, a partial DG detachment was visible 1 week after surgery. Partial DG

detachment was resolved by attachment with a simple rebubbling. A few days after DMEK, a partial detachment can occur when the air bubble in the anterior chamber disappears. This may be due to endothelial cell damage, some form of temporary endothelial dysfunction, or an overlapping of the donor DG with host DM. Overlapping is in our view the most important cause for detachment. The anterior surface of the DG contains various proteins, which could explain the adhesive properties of the DG to the posterior collagen lamellae of the corneal stroma, such as vitronectin, amyloid P, fibronectin, and osteonectin [24]. These proteins might facilitate the attachment of the DG. However, the surface of endothelial cells on the remaining DM might not support DG adhesion.

One possible way to enhance graft adhesion could be a larger descematorhexis. Larger descematorhexis results in more area of denuded stroma, which avoids overlapping and leads to better graft adhesion.

Minor peripheral detachments may be left alone, and most of them will automatically reattach over time. This means that a rebubbling of small peripheral detachments is unnecessary. Bucher et al. described that peripheral laminar detachments could attach spontaneously even months after surgery; however, peripheral rolls usually do not change [24]. Tourtas et al. showed in accordance with our results that an overlapping zone between host DM and donor DG correlates with higher rebubbling rates [25]. Overlapping of donor DG and host DM seems responsible for DG detachment. Positioning DG centrally may lead to a reduction of rebubbling rates and reduction of incidence of DG detachment.

Nevertheless, some points should be considered before drawing hasty conclusions.

Maier et al. showed that preoperative visual acuity significantly influenced the grade of unfolding and attaching of the graft lamella [26]. In fact, we were able to confirm these findings. Our findings indicated a relationship with disease severity. The preoperative BCVA in the group of eyes with central well-positioned DG did differ significantly from that of eyes with decentered DG. More edema could lead to decentration in two ways; one is that the surgeon's lower visualization of the anterior chamber might lead to a misplacement, the other is that in cases of very thick cornea, after the surgeon has put in a graft and the edema has decreased, a steeper host bed occurs which results in a mismatch of position between the graft and stroma, creating a gap which could lead to graft movement. For this reason, patients with advanced EC disorders should not wait too long for surgery, which is easier said than done, because there is a critical shortage of donor corneas [27].

No relationship was found with demographic characteristics in either group. Age and female:male ratio did not differ significantly.

In conclusion, the present findings demonstrate the importance of central well-positioned DG and the relationship with disease severity. Additionally, it was possible to observe a faster recovery of corneal transparency and a lower rebubbling rate after central positioned DG.

Competing interests None; no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

Patient consent Obtained.

Ethics approval This study was approved by the institutional review board of the University of Tübingen, and adhered to the tenets of the Declaration of Helsinki.

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