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Long-Term Clinical Outcomes and Anterior Segment Optical Coherence Tomography Findings After Artificial Endothelial Replacement Membrane Implantation

Luigi Fontana, MD, PhD,† Natalie di Geronimo, MD,*† Piera Versura, BSD,*† and Antonio Moramarco, MD*†*

Purpose: This study examines the long-term clinical outcomes of an artificial endothelial replacement membrane implant used to treat corneal edema. It also explores the interaction between the device and the posterior surface of the cornea.

Methods: Patients suffering from late endothelial keratoplasty failure (5 patients) or bullous keratopathy (2 patients) after multiple surgeries underwent EndoArt (EyeYon Medical, Israel) implantation. Before surgery and at 1-, 3-, 6-, 12-, 18-, and 24-month intervals, corrected distance visual acuity and central corneal thickness were measured. High-resolution anterior segment optical coherence tomography images were analyzed at each interval to detect device detachment and evaluate the implant interaction with the corneal tissue over time.

Results: Corrected distance visual acuity improved from a mean of 1.32 ± 0.23 (logarithm of the Minimum Angle of Resolution) preoperatively to 0.95 ± 0.28 (logarithm of the Minimum Angle of Resolution) 2 years after surgery (P = 0.03). Central corneal thickness significantly decreased from 805 ± 131 μm preoperatively to 577 ± 90 μm postoperatively (P = 0.002). Four of the 7 patients experienced device detachment, requiring 1 or more rebubblings to achieve stable implant adhesion. Anterior segment optical coherence tomography showed annular fibrosis developing between the device margin and the host cornea in most patients, particularly those who had never experienced detachment.

Conclusions: This study suggests that EndoArt is effective in the long term for improving corneal transparency and visual acuity in patients with chronic corneal edema with a limited prognosis for endothelial keratoplasty. The formation of fibrotic tissue between the periphery of the device and the host cornea may explain the strong adhesion of the implant.

Key Words: artificial endothelial keratoplasty, endothelial transplantation, corneal edema, anterior segment optical coherence tomography

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Endothelial keratoplasty (EK), which encompasses procedures like Descemet stripping endothelial keratoplasty (DSEK) or Descemet membrane endothelial keratoplasty (DMEK), stands as the preferred treatment for individuals experiencing various forms of corneal endothelial dysfunction.[1] This advanced technique offers several advantages, including minimal invasiveness, quicker visual recovery, and enhanced safety, leading to its widespread adoption over traditional penetrating keratoplasty (PK) as the new standard of care for those patients with endothelial failure–induced corneal edema.[2] By 2022, EK had largely replaced PK in the United States, with only a small percentage (10.1%) of patients with endothelial dysfunction undergoing PK, whereas the majority (89.9%) elected some form of EK.[3] Although primary EK demonstrates high success rates, with 82.4% to 96% survival for DMEK[4,5] and 79.4% to 95% for DSEK at 5 years,[6,7] concerns persist regarding long-term graft survival in specific groups of patients. Factors like prior graft failure, bullous keratopathy, glaucoma, and complicated anterior segment surgeries negatively impact graft survival, leading to a significant likelihood of requiring repeat keratoplasty, which accounted for 15.2% of graft surgeries in 2022 in the United States and 14% in Europe,[8] with over half of these cases opting for repeat EK.[3] In this regard, repeated keratoplasties suffer from reduced expected survival, destined to decrease further after each repeated surgery.[9]

Addressing this challenge, a novel CE-approved device registered for the treatment of corneal edema, named EndoArt (EyeYon Medical, Israel), has emerged as a potential solution. This contact lens–shaped acrylic hydrophilic implant, made of flexible material measuring 50 μm in thickness and 6.5 mm in diameter, designed according to the posterior corneal curvature, acts as an artificial fluid barrier upon adherence to the inner corneal surface. Because of its water

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From the *Ophthalmology Unit, Dipartimento di Scienze Mediche e Chirurgiche, Alma Mater Studiorum University of Bologna, Bologna, Italy; and †IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy.

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Correspondence: Luigi Fontana, MD, PhD, Ophthalmology Unit, Policlinico S. Orsola di Bologna. Via Pelagio Palagi 9, Bologna 40138, Italy (e-mail: luifonta@gmail.com).

impermeability, the device stops aqueous penetration into the central corneal stroma, reducing edema and improving corneal transparency. Although only a few outcome reports are available in the literature, all confirm the short-term effectiveness of EndoArt in promoting corneal deturgescence, reducing stromal thickness, and consequently improving visual acuity.[10–12] However, 1 concern regards the long-term device's efficiency in achieving complete and lasting adherence to the posterior corneal surface. Indeed, after implantation, most of the patients reported in the literature experienced 1 or more detachments, requiring further injection of an air/gas bubble into the anterior chamber to accomplish complete adhesion.[10–12] The mechanism behind device adhesion to the posterior cornea is not yet understood.

This study reports the long-term clinical outcomes of consecutive patients with chronic corneal edema secondary to failed EK grafts and bullous keratopathy who underwent artificial replacement membrane implantation. Furthermore, using anterior segment optical coherence tomography (AS-OCT), we investigated the interaction between EndoArt and the posterior corneal surface developing over time.

MATERIAL AND METHODS

This retrospective study received approval from the hospital's Institutional Review Board (Registration No. 901/2022/Oss/AOUBo) and adhered to the tenets outlined in the Declaration of Helsinki. All participants provided specific informed consent for EndoArt implantation and personal data collection. EndoArt implantation was performed on 7 consecutive patients, 3 men and 4 women. The mean age was 76 ± 4 years. Five patients shared the diagnosis of chronic corneal edema after late EK failure, whereas the other 2 had bullous keratopathy secondary to previous cataract and glaucoma surgery (glaucoma drainage device). We defined late transplant failure as a gradual loss of graft transparency without recent rejection or corticosteroid responsiveness. As a tertiary referral center, many patients arrive months after graft decompensation, making it difficult to determine the exact interval between failure onset and EndoArt implantation.

Five patients with late EK failure had 2 previous DSEK and 1 had 2 DMEK. The patients' characteristics are summarized in Table 1.

The 6-month outcomes of 5 of the 7 patients reported in this study were previously documented (patients 1–5).[11]

The surgical technique of EndoArt implantation is described in detail elsewhere.[11] In brief, after Descemet membrane or EK removal, the device is introduced into the anterior chamber using the "pushed through technique" using a blunt spatula. After confirmation of the correct device orientation, a bubble of air mixed with 10% perfluoropropane (C3F8) is used to promote adhesion to the posterior corneal surface. A single superior 10.0 nylon transfixing suture (5 patients) or 3 reversed Y-shaped sutures (2 patients) were used to secure the device to the cornea for 3 months and then removed (Fig. 1) (Video 1).

Postoperative medication included tobramycin 0.3% and dexamethasone phosphate 0.1% eye drops 4 times daily for the first month, twice daily for the second and third months, and then suspended.

Corrected distance visual acuity (CDVA) [logarithm of the Minimum Angle of Resolution (logMAR)] and central corneal thickness (CCT), calculated using AS-OCT (Casia II, Tomey Corp, Nagoya, Japan) by measuring the distance between the external and internal corneal surfaces at the apex using calipers excluding the EK graft (before surgery) and the EndoArt implant (after surgery), were collected for all patients preoperatively and at 3, 6, 12, 18, and 24 months after surgery.

High-resolution AS-OCT images were captured at the same time intervals and, where required, after each rebubbling procedure. Our analysis focused on identifying the AS-OCT features of the implant adhesion and detachment, delineating their most frequent localization and extent. Furthermore, we investigated the interaction at the implant's edge and the posterior cornea with time.

Statistical Analysis

Clinical variables, CDVA and CCT, were expressed using the mean ± SD. Variables were compared using a paired sample *t* test. Statistical significance was set at $P < 0.05$. Statistical analyses were performed using SPSS for Windows version 25 (IBM Corp, Armonk, NY).

RESULTS

After artificial endothelial membrane implantation, CDVA improved from a mean of 1.32 ± 0.23 logMAR preoperatively to 0.95 ± 0.28 logMAR 2 years postoperatively ($P = 0.03$).

Two patients without relevant comorbidities improved 11 lines, achieving final visual acuities of 20/50 and 20/32 (Snellen), respectively. The mean CCT significantly changed from 805 ± 131 μm preoperatively to 577 ± 90 μm at the last follow-up visit ($P = 0.002$), with a CCT reduction and improvement in central corneal transparency occurring in all patients (Fig. 2). The implants were retained in all cases 2 years after surgery. One glaucomatous patient (patient 4), with advanced optic nerve cupping, experienced worsening vision because of intraocular pressure decompensation and progression of optic nerve damage, although the central cornea remained clear postoperatively. After implantation, device detachment occurred in 4 out of 5 patients in whom the implant was sutured to the cornea with a single transfixing suture. Six rebubbling procedures were required to achieve complete adhesion to the posterior corneal surface during the first 3 to 4 months after surgery. Patients with implants sutured using 3 reversed Y-shaped transfixing sutures did not experience device detachment. Six months after surgery and up to the end of this study, EndoArt implants remained stably attached to the cornea in all patients. Characteristically, when the implant adheres to the posterior corneal surface, only the inner surface of the device is visible as a hyperreflective line at the AS-OCT examination. This feature was named the "single rail sign," indicating that the implant was fully attached to the posterior corneal surface (Fig. 3A). Partial

TABLE 1. Patients' Characteristics

Patient	Sex, Age	N° Keratoplasties	Glaucoma	Filtering Surgery	Pseudophakia	Current Diagnosis	Preoperative VA (LogMAR)	Final VA (LogMAR)	Preoperative CCT (μm)	Final CCT (μm)	Visual Potential
1	F, 76 yrs	2 DSEK	No	No	Yes	Late transplant failure	1.5	0.4	775	528	Moderate (multiple EK)
2	M, 75 yrs	2 DSEK	Yes	No	Yes	Late transplant failure	1	0.8	787	694	Low (chronic CME)
3	F, 74 yrs	2 DSEK	Yes	Yes	Yes	Late transplant failure	1.5	1	1036	712	Low (multiple EK, glaucoma)
4	F, 72 yrs	2 DMEK	Yes	Yes	Yes	Late transplant failure	1	1.3	691	475	Low (subterminal glaucoma)
5	M, 78 yrs	2 DSEK	No	No	Yes	Late transplant failure	1.3	0.2	734	527	Moderate (multiple EK)
6	F, 85 yrs	0	Yes	Yes	Yes	Bullous keratopathy	1.5	0.9	681	568	Moderate (glaucoma)
7	M, 73 yrs	0	Yes	Yes	Yes	Bullous keratopathy	1.5	0.8	931	538	Moderate (glaucoma)

The 6-month outcomes of patients 1 to 5 were previously documented.[11]
CME, cystoid macular edema; VA, visual acuity.

device detachment manifests with a portion of the implant not adhering to the posterior stromal surface (Figs. 3B–D). In these cases, the hyperreflective anterior and posterior surfaces of the device are visible at the AS-OCT, showing the characteristic "double rail sign." This sign is helpful in case of a shallow implant detachment, not always visible at the slit lamp but well recognizable at the AS-OCT (Fig. 3B). In correspondence to the detached area, corneal pachymetry is increased because of aqueous contact with the posterior stroma (Figs. 3C, D). After rebubbling, corneal deturgescence is restored through the adherence of the device (Fig. 4). Inferior detachments typically manifested within 3 months of follow-up after air-gas tamponade reabsorption when the single superior suture was still in place. Removal of this suture was followed by the development of superior detachments in some cases. Starting 3 months after surgery, AS-OCT showed a hyperreflective circumferential band, developing between the edge of the implant and the posterior stroma, typically starting superiorly and eventually extending to the other quadrants (Fig. 5). This band did not constantly develop evenly around the implant, especially in patients who experienced multiple detachments. At 2 years, 5 patients exhibited a complete circumferential band; of these, 3 never experienced device detachments, whereas the other 2 had partial detachments. In the latter group, after rebubbling, the hyperreflective band eventually extended to the entire perimeter of the device within a few months (Table 2). In the remaining 2 patients, the band did not extend fully around the circumference of the implant at the 2-year follow-up, and these patients experienced more detachments.

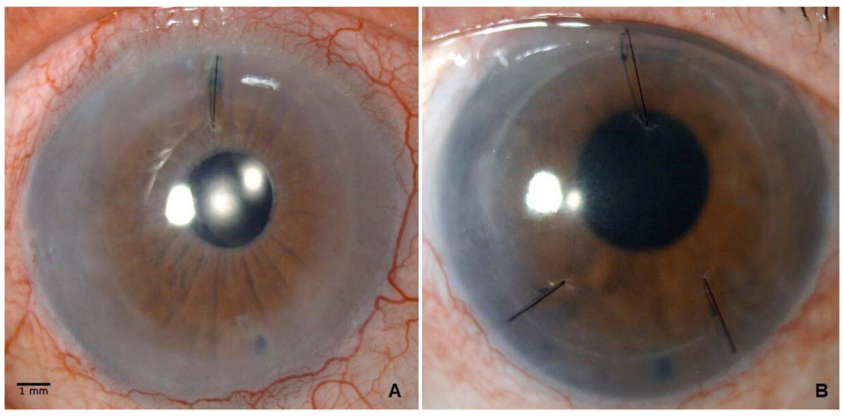

FIGURE 1. Slit-lamp photographs 2 months after artificial endothelial layer implantation showing the 2 techniques used to secure the implant to the cornea: (A) single transfixing 10-0 nylon suture (patient 2), (B) 3 reversed Y-shaped transfixing 10-0 nylon sutures (patient 6). The pictures show a clear central cornea (5–6 mm diameter) corresponding to the area of the implant. The peripheral cornea is edematous and opaque.

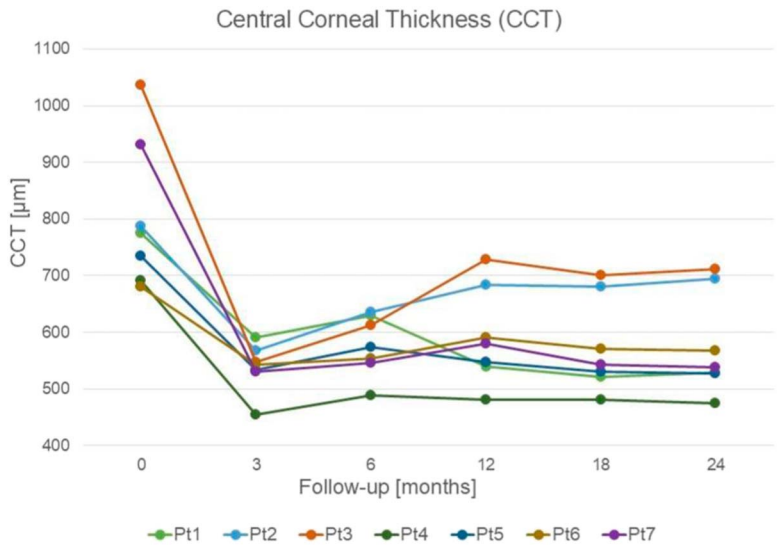

FIGURE 2. Graph illustrates the trend of CCT from preoperative values (time 0) to 1, 3, 6, 12, 18, and 24 months postoperatively.

DISCUSSION

Given the expanding number of posterior lamellar keratoplasty procedures worldwide and the application of EK to the treatment of complicated anterior segment conditions,[13] the number of individuals who might eventually require repeat procedures will also increase. With each additional keratoplasty, the likelihood of complications and graft failure rises, leading to more patients needing repeat graft surgeries. For these reasons, the global burden of repeat EK is expected to increase.

In this scenario, EndoArt presents a promising solution, particularly for patients with limited prospects of achieving long-term success with a human graft. This includes individuals with multiple failed grafts, where repeat procedures have a low likelihood of success,[8,9] or those with a history of glaucoma surgery, both of which are associated with reduced graft survival after EK.[13] Notably, the 2 patients with bullous keratopathy in our study had previously undergone glaucoma surgery with glaucoma drainage device implantation. As a result, we proposed an alternative surgical solution that offers the potential for a longer-lasting effect while preserving the option of a future EK procedure if needed. This device has already been demonstrated to reduce corneal thickness and improve corneal transparency in the short term.[10–12] In the present case series, we showed its effectiveness in maintaining corneal deturgescence up to 24 months postimplantation. In previous studies,[10–12] the impact on visual acuity was limited by the selection of patients with low visual potential because of several comorbidities, an inherent consequence of the restrictive therapeutic indication used for this novel device. However, it is important to consider that more significant CDVA improvements were observed in some patients with few or no ocular comorbidities, suggesting that the visual potential benefit of this implant may exceed the outcomes observed so far. Our study presented long-term evidence to support the high compatibility profile of the device, as no cases of corneal vascularization, melting, or intraocular inflammation were observed at 2 years. These findings indicate that EndoArt implantation does not seem to alter corneal homeostasis, which is likely responsible for the high retention rate observed with this device.

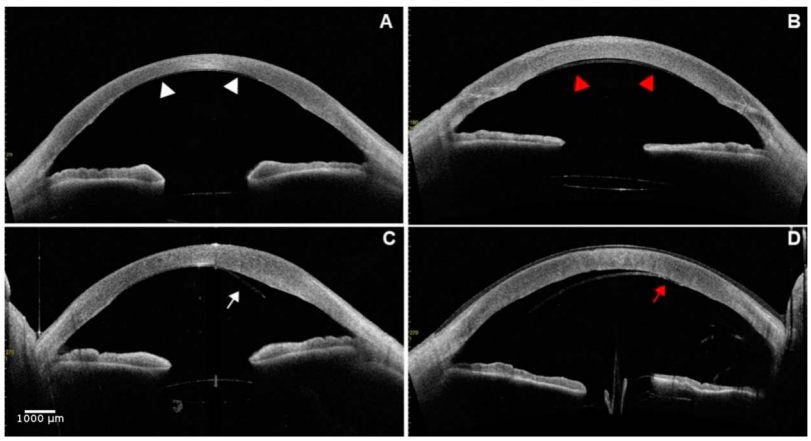

FIGURE 3. A, AS-OCT image demonstrating an artificial endothelial layer adherent to the posterior surface of the cornea (patient 2). In the AS-OCT examination, only the inner surface of the device is observed as a hyperreflective line (arrowheads). B, AS-OCT image demonstrating a shallow artificial endothelial layer detachment (patient 3) (arrowheads). C, AS-OCT image demonstrating partial implant superior detachment (patient 2). D, AS-OCT image demonstrating subtotal implant detachment (patient 1). The device is secured to the cornea by the single transfixing suture (arrow).

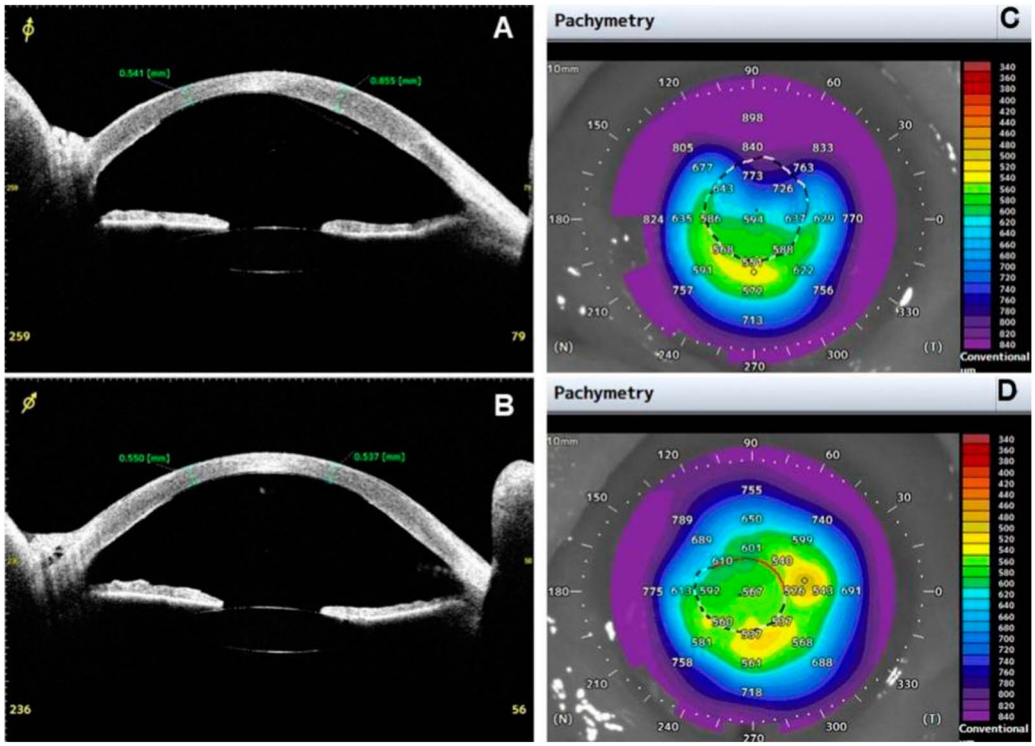

FIGURE 4. A, B, AS-OCT image demonstrating partial artificial endothelial layer detachment and the corresponding pachymetry map (patient 1). C, D, AS-OCT image and pachymetry map of the same eye after rebubbling. Observe the deturgescence effect of the device once it adheres to the posterior surface of the cornea. Pachymetry measurements include the device (50 μm).

The most frequent complication reported after surgery is implant detachment. Auffarth et al[10] documented 2 cases of patients undergoing EndoArt implantation, both necessitating rebubbling after the initial surgery. In a prior study conducted by our group, 4 out of 5 patients required additional rebubbling within 3 to 4 months after implantation.[11] In the present study, 6 months after surgery and up to 2 years after implantation, EndoArt remained fully adherent to the cornea, suggesting that the implant may require more than 3 months to accomplish stability. Successful adhesion is critical for the implant's stability, functionality, and long-term integration with the host tissue. Still, the mechanism of EndoArt adhesion to the cornea is yet to be understood. After implantation, the device is kept adherent to the cornea by the intraocular air-gas bubble and the transcorneal suture. Once the bubble is reabsorbed (2–3 weeks), the implant may become unstable, and detachments may occur, requiring rebubbling to regain complete contact between the device and the posterior corneal surface. We observed that the characteristics of detachments varied before and after removing the anchoring suture at noon. Detachments were primarily localized in the inferior and temporal sectors in the initial months. Likewise, after EK, detachments often occur in the inferior sector, as this area is typically the first to lose the tamponade effect of the air or gas introduced at the end of the procedure.[14] Temporal detachments might somehow correlate with irregularities in the posterior corneal surface, which can be attributed to the corneal tunnel and suture point. Twelve weeks after surgery, the upper anchoring suture was removed. After this, there was a reversal in the incidence of inferior detachments. After suture removal 3 months after surgery, there was a shift in the pattern of detachment incidence. Although inferior detachments were initially more common, most detachments subsequently occurred in the superior sectors, likely because of the downward forces exerted by the aqueous humor on the device. Our observations suggest that 3 to 4 months may be too short for the device to accomplish stability, and a longer time, up to 6 months, may be necessary to acquire firmness. For this reason, maintaining the sutures up to 6 months postoperatively may reduce the frequency of detachments. Our AS-OCT analysis seems to

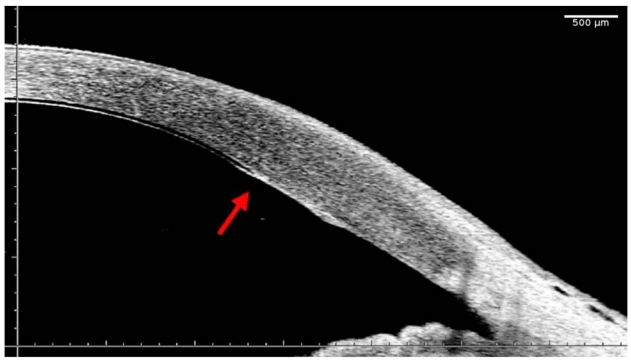

FIGURE 5. AS-OCT image showing a hyperreflective band extending between the edge of the implant and the posterior stroma (patient 5).

TABLE 2. Number of Detachments, Rebubbling Procedures, and Fibrosis Characteristics

Patient	N° Detachments	N° Rebubbling	Fibrosis	Months of Follow-Up	EndoArt Explantation
1	1	1	Yes, 360 degrees	24	No
2	2	2	Yes, 360 degrees	24	No
3	1	1	Yes, partial	24	No
4	2	2	Yes, partial	24	No
5	0	0	Yes, 360 degrees	24	No
6	0	0	Yes, 360 degrees	24	No
7	0	0	Yes, 360 degrees	24	No

support this hypothesis. A hyperreflective circular band extending from the device margin to the adjacent posterior stroma was observed in all patients after at least 3 months of follow-up. One possible explanation is that this band consists of fibrous tissue forming between the margin of the implant and the host cornea, beginning in the superior quadrant and extending circumferentially. This circumferential fibrosis may be the reason for the stable bond between the EndoArt and the cornea that establishes approximately 6 months after surgery. This finding may explain why, in our patients, device detachments did not occur after this time frame. Interestingly, we observed a correlation between the completeness of the circular fibrosis and the occurrence of detachments. In correspondence with the detached quadrants, annular fibrosis became complete only after rebubbling.

After DSEK, fibrocellular scar formation occurs at the edges of the lenticules, helping the graft adhere to the recipient stroma.[15] This process likely resembles the circumferential fibrosis seen with the EndoArt implant, highlighting the significance of tissue integration for the stability and long-term success of this corneal implant. Because fibrosis did not extend to the interface, it did not impact visual function. This absence of involvement at the interface is essential, as it helps to maintain a clear optical zone. Questions may arise regarding whether EndoArt may eventually become fully enveloped by a fibrotic membrane over time. Two years after implantation, none of our patients exhibited signs of implant opacification or deformation because of fibrotic capsule contraction. Similarly, we did not observe any AS-OCT signs suggesting the development of a fibrotic envelope over the posterior surface of the implant. However, histological examinations conducted on devices explanted long after implantation are necessary to exclude this hypothesis.

Using 3 reversed Y-shaped transfixing sutures instead of a single suture may enhance the stability of the EndoArt implant by ensuring steady contact with the posterior cornea. This approach may ensure consistent contact of the device with the posterior cornea and facilitate the development of annular fibrosis, which is important for maintaining implant adherence. By providing more anchorage, the risk of detachment may decrease once the air-gas tamponade is reabsorbed, promoting better long-term stability and integration with the corneal tissue. Further studies, including a more significant number of patients, are essential to demonstrate the advantages of using 3 reversed Y-shaped transfixing sutures over a single suture for EndoArt implants.

In conclusion, our study presents long-term evidence of EndoArt's efficacy in promoting stromal deturgescence and enhancing corneal transparency and visual acuity in patients with chronic corneal edema who have a poor prognosis after EK. The results indicate a favorable acceptance profile for the device, demonstrating good tolerance by the recipient's cornea. However, further efforts are needed to refine the implantation technique to reduce the frequency of device detachment and the necessity for rebubbling procedures.

Further prospective studies involving a larger cohort of patients are warranted to thoroughly investigate the risk of complications associated with this device implantation. A particular focus should be placed on evaluating the potential for corneal melting, a concern raised because of the device's impermeable nature and its potential to disrupt corneal hydration dynamics. In addition, long-term follow-up is essential to evaluate the biomechanical stability of the cornea, the development of any fibrotic encapsulation, and other potential late-onset adverse events. These data will help establish safety profiles, inform design improvements, and optimize postoperative management strategies to minimize risks.

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