

Adult keratoplasty: has the prognosis improved in the last 25 years?

Francis W. Price · Marianne O. Price

Received: 8 February 2007 / Accepted: 11 December 2007 / Published online: 15 January 2008
© Springer Science+Business Media B.V. 2007

Abstract Adult keratoplasty outcomes have significantly improved in the past quarter century as a result of new pharmaceuticals, advanced surgical devices, better understanding of what causes graft failure, and targeted techniques for selective replacement of only diseased corneal layers. Prevention and treatment of graft rejection, which has long been a leading cause of graft failure, has improved with the development of innovative topical and systemic immuno-suppressants. New methods for preventing and treating ocular surface complications have been devised, and limbal stem cell grafts have significantly improved management of severe ocular surface disease. Improved intraocular lens designs cause less corneal damage and have increased corneal graft survival. Non-steroidal anti-inflammatory (NSAID) eyedrops and more complete vitrectomies have reduced the incidence of chronic cystoid macular edema, which could prevent eyes with clear grafts from regaining useful vision. Patients with keratoconus or corneal scars can now benefit from advanced anterior lamellar keratoplasty techniques, which reduce the risk of immunologic rejection and endothelial failure, while matching the visual outcomes

achieved with penetrating keratoplasty. Patients with endothelial dysfunction can now benefit from advanced endothelial keratoplasty techniques, which provide more rapid visual recovery, minimize induced astigmatism and ocular surface problems, and virtually eliminate the risk of wound rupture from minor trauma. Finally, femtosecond lasers now provide transplant surgeons with a precise tool for creating complex, interlocking corneal incisions that may facilitate wound healing.

Keywords Penetrating keratoplasty · Endothelial keratoplasty · Posterior lamellar keratoplasty · Anterior lamellar keratoplasty · Limbal stem cell graft · Femtosecond laser

Introduction

Recent developments in keratoplasty techniques, including limbal stem cell grafts, anterior lamellar keratoplasty (ALK), endothelial keratoplasty (EK), and femtosecond laser contoured incisions, are significantly improving keratoplasty outcomes. Beginning long before the burgeoning use of specialized keratoplasty techniques, advances in drugs, devices, and treatment regimens were gradually improving outcomes, helping to set the stage for what appears to be an exciting time for corneal

F. W. Price · M. O. Price (✉)
Price Vision Group, 9002 North Meridian Street, Suite
100, Indianapolis, IN 46260, USA
e-mail: mprice@cornea.org

transplants, as we celebrate in this special keratoplasty issue.

Twenty-five years ago we had the operating microscope, small monofilament sutures, and topical corticosteroid drops. Since then, new treatments for graft rejection and ocular surface disease have increased graft survival rates. Visual outcomes have also improved with better understanding of lens implants, methods to prevent or treat cystoid macular edema (CME), and new treatments for glaucoma. In addition, the indications for successful corneal transplantation are rapidly expanding with the refinement of new keratoplasty techniques. Let's consider each of these advances in greater detail.

Graft rejection

While topical corticosteroids remain the mainstay for prevention and treatment of immunologic corneal graft rejections [1, 2], formulated cyclosporine A and tacrolimus now provide additional topical treatment options, which can be particularly helpful in eyes susceptible to steroid-responsive intraocular pressure (IOP) increase [3–7]. High-risk eyes with a history of immunologic rejection can also be managed with systemic immunosuppression, which has improved dramatically with new medications including mycophenolate mofetil, cyclosporine A, and tacrolimus [8–10]. In addition, an investigational slow-release drug implant now provides a means for achieving significantly higher local concentration of cyclosporine A in transplanted eyes, compared with levels achieved by either topical or systemic delivery.

Ocular surface problems

Standard penetrating keratoplasty (PKP) cuts the corneal nerves, reducing the tendency to blink and produce tears, so PKP eyes are susceptible to exposure and ulceration. The risk of graft failure from ocular surface disease is highest during the first year after a PKP, while the nerves regenerate and sutures are in place [11]. The risk of graft failure from ocular surface problems can now be reduced by aggressive treatment with ocular lubricants, bandage soft contact lenses, lateral tarsoraphies, and topical cyclosporine A. Twenty-five years ago, the first non-

preserved artificial tears were just being introduced. Now we have a whole host of non-preserved, or less toxically preserved ocular lubricants, which help maintain the ocular surface in grafted eyes. The need for corneal sutures that stay in place for months to secure the PKP incision can contribute to ocular surface problems as well, because the sutures can provide a route for infection as they loosen. In fact, suture-related infections may still be one of the most common problems with graft survival in less developed areas of the world, where it can be difficult for patients to obtain quick follow-up when sutures loosen and become irritated. New keratoplasty techniques can minimize or eliminate the need for sutures and thereby prevent suture-related complications.

Glaucoma

Glaucoma has long been recognized as an important factor in corneal graft survival [12, 13]. An analysis of 4,000 grafts from our practice showed that preexisting use of glaucoma medications increased the risk of all three leading causes of graft failure: ocular surface disease, immunologic graft rejection, and endothelial failure without any history of immunologic graft reactions [14]. High intraocular pressure not only damages the optic nerve causing visual loss, it may also increase the rate of endothelial cell attrition [15].

In the last 25 years, more effective pressure control has become possible with the development of tube shunts and various topical medications, including beta-blockers, anticholinesterase agents, carbonic anhydrase inhibitors, and prostaglandin analogues [16]. Younger surgeons probably cannot imagine treating glaucoma without these agents, but 25 years ago, beta-blockers were just being introduced.

Studies suggest that chronic use of glaucoma medications containing benzalkonium chloride (BAK) preservative can lead to corneal and conjunctival inflammation [17, 18], which may cause endothelial damage and incite immunologic graft reactions, so other less toxic preservatives are now in use and under development. Shunts have also been associated with increased endothelial cell loss and possibly a higher incidence of immunologic reactions [19–22]. Proper tube placement and use of implants with valves to reduce backflow of inflammatory mediators from the filtering bleb may help reduce

endothelial cell damage and prolong graft survival. Even though use of glaucoma medications or shunts may shorten the life of the graft, this is a worthwhile tradeoff for patients because pressure reduction is essential for preservation of visual potential.

Cataracts and intraocular lenses

Changes in cataract treatment techniques and IOL design/manufacturing have dramatically influenced corneal transplantation. Twenty-five years ago, aphakic and pseudophakic corneal edema were leading indications for adult PKP in the United States [23–25]. At that time, anterior chamber lenses were frequently implanted with cataract surgery. Many, if not all, of these lenses caused chronic inflammation, endothelial damage, and damage to angle structures, leading to peripheral anterior synechiae (PAS), glaucoma, and progressive disfigurement of the iris [26, 27]. Increased use of posterior chamber lenses, elimination of most anterior chamber lens implants, and better lens designs have improved the long-term prognosis for corneal grafts and reduced the overall incidence of aphakic and pseudophakic corneal edema, particularly in developed areas of the world [11, 28].

Cystoid macular edema

During the past quarter century, we have developed a better understanding of what causes chronic inflammation in the eye and devised techniques to help avoid it, such as more complete vitrectomies to remove traction bands to the retina and suture-fixation of posterior chamber lenses in eyes lacking capsular support [29]. Also, non-steroidal anti-inflammatory (NSAID) eyedrops are now available to prevent and treat CME [25, 30]. Before the widespread use of more complete vitrectomies and NSAIDs, chronic CME prevented many eyes with clear grafts from regaining useful vision [29].

Limbal stem cell grafts

Development of limbal stem cell grafting techniques has significantly improved management of severe ocular surface disease [31]. This area was not

thoroughly understood 25 years ago, nor did we have consistently effective systemic immunosuppression for these cases. Use of limbal stem cell grafts to provide a healthy ocular surface allows the surgeon to perform a subsequent PKP and achieve excellent outcomes in eyes that previously had no chance of graft survival because the corneal surface could not be maintained [32].

Anterior lamellar keratoplasty

Improved anterior lamellar keratoplasty techniques are allowing more people with corneal ectasia or stromal scars to have a keratoplasty without the risk of immunologic rejection and endothelial failure. The last 25 years have seen significant improvements in mechanical microkeratomes and accompanying artificial anterior chambers, allowing anterior lamellar grafts to be performed with higher quality dissections [33]. Some surgeons are cutting relatively superficial anterior lamellar grafts with microkeratomes or femtosecond lasers and attaching the donor tissue without sutures, thereby facilitating more rapid visual recovery for the patient. Interface haze can limit visual acuity after ALK, so various deep anterior lamellar keratoplasty (DALK) techniques have been developed, such as peripheral lamellar dissection with central peeling, visco-dissection, and the “big bubble” technique [34, 35]. Although DALK carries the risk of perforation with the subsequent need to convert to a PKP intraoperatively, visual acuity of 20/20 has been attained with methods that expose recipient Descemet’s membrane [36, 37].

Endothelial keratoplasty

Treatment of endothelial dysfunction has been revolutionized by improved endothelial keratoplasty (EK) techniques developed in the last decade. Melles showed that a donor button, consisting of posterior stroma and healthy endothelium, could be implanted into a recipient eye without use of any sutures to hold the donor in place [38–40]. Totally sutureless EK is now routinely performed through a 5-mm or smaller corneal, limbal, or scleral incision, often with topical anesthesia [41, 42]. EK provides: (1) rapid visual recovery, (2) refractive neutral outcomes, (3) reduced

risk of losing the eye to intraoperative suprachoroidal hemorrhage because the small incision is easily closed, and (4) fewer ocular surface problems because corneal innervation is maintained and no sutures are required [42–45]. Probably the single most important reason we began performing EK is because it virtually eliminates the risk of wound rupture from minor trauma. After seeing many young males and older adults lose eyes after traumatic rupture even a decade or more after a standard PKP, EK seemed to provide a welcome improvement in long-term prognosis.

Favorable EK outcomes are causing an increase in the number of transplants for treatment of endothelial dysfunction. Previously, patients with Fuchs' dystrophy or pseudophakic corneal edema tended to postpone or even decline PKP because they did not want to endure the activity restrictions and prolonged recovery period necessitated by the long, full-thickness incision. Some didn't want to risk possible post-PKP anisometropia or irregular astigmatism and the associated necessity for a hard contact lens to achieve best vision. Furthermore, some Fuchs' patients chose not to have their second eye treated after experiencing a PKP on the first eye. In contrast, many Fuchs' patients now request EK for their second eye within a month of having the first eye treated, and they want their first eye treated earlier. They now choose to have EK when glare makes it difficult to drive at night or perform their job, even if their Snellen acuity, as measured in a darkened room, is 20/30 or 20/40 [43]. This significant change in patient preferences is probably the greatest testimony to an improved prognosis for transplant surgery. Overall, adults with endothelial dysfunction are tending to choose earlier treatment, perhaps as much as a decade earlier for Fuchs' corneal dystrophy, and this is already increasing the demand for donor tissue.

Endothelial keratoplasty is also changing treatment of cataracts in patients with endothelial dysfunction. Previously, many Fuchs' patients would plod along with markedly worsening cataracts because they feared that cataract surgery would precipitate corneal decompensation. In fact, cataract surgery was often postponed until after PKP so that it could be used to help address unpredictable PK refractive outcomes. Now, EK has significantly improved visual outcomes and reduced the risks of having a transplant [42, 45]. Also, EK is refractive-neutral and easier to perform

with a deep anterior chamber, so it's preferable to remove the cataract first, and cataract surgeons no longer have to agonize over removing cataracts in those with low cell counts or guttata.

Femtosecond laser-assisted keratoplasty

Use of the femtosecond laser to create complex PKP wound designs is one of the most recent technological advances to impact corneal transplantation [46]. Just as the circular trephine was a major advance compared with free-hand PKP dissections with blades or scissors, the femtosecond laser is ushering in a whole new era in PKP surgery. With the traditional metal or ceramic blades used for corneal surgery, a certain degree of hand-crafting was required to create any complex incision, and a only limited repertoire of incision styles could be even be attempted because of limitations imposed by the trephine dimensions or by the ability of the surgeon to create precisely matched donor and recipient incision contours [47, 48]. In contrast, the femtosecond laser allows the surgeon to consider any imaginable incision shape and to easily match donor and recipient dimensions. Early femtosecond laser-assisted penetrating grafts utilized stepped incisions, with "top hat" (drain plug) or "mushroom" (inverted top hat) shapes, and Z-shaped "zigzag" incisions. The latter could probably not even be created without some type of computer-controlled device, such as the femtosecond laser. We have been doing femtosecond laser-assisted PKPs for over 2 years, and they are already changing the prognosis for patients. Laser-contoured PKP incisions have more wound surface area to better resist rupture, plus the laser seems to induce a fibrotic healing response along the vertical portion of the corneal incision, a feature not seen with traditional blade-cut incisions in non-vascularized corneas. At this time the nature of the enhanced healing response has not been completely elucidated. The laser may create a more textured surface and/or cause keratocyte activation that contributes to healing. In any event, healing appears to be more rapid with laser-contoured grafts; for example, in the first group of treated patients, wound healing and suture removal occurred within 7 months, even in recipients over 80 years of age who were using topical prednisolone acetate 1% four times daily. In contrast, complete wound healing

often takes a year or longer in older patients with traditional PKP incisions.

Femtosecond laser-assisted grafts can also help restore a more normal peripheral corneal topography and thickness to eyes with prior scarring and loss of anterior stromal tissue. The anterior surface of the cornea is applanated prior to the laser treatment, so the complete lamellar dissection component of a top hat-shaped incision occurs at a fixed distance from the anterior surface of the recipient cornea. Placement of the donor “top hat” then lifts the anterior surface of the recipient stepped incision to a uniform level, creating a more consistent ocular surface and facilitating wound closure and suturing in areas where the recipient cornea was previously thinned. Again, these features contribute to better visual recovery and earlier suture removal. Improved outcomes with femtosecond laser-assisted grafts may well increase the demand for transplants in patients who had previously postponed surgery.

Donor tissue

In closing, these advances would not have been as readily available to patients without an ample supply of donor corneas. Improved storage solutions now provide good tissue preservation for up to 2 weeks [49–50], compared with 3 days or less 25 years ago. This facilitates placement and allows tissue to be shipped almost anywhere in the world. The increase in anterior lamellar grafts has also allowed use of donor corneas that do not have sufficient endothelial cell density for PKP. Although the US has traditionally had an adequate supply of donor corneas, many countries have a shortage. To help alleviate this shortfall, several research centers are developing improved artificial corneas as well as cultured epithelial and endothelial cell sheets suitable for transplantation [51–54].

The prognosis for adult penetrating keratoplasty has certainly improved in the last 25 years and seems poised to improve even more rapidly going forward.

References

- Bertelmann E, Reinhard T, Pleyer U (2003) [Current practice of immune prophylaxis and therapy in perforating keratoplasty. A survey of members of the Cornea Section of the German Ophthalmological Society]. *Ophthalmologe* 100:1031–1035
- Price MO, Price FW Jr (2006) Efficacy of topical cyclosporine 0.05% for prevention of cornea transplant rejection episodes. *Ophthalmology* 113:1785–1790
- Perry HD, Donnenfeld ED, Acheampong A et al (1998) Topical Cyclosporine A in the management of postkeratoplasty glaucoma and corticosteroid-induced ocular hypertension (CIOH) and the penetration of topical 0.5% cyclosporine A into the cornea and anterior chamber. *CLAO J* 24:159–165
- Cosar CB, Laibson PR, Cohen EJ, Rapuano CJ (2003) Topical cyclosporine in pediatric keratoplasty. *Eye Contact Lens* 29:103–107
- Belin MW, Bouchard CS, Frantz S, Chmielinska J (1989) Topical cyclosporine in high-risk corneal transplants. *Ophthalmology* 96:1144–1150
- Inoue K, Amano S, Kimura C et al (2000) Long-term effects of topical cyclosporine A treatment after penetrating keratoplasty. *Jpn J Ophthalmol* 44:302–305
- Randleman JB, Stulting RD (2006) Prevention and treatment of corneal graft rejection: current practice patterns 2004. *Cornea* 25:286–290
- Reis A, Reinhard T, Voiculescu A et al (1999) Mycophenolate mofetil versus cyclosporin A in high risk keratoplasty patients: a prospectively randomised clinical trial. *Br J Ophthalmol* 83:1268–1271
- Reinhard T, Reis A, Bohringer D et al (2001) Systemic mycophenolate mofetil in comparison with systemic cyclosporin A in high-risk keratoplasty patients: 3 years' results of a randomized prospective clinical trial. *Graefes Arch Clin Exp Ophthalmol* 239:367–372
- Reinhard T, Mayweg S, Reis A, Sundmacher R (2005) Topical FK506 as immunoprophylaxis after allogeneic penetrating normal-risk keratoplasty: a randomized clinical pilot study. *Transpl Int* 18:193–177
- Thompson RW Jr, Price MO, Bowers PJ, Price FW Jr (2003) Long-term graft survival after penetrating keratoplasty. *Ophthalmology* 110:1396–1402
- Ing JJ, Ing HH, Nelson LR et al (1998) Ten-year postoperative results of penetrating keratoplasty. *Ophthalmology* 105:1855–1865
- Boisjoly HM, Tourigny R, Bazin R et al (1993) Risk factors of corneal graft failure. *Ophthalmology* 100:1728–1735
- Price MO, Thompson RW Jr, Price FW Jr (2003) Risk factors for various causes of failure in initial corneal grafts. *Arch Ophthalmol* 121:1087–1092
- Wilson SE, Kaufman HE (1990) Graft failure after penetrating keratoplasty. *Surv Ophthalmol* 34:325–356
- Lee DA, Higginbotham EJ (2005) Glaucoma and its treatment: a review. *Am J Health Syst Pharm* 62:691–699
- Baudouin C, Pisella PJ, Fillacier K et al (1999) Ocular surface inflammatory changes induced by topical anti-glaucoma drugs: human and animal studies. *Ophthalmology* 106:556–563
- Burstein NL (1980) Corneal cytotoxicity of topically applied drugs, vehicles and preservatives. *Surv Ophthalmol* 25:15–30
- Beebe WE, Starita RJ, Fellman RL et al (1990) The use of Molteno implant and anterior chamber tube shunt to

- encircling band for the treatment of glaucoma in keratoplasty patients. *Ophthalmology* 97:1414–1422
20. McDonnell PJ, Robin JB, Schanzlin DJ et al (1988) Molteno implant for control of glaucoma in eyes after penetrating keratoplasty. *Ophthalmology* 95:364–369
 21. Coleman AL, Mondino BJ, Wilson MR, Casey R (1997) Clinical experience with the Ahmed Glaucoma Valve implant in eyes with prior or concurrent penetrating keratoplasties. *Am J Ophthalmol* 123:54–61
 22. Kwon YH, Taylor JM, Hong S et al (2001) Long-term results of eyes with penetrating keratoplasty and glaucoma drainage tube implant. *Ophthalmology* 108:272–278
 23. Brady SE, Rapuano CJ, Arentsen JJ et al (1989) Clinical indications for and procedures associated with penetrating keratoplasty, 1983–1988. *Am J Ophthalmol* 108:118–122
 24. Robin JB, Gindi JJ, Koh K et al (1986) An update of the indications for penetrating keratoplasty. 1979 through 1983. *Arch Ophthalmol* 104:87–89
 25. Smith RE, McDonald HR, Nesburn AB, Minckler DS (1980) Penetrating keratoplasty: changing indications, 1947 to 1978. *Arch Ophthalmol* 98:1226–1229
 26. Smith PW, Wong SK, Stark WJ et al (1987) Complications of semiflexible, closed-loop anterior chamber intraocular lenses. *Arch Ophthalmol* 105:52–57
 27. Price FW Jr (1988) Factors contributing to corneal decompensation with the Stableflex lens. *J Cataract Refract Surg* 14:53–57
 28. Kang PC, Klintworth GK, Kim T et al (2005) Trends in the indications for penetrating keratoplasty, 1980–2001. *Cornea* 24:801–803
 29. Price FW Jr, Whitson WE (1990) Natural history of cystoid macular edema in pseudophakic bullous keratopathy. *J Cataract Refract Surg* 16:163–169
 30. Solomon KD, Cheetham JK, DeGryse R et al (2001) Topical ketorolac tromethamine 0.5% ophthalmic solution in ocular inflammation after cataract surgery. *Ophthalmology* 108:331–337
 31. Ang LP, Tan DT (2004) Ocular surface stem cells and disease: current concepts and clinical applications. *Ann Acad Med Singapore* 33:576–580
 32. Holland EJ, Djalilian AR, Schwartz GS (2003) Management of aniridic keratopathy with keratolimbal allograft: a limbal stem cell transplantation technique. *Ophthalmology* 110:125–130
 33. Busin M, Zambianchi L, Arffa RC (2005) Microkeratome-assisted lamellar keratoplasty for the surgical treatment of keratoconus. *Ophthalmology* 112:987–997
 34. Melles GR, Remeijer L, Geerards AJ, Beekhuis WH (2000) A quick surgical technique for deep, anterior lamellar keratoplasty using visco-dissection. *Cornea* 19:427–432
 35. Anwar M, Teichmann KD (2002) Big-bubble technique to bare Descemet's membrane in anterior lamellar keratoplasty. *J Cataract Refract Surg* 28:398–403
 36. Anwar M, Teichmann KD (2002) Deep lamellar keratoplasty: surgical techniques for anterior lamellar keratoplasty with and without baring of Descemet's membrane. *Cornea* 21:374–383
 37. Fogla R, Padmanabhan P (2006) Results of deep lamellar keratoplasty using the big-bubble technique in patients with keratoconus. *Am J Ophthalmol* 141:254–259
 38. Melles GR, Eggink FA, Lander F et al (1998) A surgical technique for posterior lamellar keratoplasty. *Cornea* 17:618–626
 39. Melles GR, Lander F, Beekhuis WH et al (1999) Posterior lamellar keratoplasty for a case of pseudophakic bullous keratopathy. *Am J Ophthalmol* 127:340–341
 40. Melles GR, Wijdh RH, Nieuwendaal CP (2004) A technique to excise the Descemet membrane from a recipient cornea (descemetorhexis). *Cornea* 23:286–288
 41. Melles GR, Lander F, Nieuwendaal C (2002) Sutureless, posterior lamellar keratoplasty: a case report of a modified technique. *Cornea* 21:325–327
 42. Price MO, Price FW Jr (2006) Descemet's stripping with endothelial keratoplasty comparative outcomes with microkeratome-dissected and manually dissected donor tissue. *Ophthalmology* 24:24
 43. Price FW Jr, Price MO (2005) Descemet's stripping with endothelial keratoplasty in 50 eyes: a refractive neutral cornea transplant. *J Refract Surg* 21:339–345
 44. Price FW Jr, Price MO (2006) Descemet's stripping with endothelial keratoplasty in 200 eyes: early challenges and techniques to enhance donor adherence. *J Cataract Refract Surg* 32:411–418
 45. Terry MA, Ousley PJ (2005) Deep lamellar endothelial keratoplasty visual acuity, astigmatism, and endothelial survival in a large prospective series. *Ophthalmology* 112:1541–1548
 46. Ignacio TS, Nguyen TB, Chuck RS et al (2006) Top hat wound configuration for penetrating keratoplasty using the femtosecond laser: a laboratory model. *Cornea* 25:336–340
 47. Barraquer J (1965) Special methods in corneal surgery. In King H Jr (ed) *The cornea world congress*. Rutterworths, Washington, DC, pp 586–604
 48. Busin M, Arffa RC (2005) Microkeratome-assisted mushroom keratoplasty with minimal endothelial replacement. *Am J Ophthalmol* 140:138–140
 49. Lindstrom RL, Kaufman HE, Skelnik DL et al (1992) Optisol corneal storage medium. *Am J Ophthalmol* 114:345–356
 50. Wagoner MD, Gonnah ES (2005) Corneal graft survival after prolonged storage in Optisol-GS. *Cornea* 24:976–979
 51. Hicks CR, Crawford GJ, Lou X et al (2003) Corneal replacement using a synthetic hydrogel cornea, AlphaCor: device, preliminary outcomes and complications. *Eye* 17:385–392
 52. Zerbe BL, Belin MW, Ciolino JB (2006) Results from the multicenter Boston Type 1 keratoprosthesis study. *Ophthalmology* 113:1779–1786
 53. Tanioka H, Kawasaki S, Yamasaki K et al (2006) Establishment of a cultivated human conjunctival epithelium as an alternative tissue source for autologous corneal epithelial transplantation. *Invest Ophthalmol Vis Sci* 47:3820–3827
 54. Sumide T, Nishida K, Yamato M et al (2006) Functional human corneal endothelial cell sheets harvested from temperature-responsive culture surfaces. *FASEB J* 20:392–394