Original Article

Management of Upside-Down Descemet Membrane Endothelial Keratoplasty: A Case Series

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Abstract

Purpose: To present the management of upside-down Descemet membrane endothelial keratoplasty (DMEK) following combined phacoemulsification with DMEK (phaco-DMEK) in cases of Fuchs endothelial dystrophy (FED).

Methods: This is a comparative interventional case series extracted from a prospective interventional case series (clinical outcome of DMEK combined with phacoemulsification for FED). We report five cases of upside-down DMEK. Two cases of upside-down DMEK were managed with re-orientation and the other two with repeat DMEK. The 5th case underwent an initial re-orientation and then a subsequent repeat graft. Graft re-orientation and repeat surgery were performed 9–20 days after initial phaco-DMEK. All the five cases were followed up over a 6-month period, and the following outcomes were assessed: best corrected visual acuity (BCVA), contrast sensitivity (CS), central corneal thickness, endothelial cell density (ECD), and central macular thickness.

Results: At the final 6-month postoperative follow-up, all the five cases achieved good outcomes in terms of BCVA and CS. Overall, the results were comparable to 32 control cases. One case of re-orientation and the case of re-orientation with subsequent repeat DMEK performed slightly less well than control cases in terms of postoperative ECD.

Conclusions: Re-orientation of the original DMEK scroll in cases of upside-down DMEK can be a safe and cost-effective alternative to repeat DMEK. If re-orientation does not result in corneal deturgescence, a repeat DMEK may be done subsequently.

Keywords: Descemet membrane endothelial keratoplasty, Endothelial keratoplasty, Liu vents, Moutsouris sign, Upside-down Descemet membrane endothelial keratoplasty

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Introduction

Descemet membrane endothelial keratoplasty (DMEK) is one of the most popular procedures for treating corneal endothelial failure in cases of Fuchs endothelial dystrophy (FED) and pseudophakic bullous keratopathy (PBK).[1] One of the most significant complications after DMEK is primary graft failure, as it has a major impact on the patient's visual outcome and recovery. Causes of primary graft failure include poor-quality tissue, tissue handling during peeling, transport, and surgical procedure, leading to damage of endothelial cells.[2] One iatrogenic cause for primary graft failure of paramount importance is upside-down orientation of the graft. The latter being preventable and correctable puts this cause at the center of discussion. Several methods have been described in the literature to identify DMEK scroll orientation and help prevent its upside-down placement. These include Moutsouris sign, peripheral marks, "S" or "F" stamps, the use

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of slit beam, and the use of intraoperative optical coherence tomography (OCT).[3-8]

Despite these clearly laid-out methods of prevention, upside-down DMEK still persists as a complication.[9-11] Described ways to correct the orientation include re-orientation with or without explantation of original DMEK graft from the eye and repeat DMEK with fresh donor tissue. Previous evidence suggests that repositioning of the existing graft would prove more advantageous and feasible in terms of economical use of donor tissue and reduced exposure to corneal antigens.[12]

Methods

This is a comparative interventional case series quoted from a prospective interventional case series study on the clinical outcome of DMEK combined with phacoemulsification (Phaco-DMEK) for FED cases. We present the management of five cases of primary DMEK failure due to upside-down orientation. The study was conducted at Sussex Eye Hospital, United Kingdom, after ethical approval from the audit and research department and after all the study participants agreed to be enrolled in the study and signed an informed consent form. The study followed all the tenets of the Declaration of Helsinki.

The original study consisted of 37 patients and included patients with FED associated with cataract of any grade who sought to improve their visual function and had one of the following:

Diurnal fluctuation of the patient's symptoms, i.e., blurred vision in the morning that became clearer over the day, central corneal thickness (CCT) >620 μ, and/or endothelial cell density (ECD) <1000 cells/mm^2.

Patients with a history of glaucoma, coexisting retinal problems, and amblyopia and patients with advanced corneal stromal scarring due to long-standing corneal decompensation were excluded from the study.

The five cases of primary DMEK failure due to upside-down orientation, suggested by failure of attachment, postoperative anterior segment-OCT (AS-OCT), and/or surgical slow-motion video-analysis, were studied as a separate group. Statistical analysis was performed using SPSS V26 software (IBM, United Kingdom). Results of the five cases were compared to a control group of 32 cases that underwent uneventful triple DMEK from the same original study.

Results

Thirty-seven eyes of 21 patients were enrolled in the original case series to study the outcomes of combined phacoemulsification and DMEK. The mean age of the participants was 64.63, with a standard deviation of 14.79. Forty-three percent were male, and 57% were female. Five eyes that were diagnosed with upside-down DMEK graft were analyzed individually and compared to the group of 32 eyes that had an uneventful procedure. Table 1 shows a summary of the main demographic and outcome measures.

Case 1

A 62-year-old male presented with reduced visual acuity (VA) in the left eye. LogMAR best corrected visual acuity (BCVA) was 0.1. His main concern was loss of contrast sensitivity (CS) and inability to focus on fine details at work. The logarithm of CS (logCS) was 0.45. Slit-lamp examination revealed Stage 2 FED with central corneal guttae, along with Grade 1 nuclear sclerotic (NS) cataract. Fundus examination was unremarkable. CCT was 597 μ, and ECD was 610/mm^2. A phaco-DMEK was performed on the left eye. Preparation of DMEK (8.0 mm graft with 2700/mm^2 ECD, from a 74-year-old donor) was performed in the theater, using a modified technique described by Kruse *et al*.[8] The DMEK scroll was loaded into a DMEK glass injector (Geuder AG, Heidelberg, Germany). Routine phacoemulsification and intraocular lens (IOL) implantation proceeded unremarkably. Descemetorhexis was performed under a viscoelastic material (Amvisc; Bausch and Lomb Inc., Laval, Quebec, Canada) with its subsequent removal from the anterior chamber by irrigation aspiration. Graft injection and unfolding followed with the standard "no touch" technique. The anterior chamber was filled with 100% air bubble, which was maintained for 5 min, and then air was released to leave 90% fill. The orientation seemed correct at the conclusion of the procedure. On the 1st postoperative day, there was partial graft detachment and 60% of the air bubble was confirmed

Table 1: Summary of demographic and outcome measures of the five cases and control group at postoperative follow-up

	Age	Sex	LogMAR BCVA 6 months	LogCS 6 months	ECD 6 months	CCT 6 months	CMT 1 month	CMT 3 months
Case 1	62	M	0.1	1.05	650	645	312	312
Case 2	65	M	0.1	1.2	1403	518	368	365
Case 3	83	M	0	1.2	1026	550	279	277
Case 4	50	F	0.1	1.5	1337	571	280	276
Case 5	73	F	0.1	1.4	630	564	270	270
Control group (32 cases) mean±SD (range)	64.1±15.8 (36.8-82.5)	43% male 57% female	0.03±0.13 (−0.2-0.4)	1.38±0.34 (0.3-1.8)	1552±329 (950-2155)	530±36 (465-585)	301±25 (270-368)	300±38 (255-415)

BCVA: Best corrected visual acuity, LogCS: Logarithm of contrast sensitivity, ECD: Endothelial cell density (cells/mm2), CCT: Central corneal thickness (unit is microns), CMT: Central macular thickness (unit is microns), SD: Standard deviation

on AS-OCT. Total graft detachment was noted on the 5th postoperative day, raising the suspicion of upside-down orientation as the free-floating graft showed posteriorly curling edge. Video analysis of the footage taken during the original surgery confirmed the upside-down orientation of the graft by observing how the graft edge scrolled. On the 20th postoperative day, re-orientation of DMEK was performed. Staining in the anterior chamber with vision blue (DORC) was carried out. Jets of balanced salt solution (BSS) were injected from a side port to detach the DMEK graft. This was reinforced by injection of BSS through corneal vent incision described by Liu *et al*.[13] A squint hook was used to tap on the cornea until the scroll completely detached, and then unfolding and air injection proceeded as per the standard procedure. One-week post re-orientation, there was marked reduction in corneal thickness on AS-OCT and partial inferior graft detachment. Re-bubbling was successful to re-attach it. One month after re-orientation, the CCT was 700 µ. ECD was 670/mm^2. Six months postoperatively, the CCT was 645 µ, and ECD was 610/mm^2. The logMAR BCVA achieved was 0.1, and the logCS achieved was 1.05 [Table 1].

Case 2

A 65-year-old male was referred with gradually worsening vision in the left eye. LogMAR BCVA was 0.48 on presentation and logCS was 0.3. Slit-lamp examination showed Stage 2 FED and NS cataract Grade 1. Fundus examination was unremarkable. The CCT was 650 µ, and ECD was 590/mm^2. A phaco-DMEK was performed in the left eye as per case 1. The donor was 81 years old with ECD of 2500/mm^2 and graft size of 8.0 mm. Total graft detachment was noted on the 5th postoperative day after the bubble had disappeared completely [Figure 1a]. It was difficult to judge whether the graft edge was curling in the correct direction due to corneal edema. Re-bubbling was done in an attempt to re-attach the graft. On the 12th postoperative day, the graft was totally detached with diffuse corneal edema [Figures 1b and c]. Imaging from AS-OCT coupled with surgical video analysis raised the suspicion of an upside-down graft. The patient was scheduled for re-orientation on the following day. Table 2 shows the surgical details. One month post re-orientation, the CCT was 540 µ, and the ECD was 1444/mm^2. Six months postoperatively, the logMAR BCVA reached 0.1, logCS was 1.2, ECD was 1403, CCT was 520 µ, and the slit-lamp examination showed a clear cornea [Figures 1d-f].

Case 3

An 83-year-old male presented with reduced VA in his left eye. His logMAR BCVA at presentation was 0.3, and his logCS was 0.45. Slit-lamp examination revealed Stage 2 FED with

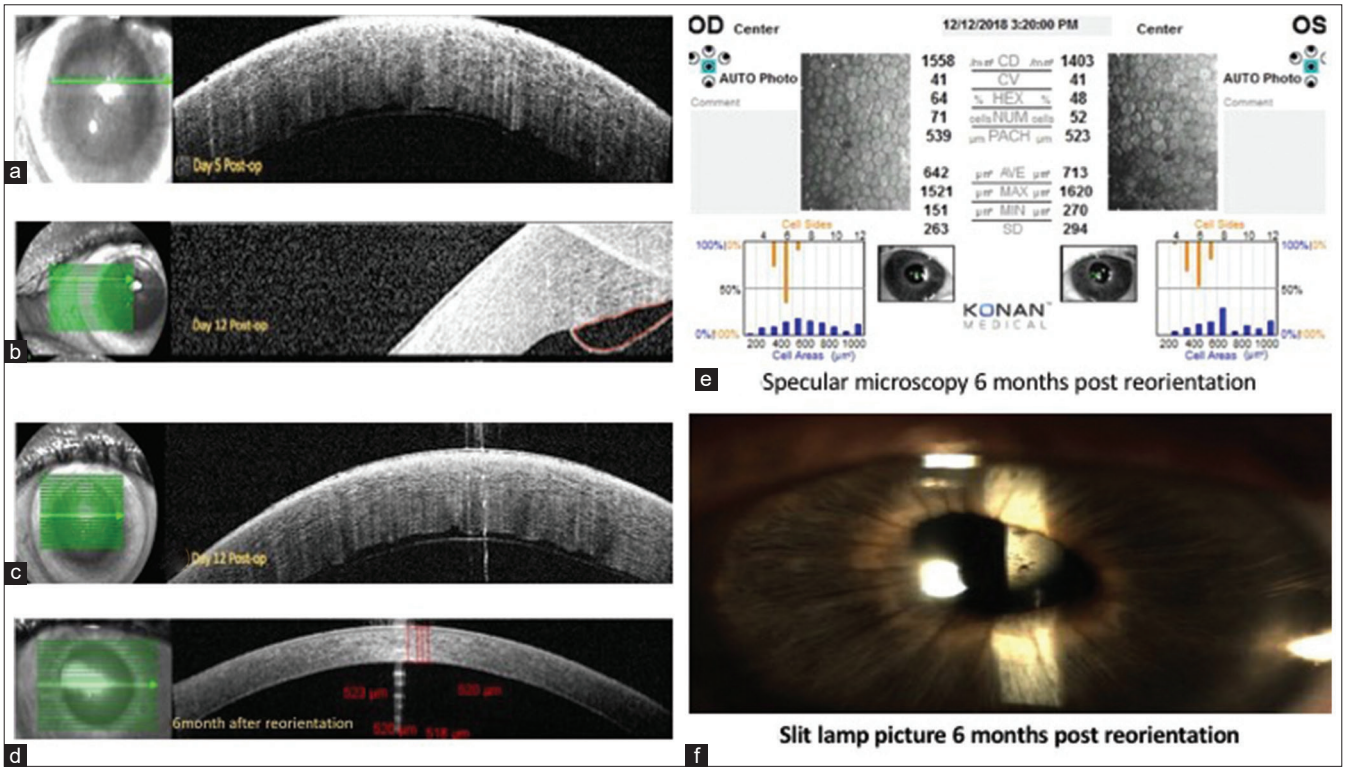

Figure 1: Case 2 (left eye). (a) Five-day posttriple Descemet membrane endothelial keratoplasty (DMEK) anterior segment-optical coherence tomography (AS-OCT) showing detachment. (b) Day 12 postoperative AS-OCT image showing peripheral graft detachment after re-bubbling. (c) Day 12 postoperative AS-OCT image showing central graft detachment despite re-bubbling. (d) The corneal thickness of the left eye on AS-OCT for case 2 at 6-month follow-up after re-orientation. The graft reattached successfully. (e) The left eye corneal specular microscopy at 6-month follow-up after re-orientation. The right eye of the same patient happened to be a part of the original prospective study where it underwent a routine uncomplicated triple DMEK. The endothelial cell density of the two eyes is comparable. (f) Slit-lamp examination and clear cornea at 6-month post re-orientation

dense central corneal guttata and NS cataract Grade 2. The fundus examination was unremarkable. Prior to the procedure, CCT was 610 μ, and the ECD was 560/mm^2. Phaco-DMEK was subsequently performed on the left eye. The DMEK was performed as per case 1, but an IOL cartridge was used to deliver the DMEK into the anterior chamber (AT, smart Kartouse and tip; Carl Zeiss Meditec AG, Jena, Germany). The orientation seemed correct during the operative procedure. On the 5th postoperative day, there was obvious total graft detachment with posteriorly curling edge. Surgical slow-motion video analysis revealed upside-down orientation of the graft. Considering the age of the patient being 83 and not willing to have more than one intervention if the first attempt failed, a decision was made to repeat the DMEK with a fresh donor tissue (7.5 mm graft with 2500/mm^2 ECD, from an 81-year-old donor). This was performed 15 days after the original DMEK. The procedure entailed explantation of the DMEK graft and replacement with a fresh one. The fresh DMEK scroll was loaded and injected into the anterior chamber using a Zeiss IOL cartridge (Carl Zeiss Meditec AG, Jena, Germany). Then, the scroll was unfolded using the standard technique described in case 1. One day after the redo, the graft was attached, and 50% of the air bubble was present, and the CCT decreased from 1100 μ before the repeat DMEK to 807 μ. One month later, the CCT was 540 μ. ECD after 1 month was 1065/mm^2. Six months postoperatively, the CCT was 550 μ, and ECD was 1026/mm^2. The logMAR BCVA achieved was 0, and the logCS achieved was 1.2 [Table 1].

Table 2: Surgical details, tips, and pearls for re-orientation

Suspect upside-down DMEK if the following is observed
Persistent corneal edema
Failure of graft attachment even after re-bubbling
Free-floating DMEK with outwardly curling edge
Review the AS-OCT and couple this with the surgical video
If these raise a strong suspicion of upside-down DMEK, proceed to re-orientation as soon as possible
Re-orientation procedure
Re-stain
Trypan blue should be administered into the anterior chamber to stain the primary DMEK
If the DMEK is attached
Re-staining should be done prior to detaching the DMEK graft to prevent staining of the recipient stroma
Attempt to detach the graft by injecting BSS through side ports (Video 2)
If complete detachment is not achieved, create an air bubble and massage it above the DMEK (Video 3)
If still partially attached, create vent incisions[13] over the area that is detached (ensure the vent is created above an air bubble so that it can act as a cushion to protect the DMEK graft) (Video 4)
Jets of BSS can then be injected through the vent to complete the graft detachment (to our knowledge, this is the first mention in the literature of using corneal vent incision[13] for this purpose) (Video 4)
If all attempts fail to detach the graft, consider repeat DMEK
If the DMEK is free floating
Encourage the scroll to attain the correct orientation and proceed as per the standard DMEK procedure
Consider repeat DMEK if the cornea does not clear after re-orientation, and the graft is attached

DMEK: Descemet membrane endothelial keratoplasty, AS-OCT: Anterior segment-optical coherence tomography, BSS: Balanced salt solution

Case 4

A 50-year-old female presented with reduced VA in her right eye. Her logMAR BCVA at presentation was 0.2. Her logCS was 0.45. Slit-lamp examination revealed Stage 2 FED with dense central corneal guttae and NS cataract Grade 1. Fundus examination was unremarkable. CCT was 618 μ, and the ECD was 1000/mm^2. Triple DMEK was performed on the right eye. The procedure was performed as in case 3. The orientation was checked using Moutsouris sign. On the 1st postoperative day, there was significant graft detachment with a 60% air bubble [Figure 2a]. The edge of the graft

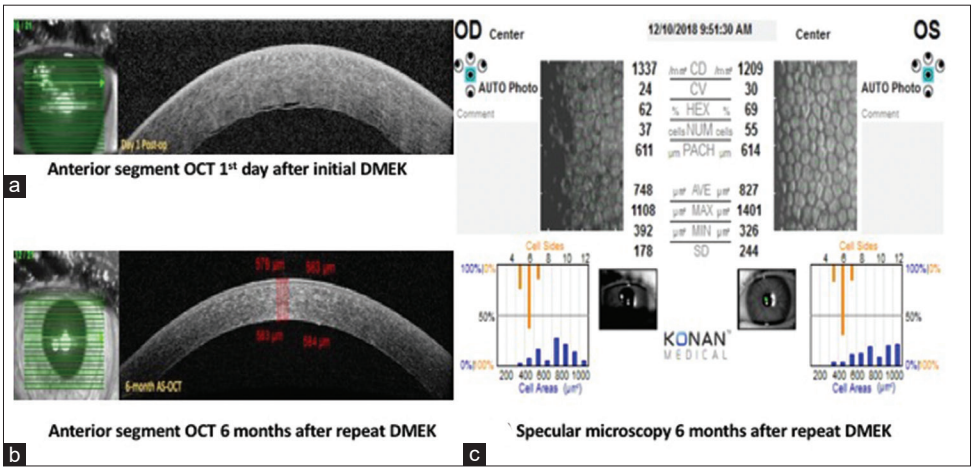

Figure 2: Case 4 (right eye). (a) Significant graft detachment in the right eye under air bubble tamponade on the 1st postoperative day. (b) The right eye corneal thickness on anterior segment-optical coherence tomography at 6-month follow-up after redo. The graft reattached successfully. (c) The right eye corneal specular microscopy at 6-month follow-up after redo. The left eye of the same patient happened to be a part of the original prospective study where it underwent a routine uncomplicated triple Descemet membrane endothelial keratoplasty. The endothelial cell density of the two eyes is comparable

was curling posteriorly. Slow-motion video analysis showed that when checking the orientation using Moutsouris sign, the cannula was passing underneath the scroll [Video 1], so it was a false-positive Moutsouris sign, and the graft was upside-down [Figure 3]. The patient's preference was toward redoing the DMEK rather than an attempt of re-orientation. This was subsequently done 14 days after the original procedure, using the technique described in case 3 with an 8.25-mm graft, ECD of 2700/mm^2 of a 21-year-old donor.

One month after the repeat DMEK, the CCT was 570 μ, and the ECD was 1411/mm^2. At 6 months postoperatively, the CCT was 582 μ, and ECD was 1337/mm^2 [Figures 2b and c]. The logMAR BCVA achieved was 0.1, and the logCS achieved was 1.5 [Table 1]. Slit-lamp examination showed clear cornea.

Case 5

A 73-year-old female presented with reduced VA in her right eye. Her logMAR BCVA at presentation was 0.2. Her logCS was 0.45. Slit-lamp examination revealed Stage 2 FED with dense central corneal guttae and NS cataract Grade 1. Fundus examination was unremarkable. CCT was 615 μ, and ECD was 630/mm^2. A phaco-DMEK was subsequently performed on the right eye, as described in case 1. The orientation seemed correct during the procedure. On the 1st postoperative day, there was partial graft detachment with a 50% air bubble. On the 8th postoperative day, the air bubble disappeared, and total graft detachment with posteriorly curling edge was seen. Surgical video analysis at this stage confirmed an upside-down graft. The following day, graft re-orientation was attempted using a similar technique as in case 2. It was very difficult to achieve due to poor view. The surgeon was not sure about the graft orientation at the conclusion of the procedure, and therefore, the patient was scheduled for repeat DMEK, which was done immediately on the following day. The standard technique was used as described in case 3 with a size 8.0-mm graft, ECD of 2500/mm^2 of a 75-year-old donor. The surgery was difficult, and the graft unfolding took longer than expected. The outcome subsequently achieved was a reasonably unfolded DMEK with two folds. At the 8th postoperative day after the second DMEK, re-bubbling had to be carried out as there was significant graft detachment. One month after redo, the CCT was 625 μ, and ECD was 640/mm^2. Six months postoperatively, the CCT was 564 μ, and ECD was 630/mm^2. The logMAR BCVA achieved was 0.1, and the logCS was 1.4 [Table 1]. Slit-lamp examination showed a clear cornea and two central folds [Figure 4].

Results of the five cases at the 6-month postoperative period were compared to a control group of 32 uneventful phaco-DMEK cases which were part of the same study on the outcomes of phaco-DMEK. The five cases were well within the range of the control group in terms of BCVA. All cases except case 1 were within the range of CS of the control group. In terms of ECD, cases 2–4 were within the range of the control group. However, cases 1 and 5 had less ECD than the range of the control group. In terms of CCT of the cornea, at 6 months postoperatively, all cases except case 1 were within the range of the control group. The results are summarized in Table 1.

Pre- and postoperative OCT of the macula was also assessed to detect any changes in central macular thickness (CMT) related to the procedure. Cases 1 and 2 showed a slight increase in the CMT, whereas cases 3, 4, and 5 showed no obvious change. However, the postoperative CMT of the five cases at 1 month and 3 months was still within the range of the control group [Table 1].

Discussion

Upside-down DMEK is a known complication resulting in primary graft failure. The incidence rates of upside-down DMEK from numerous studies ranged from 0% to 18%.[10,14,15] We report a rate of upside-down DMEK of 5/37 (i.e., 13%) in our study. This complication is underreported as it can be confused with other causes of primary graft failure. The use of sulfur hexafluoride (SF6) gas by some DMEK surgeons can force the attachment of the upside-down DMEK, but corneal clearing could not be achieved. This can be misleading

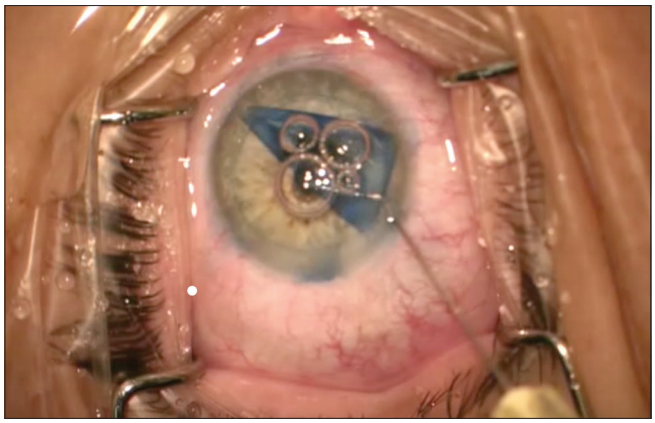

Figure 3: A false-positive Moutsouris sign. The cannula is shown to be passing underneath the scroll

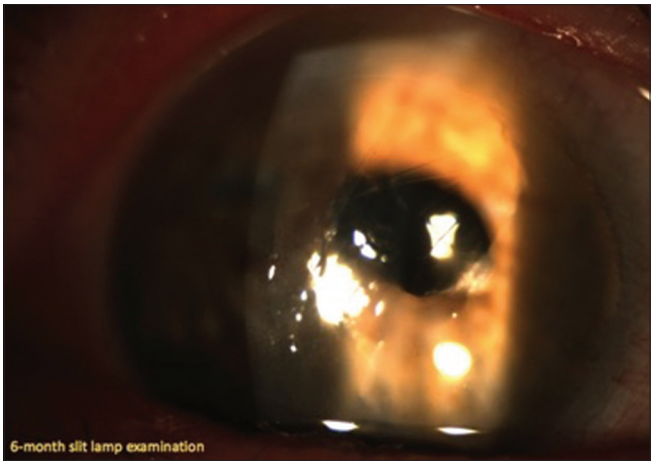

Figure 4: Six-month slit-lamp examination showing clear cornea and two central folds in case 5

as they might not consider upside-down DMEK in the differential diagnosis due to proper graft attachment. Having no current clear guidelines on the technique and time frame of its management makes upside-down DMEK an exceptional challenge for the corneal surgeon. This case series touches upon the two proposed techniques for managing this complication involving re-orientation and repeat.

It is prudent to prevent upside-down DMEK, and there have been several methods described in literature to identify the graft orientation. Central marking such as "S" and "F," peripheral marking and Moutsouris sign are examples. Some surgeons believe that Moutsouris sign is imperative during surgery regardless of the use of additional markings. However, it is important to note that it can be deceiving when the spatula passes underneath the DMEK graft rather than above it, giving a false-positive Moutsouris sign as seen in case 4 [Figure 3 and Video 5]. Extra care needs to be taken when there is poor view, such as when the DMEK edge is hidden under a peripheral corneal opacity or corneal edema. While the cannula is inserted underneath the DMEK scroll, injecting an air bubble to help un-scroll the DMEK graft can be misleading as the bubbles can travel rapidly to above the scroll [Video 5]. Removing this air bubble from above the graft can also be deceiving as the surgeon will think that it has been injected above the graft in the first place [Figure 5]. Moreover, it is extremely difficult to use this sign, especially in cloudy corneas or poorly stained donors.

The other important point to consider is whether there is an optimal size of DMEK graft that can minimize upside-down DMEK. There is no evidence in literature on a specific size of DMEK graft. The size of DMEK graft guidance relies mainly on the anterior chamber's dimensions (the eye's white-to-white diameter). An oversized DMEK graft can overlap with the paracentesis, which will make re-bubbling difficult. Moreover, if a peripheral mark is used, it may get hidden behind an arcus senilis.[15]

These methods may still be difficult to apply, such as when the host cornea is opaque. Intraoperative OCT to identify the orientation of the DMEK scroll can also be an option. However, this can be expensive and therefore not accessible to all corneal surgeons. We recommend video recording of all DMEK cases so that upside-down DMEK can be identified. Furthermore, using a slit beam to identify the direction of the graft edge curling before concluding the procedure with air injection can help confirm the orientation.

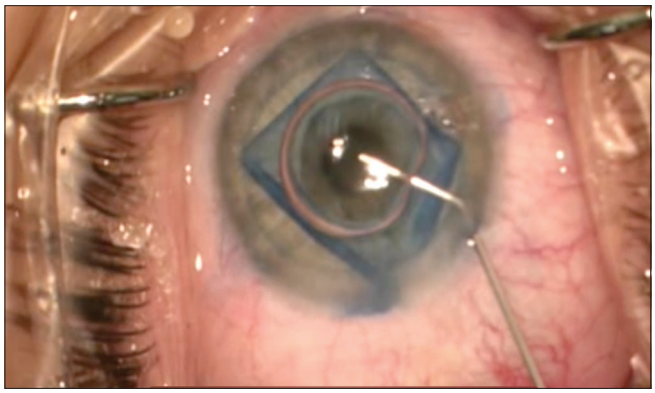

Figure 5: The cannula passing above the Descemet membrane endothelial keratoplasty graft to remove the air bubble after unfolding the scroll

The other difficulties include old donor grafts which do not scroll well. Origami scrolling of the DMEK graft, for example when some parts of the scroll are rolling up and another part down, can cause problems intraoperatively. Moreover, the graft can become stuck into the anterior chamber angle.

Once an upside-down DMEK is confirmed, timely intervention will be crucial as there is no clear evidence for how long the graft can survive the upside-down orientation. In addition, there is evidence suggesting corneal stromal scarring if left upside-down for a long time. The same principle applies for repeat, as there is strong evidence that persistent corneal edema can compromise the visual outcome, so the earlier the repeat, the better the outcome.[16-18]

Our case series is comprised of two cases that underwent re-orientation (cases 1 and 2), two cases of repeat DMEK (cases 3 and 4), and one case of attempted re-orientation which ended up with a repeat DMEK (case 5). It can be inferred from cases 1 and 2 that re-orientation can provide good visual outcomes. These results are comparable to that of the previously reported case series by Dragnea *et al*. and a case report by Yu *et al*.[9,12] They are also comparable to the results of cases 3, 4, and 5 that underwent repeat DMEK [Table 1]. Case 1 ended up with low ECD after re-orientation, which may be explained by re-bubbling being carried out while the graft was upside-down or by the surgical circumstances of re-orientation.

By comparing the results of the five cases of treated upside-down DMEK following phaco-DMEK to the results of 32 cases of uneventful phaco-DMEK, the overall outcomes were acceptable especially in terms of the final BCVA. However, two cases (1 and 5) underachieved in terms of ECD, which we believe was due to surgical circumstances.

We believe that the outcomes of the cases were mainly driven by the ease, length of surgery, and handling of donor tissue during preparation rather than the choice of re-orientation versus repeat. A good example from this case series is case 5, which ended up with the least ECD compared to other cases, although surgery was done with a fresh DMEK tissue. This may have been due to the difficulty of the procedure and longer unfolding time. Regardless of which procedure was carried out (either re-orientation or repeat graft), the five cases ended up with good outcome in terms of BCVA and CS at 6-month postoperative follow-up.

In conclusion, this case series suggests that postoperative graft re-orientation is a valid solution in cases of upside-down DMEK grafts and more economical than repeating the procedure with new donor tissue. There is no concrete evidence

of one surpassing the other in terms of final visual outcome. If re-orientation fails, the option of re-grafting can be used.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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