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Implantation of an Artificial Endothelial Layer for Treatment of Chronic Corneal Edema

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Purpose: The purpose of this study was to describe a novel device that may serve as an alternative to Descemet membrane endothelial keratoplasty (DMEK) for the treatment of chronic corneal edema.

Methods: The EndoArt (EyeYon Medical, Israel) is a flexible, 50-μm thin artificial endothelial layer that matches the cornea's posterior curvature and functions as a fluid barrier at the posterior stroma, replacing the diseased endothelium. Similar to a DMEK approach, it is implanted into the anterior chamber, carefully positioned on the posterior stroma, and secured using an air–gas mixture. Two patients with chronic corneal edema resulting from endothelial decompensation underwent implantation of the new artificial lamella.

Results: In patient 1, the central corneal thickness (CCT) decreased from 730 μm preoperatively to 593 μm at 1 day postoperatively. In patient 2, the CCT decreased from 761 μm preoperatively to 487 μm at 1 day postoperatively. Both patients reported high satisfaction and an overall brighter visual quality. Although dislocation of the lamella occurred in both cases, the CCT was promptly restored after a repositioning procedure and remained stable at the 17-month follow-up (CCT of 526 and 457 μm for patients 1 and 2, respectively). In contrast to DMEK donor tissue, the artificial lamella is sufficiently robust to allow easy intraocular manipulation without the risk of damaging the implant. It is easily removable and does not require any immunosuppressive treatment because of its nonbiological nature.

Conclusions: Implantation of the EndoArt led to rapid corneal deturgescence and CCT restoration, presenting a possible option for patients with chronic corneal edema.

Key Words: corneal edema, Fuchs endothelial dystrophy, pseudophakic bullous keratopathy, endothelium, DMEK

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In recent decades, there has been an increase in the number of keratoplasties performed worldwide.[1–3] In particular, a growing trend toward posterior lamellar procedures became evident, with endothelial keratoplasties surpassing the penetrating ones for the first time in the United States in 2012.[3] According to a report of the German Keratoplasty Registry, posterior lamellar transplantations accounted for approximately 60% of all keratoplasties performed in Germany in 2016, 92% of which were Descemet membrane endothelial keratoplasties (DMEK).[1]

First introduced by Melles et al[4] in 2006, DMEK describes selective transplantation of the Descemet membrane (DM) and corneal endothelium, and it has become a standard procedure for the treatment of endothelial dysfunctions.[1,5–7] Yet, despite its proven efficacy, DMEK is associated with a number of postoperative complications, such as primary or secondary graft failure, immunological graft reaction, or interface keratitis, which may compromise the quality of surgical outcomes.[7–9] Furthermore, with a global shortage of available donor corneas, there is a struggle to meet the increasing demand.[10]

Recently, an artificial endothelial layer, the EndoArt (EyeYon Medical, Ness Ziona, Israel), was introduced and awarded Breakthrough Therapy Designation by the US Food and Drug Administration. Composed of flexible, hydrophilic acrylic material, the EndoArt is a dome-shaped implant with a 6.0-mm diameter and 50-μm thickness that matches the cornea's posterior curvature and functions as an artificial fluid barrier at the recipient's posterior stroma, replacing the diseased endothelium (Fig. 1). The epithelial evaporation and decrease of aqueous influx into the central stroma ultimately reduce the edema and reestablish corneal homeostasis.

We describe the novel artificial endothelial layer for implantation in patients with endothelial decompensation. The device may serve as an alternative to the conventional DMEK and reduce the number of corneal transplantations.

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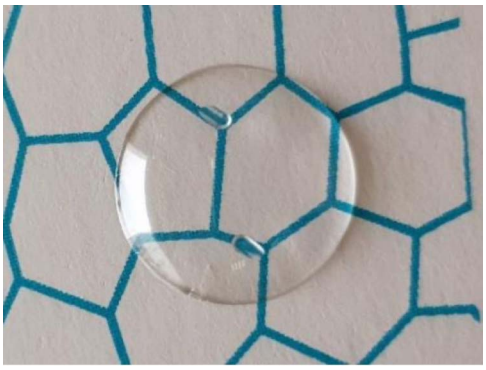

FIGURE 1. The EndoArt is dome-shaped, 50 μm thick, has a 6.0 mm diameter, and is composed of a flexible, hydrophilic–acrylic material. (The full color version of this figure is available at www.corneajrnl.com.)

SURGICAL TECHNIQUE

Patient Selection

Suitable candidates for this procedure include patients with chronic corneal edema resulting from endothelial dysfunction due to Fuchs endothelial dystrophy, pseudophakic bullous keratopathy, or failed endothelial grafts. As with DMEK, patients may not be suitable if there are coexisting diseases, such as a severely scarred cornea unfit for regular endothelial keratoplasty, irregular posterior cornea, band keratopathy, limbal stem cell deficiency, and phthisis. Patients with a history of ocular herpetic keratitis should be avoided because of the risks of Herpes simplex virus recurrence that may, in turn, give rise to endothelial decompensation, corneal scarring, and surgical failure.[11,12] Furthermore, patients with a glaucoma shunt may be suboptimal candidates because the shunt can decrease the efficiency of the air bubble in the anterior chamber and thus interfere with the device attachment.

Technique

Supplemental Digital Content 1 (see Supplemental Video, http://links.lww.com/ICO/B233) shows the surgical technique. A 9.0-mm ring-shaped marking (Geuder AG, Heidelberg, Germany) was applied to the central corneal surface to outline the peripheral extent of DM excision. Two paracentesis incisions were made at 10 o'clock and 2 o'clock, and a 2.4-mm clear corneal incision was made at 12 o'clock. Using a reverse Sinskey hook (Storz Ophthalmic Instruments, Bausch + Lomb GmbH, Heidelberg, Germany), the patient's DM and endothelium were peeled from the posterior stroma, creating a 9.0-mm descemetorhexis.

The artificial endothelial layer was placed in the cartridge of an intraocular lens injector, the Accuject (Medicel AG, Altenrhein, Switzerland), and manually implanted into the anterior chamber. Once the artificial lamella was gently spread out over the iris, it was carefully levitated and positioned on the recipient's posterior stroma using a Sautter cannula (Geuder AG). A bubble of air and then a bubble of air mixed with 20% sulfur hexafluoride were injected into the anterior chamber to secure the graft and support adherence. A digital microscope with integrated intraoperative optical coherence tomography (OCT) for the anterior segment (ARTEVO 800; Carl Zeiss Meditec AG, Jena, Germany) was used to visualize and verify the lamella's position.

The postoperative topical regimen included an antibiotic eye drop 3 times daily for 1 week and a low-dose corticosteroid eye drop 3 times daily as a long-term treatment. Immunosuppressive treatment was not necessary.

In both of our clinical cases, the artificial endothelial layer was implemented as a compassionate use. This study adhered to the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board/Ethics Committee at the Ruprecht Karl University of Heidelberg, Germany.

CASE REPORTS

Case 1

A 58-year-old woman presented to our clinic complaining of cloudy and fluctuating vision in her right eye. This eye had already undergone a DMEK 5 years earlier to treat endothelial decompensation caused by previous intraocular procedures including anterior chamber lavage and pars plana vitrectomy for the treatment of endophthalmitis that occurred after cataract surgery. At presentation, the uncorrected distance visual acuity (UDVA) was finger count at 1 m and the manifest refraction did not lead to any visual improvement. The slit-lamp examination showed bullous pseudophakic keratopathy with diffuse epithelial and stromal corneal edema and pupillary atrophy (Fig. 2A). The DMEK lamella was still attached to the patient's stroma. The central corneal thickness (CCT)

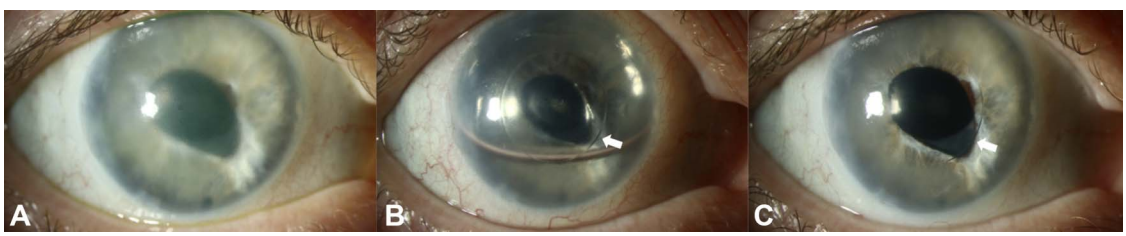

FIGURE 2. A, Preoperative slit-lamp image of case 1 with diffuse pseudophakic bullous keratopathy. B, One-day postoperative slit-lamp image of the same patient with the artificial endothelial layer implant (white arrow) attached to the central stroma and gas bubble in the anterior chamber. The central corneal edema is already beginning to reduce. C, Three-month postoperative slit-lamp image of the same patient showing a considerable regression of the central corneal edema. The artificial endothelial layer is in place (white arrow). (The full color version of this figure is available at www.corneajrnl.com.)

TABLE 1. The Measured Central Corneal Thickness Values Preoperatively and Postoperatively for Case 1

		Postoperatively					
	Preoperatively	1 d	1 mo	6 mo*	6 mo†	12 mo	17 mo
Case 1	730 μm	593 μm	430 μm	680 μm	527 μm	510 μm	526 μm

*One day before the repositioning procedure.
†One day after the repositioning procedure.

measured by the swept-source OCT scan was 730 μm. The examination of the posterior segment showed optic neuropathy and central retinal atrophy because of endophthalmitis. After detailed consultation, the patient agreed to undergo implantation of the artificial endothelial layer.

Table 1 shows the postoperative course of the CCT. Figures 2B, C show postoperative slit-lamp findings. Figure 3 displays the anterior segment OCT images preoperatively and at 3 month postoperatively. The 17-month follow-up swept-source OCT finding is illustrated in Figure 4.

At 1 day postoperatively, the UDVA was 1.7 logMAR and the CCT was 593 μm. At 6 months postoperatively, an inferior detachment of the artificial endothelial layer from the posterior corneal stroma could be observed as an incidental finding, and the CCT was 680 μm. The patient did not report to have noticed any difference in her visual perception. A day later, the lamella could be repositioned successfully using air. One day after the repositioning procedure, the CCT was reduced to 527 μm. The CCT remained stable at the 17-month follow-up examination. There was no migration of endothelial cells over the border of the descemetorhexis nor any overgrowth of endothelial cells across the device.

Case 2

An 82-year-old man presented to our clinic with persisting cloudy vision in his right eye. This eye had already received a DMEK procedure 2 years earlier to manage Fuchs dystrophy and a rebubbling procedure a month after DMEK. The UDVA was 1.1 logMAR at presentation, which did not improve with manifest refraction. The slit-lamp examination showed primary graft failure accompanied by epithelial bullae, subepithelial fibrosis, and stromal edema. The DMEK lamella remained attached to the patient's stroma. The patient agreed, after detailed consultation, to undergo EndoArt implantation.

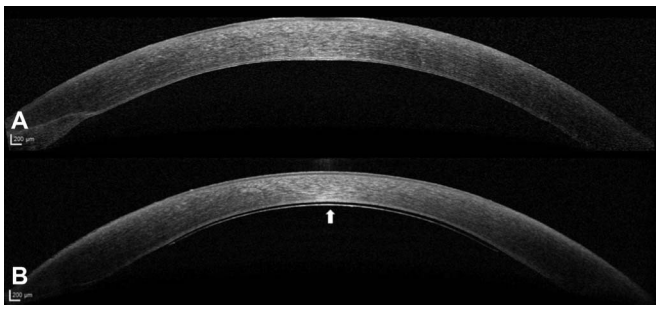

FIGURE 3. A, Preoperative anterior segment OCT image of case 1 with chronic corneal edema. B, Three-month postoperative anterior segment OCT image of the same patient with the artificial endothelial layer implant attached to the central stroma. The white arrow shows the artificial endothelial implant in place.

Table 2 shows the postoperative course of the CCT. Figure 5 displays the 17-month follow-up image of the swept-source OCT.

At 1 day postoperatively, the CCT decreased to 487 μm. At 24 days postoperatively, the artificial endothelial layer was detached from the posterior stroma inferiorly and the CCT was 593 μm. The patient did not notice any worsening of his vision on the affected eye. At 25 days postoperatively, it was repositioned using air. At 27 days postoperatively, the UDVA improved to 1.0 logMAR and the CCT was reduced to 507 μm. The CCT had remained stable at the 17-month follow-up examination. There was no migration of endothelial cells over the border of the descemetorhexis, nor any overgrowth of endothelial cells across the device.

DISCUSSION

Generally, there are 2 common underlying pathophysiological mechanisms of corneal edema. It can result from a primary (eg, Fuchs dystrophy) or a secondary endothelial failure (eg, pseudophakic bullous keratopathy, graft failure after penetrating or endothelial keratoplasty, or endothelial decompensation after glaucoma surgery) or from high intraocular pressure (IOP) that overwhelms its pumping capacity.[13] Although the causative treatment of the latter involves lowering of the IOP, the former often ultimately requires surgical restoration of the malfunctioning endothelium.

The concept of DMEK was first introduced more than a decade ago by Melles et al.[4] Numerous studies have since confirmed the clinical efficacy and safety profile of transplanting the ultrathin DM and endothelium as a substitute for the dysfunctional endothelium.[6,7,10,14–16] Vasiliauskaitė et al[16] published the long-term clinical outcomes of the first DMEK cohort in 100 eyes of 88 patients and observed excellent visual outcomes, with 89% reaching best-corrected Snellen visual acuity of 20/25 or better at the 10-year follow-up. Furthermore, no primary graft failures occurred within 10 years, whereas 4% of eyes developed allograft rejection.[16] Their findings accord with the results from other studies, which found that DMEK provided the most rapid and optimal visual recovery and held a much lower risk of immunologic rejection than other endothelial keratoplasty procedures.[15] The resulting widespread adoption of this method is clearly reflected by the expanding number of DMEKs performed worldwide.[1–3]

Notwithstanding these reports on promising results, DMEK's success is profoundly dependent on a number of vulnerable factors that may compromise its outcome.

A key factor is the integrity of the donor tissue, and it is therefore of utmost importance that the tissues undergo a stringent safety and quality control at the eye bank.[7,14,17] Laaser et al[17] also highlighted the importance of good tissue

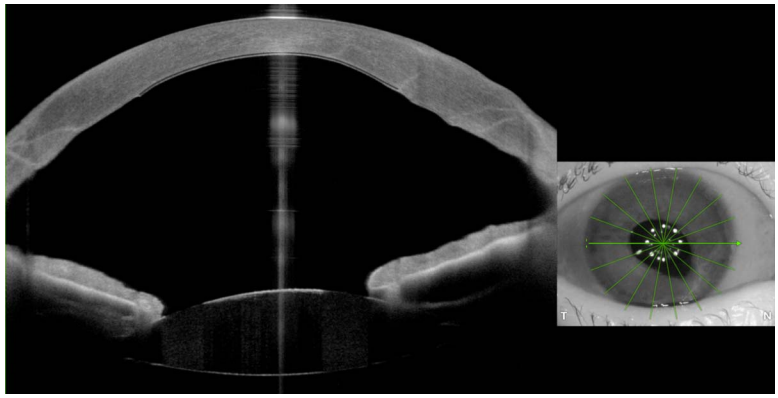

FIGURE 4. Seventeen-month postoperative swept-source OCT image of case 1. (The full color version of this figure is available at www.corneajrnl.com.)

culture methods because they affect not only the endothelial cell viability but also the DM's biophysical properties that contribute to graft adhesion. Eyes with DMEK tissues require long-term immunosuppressive therapy and frequent follow-up examinations to avoid or control complications such as developing primary or secondary graft failure, immunological graft reaction, or interface keratitis.[8,9] Furthermore, both preoperative donor graft preparation and intraoperative tissue handling require extreme delicacy of a skillful surgeon because the exceedingly thin (<20 μm) donor tissue renders it very susceptible to endothelial cell loss or tears.[7,14,17] Consequently, in practice, DMEK has become reserved for highly specialized corneal centers with experienced surgeons who work closely with responsible eye banks.[7,17]

However, such facilities are not prevalent enough, especially in developing countries. Furthermore, the global scarcity of available donor corneas further restrains access to appropriate surgical care. The most recent global survey of corneal transplantation and eye banking found that an estimate of 12.7 million patients are waiting for a corneal donor tissue worldwide and that only 1 in 70 of the needs is met, emphasizing the serious imbalance in current supply and demand.[10] The study also revealed that 53% of the world's population simply lacks access to corneal graft tissues,[10] calling for a timely alternative to corneal transplantations.

In a recent uncontrolled, single-group study, Kinoshita et al[18] showed that injection of cultured human corneal endothelial cells supplemented with a rho-associated protein kinase inhibitor into the anterior chamber of 11 patients with endothelial dysfunction led to a marked increase in corneal endothelial cell density, suggesting that it is a viable alternative to DMEK. Furthermore, the recently reported technique termed the Descemet stripping only, in which only the central 4-mm zone of the DM is removed and the central posterior stroma is left without an endothelial graft, has been shown to provide encouraging results for up to 5 years, with less adverse events, less need for additional procedures, and no need for donor tissues.[19,20] However, the clinical efficacy and safety of both techniques must await longer-term results.

Implanting an artificial endothelial layer offers a range of advantages over using a donor DMEK tissue. The EndoArt is a potential substitute for a human tissue, but unlike a DMEK tissue, it provides a water-impermeable barrier designed to be attached to the patient's posterior stroma, impeding the inflow of the aqueous humor and thus preventing stromal imbibition. It is made of an optically clear CI26 material (Contamac Ltd, Saffron Walden, United Kingdom) or a copolymer of hydroxyethyl methacrylate and methyl methacrylate, the same material that also composes commercial hydrophilic acrylic intraocular lenses, giving it biocompatible and biostable properties.

This material is sufficiently robust to allow smooth and controlled insertion and easy intraocular manipulation without the risk of damaging the implant, which is always a potential problem with a donor tissue. It is easily removable or exchangeable and does not require any immunosuppressive treatment thanks to its nonbiological nature. The aforementioned postoperative topical regimen in our cases did not lead to any complications, such as graft rejection or IOP elevation. Because the device is not implanted into the corneal stroma as in, for example, corneal inlays, complications, such as corneal melting or haze, are not expected. Importantly, because it is merely a water-impermeable plate, it neither requires harvesting or processing steps in an eye bank, nor is subject to legal, ethical, or cultural restrictions that often complicate organ transplantations. It can also be stored for years before use and then used immediately. Its cost-effectiveness and the lack of a waiting list are also of particular interest to surgeons in

TABLE 2. The Measured Central Corneal Thickness Values Preoperatively and Postoperatively for Case 2

		Postoperatively						
	Preoperatively	**1 d**	**24 d***	**27 d†**	**1 mo**	**6 mo**	**12 mo**	**17 mo**
Case 2	761 μm	487 μm	593 μm	507 μm	480 μm	476 μm	510 μm	457 μm

*One day before the repositioning procedure.
†Two days after the repositioning procedure.

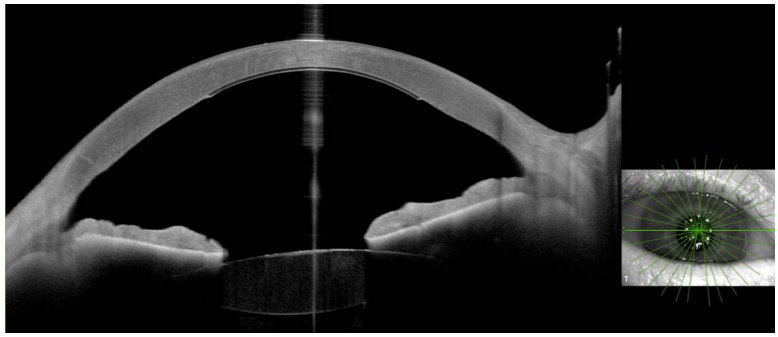

FIGURE 5. Seventeen-month postoperative swept-source OCT image of case 2. (The full color version of this figure is available at www.corneajrnl.com.)

countries with limited access to human donor corneas. In such regions, the EndoArt may also serve as a temporary treatment option until donor grafts become available.

In DMEK, the graft detachment has been reported as one of the most common postoperative complications that requires repositioning through rebubbling procedures.[21,22] Inward folds of the DM graft's edges, irregularities at the graft–stroma interface, and insufficient support of the intracameral air bubble are among the factors that have been discussed as potential causes of graft detachment.[21,22] Furthermore, thin graft thickness has been suggested as another risk factor for graft failure owing to its susceptibility to damage and its tendency to fold intraoperatively.[23] By contrast, the artificial endothelial layer is thicker than a typical DM donor tissue and more rigid, which may account for better graft adherence. Its nonbiological nature lacking any collagen or proteoglycan may also contribute to a lower graft detachment rate.

In our clinical cases, the artificial endothelial layer led to a rapid reduction of the CCT. Although the visual acuity did not experience a significant increase, both patients reported high satisfaction and an overall brighter visual quality on the operated eye. Although a dislocation of the artificial endothelial layer occurred in both cases, the CCT was promptly restored after a repositioning procedure through rebubbling using air. As there were no other concurrent complications such as intraocular inflammation, we believe that the dislocation was most likely the result of a mechanical cause (eg, eye rubbing).

Reports of rebubbling rates after DMEK show wide differences. In a prospective, interventional case series comprising 500 eyes of 393 patients, Rodríguez-Calvo-de-Mora et al[24] reported a clinically significant graft detachment rate of 4.8%, 58% of which required a rebubbling procedure. Tourtas et al[25] noted that 82% of 38 eyes that underwent DMEK showed partial graft dehiscence and required rebubbling during the early postoperative period. We need a larger sample size to determine the rebubbling rate of the artificial endothelial layer.

Although a long-term immunosuppressive treatment should not be necessary because of the nonbiological property of the device, a topical low-dose corticosteroid treatment was administered four times a day in this study as a precautionary measure because there are currently no data available regarding the long-term effect of the device.

There may be concerns for the influence of the EndoArt on the IOP. Because the device is very thin and only has a diameter of 6 mm, thereby not covering the entire posterior corneal surface, it is unlikely to have a clinically significant influence on the IOP. In this study, the IOP was measured using the Goldmann applanation tonometer (Haag-Streit Deutschland GmbH, Wedel, Germany) at all postoperative visits, and the values were within the normal range.

Furthermore, questions may arise concerning the corneal metabolism of the aqueous and nutrients. EndoArt is a passive barrier layer that is impermeable to both liquids and gases. When implanted, approximately 30% of the posterior cornea turns into a sealed surface, reducing the amount of fluid penetration into the cornea. Instead of active pumping of excess water (endothelial role), the device decreases the net flow of fluid into the cornea and returns the overall balance (Fig. 6). The excess fluid that has already accumulated in the cornea then evaporates through the epithelial layer.

In conclusion, this technique shows the feasibility of a novel artificial endothelial layer for the treatment of patients with endothelial dysfunction. It still needs to be Food and Drug Administration–approved and confirmed in a future study with a larger sample size and a heterogenous patient population whether this technique can offer a long-term solution. A multicenter, prospective clinical trial was launched just recently in Europe, which seeks to investigate its safety and efficacy. However, our experiences so far have shown no significant postoperative complications for up to a 17-month follow-up period, underlining its potential as a possible alternative to corneal transplantations.

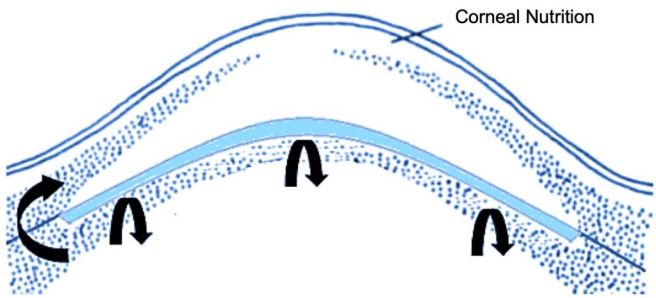

FIGURE 6. Once implanted, the EndoArt device reduces fluid transfer from the aqueous and returns the overall balance of stromal metabolism. (The full color version of this figure is available at www.corneajrnl.com.)

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