Advances in endothelial keratoplasty

Birbal, R.S.

Birbal RS[1-3], Ní Dhubhghaill S[1,2,4], Baydoun L[1,5], Ham L[1-3], Bourgonje VJA[1,2], Dapena I[1,2], Oellerich S[1] and Melles GRJ[1-3,6]

[1] Netherlands Institute for Innovative Ocular Surgery (NIIOS), Rotterdam, The Netherlands

[2] Melles Cornea Clinic, Rotterdam, The Netherlands

[3] Amnitrans EyeBank, Rotterdam, The Netherlands

[4] Antwerp University Hospital, Edegem, Belgium

[5] University Hospital Münster, Münster, Germany

[6] NIIOS-USA, San Diego, California, United States of America

Chapter 8

Quarter-Descemet Membrane Endothelial Keratoplasty: One- to Two-Year Clinical Outcomes

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ABSTRACT

Purpose: To report clinical outcomes of the first Quarter-Descemet membrane endothelial keratoplasty (Quarter-DMEK) case series performed for central Fuchs endothelial corneal dystrophy.

Methods: This is a prospective, interventional case series analyzing the clinical outcomes of 19 eyes of 19 patients with central FECD, that is, with guttae predominantly in the 6- to 7-mm optical zone, who underwent unilateral Quarter-DMEK at a tertiary referral center. Main outcome measures were best-corrected visual acuity (BCVA), endothelial cell density (ECD), and postoperative complications. Included eyes had up to 2 years of postoperative follow-up.

Results: At 6 months postoperatively, all eyes reached a BCVA of ≥20/40 (≥0.5); 18 of 19 eyes (95%) ≥20/25 (≥0.8) and 9 of 19 eyes (42%) ≥20/20 (≥1.0). Thereafter, BCVA remained stable up to 2 years postoperatively. The mean donor ECD decreased from 2842 ±139 cells/mm^2 (n=19) before implantation to 913± 434 cells/mm^2 (-68%) at 6 months (n=19), 869 ±313 cells/mm^2 (-70%) at 12 months (n=18) and 758 ±225 cells/mm^2 (-74%) at 24 months (n=13) after Quarter-DMEK. Visually significant graft detachment requiring re-bubbling occurred in 8 of 19 eyes (42%).

Conclusions: Quarter-DMEK surgery yields visual outcomes similar to those of conventional DMEK and may potentially quadruple the availability of endothelial grafts. Further modifications of the graft preparation and the surgical technique may improve clinical outcomes in terms of lower ECD decrease and fewer graft detachments.

INTRODUCTION

Descemet membrane endothelial keratoplasty (DMEK) may currently be the most advanced technique in the management of corneal endothelial disorders.[1,2] In an effort to further increase donor tissue availability, in particular of endothelial grafts, Hemi-DMEK (semi-circular, 'half-moon' shaped graft instead of a conventional, circular graft of same surface area) was introduced in 2014 as a DMEK modification.[3] In 2016, this technique was further refined into Quarter-DMEK, where only a smaller graft, that is, one quadrant of a full-diameter donor Descemet membrane (DM) graft was transplanted into eyes with Fuchs endothelial corneal dystrophy (FECD), provided that it was limited to the central 6- to 7-mm optical zone of the cornea.[4]

We previously reported the 6-month clinical outcomes of the first 12 eyes that underwent Quarter-DMEK in our center and showed that this new technique was not only feasible but also resulted in good clinical outcomes in terms of best-corrected visual acuity (BCVA) up to 6 months postoperatively.[5] If longer-term outcomes would mimic those of conventional DMEK, Quarter-DMEK may have the potential to provide a far more efficient use of donor tissue. The aim of this study was therefore to evaluate the clinical results of the first Quarter-DMEK cohort of 19 eyes up to 2 years postoperatively.

METHODS

Patient data

A series of 19 eyes from 19 patients [mean age 66 (±9) years; range 56-82 years] underwent Quarter-DMEK for clinically significant central FECD, that is, with guttae predominantly in the central 6- to 7-mm optical zone of the cornea. Additional patient selection criteria entailed 1) mild to no FECD in the corneal periphery and 2) no other ocular comorbidities. Twelve eyes were pseudophakic and 7 eyes phakic (Table 1). All eyes had completed the 6-month follow-up, 18 eyes had completed the 12-month follow-up, and 13 eyes had completed the 24-month follow-up. The study received ethical approval (METC Zuidwest Holland), an institutional review board-approved informed consent was obtained from all patients before surgery and the study adhered to the tenets of the Declaration of Helsinki.

Donor tissue preparation

Quarter-DMEK donor tissue preparation was performed by a single experienced eye bank technician, as previously described.[4] In short, from whole donor globes obtained less than 24 hours postmortem, corneoscleral buttons were excised and stored in organ culture medium at 31°C (CorneaMax, Eurobio, Courtaboeuf, France) until graft preparation. The corneoscleral buttons were mounted endothelial side up on a custom-made holder with a suction cup and using a hockey stick knife (DORC International, Zuidland, The Netherlands) peripheral DM with its adjacent trabecular meshwork was loosened over 360 degrees. Using a surgical blade (no. 24 knife, Swann-Morton, Sheffield, UK), the buttons were then dissected into 4 equally sized quarters. DM was centripetally peeled from the underlying posterior stroma of each quarter, yielding four DM rolls. Endothelial cell morphology and viability were evaluated before and after graft preparation. Quarter-DMEK grafts were then stored in organ culture medium until the time of transplantation. After preparation, the mean Quarter-DMEK graft storage time was 5.9 (±1.7) days (Table 1). The 19 Quarter-DMEK grafts were prepared from 15 corneal buttons of 14 donors with a mean age of 69 (±9) years (range 51-84), that is, from 4 donor corneas, 2 Quarter-DMEK grafts were transplanted, while from the other 11 donor corneas, only a single Quarter-DMEK graft was used (Table 1). The other potential Quarter-DMEK grafts (n=41) were used either as back-up grafts during surgery or for research purposes.

Table 1. Demographics Quarter-Descemet membrane endothelial keratoplasty eyes and donors.

		(n)
Number of eyes/patients		19/19
Gender (female/male)	68% / 32%	(13/6)
Mean age (±SD) in years	66 (±9)	
Preoperative lens status		
Pseudophakic	63%	(12)
Phakic	37%	(7)
Number of corneas/donors		15/14
Donor age (±SD) in years	69 (±9)	
Donor gender (female/male)	29% / 71%	(4/10)
Donor death cause		
Cancer	29%	(4)
Cardiovascular/Stroke	50%	(7)
Respiratory	7%	(1)
Trauma	7%	(1)
Other	7%	(1)
Graft storage time in medium (±SD) in d		
Total	18.7 (±27.5)	
From preparation to surgery	5.9 (±1.7)	

d=days; n= number; SD= Standard deviation

Quarter-DMEK surgery

Quarter-DMEK surgery was performed according to the standardized no-touch DMEK technique with a few modifications.[4-6] Using a reversed Sinskey hook (DORC International), a descemetorhexis of approximately 7 to 8 mm was made under air. The Quarter-DMEK graft was thoroughly rinsed with balanced salt solution to fully eliminate the organ culture medium and stained with 0.06% Trypan blue (VisionBlue; DORC International). The graft was then aspirated into a curved glass injector (Melles glass inserter, DORC International) and injected into the recipient's anterior chamber. The Moutsouris sign was confirmed to ensure correct graft orientation, that is, with the endothelium facing the iris. The graft was unfolded and centered over the iris by indirect manipulations of the tissue through air, balanced salt solution and strokes on the outer corneal surface; and then elevated to the posterior corneal surface using an air bubble. At conclusion of the operation, a complete air fill of the anterior chamber was maintained for a period of 60 minutes, after which a partial air-fluid exchange was carried out to leave an estimated residual air bubble of 30% to 50% of the anterior chamber volume. Postoperative topical medication was identical to the protocol following conventional DMEK.[6]

Data collection and statistical analysis

Recipient eyes underwent ophthalmic examination at 1 day, 1 week, 1, 3, 6, 9, 12 and 24 months postoperatively. BCVA was measured using a Snellen letter chart, and the outcomes were converted to logarithm of the minimum angle of resolution (logMAR) units to enable statistical analysis. BCVA was defined as stable for changes ≤1 Snellen lines, and as improving or deteriorating for changes ≥2 Snellen lines. Intraocular pressure (IOP) was measured with applanation tonometry and increased IOP after Quarter-DMEK was defined as an IOP ≥24 mm Hg or an increase in IOP of ≥10 mm Hg from baseline. The eyes were examined with slit-lamp biomicroscopy, anterior segment ocular coherence tomography (Slit-lamp-OCT; Heidelberg Engineering, Heidelberg, Germany) and rotating Scheimpflug corneal tomography (Pentacam HR, Oculus Optikgeräte, Wetzlar, Germany). In addition, non-contact autofocus specular microscopy (Topcon SP3000p, Topcon Medical Europe, Capelle a/d IJssel, The Netherlands) was performed to evaluate postoperative endothelial cell density (ECD). Images of the central corneal window were analyzed and manually corrected by a trained technician; for each follow-up time point, up to 3 measurements of ECD were averaged. The independent paired Student *t* test was applied to assess differences between consecutive follow-up time points. $P < 0.05$ was considered statistically significant.

RESULTS

Clinical outcomes

At 6 months postoperatively, BCVA improved in 14 of 19 eyes (74%) and remained stable in 5 of 19 eyes (26%). The latter eyes all had a preoperative BCVA of 0.7 or higher. At 6 months after Quarter-DMEK, 19 of 19 eyes (100%) reached a BCVA of ≥20/40 (≥0.5); 18 of 19 eyes (95%) ≥20/25 (≥0.8) and 9 of 19 eyes (42%) ≥20/20 (≥1.0) (Table 2; Fig. 1A). Thereafter, BCVA remained stable up to 2 years postoperatively ($P \geq 0.05$).

Table 2. Clinical outcomes up to 2 years after Quarter-Descemet membrane endothelial keratoplasty for central Fuchs endothelial corneal dystrophy.

Clinical outcome	Preoperative (n=19)	At 6-Month Follow-up (n=19)	At 12-Month Follow-up (n=18)	At 24-Month Follow-up (n=13)
BCVA				
<20/40 (< 0.5)	31.6%	-	-	-
≥ 20/40 (≥ 0.5)	68.4%	100%	100%	100%
≥ 20/25 (≥ 0.8)	26.3%	94.7%	88.9%	84.6%
≥ 20/20 (≥ 1.0)	5.3%	42.1%	50.0%	38.5%
≥ 20/17 (≥ 1.2)	-	15.8%	22.2%	7.7%
Mean BCVA (±SD), (logMAR)	0.28 (±0.19)	0.04 (±0.08)	0.03 (±0.09)	0.05 (±0.07)
Change in BCVA from preoperative to FU, n (Percentage)				
Improved (≥2 Snellen lines)		14 (74%)	13 (72%)	11 (85%)
Unchanged (≥ 1 Snellen line)		5 (26%)	5 (28%)	2 (15%)
Worsened (≤ 2 Snellen lines)		0 (0%)	0 (0%)	0 (0%)
ECD (±SD), (cells/mm²)	2842 (±139)	913 (±434)	869 (±313)	758 (±225)
ECD Decrease (±SD), (%) *		68 (±15)	70 (±11)	74 (±7)
Pachymetry (±SD), (μm)	639 (±89)	550 (±49)	555 (±51)	548 (±38)
Pachymetry Decrease (±SD), (%) *		12 (±14)	12 (±14)	15 (±14)

*Decrease as compared to preoperative values
BCVA: Best-corrected visual acuity
ECD: Endothelial cell density

Donor ECD averaged 2842 (±139) cells/mm^2 before surgery (n=19) and 913 (±434) cells/mm^2 (-68%) at 6 months (n=19), 869 (±313) cells/mm^2 (-70%) at 12 months (n=18) and 758 (±225) cells/mm^2 (-74%) at 24 months after surgery (n=13) (Table 2, Fig. 1B). The annual ECD decrease rate from 12 to 24 months was 12.8% (Fig. 1B).

Mean pachymetry decreased from 639 (±89) μm (n=19) before surgery, to 550 (±49) μm at 6 months (n=19), 555 (±51) μm at 12 months (n=18) and 549 (±38) μm at 24 months after Quarter-DMEK (n=13).

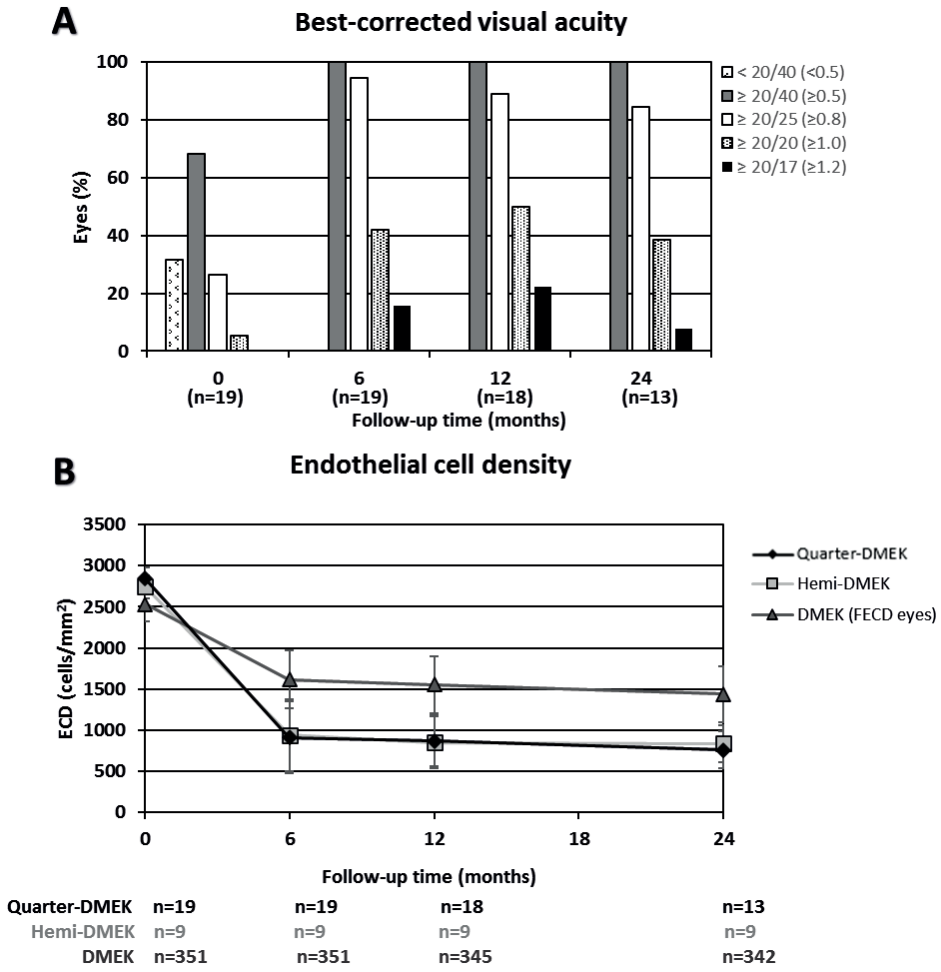

Figure 1. Best-corrected visual acuity and endothelial cell density before and up 2 years after Quarter-Descemet membrane endothelial keratoplasty. (A) Bar graph displaying best-corrected visual acuity (BCVA) for all time points. (B) Graphs displaying mean endothelial cell density (ECD) for all time points. For comparison, ECD values for Hemi-DMEK (extracted from Ref. 7) and conventional DMEK (taken from Ref. 8) are also included.

Postoperative complications and graft survival

In the early postoperative phase, 8 of 19 eyes (42%) showed visually significant graft detachment requiring a re-bubbling procedure, which was successful in all eyes. At the latest available follow-up visit, 12 of 19 eyes (63%) showed complete corneal clearance (Fig. 2), while 7 of 19 eyes (37%) showed a clear corneal center but persistent edema, sometimes accompanied by bullae, along the limbal round edge of the Quarter-DMEK graft or in one of the de-

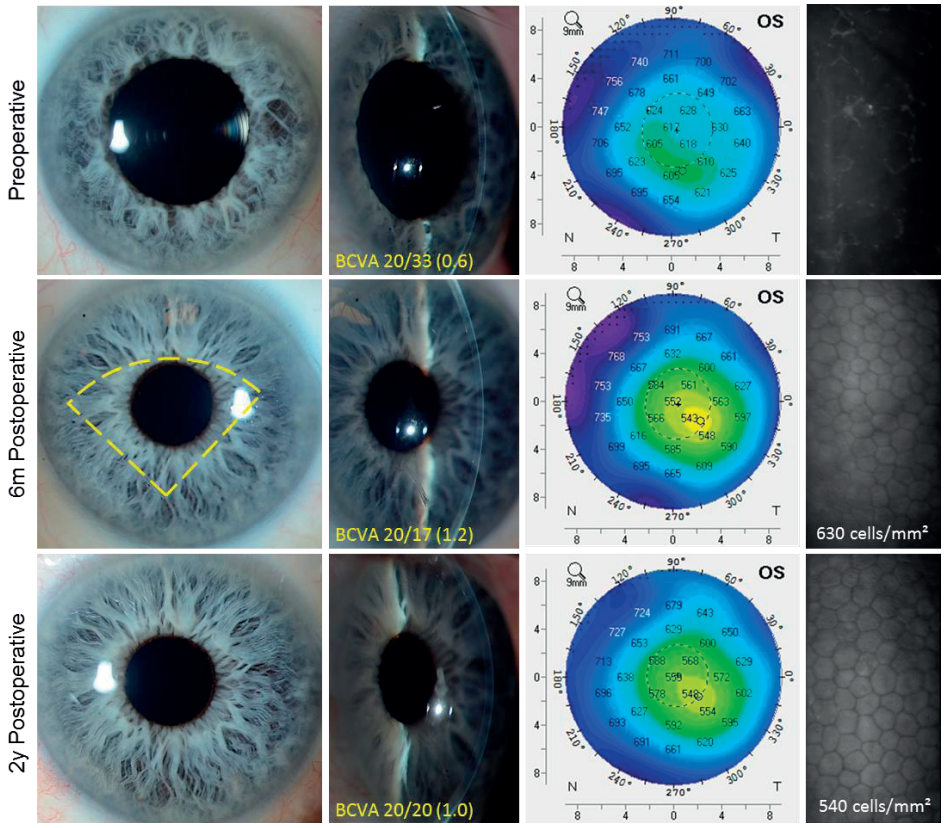

Figure 2. Slit-lamp images, pachymetry maps and central specular microscopy images before and after Quarter-Descemet membrane endothelial keratoplasty. Images are shown preoperatively (top row), at 6 months (middle row) and at 2 years (bottom row) after Quarter-DMEK. The intermitted yellow triangle outlines the approximate position of the Quarter-DMEK graft. Best-corrected visual acuity (BCVA) values in the second left column are reported in Snellen (Decimal); OS= oculus sinister.

nuded areas adjacent to the graft (Fig. 3). None of the patients with persistent peripheral corneal edema experienced any discomfort from it, and none of them developed any complications possibly related to the edema. In 2 of 19 eyes (11%) subtle graft fibrosis was observed along the round edge of the Quarter-DMEK graft (Fig. 3).

Two patients displayed persistent steroid-induced ocular hypertension after Quarter-DMEK. In both cases, the pressure was managed by instituting topical anti-glaucoma medication and an expedited tapering of the topical corticosteroids for the first patient and earlier transitioning from topical dexamethasone to topical fluorometholone for the second.

Allograft rejection and secondary graft failure did not occur throughout the study period, and none of the eyes required re-transplantation.

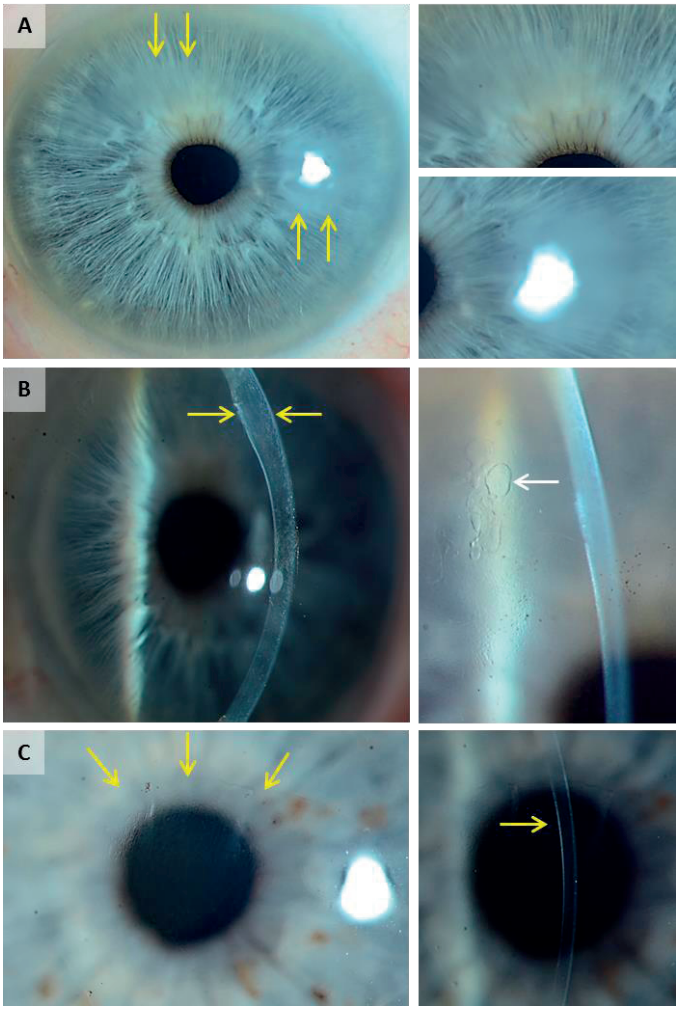

Figure 3. Slit-lamp images of an eye at 2 years after Quarter-Descemet membrane endothelial keratoplasty. (Top row, A) The intermitted white triangle outlines the approximate position of the Quarter-Descemet membrane endothelial keratoplasty (Quarter-DMEK) graft, and the yellow arrows indicate areas with persisting edema; along the round limbal edge of the graft and in the bare area temporal of the graft. (Middle row, B) The yellow arrows highlight edema in the superior part of the cornea, which in this eye is accompanied by bullae, highlighted with the white arrow. (Bottom row, C) The yellow arrows indicate graft fibrosis along the round limbal edge of the Quarter-DMEK graft.

DISCUSSION

The past 20 years of corneal endothelial transplantation techniques have been focused on reducing the amount of tissue transplanted, so that only the damaged layer of the cornea is replaced.[2,9] In Quarter-DMEK, the aim was to go one step further in patients with central FECD.[4] In these cases, only the central portion of the corneal endothelium was removed and replaced with a smaller graft, preserving more of the patient's own peripheral endothelial cells. This has the theoretical benefit of reduced donor antigen load, and the benefit of potentially quadrupling the amount of donor tissue available for transplantation.[5] In the current study, we reported clinical outcomes of 19 consecutive Quarter-DMEK cases up to 2 years postoperatively.

BCVA values after Quarter-DMEK reflected those after conventional and Hemi-DMEK. Fast visual rehabilitation within the first 6 months postoperatively was followed by a stabilization of BCVA throughout the study period. As expected, corneal clearance was less rapid after Quarter-DMEK compared to conventional DMEK and, in particular, lagged behind along the round limbal edge of the Quarter-DMEK graft and the adjacent bare stromal areas.[5] Recently, we showed that asymmetrical endothelial cell migration of Quarter-DMEK grafts *in vitro* may explain this corneal clearance pattern, with cell migration predominantly occurring from the radial cut edges, but not the round edge.[10] Additional studies investigating whether these peripheral cells constitute a valuable cellular reserve are required to optimize this technique.

Visually significant graft detachment requiring re-bubbling (42%) occurred in a similar rate compared with after Hemi-DMEK (40%), but a slightly higher rate compared with the first 25 cases of the initial conventional DMEK case series (36%).[7,11] This may be related to more difficult graft handling during surgery, but it may also be because edge detachments of these grafts almost always involve the visual axis, prompting re-bubbling more quickly.

A larger concern is the 68% drop in ECD in the early postoperative phase. In the first 6 months after Quarter-DMEK surgery, ECD decreased more steeply compared with that after conventional DMEK but resembled the sharp initial decline after Hemi-DMEK. Thereafter, all three DMEK-techniques showed a similar gradual yearly decline.[7,8] Eliminating the method error as a confounding variable, it was shown before for DMEK eyes that the largest drop in ECD from 1 day postoperative to 6 months postoperative may occur in the first week

postoperatively, and that a large proportion of the decrease from preoperative to 1 day postoperative may be because of preoperative overestimation of the viable cell count and increased surgical manipulation.[12] Another explanation could be a mismatch between the larger descemetorhexis and the smaller triangular-shaped Quarter-DMEK graft, resulting in larger areas of bare stroma that must be colonized by migrating donor cells. To date, no Quarter-DMEK graft has decompensated or required a re-operation but longer-term studies are required to determine how long the current BCVA outcomes can be maintained.

Before implementing Quarter-DMEK into clinical practice on a larger scale, it should be considered that the Quarter-DMEK technique may still be in progress and studies are underway to evaluate whether the procedure would benefit from a smaller descemetorhexis (diameter) aiming to reduce the surface of the bare areas that need to be repopulated by endothelial cells, adapting graft preparation to reduce the loss of cells along the radial cut edges of the graft, and/or removing the round peripheral edge of the Quarter-DMEK graft to promote cell migration toward the adjacent bare area in the corneal periphery.

In conclusion, Quarter-DMEK yields visual outcomes similar to those after conventional DMEK and may potentially increase availability of endothelial donor tissue. However, to obtain improved clinical outcomes, endothelial cell counts, and graft longevity, the acute drop in ECD must be addressed. If this can be improved to the level of conventional DMEK, the potential benefit from a single corneal donor could, in theory, be quadrupled for these central FECD cases.

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