

State of the Art of Corneal Transplantation



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Abstract

Corneal transplantation has undergone important advances in the last 20 years. Penetrant keratoplasty has been the dominant procedure for more than half a century and it successfully covers most causes of corneal blindness. The adoption of newer forms of lamellar transplantation surgery has been an essential change in recent years. Endothelial keratoplasty has resulted in more rapid and predictable visual outcomes. Deep anterior lamellar keratoplasty is replacing penetrant keratoplasty for diseases affecting the stromal corneal layers while avoiding the risk of endothelial rejection. Other emerging therapies like ocular surface reconstruction, femtosecond-laser assisted surgery, bioengineered corneas and medical treatment for endothelial disease are also likely to play a part in the future.

Keywords: Descemet Membrane Endothelial Keratoplasty (DMEK), Descemet Stripping Endothelial Keratoplasty (DSAEK), Deep Anterior Lamellar Keratoplasty (DALK), Penetrating Keratoplasty (PKP), Keratoconus

Abbreviations: PKP: Penetrant Keratoplasty; BCVA: Best Corrected Visual Acuity; ALK: Anterior Lamellar Keratoplasty; DALK: Deep Anterior Lamellar Keratoplasty; EK: Endothelial Keratoplasty; DSAEK: Descemet Stripping Automated Endothelial Keratoplasty; UT-DSAEK: Ultrathin-Descemet Stripping Automated Endothelial Keratoplasty; DMEK: Descemet Membrane Endothelial keratoplasty; IOCT: Intra-operative Optical Coherence Tomography

Introduction

Corneal blindness may be due to numerous dystrophic, degenerative, infectious, inflammatory or traumatic conditions [1,2]. Once corneal transparency is lost, transplantation is the current therapeutic intervention of choice with the aim of improving visual acuity. Corneal transplantation or keratoplasty is the most successful allogenic transplant worldwide and also the most frequently performed [3,4]. It has evolved from the replacement of full-thickness cornea to selective layers of it. This has been possible due to the improvement in understanding of corneal anatomy, advanced surgical techniques, instruments and microscopes.

Cornea: Structure and Function

The cornea is a transparent and avascular structure that provides protective and refractive functions. It forms, together with the sclera, the outer shell of the eyeball. It consists of six discernible layers. The anterior-most is epithelium consisting of four to six layers of stratified, non-keratinizing squamous cells [5]. Its

regeneration is enabled by limbal epithelial stem cells, a group of cells that accomplish three characteristics: lack of differentiation, slow-cycling and high proliferative activity [6]. These cells reside in the palisades of Vogt, a radially orientated fibrovascular ridge and when activated they proliferate, differentiate and migrate to the central cornea [7].

Beneath the corneal epithelium, the Bowman's layer is acellular, and it does not regenerate. The third layer is the stroma, which constitutes a major part of the cornea and contains proteoglycans and keratocytes surrounding collagen lamellae. Posterior to the stroma, the Descemet membrane provides a base for endothelial cells whose main role is maintaining corneal transparency.

Evolution and Types of Corneal Transplantation

Eduard Zirm performed the first successful corneal transplant in 1905 [8]. However, penetrant keratoplasty was not established as the mainstay of corneal transplantation until mid-1950s, when surgical improvement was achieved, and topical steroids were introduced. In the last 20 years, the concept of selective lamellar

keratoplasty has emerged, leading to fundamental changes in this procedure [3,4]. Keratoplasty can be performed for various aims and is classified as therapeutic, optical or tectonic. Therapeutic is done to remove the infective portion of the cornea. Optical restores vision and tectonic provides support and maintains the integrity of the globe. There are different clinical and anatomical parameters that need to be evaluated before planning the type of corneal transplantation. The selective replacement of the damaged part has many advantages compared to penetrating keratoplasty in terms of intraoperative complications and postoperative graft rejection.

Penetrant Keratoplasty (PKP)

Until recently, PKP was the most frequently performed corneal transplantation technique all around the world. Nowadays, PKP has limited its use in diseases where the benefit of replacing the whole cornea, compared with lamellar keratoplasty, will provide the best optical or therapeutic result [9]. It is mainly done in corneal decompensation with anterior stromal scarring, corneal dystrophies with endothelial involvement or in full thickness opacities due to healed keratitis or traumatic scars. Common indications also include tectonic grafts for acute ulcerating or infectious keratitis, previous graft failure or an advanced keratoconus not suitable for deep anterior lamellar keratoplasty [3]. PKP is an effective and successful treatment for improving visual function. Some studies have demonstrated a survival rate higher than 70% at 10 years follow-up [10-12] and others 90% at 5 years and 82% at 10 years [13]. Surgical indication plays a major role in influencing the graft survival rate, keratoconus patients achieving the best long-term results [14]. In developing countries, graft survival rate was lower than in many western countries. This is probably due to the higher percentage of patients with high-risk indications, lower quality of donor corneas and reduced access to medicines and expert care [15,16].

There have been several studies in order to evaluate the visual outcomes after PKP. Beckingsale et al described half of patients with a visual acuity better than 6/18 [17]. Paglen et al and Pramanik et al reported a best corrected visual acuity (BCVA) of more than 6/12 in 73% of patients at more than 10 years of follow up [14,18]. However, only 48% of patients achieved 6/12 at 5 years in a case-series by Rahman et al [19]. Brahma et al did a study on 18 patients with keratoconus to evaluate the visual outcome after PKP and found an improvement in visual acuity, contrast sensitivity and glare [20].

Graft rejection is the most common complication after PKP [21]. Rahman et al reported an incidence of 21% of graft rejection episodes, of which 7.4% could not be solved and went into graft failure [19]. Pramanik et al found early graft failure to be rare [14] and Olson et al reported allograft rejection in 31% of cases but none progressed to graft failure [22]. Even in the absence of rejection, donor corneal endothelial cell loss is progressive for 10

years post-PKP, which causes late failure of the graft [23]. In fact, the rate of endothelial cell loss was reported to be about 33% to 40% within the first 2 years [24-26].

The incidence of post-PKP glaucoma is estimated to be 21.5% [27]. It is caused by surgical changes of the anterior chamber angle and/or corticosteroid induced IOP elevation. Its treatment with topical drops and/or surgery is associated with graft failure as well [28]. Re-epithelization after PKP is altered due to the use of topical steroids and corneal denervation. Ocular surface complications constitute 18% of graft failure. Microbial keratitis after PKP is frequently caused by gram-positive organisms. The prolonged use of corticosteroids and the presence of loose sutures increased the risk of infection, and more than a half of the grafts affected progress to failure [29].

Anterior Lamellar Keratoplasty (ALK)

The lost technique of ALK was brought back in 1948 by Paufigue et al [30] and microkeratome was introduced by Barraquer in 1964 [31]. Microkeratome was able to give a more regular cut and thus avoid the poor visual gain because of the irregular interface. Kaufman modified the technique and introduced epikeratophakia, which described the use of lamellar graft without the need to perform host corneal dissection [32]. ALK has come a long way from manual dissection to microkeratome assisted and now to femtosecond laser-assisted keratoplasty. There are a variety of techniques described for ALK depending upon the depth of corneal opacity.

Deep Anterior Lamellar Keratoplasty (DALK)

DALK has become a popular surgical technique to treat stromal diseases, reducing the risk of endothelial graft rejection. The most challenging step of this surgery remains the separation of corneal stroma from Descemet membrane. The most widely used technique is "Big Bubble", where air is injected into the deep stroma and cleaves Descemet membrane from the rest of the host tissue [33]. Finally, a donor corneal bottom with no Descemet membrane is then sutured to the host cornea. Keratoconus is the main indication for DALK. It also offers a treatment for infectious keratitis, corneal dystrophies and stromal scarring.

Long term follow-up data report a mean BCVA of 6/7.5 at 4 to 6 years follow-up after DALK procedure and 29% of patients with BCVA of 6/6 at 5 years [34,35]. There are several studies comparing DALK and PKP in terms of visual outcome. Recently, a systematic review by Henein and Navanaty demonstrated strong evidence of superior post-operative refractive astigmatism following DALK [36]. However, a recent meta-analysis by Song et al concluded that there was no significant difference in postoperative astigmatism and best corrected visual acuity in comparison to PKP, but spherical equivalents were greater in DALK [37].

As the host endothelial cells are preserved in DALK,

endothelial immune rejection cannot occur, although stromal and epithelial rejections are still possible. In one study reported by Feizi et al [38], the rate of subepithelial and stromal rejections are 10.9% and 3.1 % respectively. The systematic review made by Keane et al [39] and the recent Song et al meta-analysis [37], conclude that graft rejection episodes were more likely to occur in PKP than in DALK. Moreover, comparative studies showed lower levels of endothelial cell loss after DALK compared to PKP at different times of post-surgery follow-up [40]. In contrast to PKP, endothelial cells seem to decrease in the immediate postoperative period after DALK but tended to stabilize at around 6 months to 1 year and remain stable for 10 years after DALK [35]. Then late corneal failure due to endothelial decay is less likely after DALK.

Glaucoma was observed to be less than 5% after DALK, much lower compared to PK because the distortion of the iridocorneal angle is diminished in DALK [41]. There is a group of complications unique to DALK. Intraoperative micro-perforations may occur when trying to split Descemet membrane (DM) from the stroma. Those of 1 mm or less can be managed intraoperatively and does not prevent the conversion to PKP [42]. In cases of macroperforations, conversion is usually required during surgery. This happens in approximately 60% of cases, according to a study performed in 2010 [43]. As the use of DALK gained popularity, the rate of complications reduced to 16.2 % to 20.7% [44-46].

Endothelial Keratoplasty (EK)

Descemet Stripping Automated Endothelial Keratoplasty (DSAEK)

Melles et al used a small, self-sealing 5-mm tunnel to perform a novel step which was called descemetorhexis, which is based in the replacement of pathological DM and endothelium from the recipient cornea by a “taco-folded” donor tissue with endothelium, DM and a layer of stroma adhered to the recipient cornea by air injection [47]. This technique was called Descemet stripping endothelial keratoplasty and evolved to DSAEK when Gorovoy started with the use of an automated microkeratome [48]. In DSAEK only the posterior lamella is replaced. Some authors observed that thinner grafts led to better BVCA due to less change in the relationship between anterior and posterior corneal curvatures of the recipient cornea and based on this principle Ultrathin-DSAEK (UT-DSAEK) was developed, which used grafts of half of the conventional graft thickness, of about 100 μm [49,50]. Then, this type of corneal transplantation gives the patient the benefit of faster and early visual recovery. Suture-related problems are also reduced.

DSAEK provides predictable and superior visual outcomes in comparison to PKP [51]. The average visual acuity is about 20/40 as described in different studies [52-54]. Van Rooij et al [55] found that BCVA of DSAEK patients was significantly better than those who had PK at 2-year follow-up and Woo et al reported 23.6% of the patients had BCVA 6/7.5 or better 3 years after DSAEK. Significantly less postoperative astigmatism was

observed in DSAEK but spherical equivalent was not significantly different. As for the complications, graft failure has been reported to be approximately 10 per cent [56]. Most single centre studies showed a graft survival rate of 93% or above at 5 years after DSAEK [57,58]. A decrease of 36% in endothelial cell density after DSAEK has been observed by Terry et al [59], similar results to the ones documented by Price and Price [60]. The initial endothelial cell loss in DSAEK was reported to be higher than in PKP, followed by constant low-grade cell loss at a rate of 11.7% per year over 5 years [57]. The latest modification of this surgery, UT-DSAEK, demonstrated a survival rate of 94.5% at 5 years, comparable to conventional DSAEK [61].

Immunological graft rejection rates in DSAEK are much lower than PKP as the lesser amount of corneal tissue is transplanted as compared to the full thickness graft. Different authors have reported similar rejection rates. Price et al [54] published a 5-year graft rejection rate of 7.9% after DSAEK, Jordan et al [62] found a rate of 9 per cent in a study with almost 600 patients, while Madi et al [62] reported on 3.9% of rejection episode after UT-DSAEK.

Graft detachment is the most common complication after DSAEK, which requires rebubbling in the immediate to early postoperative period. While most of them are recognized by corneal oedema or direct visualization of a double anterior chamber on slit-lamp bio microscopy, the anterior segment coherence constitutes the most effective way of confirming detachments. Its rate of occurrence is between 0.7% and 14.8%, according to recent literature reports [52,60].

Descemet Membrane Endothelial Keratoplasty (DMEK)

After the introduction of DSAEK, Melles et al described a new endothelial graft of 10-15 μm of tissue consisting of only DM and endothelium obtained by descemetorhexis, called DMEK [63]. It provides faster visual rehabilitation, better visual outcomes and lower immune rejection rates than DSAEK [64,65]. One of the most difficult steps in this surgery is the orientation of the graft. Intra-operative optical coherence tomography (IOCT), stamping, staining or tearing the lenticule may help us for correct position. DMEK enhances visual outcome compared to DSAEK due to a reduced interface effect. Several studies have reported 32-85% of patients achieving BVCA of 6/7.5 or better at 6 months after DMEK and significantly better BCVA compared to PKP, DSAEK and even UT-DSAEK at 1 year [65]. 5-year survival rates are between 90 to 95% in eyes that underwent DMEK. It diminishes in the presence of glaucoma drainage device implant, prior trauma, or previous failed keratoplasty. Graft rejection rates are the best in corneal transplantation. They are about 0.7-1.5%.

Recent Advancements

Several techniques have helped to improve the outcomes of keratoplasty, being the intra-operative optical coherence tomography, the femtosecond laser and bioengineered corneas the most important ones.

Intra-operative Optical Coherence Tomography (iOCT)

iOCT provides continuous details of the surgery, and it is very useful in lamellar keratoplasty such as DALK, DSAEK or DMEK. It measures the central corneal thickness of both the donor and the host cornea, an important parameter for deciding the blade size of the microkeratome for dissection. Moreover, it acts as a tool to minimize complications. In DALK procedure it guides every step of the surgery starting from depth of trephination to graft-host apposition [66]. In cases of DSAEK and DMEK, it helps in identifying the right orientation of graft and ensures the adequate apposition of host and donor cornea at the end of the surgery [67,68].

Femtosecond Laser-Assisted Lamellar Keratoplasty

Full thickness PKP as well as lamellar keratoplasty can be performed using femtosecond laser. It leads to better incision geometry, an accurate graft-host apposition and better wound healing, decreasing the risk for graft dehiscence. It is also associated with less endothelial cell loss at the margin of the graft [69,70].

Bioengineered Corneas

They are designed to replace the full or part of the diseased cornea and range from keratoprosthesis to the recent development of tissue-engineered hydrogels, which help in the regeneration of host tissues [71]. There are also lenticules that can be used to correct the refractive errors by their implantation into the cornea.

Discussion

Corneal transplantation remains the only available and effective therapy of corneal blindness worldwide and there has been no turning back since the first corneal transplantation surgery was performed in Europe in 1905 [8]. More than 95 per cent of corneal tissues were used for PKP over a period from 1980 to 2004 and the major indications were pseudophakic bullous keratopathy, keratoconus, Fuchs' endothelial corneal dystrophy and failed grafts [72]. Even though the number of PKP remained the same, the number of DMEK and DSAEK increased significantly from 2008 to 2016. DMEK is well-established and was first reported in 2006 by Melles [73,74], providing several advantages over PK based on its minimal invasiveness, lower intraoperative risks and minimal refractive shift with fast visual recovery [75-77]. Many more patients with endothelial disorders have benefited from the high success of the DMEK in recent years, being treated with keratoplasties earlier than before. Corneas that had been considered not suitable for PKP are now qualified for DMEK. By contrast, Afshari et al reported in 2006 that eyes with Fuchs' dystrophy and a visual acuity better than 0.5 were not still candidates for a keratoplasty [78].

In another sense, DMEK is a sophisticated surgery, presenting the challenges of stripping the donor graft and then manipulate it after injection into the anterior chamber to identify the endothelial

layer for correct orientation. All these procedures have to be carried out without touching the Descemet membrane. Novel surgeons are sometimes reluctant to use the DMEK procedure because of the lack of donor corneas in some hospitals and the higher probability of graft preparation failure compared to DSAEK. However, experienced ophthalmologists tend to use almost always DMEK even in difficult surgical scenarios such as glaucoma drainage devices or previous failed keratoplasties due to DMEK better BCVA results comparing to DSAEK. As one important factor for the outcome of DMEK is the waiting time until surgery [79,80], pressure on eye banks to procure more suitable corneal grafts has been growing enormously in the last years. The knowledge and awareness of corneal donation through education is important to gain more corneal donors to help visually impaired patients in sufficient number with corneal transplantations.

Regarding anterior lamellar keratoplasties, the moderate introduction of DALK is probably due to its longer surgical time and higher technical challenge with the big bubble, the introduction of collagen crosslinking in patients with progressive keratoconus [81], a lower number of patients with the indication for DALK and, consequently, a slower and more difficult learning curve for the surgeon. There are no significant differences in BCVA comparing to PKP in recent studies [37] but graft rejection episodes are less likely to occur [37,39] so DALK should be the elective surgery in corneal anterior pathologies when the descemetic and endothelial layers are respected.

Conclusion

Nowadays, conventional PKP procedures are being replaced by selective lamellar keratoplasty, such as endothelial and deep anterior lamellar keratoplasty. The use of the iOCT and the femtosecond laser, together with the improvement in instrumentation and engineering devices help to reach better anatomical and functional results, reducing complications during surgery. Further developments in artificial cornea technology, endothelial therapies and stem-cell transplants are on the horizon in this fast-evolving ophthalmic field.

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