Keratoconus: Surgical Interventions

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Keratoconus *(Greek: kerato – horn, cornea; and konos – cone)* is a degenerative, non-inflammatory corneal disorder, characterised by central and para-central stromal thinning and conical ectasia. The management of keratoconus depends on the degree of ectasia. Early cases can be corrected effectively with astigmatic spectacle correction and soft toric contact lenses. As the condition progresses rigid contact lenses become the mainstay of treatment and in the majority of eyes provide satisfactory visual rehabilitation. However, discomfort, poor fitting and patient preference may limit their usage. In addition, corneal scarring associated with advanced ectasia can limit the amount of visual rehabilitation achieved by rigid lenses and there is a body of evidence suggesting that repeated minor trauma caused by the wearing of such lenses may be responsible for the acceleration of the condition.[1]

For these various reasons, between 10-20% of patients with keratoconus progress to a point where rigid lenses no longer provide an adequate management solution and surgical intervention is required for adequate visual rehabilitation.[2,3] Current surgical options are multiple and varied, and include:

- Corneal transplantation
  - Penetrating keratoplasty
  - Deep anterior lamellar keratoplasty
  - Epikeratophakia
- Intra-corneal ring segment insert
  - Intacs
  - Ferrara Rings
- UVA / riboflavin corneal cross linkage (CR3)
- Thermokeratoplasty
- Lenticular refractive surgery
  - Refractive lens exchange with toric intraocular lenses
  - Toric phakic intraocular lenses
- Contraindications to surgery in individuals with pre-existing sub-clinical or overt keratoconus
  - Astigmatic and radial keratotomies
  - Refractive laser surgery

Corneal transplantation

Penetrating keratoplasty

In the past, there has been only one realistic surgical option for keratoconus – a full thickness corneal transplant or penetrating keratoplasty (PK). Indeed, keratoconus is still one of the most common indications for PK accounting for 15-25% of cases.[4,5] Reported risk factors for progression to PK include young age of presentation (less than 20) and keratometry measurements >55 diopters.[6] Being an intraocular procedure with an open eye during much of the surgery and a large surgical wound, the procedure is best conducted under sedation or general anaesthesia. It necessitates an experienced corneal surgeon and viable donor material with satisfactory endothelial cell counts. Visual recovery takes several weeks / months, with full stabilisation not occurring until a year, after which time the sutures can be removed.

As keratoconic eyes do not typically exhibit corneal neovascularisation (unless there is associated atopic disease) and other ocular pathologies (such as glaucoma and intercurrent infection), PK in keratoconus in comparison to other indications is considered low risk in terms of graft rejection, graft survival and postoperative complications. The outcomes of PK for keratoconus are generally very good. Published series report average final best spectacle corrected visual acuities (BSCVA) of 20/25-20/32 with 73-91% of eyes achieving 20/40 or better.[2,3] Long-term studies have documented five and 10-year graft survival rates of over 90% in primary transplants.[7-9]

Immunological graft rejection does occur and has been reported in 4-31% of eyes postoperatively, depending on length of follow-up and the postoperative corticosteroid regimen. Published series suggest that such episodes typically occur in the first year, are usually endothelial and usually comprise single episodes only. They invariably respond to medical management, usually topical and systemic corticosteroids, with few cases resulting in graft failure.[2,3,7-9]

Iatrogenic astigmatism can and does limit visual rehabilitation, with many patients (up to 30%) requiring further keratorefractive surgical procedures such as astigmatic keratotomies or excimer laser techniques.[2,3,9,10] There is little convincing evidence to choose interrupted over continuous suturing for an effect on final sutures-out astigmatism.[11] Postoperative myopic shift does appear to be reduced by lessening the graft host size disparity.[12]

Increased rates of endothelial cell loss have been reported up to 17 years following PK, casting doubt on long-term graft survival.[13-15] Recurrence of keratoconus in the donor has been documented as early as two months and as late as 40 years after PK, possibly due to undetected keratoconic disease in the donor, a systemic condition associated with keratoconus or true recurrence.[14-16] A reported mean time to recurrence of about 18 years has been suggested.[14-16] Late progression of astigmatism has been documented in 70% of eyes after seven years following PK, due to progression of the condition in the host cornea and associated with thinning at the graft host junction.[17]

Deep anterior lamellar keratoplasty

Although outcomes of PK in keratoconic eyes are generally very favourable, graft rejection, induction of vision-limiting astigmatism and late astigmatic progression are not infrequent.[2,3,9-17] In keratoconic eyes the corneal endothelium is usually intact, with good cell counts even after cases of acute hydrops.[18] Whilst corneal stromal rejection episodes can occur,[19] host keratocytes migrate and replace donor keratocytes and most rejection episodes after 12 months are endothelial in origin. For such reasons, there has been a recent trend to perform lamellar keratoplasty (LK) and in particular deep anterior lamellar keratoplasty (DALK) in keratoconic eyes. By allowing replacement of only the diseased stroma, leaving healthy endothelium and not penetrating the ocular wall, LK negates the risk of endothelial rejection, improves postoperative biomechanical corneal stability

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(which may be associated with less wound dehiscence and postoperative astigmatism) and should reduce the risk of postoperative complications associated with intraocular surgeries such as cataract, endophthalmitis, glaucoma, epithelial ingrowth, retinal detachment, cystoid macular oedema and suprachoroidal haemorrhage.

Early results of lamellar procedures, especially mid-lamellar techniques, were rather ambivalent with problems from glare and reduced BSCVA due to interface irregularities and opacities.[20] However, as techniques and experience have developed, outcomes have improved. DALK, which involves removing the pathological stroma down to descemet's membrane and transplanting a full thickness donor button devoid of endothelium and Descemet's membrane, has been shown to result in less host endothelial cell loss, less postoperative intraocular pressure problems, a reduction in rejection episodes and, in some series a reduction of induced astigmatism compared to PK.[21-27] Published series indicate that 80-100% of eyes achieve a BSCVA of 20/40 or better. There appears to be a postoperative endothelial cell loss of approximately 10% during the first six months, which is 50% less than that seen after PK,[28] followed by a physiological rate of cell loss (1-2% per annum) in contrast to PK, where an accelerated continuing loss has been reported (4% per annum).[13-15,18]

Whilst some series have achieved comparable visual outcomes with PK, others have demonstrated that in terms of numbers of eyes achieving a BSCVA of 20/20 or better, penetrating techniques slightly out-perform deep lamellar procedures[22-27] and that although endothelial rejection is negated, stromal rejection can very rarely occur (1-2%).[19] Further refinements in operative techniques, together with improvements in technologies, such as the implementation of femtosecond lasers and mechanical microkeratomes for DALK, will allow refinement of lamellar techniques and improve the ease of performing these procedures for both surgeons and patients alike. Lamellar keratoplasty, if not already, is likely to become the surgical intervention of choice in keratoconus providing an effective, technically easy to perform, outpatient, local anaesthetic procedure with fairly rapid visual recovery, excellent visual outcomes and long-term graft survival and stability.

Epikeratophakia

Epikeratophakia involves removing the corneal epithelium from the host and then sewing onto the corneal stromal bed a previously cryolathed lenticule of donor cornea. It was first described by Kaufman in 1980.[29] The procedure has generally resulted in less favourable outcomes than PK with reports of failure of re-epithelialisation, poor BSCVA, stromal and lenticule inflammation and opacification and interface haze.[29,30] Whilst implementation of more advanced technologies may help improve outcomes, with the development of DALK techniques this procedure has been largely rendered obsolete in the management of keratoconus.

Intra-corneal ring segment inserts (Intacs and Ferrara Rings)

The development of intra-corneal ring segments has provided a surgical alternative to corneal transplantation in some eyes with keratoconus. This technology has been available for over 10 years and was initially developed for the correction of low degrees of myopia, up to -3.0 diopters, with some success.[31] However, with the development of advanced excimer laser technologies, the procedure has not become mainstream. More recently, these ring segments have been used to reduce the irregularity of the cornea and flatten the apex of the cone in mild and moderate cases of keratoconus with some reported success.[32,33]

Two types of rings are available: Intacs which have a hexagonal cross-section and are placed more peripheral than Ferrara Rings which are triangular / prismatic in shape. Intacs were approved by the Food & Drug Administration in 1994 for low myopic corrections and extended to treatment of keratoconus in July 2004.[34] The rings are inserted into the posterior stroma (about 75% of corneal depth at the incision site) in a quick outpatient technique performed under topical anaesthesia. The circular intra-lamellar pockets for the rings are created either using a specially designed vacuum lamellar dissector or with the femtosecond laser. The exact mode of action of the rings is unknown. It is assumed that they push out against the ectatic curvature peripherally flattening the peak of the cone centrally and returning the cornea to a more spherical shape. High resolution ultrasonic studies have suggested an important role for the epithelium with hyperplastic changes adjacent to the segments having an important refractive effect.[35]

Results have generally been encouraging with most eyes achieving a flattening of the cone postoperatively accompanied by reduction in astigmatism, lessening of inferior versus superior keratometric differences and resultant improvements in best spectacle corrected and uncorrected visual acuities (UCVA).[36-40] Recent series have reported a two line or more improvement in UCVA in approximately 75% of eyes with similar improvements in BSCVA in about 45% of cases.[36-40] Whilst most series remain small, favourable and stable outcomes of up to 24-36 month follow-up have been achieved.[38,39] There is no evidence that ring insertion halts the progression of the condition which would require longer 5-10 year follow-up. The results seem to be best in eyes with mild to moderate keratoconus with average central keratometric readings of less than 53 diopters.[41] Perforation of the anterior chamber is a small risk during the procedure. Lack of efficacy, infection, sterile keratitis, late ring extrusion, chronic eye pain / irritation and scotoptic visual disturbances can account for a number of failures. Removal of problematic ring segments can easily be performed and has been necessary in 4-12% of eyes in published series.[38-42] Once the segments have been explanted the cornea returns to its preoperative state and it is still possible to perform both lamellar and penetrating keratoplasty techniques.[43]

There is some debate as to whether one or two intact segments should be inserted. Certainly most practitioners would agree that if the rings are inserted in a superior-inferior fashion, a thicker segment should be inserted inferiorly around the base of the cone. A number of practitioners are advocating insertion of only a single intac segment inferiorly, with initial studies suggesting the results are comparable, if not better, than two ring insertion.[44-46] Refinement in ring technology, in terms of diameter, shape, thickness and width, a greater understanding of corneal biomechanics and further development of treatment algorithms should allow more predictable refractive outcomes. Certainly it is these authors' opinion that intacs are the treatment of choice in the contact lens intolerant eye, with keratometry less than 53 diopters and no central corneal scarring and should be attempted before considering DALK. It must be stressed, that intra-corneal ring technology does not offer a cure for the condition but can very often produce a marked improvement in unaided and best corrected visual acuity and allow eyes to be corrected with spectacles and / or soft rather than rigid lenses.

Riboflavin / UVA corneal cross-linkage (CR3)

Corneal collagen cross-linkage (CR3) using riboflavin (vitamin B2) / ultraviolet A (UVA) [370nm] light is a new therapeutic modality which may be the first available treatment to

halt and stabilise the keratoconic process.[47] Its aims are to increase the biomechanical stability of the corneal stroma, in terms of its tensile strength and its resistance to enzymatic digestion, by inducing and increasing cross-linkages between the stromal collagen fibres. Photochemical collagen cross-linking by riboflavin / UVA is a simple and technically easy to perform outpatient procedure. The riboflavin has the dual function of acting as a photosynthesiser for the production of oxygen free radicals as well as absorbing the UVA irradiation and preventing damage to deeper ocular structures such as the corneal endothelium, the lens and the retina. The production of oxygen free radicals by this photochemical process is thought to induce collagen cross-linkage by the natural lysyl oxidaze pathway.

The technique is performed under topical anaesthesia. Riboflavin does not penetrate the normal healthy corneal epithelium and has to be removed using a blunt spatula (although some surgeons advocate the use of minor epithelial trauma only, as sufficient to allow riboflavin penetration into the corneal stroma). Riboflavin eye drops 0.1% are applied to exposed stromal surface five minutes prior to the CR3 procedure and then every five minutes during the treatment, which involves exposing the corneal stromal surface to UVA radiation (370nm) at a radiance of 3mW/cm^2 for 30 minutes. At this low energy level, UV wavelength and using this concentration of riboflavin, the technique has been shown to be safe with no endothelial toxicity provided the cornea is thicker than 400µm and no damage to deeper ocular structures.[48] In laboratory studies riboflavin / UVA CR3 has been shown to improve stress-strain measurements, reduce the swelling rates and increase shrinkage temperature and the resistance against enzymatic degeneration of corneal stromal tissue.[49-51] An increase in the diameter of the collagen fibres following the procedure has been documented with most changes occurring in the anterior 200µm.[52-53] Clinical studies have indicated stabilisation of the keratoconic process in treated eyes with no evidence of progression with up to five years follow-up.[54] In addition 70% of eyes have shown some slight regression of the ectasia by an average of two diopters. No long-term problems in terms of loss of transparency of the cornea or lens have occurred and endothelial counts have been unchanged postoperatively.[54-55]

Whilst this technique is still under laboratory and clinical evaluation, it does appear to offer promise. It is the first treatment modality to possibly stabilise the keratoconic process. The ability to halt disease progression at the earliest stages of the condition, when full visual rehabilitation can still be achieved with spectacles and soft contact lenses, offers great hope for future generations suffering with this not infrequent and often visually devastating condition.

Thermokeratoplasty

As early as 1869 the Swiss ophthalmologist Johan Horner described attempts to reshape the cornea by chemical cauterisation.[56] Knapp in 1928 reported improvement in visual acuity after thermal cauterisation in eyes with keratoconus.[57] In 1975 Gassett and Kaufman published encouraging results with a thermokeratoplasty technique applied to the apex of the cone, allowing more controlled collagen shrinkage and apical flattening.[58] Problems associated with thermokeratoplasty, both for the treatment of keratoconus and hyperopia, include limited efficacy, poor predictability, poor medium and long-term stability and postoperative corneal scarring and have limited the efficacy of these techniques. Recently, the advent of laser and conductive keratoplasty technologies, have offered greater control for thermokeratoplasty in terms of temperature regulation and shrinkage depth. Published results have indicated encouraging results for the correction of low degrees of hyperopia of up to +1.50D and have led a number of investigators to re-consider using such techniques for keratoconus. Thus far, there have been few published studies, although limited success has been reported.[59,60]

Refractive lens exchange (phakic / toric intraocular lenses)

Corneal surgery in keratoconus can be problematic, often requiring specialised equipment and being technically difficult to perform. In addition, corneal surgical techniques may be associated with further destabilisation of the cornea and acceleration of the ectatic process as in the case of laser refractive and incisional surgery. Whilst not addressing the correction of the irregular nature of the induced astigmatism in keratoconus, refractive lens exchange and toric phakic intraocular lens insertion may be of some benefit in correcting myopia and astigmatism in selected eyes with early / mild disease with good BSCVA. Published studies have reported significant improvements in unaided visual performance with good safety and efficacy indices both for refractive lens exchange and toric phakic intraocular lens insertion.[61-63] Such treatment modalities are relatively easy to perform, with technologies that are widely available to the majority of ophthalmologists and may offer an alternative in selected contact lens intolerant keratoconic before considering keratoplasty. Further refinements in positioning and implantation of toric intraocular lenses and biometry techniques in these irregular eyes may allow the greater use of lenticular refractive techniques for the future management of some keratoconic patients.

Keratoconus as a contraindication to corneal surgical procedures

Excimer laser keratorefractive surgery has heralded a new era in ophthalmology. Techniques such as laser in situ keratomileusis (LASIK), photorefractive keratectomy (PRK) and laser epithelial keratomileusis (LASEK) have been shown to be safe and effective for the correction of low to moderate degrees of myopia, hyperopia and astigmatism with millions of patients having been treated worldwide. However, one of the major contraindications to such surgeries appears to be the presence of overt and even sub-clinical (forme fruste) keratoconus. An association between the development and acceleration of corneal ectasia in such eyes and LASIK has been clearly established and overt and forme fruste keratoconus are an absolute contraindication to LASIK surgery.[64] Whilst a number of investigators have actually proposed excimer laser phototherapeutic keratectomy (PTK) and PRK procedures as possible treatment modalities for keratoconus, with encouraging reported results and good five-year stability,[65] two recent reports of corneal ectasia following PRK[66,67] strongly suggest that such surface ablation procedures (PRK, LASEK and wide area PTK) are not advisable in these eyes and that keratoconus in all its forms should be regarded as a relative, if not an absolute, contraindication.

Similarly, some surgeons advocate the use of radial keratotomy for the correction of selective patients with mild to moderate keratoconus.[68] Such procedures, which are known to mechanically de-stabilise the cornea, are not advisable and must have the potential to exacerbate the ectatic process in the medium to long-term. Indeed, ectasia has been reported after radial keratotomy.[69]

Whilst many surgical interventions for keratoconus are still at an evolving stage, the use of techniques which are additive (such as intacts), mechanically and chemically stabilise the cornea (riboflavin / UVA corneal collagen cross linkage), assumed to be neutral (conductive keratoplasty) or that replace the diseased corneal tissue (keratoplasty techniques) must be deemed preferable to procedures that remove tissue (excimer laser) and mechanically de-stabilise the cornea (astigmatic and radial keratotomies), particularly in a condition where the cornea is known to be thin, ectatic and mechanically unstable.

Conclusion

Keratoconus is a common condition with severe ocular morbidity that presents in young individuals. It can significantly limit lifestyle choices as a result of visual handicap. The development of new surgical

treatment modalities and the refinement of older techniques with the introduction of new technologies offer the promise of improved visual outcomes for future generations with this condition. ■

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Declaration of Competing Interests
None declared.