EDITORIAL

Corneal transplantation: Beyond the horizon

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Abstract

Evolving techniques in keratoplasty have undoubtedly led to thinner corneal grafts. These newer iterations of keratoplasty aim to reduce graft rejections, improve visual acuity and visual rehabilitation. Each technique poses its own advantages and disadvantages; the surgeon should select patients suitable for a particular technique while accounting for their surgical competency given the learning curve associated with these newer techniques. Alternatives to corneal transplant may have a role in addressing the shortages of corneal graft, these bioengineered material and medical treatment still need further studies to demonstrate its clinical applicability.

Key words: Cornea; Cell therapy; Keratoplasty; Bullous keratopathy; Techniques

Core tip: Review of the current status of corneal transplant, the issues encountered with current techniques, the potential and future treatment on the horizon.

INTRODUCTION

Corneal transplantation remains the mainstay of treatment for visual rehabilitation for any corneal disease affecting its clarity. In the past decade, we have witnessed great strides in the advancement of lamellar keratoplasty, which involves removing and replacing only the diseased portions, gaining popularity over the tradition penetrating keratoplasty (PK) or full thickness keratoplasty. Ongoing refinements resulted in better equipment, harvesting and transplanting techniques. In this editorial, we will highlight the recent major advances in corneal grafting and other ongoing potential developments such as artificial cornea and cellular transplantation.

ANTERIOR LAMELLAR KERATOPLASTY

Deep anterior lamellar keratoplasty (DALK) aims to replace the diseased epithelium and corneal stroma while retaining the unaffected Descemet's membrane (DM) and endothelium. It has been used as an alternative to PK in corneal diseases that is confined to the anterior layers, such as keratoconus, corneal dystrophies and scars. As an extraocular procedure, the advantages include preserving the host endothelium, reducing surgical trauma, minimizing the risk of endothelial rejection, and achieving faster visual recovery compared with PK[1]. However, conversion to PK may be inevitable if there is intraoperative DM perforation, which is the most common complication. A major optical disadvantage compared with PK is the corneal stromal bed irregularity following manual lamellar dissection techniques, limiting the postoperative best corrected visual acuity (BCVA). Different techniques for DALK have been suggested to overcome this issue to remove the stroma with baring of the DM. Of these techniques, Anwar's big-bubble technique is one of the most popular techniques among corneal surgeons. Based on level II evidence in 1 study and level III evidence in 10 studies, DALK is found to have equivalent BCVA outcome with no advantage for refractive errors if the surgical technique yields minimal residual host stromal thickness[1]. Retrospective comparative case series with subgroup analysis revealed that the big-bubble technique gives better results than manual dissection and PK (2.2-2.5 lines difference), but manual dissection has lower BCVA compared with PK (1.0-1.8 lines difference)[2]. This study also demonstrated that DALK has better overall long-term, model-predicted graft survival (49.0 *vs* 17.3 years) and endothelial cell loss (-22.3% *vs* -50.1%) than PK.

Newer technology with the femtosecond laser allows more precise incision with customized graft shape, edge and lamellar plane to improve the matching of donor-recipient fit, and increased donor-recipient junction surface area contact interface[3]. Femtosecond laser assisted keratoplasty was first described in 2006 by Suwan-Apichon *et al*[4] and later by Price *et al*[5] and others[6]. Configuration such as "zigzag" or "mushroom" shaped wounds in both the donor and host were aimed at reducing postoperative astigmatism, improving wound integrity, and allowing earlier suture removal. Prospective studies using femtosecond laser-assisted PK found that the wound is more stable, particularly with the top hat and mushroom wound configurations[7], but refractive outcomes are not superior when compared to the conventional techniques[8]. Retrospective review comparing femtosecond laser mushroom configuration and manual trephine straight edge configuration using Melles' or Anwar's technique found that femtosecond laser assisted DALK achieves faster visual rehabilitation with a better BCVA at 3 mo, which was not significant at 6 or 12 mo; whereas mean spherical equivalent, cylindrical astigmatism, and keratometric cylinder were similar for all follow up[9]. Further well designed controlled trials are warranted to elucidate the role of femtosecond laser in DALK. It may have a complementary role when combined with manual stromal dissection or air injection to expose the DM in cases with irregular corneal thickness, such as keratoconus, corneal ectasia, and corneal scar, in order to facilitate a more uniform fashion of stromal excision to the DM[1]. Such potential technology for achieving better visual outcome is encouraging, but current use is limited by the high costs, especially in non-institutional practices or less developed economies.

EVOLUTION IN ENDOTHELIAL KERATOPLASTY

Modern day posterior lamellar keratoplasty (PLK) reached a breakthrough when Melles described an essentially sutureless technique to replace the posterior lamella using an air bubble for graft fixation in 1998[10]. A few years later, Terry and Ousley modified and simplified the PLK technique and coined the term deep lamellar endothelial keratoplasty (DLEK)[11]. Following the successes of DLEK, Melles introduced a Descemet's stripping technique in 2002 where a "Descemet roll" was obtained by stripping the DM with its endothelial layer from the posterior stroma in the donor, and implanted it after a "descemetorhexis" to prepare the recipient bed for transplanting this manually dissected donor lamellar button[12,13]. Further improvements continued in 2005 when Price modified the technique and named it Descemet stripping endothelial keratoplasty (DSEK)[14] a year later, Gorovoy simplified the challenging and time consuming manual dissection of donor tissue by using a microkeratome and named it Descemet stripping automated endothelial keratoplasty (DSAEK)[15]. In essence, DSAEK allows replacing the recipient's diseased endothelium and DM by the donor's healthy endothelium and DM attached with a thin section of corneal stroma.

Over the last decade, DSAEK has become the procedure of choice in treating corneal endothelial dysfunction, such as Fuchs endothelial dystrophy and pseudophakic bullous keratopathy. A systematic review by the American Academy of Ophthalmologist found that DSEK/DSAEK were similar to PK in terms of surgical risk, complication rate, graft survival, BCVA and endothelial cell loss, but superior to PK in allowing for much faster visual recovery, refractive stability, refractive outcomes, fewer wound and suture related complications, intraoperative and late suprachoroidal haemorrhage risk[16]. Although DSAEK produced good visual outcome in most cases, it is not as high as one would have hoped for. Part of this is attributed to the disturbed natural corneal posterior anatomy where the stromal donor-recipient interface results in higher order aberration and light scattering[17,18]. The thickness of the donor's stroma in DSAEK will also accentuate any mismatch between

the donor and recipient corneal curvatures. Compressive folds can also form between this interface when there is a mismatch between the curvature of the donor and recipient's cornea[19]. To overcome these challenges, modifications of endothelial keratoplasty to transplant only a strip of endothelial cells layer with the DM without the stroma was developed and named Descemet's membrane endothelial keratoplasty (DMEK) by Melles[20].

Eliminating this stromal interface and thickness variation, DMEK provides improved visual outcome, smaller incision width, and reduced risk of immunological graft rejection as compared with DSAEK[17,21,22]. The DSAEK graft thickness is about 70-250 μm while DMEK is about 14-20 μm, thus reducing the volume of donor tissue by 75%-90%[23]. For DSAEK/DSEK (and DLEK), significantly more cell loss was reported when using a 3.2 mm incision when compared to a 5 mm incision[24]. However it is possible to insert the DMEK graft *via* a 2.8 mm incision with comparable endothelial cell loss with a DSAEK graft performed with a 5mm incision, thus minimizing the postoperative astigmatism[24,25]. Kruse reported that within a 6 mo follow up, DMEK achieves better and faster visual rehabilitation as compared to DSAEK, but no difference in endothelial cells survival[21]. It is not uncommon for DMEK eyes to approach near instant visual recovery, with patients having BCVA of 20/40 on the first postoperative day and 20/20 or better within the first postoperative week[26]. DMEK is believed to have less graft rejections with the absence of the donor epithelium and stroma. Price's group performed a comparative case series and found that the Kaplan–Meier cumulative probability of a rejection episode at 1 and 2 years was 1% and 1% for DMEK; 8% and 12% for DSEK; and 14% and 18% for PK respectively, with a significant level of $P = 0.004$. The DMEK eyes thus were thus 15 times less likely to experience a rejection episode than DSEK eyes ($P = 0.008$) and 20 times lower risk than PK eyes ($P = 0.006$)[27].

BATTLE OF THE ENDOTHELIAL KERATOPLASTIES

Despite the significant reported benefits of DMEK over DSAEK, the road to acceptance is relatively slow among corneal surgeons. DMEK presents the surgeon with two main technical challenges and a relatively steep learning curve, preparing and handling the donor graft. Although the preparation of the DMEK donor has improved in the last few years, potential graft wastage remains a key challenge, especially to the newer DMEK and or lower volume surgeons. It is possible for the surgeon to decide whether the graft preparation is to be outsourced to an eyebank or performed during surgery[28]. Different techniques have been proposed in harvesting the donor graft: manual peeling with forceps[29,30] hydrodissection[31] and pneumatic dissection[32]. The forceps technique is the most widely adopted technique with reproducible tissue qualities in up to 98% of donor

cornea in experienced hands[33]. The remaining 2% cornea demonstrated strong adhesions in the DM-stroma interface, either due to ultra-structural (peg-like interlocking) or biochemical abnormalities (increased staining intensities for adhesive glycoproteins)[33], which can result in multiple horseshoe shaped tears in the DM or lamellar splitting of the DM[34]. Previous case series described the successful implantation of accidental large tears in DM (torn into 2 pieces) into 3 eyes, unfolded and attached to the recipient's posterior stroma[35]. At 6 mo of follow up, BCVA ranged between 20/30 and 20/25, endothelial cell loss ranged 28%-32%, and all corneas remained clear without any signs of failure; thus even complete rupture does not preclude successful grafting.

Intraoperative handling of the graft continues to present challenges. During graft insertion, it is critical to maintain the correct orientation of the Descemet roll. Although several inserters have been well developed for DSAEK, the insertion technique in DMEK is yet to be standardized. Several designs have been published including glass injectors and intraocular lens injectors coupled with irrigation fluid under a predefined intraocular pressure to improve the success for delivery of the Descemet roll. Unfolding the graft is one of the more challenging step in DMEK, poor manipulation during insertion will traumatize the endothelial cells. The ease of unfolding depends on the tightness and orientation of the scroll, the anatomy of the anterior chamber, and the intraocular pressure. Grafts from young donors tend to have more scrolling and are thinner, hence more prone to tears; these factors make corneas from younger donor more difficult in harvesting and unrolling[36]. Liarakos *et al*[37] compiled a list of basic and auxiliary techniques along with an algorithm for selection. The high technical demands with insertion and manipulation render DMEK relatively unsuitable in eyes with shallow anterior chamber and / or complicated anatomy, such as those with anterior chamber intraocular lens, peripheral anterior synechiae, and those with an absence of a barrier between anterior chamber and vitreous[38]. Since DMEK grafts are very thin and lost to view in the anterior chamber, eyes with glaucoma shunt, large iris defect, and aphakic eyes are also some conditions less suited for DMEK. The technical challenges and complications associated with DMEK can be reduced once the surgeon has overcome his or her learning curve, but even in the hands of more experienced DMEK surgeons, reported complications rates were still not as low to the rates achieved with DSAEK[29,39,40]. Partial graft detachment requiring rebubbling is the most frequently encountered postoperative complication. Initially the rebubbling ranged between 63%-82%, with the increase in experience and technique modifications, the rebubbling rate was substantially reduced to 3%-17%[36]. The largest DMEK series reported to date evaluated the outcome of 500 consecutive cases and effect of technique standardization confirms the earlier findings that DMEK consistently gives higher visual

Table 1 Comparison between ultra thin-Descemet's stripping automated endothelial keratoplasty and Descemet membrane endothelial keratoplasty

	UT-DSAEK	DMEK
Corneal layers involved	A double microkeratome pass to achieve a thin layer of donor central posterior stroma with the Descemet membrane and endothelium attached	Donor Descemet membrane and endothelium only
Thickness	< 130 μm	14-20 μm
preparation by eyebanks	Widely available from eyebanks	Mostly prepared intraoperatively by surgeons, provided by a limited number of eyebanks
Donor selection	Same criteria as DSAEK, less stringent	Preferably in older donors, as grafts from younger donors are more difficult to harvest and unroll
Recipient selection	Same criteria as DSAEK, less stringent	Less suitable in recipient with a shallow anterior chamber or complicated anatomy
Technical challenges	Similar technique compared with DSAEK	Donor preparation, insertion and manipulation of graft present a learning curve
Operative time	Shorter	Longer
BCVA	Similar percentage of eyes achieving 20/20 at 1 yr, but DMEK allows faster visual recovery with a higher percentage at 6 mo	
Endothelial cell loss at 1 yr	Similar with around 35%	
Tissue loss	2.8%	4.2%
Primary failure	1.4%	8.1%
Rejection probability at 1 yr	2.44%	1%
Rejection rate at 1 yr	2.8%	5.7%
Graft dislocation (partial)	3.9%	9%-92%
Rebubbling rate	3.9%	3%-17%

UT-DSAEK: Ultra thin-Descemet's stripping automated endothelial keratoplasty; DMEK: Descemet membrane endothelial keratoplasty; DSAEK: Descemet stripping automated endothelial keratoplasty; BCVA: Best corrected visual acuity.

outcome and faster visual rehabilitation[41]. The overall number of partial graft detachment reduced from 21.6% in the first 250 eyes to 10% in the following 250 eyes. Approximately half of these detachments may be classified as clinically insignificant partial detachment and did not require any intervention. The decision to rebubbling depends on the extent of graft detachment and how its evolution over time[42].

Compared with DSAEK, DMEK can achieve faster visual recovery, better visual outcomes, and reduced rejection rates. However, still more than half of the patients could not return to a vision of 20/20 in the absence of comorbidities; perhaps more than the presence of stromal interface exists in determining the final visual outcome[25,40]. It has also been proposed that posterior corneal higher order aberrations may be lessened in thinner graft due to less pronounced tissue irregularities. Several retrospective studies show contradictory evidence between graft thickness and final visual outcomes[43]. In 2011, Neff *et al*[44] reported that visual outcomes in DSAEK can be better than DMEK in patients with grafts thinner than 131 μm, correlating the morphologic characteristics of DSAEK graft with the final visual outcome for the first time. Busin, introduced an ultrathin (UT) DSAEK concept using two microkeratome passes, the first pass to debulk the donor tissue, and a refinement pass to achieve a thickness of less than 100 μm[45]. Insertion, deployment, and handling techniques are similar to that of DSAEK, obviating the need of the steeper learning curve of DMEK. The authors presented their prospective findings after a 2 year follow up period[46]. Comparing their results with the longest available follow up series, UT-DSAEK has almost identical outcome in comparison to DMEK[25] in terms of percentage of eyes recovering at least 20/20 BCVA over time, whereas the percentage DSAEK[47] patients were constantly lower for all time points. Although the speed of visual recovery after UT-DSAEK is slower compared with DMEK, there is no difference in the percentage of eyes with BCVA of 20/20 1 year postoperatively[25]. Endothelial cell loss of around 35% were comparable with DSAEK[48,49] and DMEK[25,50], suggesting that the double microkeratome technique does not adversely affect endothelial cell survival. Graft perforation were reported in 2.1% of the cases, which involved the use a 50 μm microkeratome head to perform the second pass in residual corneal central thickness of less than 190 μm. Inaccuracy in assessing the residual thickness through ultrasonic pachymetry can be improved *via* using anterior segment optical coherence tomography. Cases with peripheral perforation were used after eccentric punching and were managed successfully without tissue loss; there were no substantial difference in their final BCVA or endothelial cell density. Postoperative graft dislocation occurred in 3.9%, which is much less than the reported rate of 9%-92% after DMEK[25,40,51,52]. Unlike DMEK, UT-DSAEK grafts are similar to DSAEK grafts and maintain a shape on their own, making them more stable. In the event of graft detachment, they may not need rebubbling as they usually zipper down on their own, whereas the edges of DMEK detachments can continue to curl under leading to the persistence of cleft/interface[25,40]. DMEK remains the thinnest available endothelial graft and there are currently no definitive

studies comparing UT-DSAEK to DMEK. Table 1 is an overall summary of the key differences between the two techniques.

Descemet membrane endothelial transfer, where corneal clearance was noted after re-endothelialisation of the recipient's posterior stroma by a free floating donor's Descemet roll in the recipient anterior chamber after descemetorhexis has been reported[53]. This effect may have been due to the migration of endothelial cells to repopulate the recipient's stroma[54].

ENDOTHELIAL KERATOPLASTY REIGNS SUPREME?

Bullous keratopathy secondary to endothelial decompensation is one of the commonest causes of corneal transplantation. As grafts may be limited in some localities and or in eyes with poor potential, alternatives such as conjunctival flaps, anterior stromal puncture, amniotic membrane transplantation, photokeratectomy, bandage contact lens, collagen cross-linking, and endothelia cell injection are useful options[55].

Despite the promising reported results in lamellar keratoplasty literature, Coster *et al*[56] analysed long-standing Australian national corneal transplantation registry data, and contrary to previous findings, they found that lamellar procedures, whether endothelial or deep anterior, were associated with worse graft survival and visual acuity compared with PK for the same indications and over same time periods. The authors attributed their findings to the differences between a real world registry data from multiple surgeons versus data from a few single centre high volume surgeons, with a defined set of inclusion and exclusion criteria. Coster *et al*[56] also addressed the issue of learning curve, which can explain the poorer outcomes in the early stages of a new technique. They found that experienced surgeons (> 100 registered keratoplasties) achieved significantly better survival of endokeratoplasties ($P < 0.001$) than surgeons who had performed fewer grafts (< 100 registered keratoplasties). However, even in the hands of experienced, high-volume surgeons, endokeratoplasty failures can still occur. Registries provide large volume data over time, but are not without flaws. Changes in practice over time, such as patients selection and widely varying numbers of transplants between different hospitals, are factors that will influence the data[57]. The multicentre Cornea Preservation Time Study will soon provide us with the 3 year standardized graft survival data after. The results from this Australian registry study serves to remind us the importance in monitoring outcomes of newer techniques on a larger and broader scale.

ON THE HORIZON

Many patients will benefit from corneal transplant, however there is a limited supply of donors worldwide[58]

and given sufficient time, allografts will eventfully fail. There has been a long interest in developing alternatives for restoring the corneal tissue structure and function. Keratoprosthesis such as Boston KPro and osteo-ondo-keratoprosthesis have helped patients save their vision in cases where keratoplasty have failed or contraindicated. The original Boston KPRo pioneered by Claes Dohlman is made up of polymethylmethacrylate (PMMA) consisting of a solid front plate and a porous back plate. With advances in the design by having pores in the back plate, a thread-less design, and complimenting it with soft contact lens use, the rates of corneal melt have decreased[59]. Retention rates ranging from 83%-100% have been reported within the first 2 years of implantation[60]. Recent studies have shown that a titanium design as compared to PMMA results in less postoperative inflammation, lower rates of frequency and severity or retroprosthetic membrane[61]. In 2013, the United States Food and Drug Administration approved a revised design of both Type Ⅰ and Ⅱ Boston KPro that eliminates the need for a locking ring use and uses titanium instead of PMMA as a back plate. The metallic appearance due to back plate may be cosmetically dissatisfactory for the patients; there is currently ongoing research on fabrication techniques to add brown or blue hue to improve the cosmetic appearance.

More recently, the use of decellularised extracellular matrixes (ECMs) have been proposed as a scaffold for corneal cell regeneration as it contains many structural and instructional macromolecules for organogenesis, where in wound healing such as corneal wound healing, the same ECM macromolecules contribute to tissue repair[62]. Cultured fibroblasts can secrete their own ECM to form sheets to reconstruct a stromal tissue with endothelial and epithelial cells seeded on each side of the reconstructed stroma[63]. However, the main drawback of this technique is the long duration needed to produce the thickness as seen in the human cornea.

Since collagen is the main structural component in ECM, this has been a target of interest. Recent rabbit experiments have demonstrated a biocompatible plastically compressed collagen scaffold in producing a translucent stroma with no oedema, inflammation or neovascularization, which can be a promising corneal scaffold for future artificial cornea[64]. Recombinant collagen has also been produced and is commercially available, which mimics the same amino acid sequence as human collagen. Type Ⅲ recombinant human collagen has been fabricated into corneal implants to enable corneal regeneration by endogenous cell recruitment in a phase I study involving 10 patients[65]. During the four year follow up period, there were no signs of inflammatory dendritic cells recruitment and rejection even in the absence of immunosuppression. Continued nerve and stromal cell repopulation to approximate the microarchitecture of normal cornea were reported, resulting in an average BCVA of 20/52

gained and more than 5 Snellen lines.

Co-emergent techniques, such as 3-D printing can enable printing of live cells, tissues and even organs for implantation. This is a new technology that involves creating physical objects from digital files. This is still an active and ongoing field of research, and thus far 3D bioprinting has resulted in successful printing of blood vessels and vascular networks[66], bones[67], ears[68] and so on. Its application in ophthalmology is currently limited, but recent progresses in exploiting naturally biomaterials with 3D bioprinting have a potential in generation of ocular tissues. In the future, this technology may one day play a role in producing cornea and other organs to be custom-tailored to the patients' needs.

The emergent strategies in cellular biology and tissue cultivation of corneal endothelial cells (CEC) aim to produce transplantable corneal endothelial cell sheets. It focuses on the culture of CEC retrieved from the donor's cornea, followed by transplantation into the recipient. *Ex vivo* human CEC models can overcome the G1 phase and complete the cell cycle; this occurs in the presence of appropriate growth factors[69]. The main factors that determine the mitotic capacity of human CEC *in vitro* includes method of culture, growth factors in culture medium, and viability of donor cornea; the process of isolation, preservation and expansion are critical in engineering human corneal endothelium which remains to be optimized with ongoing research[70]. Adult stem cells found in adipose tissue, bone marrow and umbilical cord blood have self-renewal and plasticity attributes, which have been widely studied as potential therapies in degenerative diseases[71]. Early studies with short term results have supported the use of adult stem cells as potential treatment for corneal diseases in animals[72,73]. There is an abundant literature on mesenchymal stem cells (MSCs) for corneal reconstruction based on *in-vivo* and *in-vitro* studies. MSCs are a type of multipotent progenitor cell with the ability to differentiate into different lineages of mesenchymal cells. They can infuse into an allogenic host without being rejected due to the low expression of surface co-stimulatory molecules[74]. Rabbit MSCs (Rb-MSCs) transplanted onto chemically injured rabbit cornea show an expression of corneal epithelium specific marker cytokeratin 3 (CK3) and promote the healing of the cornea epithelium *in-vivo*. These Rb-MSCs *in-vitro*, differentiate into cells with a morphology similar to the corneal epithelium and expresses CK3[72]. Animal studies have demonstrated a reduction in expression of various inflammatory factors after transplantation of MSCs in chemically injured rat's cornea. Furthermore, in contrast to its angiogenic effect in ischemic tissues and tumors, MSCs can down-regulate angiogenic factors and upregulate anti-angiogenic factors[75]. Through their differentiation capability and paracrine function, MSCs can promote corneal wound healing and reduce corneal neovascularization. Further experimental studies are needed before proceeding to clinical trials with MSCs in human eyes.

A strictly pharmacological approach in treating corneal dysfunction would be a very attractive option as it eliminates the need of donor grafts and morbidities associated in artificial corneas and transplantation of CECs. A selective Rho-associated kinase (ROCK) inhibitor Y-27632 can diminish the dissociation-induced apoptosis of human embryonic stem cells[76]. *In vitro* studies on primate CEC have shown that Y-27632 promotes cell adhesion and proliferation and inhibits apoptosis[77]. The application of Y-27632 ROCK inhibitor eye drops resulted in less corneal oedema and corneal endothelial wound healing *via* stimulating proliferation of CECs in rabbit[78]. Whereas in monkey, it enhanced wound healing of the corneal endothelium with a retained high endothelial cell density and the physiological hexagonal morphology with expression of functional proteins was also demonstrated[79].

Based on these promising animal studies, a pilot clinical study recruited 4 eyes with diffuse corneal oedema secondary to bullous keratopathy and 4 eyes with late onset of Fuchs corneal dystrophy were given Y-27632 eye drops. The 4 eyes with diffuse corneal oedema did not show reduction in corneal thickness or improvement in visual acuity. However, in 3 of the eyes with Fuchs corneal dystrophy, there was a reduction in corneal thickness which was maintained overtime[79]. Furthermore, one of these eyes demonstrated recovery of corneal clarity, with a BCVA of 20/20 at 2 wk after treatment; the endothelial function and the visual acuity were maintained up to 24 mo[80].

It is hypothesized that the inhibition of ROCK signalling may manipulate cell adhesion properties. When cultivated corneal endothelial cells combined with ROCK inhibitor were injected into the anterior chamber of animal eyes, endothelial cell adhesion was promoted and the cells achieved a high cell density and morphology similar to corneal endothelial cells *in vivo*, thus enabling the transplantation of cultivated CECs as a form of regenerative medicine[81]. These promising findings may pave the way for a new approach in treating corneal endothelial dysfunction.

CONCLUSION

Evolving techniques in refining the outcomes of anterior and posterior lamellar keratoplasty in the last decade have led to improved visual acuity and reduced rejection rates. As surgeons continue to modify and share their experiences, it will become easier for corneal surgeons to master the technical challenges related different facets of modern keratoplasty. The beauty of lamellar keratoplasty allows us to focus our treatment on the specific diseased corneal layer, where we can achieve more with less. In the future, we eagerly anticipate the alternative possibilities to corneal transplantation using bioengineered material and medical treatment, obviating the need and heavy demand on donor graft availability.

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