Clinical Outcome of Rebubbling for Graft Detachment After Descemet Membrane Endothelial Keratoplasty

Nadine Gerber-Hollbach, MD,*† Lamis Baydoun, MD,*† Ester Fernández López, MD, PhD,*† Laurence E. Frank, PhD,*† Isabel Dapena, MD, PhD,*† Vasilios S. Liarakos, MD, PhD,*† Sontje-Chiao Schaal, MD,* Lisanne Ham, PhD,*†§ Silke Oellerich, PhD,* and Gerrit R. J. Melles, MD, PhD*†§

Purpose: To assess the clinical outcome after successful rebubbling procedures for visually significant graft detachment after Descemet membrane endothelial keratoplasty (DMEK).

Methods: From a total of 760 consecutive DMEK surgeries, 41 eyes required rebubbling. Of those, 33 eyes of 31 patients were successful and were included in our retrospective outcome analysis study. Main outcome measures were compared with those of matched controls with uneventful primary DMEK (attached DMEK grafts without rebubbling). Rebubbling was performed on average 25 (±20) days (range 7–91 days) after DMEK. All eyes were evaluated for best-corrected visual acuity, endothelial cell density (ECD), pachymetry, and complications up to 6 months after rebubbling.

Results: At 6 months after DMEK, best-corrected visual acuity in rebubbed eyes did not differ from that in control eyes ($P = 0.514$). The mean ECD decrease was higher in rebubbled than in control eyes (54% vs. 35%, respectively, $P = 0.001$). Pachymetry did not differ between both groups ($P = 0.153$). After rebubbling, one buphthalmic eye showed temporary intraocular pressure elevation and 5 eyes had minor graft edge detachment that did not require further treatment.

Conclusions: Rebubbling for DMEK graft detachment may result in similar visual outcomes as in uncomplicated DMEK, when performed within the first 6 to 8 postoperative weeks. However, rebubbed eyes may have lower ECD, which may be attributed to additional air bubble trauma and/or selection bias through more extensive manipulation during initial DMEK or higher risk of graft detachment in more complicated eyes.

Key Words: Descemet membrane endothelial keratoplasty, graft detachment, rebubbling, endothelial cell density, best-corrected visual acuity, pachymetry, air injection

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Descemet membrane endothelial keratoplasty (DMEK), selective replacement of Descemet membrane with its endothelium for corneal endothelial disorders, may have brought modern keratoplasty procedures to a level of minimally invasive surgery that provides unprecedented clinical outcomes. Although many complications of earlier keratoplasty techniques could be reduced and/or eliminated, graft detachment has evolved as a new complication, which has been attributed to various factors, for example, graft preparation and storage times, storage media, donor age, DMEK graft tightness.

Today, rebubbling may be the widely accepted treatment to manage graft detachment after DMEK. However, concern has been raised about potential donor endothelial cell damage caused by air reinjection and about the overall visual outcome. Because not every detachment has an impact on the visual acuity and virtually all eyes initially operated on for Fuchs endothelial dystrophy may show some degree of spontaneous corneal clearing in the area overlying the detachment, not every graft dehiscence may require rebubbling.

Hence, the aim of our study was to evaluate the clinical outcome of rebubbling procedures for visually significant graft detachment compared with control eyes (ie, DMEK eyes without rebubbling).

MATERIALS AND METHODS

From a total of 760 consecutive DMEK surgeries, 41 eyes required rebubbling. Of those, 33 eyes of 31 patients were successful (one eye required 2 rebubbling procedures) and were included in our study. Preoperative indications were...
All patients signed an institutional review board-approved informed consent form before surgery. The study adhered to the Declaration of Helsinki.

**Donor Tissue and DMEK Surgery**

From donor globes, corneoscleral buttons were excised less than 36 hours postmortem and stored in organ culture medium (CorneaMax, Eurobio, Courtaboeuf, France) at 31°C. After 1 week of culture, endothelial cell morphology and viability were evaluated and DMEK grafts were prepared as previously described. The graft size varied from 8.5 mm (n = 2), 9 mm (n = 1), 9.5 mm (n = 29), to 10 mm (n = 1). The “Descemet-rolls” were stored “free-floating” in organ culture medium until the time of transplantation.

A circular, on average 9.0-mm diameter, “descemetorhexis” in the recipients’ eyes and a DMEK procedure were performed, as previously described.

**Indication and Success of Rebubbling**

Preoperative and postoperative graft detachment status was classified as minor (≤1/3 of the graft surface area) or major detachment (>1/3 of the graft surface area). Rebubbling was indicated for persisting, progressing, and/or visually significant DMEK graft detachment with corneal edema affecting the visual axis that showed no or minimal resolution. Successful rebubbling was defined as graft reattachment providing corneal clearance, not requiring further surgical treatment.

**Rebubbling Procedure**

Rebubbling procedures were performed as previously described under topical [tetracaine (0.5%)] or local anesthesia (4 mL 1% ropivacaine hydrochloride with 150 IU hyaluronidase) followed by ocular massage, and anti-Trendelenburg positioning in all eyes. A side-port was made or reopened with a surgical knife (DORC International, Zuidland, the Netherlands) to introduce a 30-gauge cannula underneath the anterior chamber. Descemet-rolls were injected to reposition the graft against the recipient posterior stroma and to promote graft adhesion. The anterior chamber was left for 45 to 120 minutes (median: 70 minutes) with air, followed by 30% to 50% air–liquid exchange to reduce the air bubble. All procedures were performed by an experienced DMEK surgeon (L.B., I.D., V.S.L., or G.R.J.M.) and recorded on a DVD (Pioneer DVR-RT601H-S). Postoperative medication included topical antibiotics and steroids as used after primary DMEK.

**Data Collection**

All eyes were examined before and up to 6 months after DMEK and were evaluated for best-corrected visual acuity (BCVA), endothelial cell density (ECD) (Topcon 3000S specular microscope; Topcon Medical Europe BV, Capelle...
Differences between rebubbled and control eyes (n = 25) (Fig. 1 and Table 2). Mean logMAR BCVA did not differ between rebubbled and control eyes (without rebubbling) (P = 0.514).

Complete preoperative and postoperative ECD and pachymetry measurements were available for 30 and 28 eyes, respectively. At 6 months, the ECD decrease was higher in rebubbled (54%) than in control eyes (35%; P = 0.001). Pachymetry did not differ between rebubbled and control eyes (P = 0.153).

### Complications

After rebubbling, 5 eyes showed persistent detachment though minor peripheral edge detachment not affecting the visual axis, that is, that did not need any further intervention. One buphthalmic eye had intraocular pressure elevation episodes within the first 6 months after rebubbling, which was managed with topical medication.

### DISCUSSION

Our study confirms previous reports on rebubbling after endothelial keratoplasty in that BCVA and pachymetry outcomes equal those of uncomplicated DMEK eyes and that rebubbling may affect ECD.\(^{16,18,19}\) A recent study reported no difference in the ECD decrease between rebubbled and control eyes after a single rebubbling procedure performed within the first week after DMEK, but a higher ECD decrease was found with repeated rebubbling procedures in the same eye.\(^{16}\) In contrast, our study showed lower ECD in rebubbled eyes. Besides the fact that detachment may be associated with graft preparation trauma, this difference may be explained by several forms of selection bias and associated different group sizes. First, our clinic may tend to await spontaneous reattachment longer because partial detachment may be part of the wound-healing process ("dynamic graft attachment pattern").\(^{28,29}\) This might filter out the "lower potential" grafts because grafts that showed persistent detachment have been found to have lower ECDs.\(^{3}\) Second, in general, eyes with more complicated pathology and more extensive corneal decompensation might be at higher risk of postoperative graft detachment and may require more extensive manipulation during initial DMEK surgery. The difference in the ECD decrease between

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<thead>
<tr>
<th>TABLE 2. Clinical Outcomes After DMEK for Rebubbled and for Control Eyes</th>
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<td><strong>Outcomes 6 mo After DMEK</strong></td>
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<td><strong>Rebubbled Eyes</strong></td>
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<td>BCVA (n = 25)</td>
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<td>ECD (n = 30)</td>
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<td>Pachymetry (n = 28)</td>
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a/d IJssel, the Netherlands), pachymetry (Pentacam; Oculus, Wetzlar, Germany), and postoperative complications. Graft adherence status was determined using anterior segment optical coherence tomography (AS-OCT; Heidelberg Engineering GmbH, Heidelberg, Germany) and Pentacam Scheimpflug imaging. AS-OCT scans in at least 4 meridians (45, 90, 135, and 180 degrees) were performed. Scans were evaluated by 3 masked observers before and after the rebubbling procedure.

### Statistical Analysis

For the outcome analysis, matched control eyes were obtained using propensity score matching with the R package MatchIt.\(^{26,27}\) Patient and donor characteristics were covariates for matching. Multiple linear regression analysis was performed to assess differences between rebubbled and control eyes (without rebubbling). Sensitivity analyses were performed to see whether bilateral rebubbling (2 patients) and repeat rebubbling (1 patient) influenced the outcomes. LogMAR visual acuity was used for statistical analysis.

### RESULTS

A total of 33 eyes underwent a rebubbling procedure for minor (n = 6) or major graft detachment (n = 27). On average, rebubbling was performed 25 (±20 days) (range 7–91 days) after DMEK; 2 eyes underwent rebubbling performed more than 2 months postoperatively (77 and 91 days).

### Clinical Outcomes of Successful Rebubbling

After excluding 8 eyes for low visual potential (n = 5) or incomplete data (n = 3), 25 rebubbled eyes were available for visual acuity analysis (Fig. 1 and Table 2). At 6 months, 100% of eyes reached a BCVA of 20/40 (≥0.5), 68% ≥20/25 (0.8), and 20% ≥20/20 (1.0) (n = 25). For the same follow-up, 96% of control eyes reached a BCVA of 20/40 (≥0.5), 72% ≥20/25 (0.8), 40% ≥20/20 (1.0), and 20% ≥20/17 (1.2) (n = 25) (Fig. 1 and Table 2). Mean logMAR BCVA did not differ between rebubbled and control eyes (P = 0.514).
Hence, the major challenge with postoperative DMEK graft detachment may be whether to perform a rebubbling procedure and if so, to decide at what time to intervene after initial DMEK. To make these decisions, a graft detachment may repeatedly be imaged with AS-OCT to determine the extent and evolution of the detachment and if possible its cause.

In evaluating the AS-OCT images, an attempt may be made to distinguish between the 2 most common causes: mechanical displacement of the DMEK graft versus delayed endothelial function or a combination thereof (Figs. 2, 3).

A most extreme example would be a graft positioned upside-down, that is, mechanical displacement and lack of (effective) endothelial function, which obviously requires reintervention. However, if the DMEK graft is positioned right side up showing attached areas with corneal clearing (ie, functional endothelium) combined with areas of “deep” graft detachment, mechanical displacement may just be too large to allow spontaneous reattachment. Even more so when there is a “touch” between the graft and surrounding intraocular tissues, through which the graft is stuck in its position. In the event of such mechanical displacements with indicators of good endothelial function, the graft may be eligible for early rebubbling because it is not going to reattach by itself (Fig. 2B, C). However, if the graft detachment is flat and shows a lack of endothelial function, it may be considered to await spontaneous reattachment because repositioning the graft by rebubbling may not improve the endothelial cell function required for the graft to reattach (Fig. 2A).

Another relatively common reason for graft detachment is an “inward fold” that may cause the DMEK graft to spring away from the host posterior stroma (Fig. 2D). Such inward folds (and subsequent detachment) may be easily avoided by checking intraoperatively whether complete graft unfolding was obtained, and if not, by performing “bubble bumping” to undo these edge folds. However, when only recognized postoperatively, rebubbling may be postponed because inward folds commonly show a tendency to reattach after a few months (Fig. 4). Alternatively, if the detachment is enlarging within the first postoperative weeks, such eyes may be managed by rebubbling, that is, “bubble bumping” followed by complete air fill of the host anterior chamber.

The decision whether to rebubble or not may also be taken based on visual acuity measurements. If the eye shows weekly improvement, rebubbling may be postponed; however, it may be better to intervene if no improvement is seen or the condition of the eye deteriorates. It is important to note, however, that postponing rebubbling beyond 4 to 6 weeks postoperatively may result in incomplete graft unfolding owing to scarring of the DMEK graft, causing progressive rigidity of the donor tissue (Fig. 5).

In conclusion, rebubbling may be an indispensable treatment option for DMEK graft detachment. The decision whether and when to rebubble may be made by carefully analyzing consecutive AS-OCT images, to determine the most likely cause and evolution of the detachment. Because reintervention may induce additional endothelial cell damage, rebubbling may be weighed against the chance of spontaneous resolution. However, when rebubbling is indicated, it

rebubbed eyes and control eyes may also be attributed to additional air bubble trauma as any intervention may affect the intraocular structures.

FIGURE 2. Anterior segment OCT images showing 4 common DMEK graft detachment (white arrows) configurations eligible for rebubbling for different reasons. A, With flat detachment that follows corneal curvature but without any apparent tendency for the graft to adhere, spontaneous reattachment may be awaited because the graft may be a “slow responder” that does not benefit from immediate rebubbling. Such grafts may be rebubbled from 2 to 4 weeks after surgery when the endothelial function may have been restored. Note that such a graft configuration (well positioned but just slightly detached) may also be indicative of an upside-down position of the graft. B, Wavy graft detachment over several quadrants that shows areas with partial attachment (green arrows) may be rebubbled rather quickly because the detachment is too large to expect spontaneous reattachment, that is, detachment may persist owing to physical separation rather than a lack of endothelial functionality. C, Detachment protruding far into the host anterior chamber may be eligible for early rebubbling because the graft may have adhered to surrounding ocular structures such as the iris (blue arrow), so that it has to be mechanically separated. D, Inward folds (orange arrow) typically produce somewhat larger graft detachment that may spontaneously reattach over time, but sometimes requires rebubbling. Such inward folds can be easily prevented by checking full unfolding of the graft during surgery, and if necessary, by managing the fold by “bubble bumping.”
may be performed within the first 6 postoperative weeks, that is, before the graft becomes too immobile to be properly repositioned.

REFERENCES