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Review Article

Keratoplasty: The Progress from Penetrating to Cellular Transplants - Short Review

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Abstract

The cornea is a transparent membrane that acts as a protective barrier to the eye and refracts light. Corneal disorders (diseases, dystrophies, degenerations, injuries) can lead to a loss of translucency. Corneal opacity is a one of major causes of blindness, affecting approximately 6 million people worldwide. For patients with corneal blindness, the only method of regaining vision is corneal transplantation (keratoplasty). Keratoplasty has evolved to include various methods such as penetrating keratoplasty (PK), anterior lamellar keratoplasty (ALK), and posterior/endothelial keratoplasty (PK/EK). Lamellar keratoplasty has gained popularity due to its improved outcomes and reduced risks compared to penetrating keratoplasty. Modern keratoplasty benefits from additional tools like optical coherence tomography and femtosecond lasers, which enhance surgical precision and decision-making. Future for corneal disease treatment assumes partial EK, Descemet membrane endothelial transfer, descemetorhexis stripping without endothelial keratoplasty, using ROCK inhibitors, cell therapy, tissue engineering grafts, stem cells and combination of all of them. Further studies are necessary to confirm advantages of those trends.

Keywords: *Cornea; Corneal Transplantation; Keratoplasty; Corneal Grafting*

Introduction

The cornea, along with the sclera, makes up the outer membrane of the eyeball (the cornea constitutes 1/6 of the anterior surface, the sclera - 5/6 at the posterior part of the eye). The cornea is a transparent, avascular structure consisting of five layers: corneal epithelium, Bowman's layer, stroma, Descemet's membrane (DM) and corneal endothelium. Furthermore, it plays a pivotal role in optical refraction [1,2]. Diseases of the anterior corneal layers result in corneal opacities or scars, leading to visual loss. Moreover, corneal endothelium malformations (diseases, dystrophies, degenerations, rejections) lead to disfunction of it as a pump constantly removing fluid from the stroma and result in loss of visual acuity secondary to corneal oedema [2].

According to the World Health Organization's 2019 World Report on Vision, about 285 million people in the world suffer from visual impairment, while 14% (about 39 million) of them are blind. Corneal opacity is one of commonest causes of blindness worldwide and affects about 6 million people [3,4].

Corneal transplantation/keratoplasty is the main treatment modality for visual rehabilitation in eyes with reduced corneal clarity. Keratoplasty is one of the most common transplantations performed in humans [5,6]. According to data from the year 2012, about 12.7 million people worldwide are waiting for corneal transplantation. The procedure was performed 185 thousand times in 116 countries and 284 thousand corneas were harvested in 82 countries [7]. In the year 2021 in Poland, 2971 patients were waiting for transplantation, while 1000 keratoplasty procedures are performed per year [8].

Until relatively recently, penetrating keratoplasty has been the most common surgical technique. In the last 15 years selective replacement of the diseased corneal layers has been observed. It was possible because of advancements in microsurgical equipment, refinements in grafting techniques. Lamellar keratoplasty techniques allow better visual outcomes and less tissue rejection [6-9]. We would like to present short review on current techniques and advantages of keratoplasty.

Current methods in keratoplasty

The history of keratoplasty begins in 1813 and was pioneered by Karl Himley, who was the first to suggest using corneas between animals and - as he claimed - describe penetrating keratoplasty (PK) [10]. Within almost the century the idea of corneal transplantation was investigated (animal models of surgery) but the first successful corneal human transplantation was performed in 1905 by Eduard Zirm [2,6,10,11]. Progress in anesthesiology, antiseptic rules, surgical techniques, immunology resulted in new technology and instrumentation, upgraded surgery methods, new strategies in postoperative management and better visual outcomes [10,11].

Penetrating keratoplasty (PK)

PK is well-known technique that remains the most common type of keratoplasty worldwide [8,11,12]. During surgery full-thickness donor corneal button replaces damaged host cornea. The long-term survival of those grafts is high: in 10 years observation it has been described even in 70 - 90% in low-risk cases [11-13]. Regardless of achievements in survival and visual outcomes, PK is fraught with a risk of complications. “Open-sky” surgery can be complicated with expulsive hemorrhage or iris prolapse. After surgery anterior synechiae, raised intraocular pressure (IOP), loosed or broken sutures, corneal allograft rejection, endophthalmitis were described. Prolongated topical corticosteroids could be responsible for raised IOP and cataract. Corneal astigmatism is the reason of suboptimal visual acuity with clear cornea after PK (approximately one third of eyes with astigmatism >/= 5 diopters) [11,14,15].

Lamellar keratoplasty (LK)

First data on the lamellar keratoplasty come from the 19th century: in 1888 von Hippel perform anterior lamellar keratoplasty (ALK) in dog [10]. Unfortunately visual outcomes were not satisfying because after manual dissection the interface was irregular and revealed residual stromal opacities. Consequently, LK was abandoned for decades and PK was the predominant technique [2,11]. The development of better equipment (microscopes, tailored instruments, microkeratomes, lasers) facilitates precise tissue dissection and renewed interest in lamellar techniques. Better knowledge on transplant immunology and postoperative immunosuppression improve prevention and treating graft rejection. As studies show ALK needs shorter steroid therapy then PK [2,11,16]. Depending on the procedure’s relation to the DM we can divide them to the anterior lamellar keratoplasty (ALK) (anteriorly to DM) and endothelial keratoplasty (EK) (posteriorly to DM) [17,18].

Anterior lamellar keratoplasty (ALK)

ALK is reserved for replacement of anterior layers of the cornea without disturbing host endothelium [2]. Studies have shown that even more than half of all PK graft failures are related to acute endothelial graft rejection or endothelial decompensation. Preserving healthy host endothelium ALK is in charge of improvement in terms of graft survival. As an extra-ocular surgery ALK exclude complications connected with open-globe surgery [2,15,16,19,20]. ALK is suitable for corneal stromal diseases, superficial scarring, corneal dystrophies affecting

epithelium, Bowna's layer, stroma and ectatic disorders (as keratoconus and post LASIK/laser assisted stromal *in-situ* keratomileusis/ectasia). For the superficial disorders anterior layers of the host's cornea are replaced by donor button (superficial anterior lamellar keratoplasty - SALT) (30 - 40% of anterior cornea) and deeper layers of the recipient cornea, recipient endothelium and anterior chamber remain intact. In condition damaging deeper layers both epithelium and deep stroma are replaced with healthy donor tissue (deep anterior lamellar keratoplasty DALK) [2,16,19,23]. DALK we can divide to pre-descemetic DALK (pdDALK) (10% of stroma remains on the DM) and maximum depth/descemetic DALK (MD-DALK/dDALK) (completely bare DM) [2,24]. The visual results improve with deeper and smoother tissue dissection during ALK. That is why MD/dDALK have smoother stromal bed and visual outcomes are better with less interface haze or residual scarring. But on the other hand, it remains very difficult technique with the high risk of inadvertent rupture of the DM and consequently to conversion to PK [2,4-26].

Within last years new technologies have been implemented to lamellar surgery: automated microkeratome and femtosecond laser machine.

The microkeratome-assisted ALK (automated lamellar therapeutic keratoplasty) enables to perform automated lamellar dissection of both donor and recipient cornea. Depending on the head size variable depths of dissection can be selected. The surface of dissection is smoother and enhanced compared to manual one. It is used for treatment anterior and midstromal changes [2,27].

Femtosecond laser - assisted ALK (Femto/FS ALK/FALK) allows to dissect corneal stroma as close as 100 microns from the anterior chamber. It is useful in pre-descemetic ALK. Studies on assessing this technology in deeper lamellar ablations are ongoing. In combination with intra-operative OCT, it helps in a more accurate analysis of the depth of opacity and preparation of customized grafts [2,27].

Bowman's layer (BL) of the cornea is the most anterior, compact collagen of the stroma. It is responsible for biomechanical strength and shape to the anterior cornea. In some diseases BL thins and disrupts, weakening the cornea. Recently the BL transplantations (BLT) are performed. The technique does not carry any risk of allograft rejection because no biological material is used. BLT leads to decrease in keratometry values, improved corneal thickness, better tolerance of contact lens and visual acuity [28-31].

Posterior lamellar keratoplasty (PLK)/endothelial keratoplasty (ED)

PLK/EK is the procedure of choice for endothelial problems (e.g. Fuchs endothelial dystrophy, posterior polymorphous dystrophy, iridocorneal endothelial syndrome, failed PK, bullous keratopathy) in corneas with healthy anterior surface and stroma. Compared to PK, EK introduces fewer foreign antigens, improves vision regeneration and surgery results, minimizes the risk of astigmatism and results in better stability of the globe [2,23,28].

Nowadays, the most commonly used methods of EK include DMEK, DSEK, and DSAEK, but performed may also be: deep lamellar endothelial keratoplasty (DLEK), pre-descemet endothelial keratoplasty, descemetorhexis without endothelial keratoplasty, descemet stripping only, and descemet membrane endothelial transfer [17,20].

DSEK was introduced in the year 2004, which led to rapid progress in corneal transplantation. During this procedure, specific strippers are used to peel off the patient's DM and then the diseased endothelium and DM are replaced with the donor's posterior corneal stroma, DM, and endothelium [20,32]. Over time, DSEK became an increasingly popular surgical treatment for corneal endothelial diseases, due to easy preparation and manipulation of the donor's cornea and a short learning curve, which resulted in good and reproducible clinical results [33]. However, it should be remembered that postoperative visual quality may be reduced due to the presence of additional stroma layers transplanted during the DSEK procedure [34].

DSAEK and DSEK procedures are very similar to each other, and the main difference between them is that in DSAEK, the tissues are dissected with a mechanical microkeratome, used to separate a thin layer of tissue from the back of the donor's cornea [34]. A microkeratome enables greater precision by cutting with an oscillating blade [35]. This is a significant advantage over DSEK because every contact of the endothelium with surgical instruments can damage it, and, as a result, damage the graft, which can be effectively limited when using a microkeratome. DSAEK was the most frequently performed technique in Europe in the year 2021 and accounted for approximately 46% of the keratoplasties performed [36]. There are four general categories of graft thickness: nano-thin DSAEK (15 - 49 μm), ultra-thin DSAEK (50 - 99 μm), thin DSAEK (100 - 149 μm), and conventional DSAEK (150 - 250 μm). The nano-thin DSAEK ensures fastest visual recovery [37]. Ultrathin DSAEK enables better vision results compared to the standard DSAEK without increasing the risk of postoperative complications [34].

DMEK is one of the most modern keratoplasty techniques, and in Europe, in the year 2021, it accounted for 9% of all keratoplasty procedures performed [36]. Introduced in 2006 by Melles, the procedure showed very promising results [38]. The grafted material used in this technique does not contain the corneal stroma, but only the endothelium and DM, which distinguishes it from DSAEK and makes it a pure anatomical substitution of the diseased endothelial tissue [39,40. The graft is prepared by descemetorexia on the donor's eye and is approximately 10 - 15 μm thin [20]. The graft placed in the anterior chamber can be applied to the stroma by injecting an air bubble into the chamber [39]. The DMEK procedure is superior to the DSAEK in the aspects of faster visual recovery, better visual quality, and better visual results [40]. Moreover, the choice of the DMEK procedure increased the patients' satisfaction with the results of the surgery [41]. The rejection rate for DMEK ranges from 0% to 7%, which is significantly lower than the DSAEK and PK rejection rates, which are between 10% and 22% [40]. Although the loss of endothelial cells in the first 6 months is greater with DMEK than with DSAEK, studies show that long-term (5 years) cell loss is comparable for the two procedures [40]. However, despite the significant advantages of DMEK over other techniques, it is still used less frequently than DSAEK due to the technical difficulties of transplanting such a thin graft [39]. DMEK can be combined with phacoemulsification and implantation of an intraocular lens, forming the so-called triple procedure, which is a safe and cost-effective solution for patients qualified for DMEK with coexisting cataracts, or at high risk of its occurrence. It should be remembered that the DMEK procedure itself accelerates the formation of cataracts, so by using the triple procedure, you can avoid the need for reoperation, especially in people over 50. This procedure allows for obtaining excellent refractive outcomes [41,42].

DLEK was performed for the first time in the year 2000 by Mark Terry. This technique involves dissection and formation of a lamellar pocket over the entire area of the cornea, followed by removal of the recipient's posterior lamellae and implantation of hand-prepared donor tissues containing stroma, DM, and endothelium. Air bubble injection into the anterior chamber is used to fix the tissues together. The use of sutures is avoided and the complications resulting from open-globe surgery are limited. However, the duration and complexity of this method and - in particular - the need for manual preparation of tissues, limited its use, despite obtaining better visual outcomes compared to PK [40].

Additional tools used for better keratoplasty results

Modern keratoplasty can be assisted by specific tools, which enable better results of surgery and include optical coherence tomography (OCT) and femtosecond lasers (FS).

OCT is a non-invasive diagnostic technique with an accuracy of at least 10 - 15 microns, which relies on the use of interferometry [43]. It is widely used in ophthalmology and supports preoperative diagnostics, intraoperative decision-making, and postoperative monitoring. Intraoperative OCT (iOCT) provides dynamic real-time feedback, which is used during crucial surgical steps [43]. The iOCT used during DALK helps to confirm the presence of bubbles during stroma dissection. During PK, it enables the assessment of the graft-host relationship, allowing the surgeon to refrain from prolonged pressure on the globe after the transplant has been inserted [4,45]. A

microscope-integrated intraoperative OCT is a useful addition to the standard surgical microscope, especially for operating patients with clouded corneas or in the case of novel lamellar transplantations procedures [46]. The landmark DISCOVER study found that the use of iOCT changes the surgeon's decision in 38% of cases during lamellar keratoplasty [47]. However, the use of iOCT requires the surgery to be stopped to capture the images, which prolongs the procedure [44,48].

FS is an infrared laser that emits light pulses of short duration at a 1053 nm wavelength and works by producing photodisruption or photoionization of the optically transparent tissue. FS is mainly used in corneal surgery, keratoplasty, refractive procedures, and cataract surgery [49,50]. During DALK, FS can be used to accurately cut tissues, which results in lower astigmatism, better wound healing, and more precise matching of the donor to the recipient [51]. The procedures performed with the use of FS are characterized by accuracy, safety, and repeatability.

Future trends in endothelial keratoplasty

Possibilities in EK evolved over last years but there are still limitations. The most important the luck of enough donor tissue is. As statistic shows there is only 1 cornea available for potentially 70 recipients [52]. That is why new, alternative methods in corneal endothelial disease treatment are sought.

Partial DMEK

To make use of available donor corneas the trials of using partial DMEK were performed. During surgery half (hemi-DMEK) or quarter (quarter-DMEK) sized grafts were inserted after circular Descemetorhexis in patients with Fuchs' endothelial cell dystrophy (FECD). After 6 months in both studies BCVA of treated eyes was 20/40 or better and central corneas thickness (CCT) was reduced, endothelial cells filled in denuded areas [53,54]. Authors suggest the corneal endothelium has some regenerative capacity *in vivo*. It is not clear if regeneration is connected with the donor or the recipient endothelium.

Descemet membrane endothelial transfer (DMET)

In literature we can find some studies on using "free-floating" Descemet roll, sutured to the corneal incision to establish area of contact. In patients witch FECD the results of DMET were improved (thinner CCT, increase in endothelial cell density), unfortunately in patients with bullous keratopathy no improvement was observed [11,55]. That suggests the necessity of relatively healthy peripheral recipient endothelium though it doesn't rule out contribution from the donor endothelial cells toward reendothelialization [11].

Descemetorhexis stripping without endothelial keratoplasty (DWEK)

After intentional or accidental descemotorhexis the peripheral cornea is able to repopulate damaged area. In some studies conditions for successful DWEK were analysed: healthy peripheral endothelium and small diameter of descemetorhexis are the key to success. The migratory and/or proliferative capacity of the peripheral endothelium depends on patients age, activity of the disease, type and severity of the disease, genetic variations of the FECD [11,56,57]. Wherefore DWEK is worth considering in patients with central corneal guttae in FECD. It doesn't need donor tissue, rejection isn't induced, topical corticosteroid therapy is shorter and the possibility of EK persists [11,58].

Other therapeutic possibilities

New trends in corneal diseases treatment focused on peripheral endothelium stimulation, cell therapy, tissue engineered grafts and stem cells [11].

Stimulation of the peripheral endothelium was achieved with Rho-associated coiled-coil serine/threonine protein kinase (ROCK) inhibitor. In culture ROCK inhibitor Y-27632 improved corneal cell proliferation, adhesion and decreased apoptosis. In animals, it enhanced

wound healing and endothelial proliferation. In humans with corneal oedema in some cases with FECD improvement was observed. But the peripheral endothelium was healthy [11,58-61]. Those studies suggest that endothelial wound healing can be supported by ROCK inhibitor Y-27632 when the peripheral endothelium is proper [11,60]. Another indication for ROCK inhibitors is cell therapy. Cultivated human corneal endothelial cells suffer from the poor attachment to the cornea when they are injected. In the study they were injected in Y-27632 containing medium, patient spent 3 hours in prone position for cells to attach. In further observation central endothelial density, CCT, BCVA improved. No inflammation or immunogenic reaction were observed [11,61-63].

In those cases with DM problems: irregularities, ruptures, isolated detachment or detachment associated with ruptures (FECD, bullous keratopathy) replacement of DM may be required to enable corneal endothelial cell migration [11,63-65]. Tissue engineering keratoplasty requires transplantation of a thin (100 μm) layer of human stroma and DM with some endothelial cells. In animals it has shown promising results [11,66].

Human endothelial cells could be used for cell therapy but reprogramming of stem cells (SCs) from other sources are sought. Adult SCs for the corneal endothelium are located at the peripheral part of the cornea (so called "transition zone") and might be dual stem cells for both corneal endothelium and trabecular meshwork. Those cells seem to be an important source for corneal endothelium [11,67-70].

Conclusion

Keratoplasty remains the primary option for patients with corneal disorders leading to vision loss. Surgical procedures evolved from full thickness corneal transplantation to lamellar techniques. It is favorable for faster visual recovery and improve visual outcomes. Moreover, shortage of donor cornea is responsible for development of alternative forms of treatment. Future choice of the method will be dependent on recipients age, presence/absence of endothelial disease, type and severity of the disease. Disorders that damage peripheral endothelium will be treated with transplantation of cells/tissues in conjunction with ROCK inhibitors or a traditional grafts. In diseases with spared peripheral endothelium hemi-/quarter-DMEK, DMET, DWEK, ROCK inhibitors or combined DWEK with ROCK inhibitors could be used. Further studies are necessary to clarify patients selection criteria for each kind of treatment.

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Volume 15 Issue 5 May 2024