Management of keratoconus: current scenario

Vishal Jhanji,1,2 Namrata Sharma,3 Rasik B Vajpayee2

ABSTRACT

Keratoconus is an ectatic corneal dystrophy and is a leading indication for corneal transplantation surgery worldwide. The disease was first described in detail more than 150 years ago by Dr John Nottingham, but the understanding of the disease and its management have undergone significant changes over the last few decades. Corneal specialists have adopted new techniques and technologies for the effective management of keratoconus, while adhering to the age-old concepts of contact lens fitting and penetrating keratoplasty. Lamellar keratoplasty has been revived with improved outcomes and devices such as intracorneal ring segments are being used to treat cases of early keratoconus effectively. This review article discusses the current scenario on the surgical as well as non-surgical management of keratoconus with a focus on the established, novel and emerging treatment modalities.

INTRODUCTION

Keratoconus is a non-inflammatory disease of the cornea characterised by thinning of the corneal stroma that may or may not lead to irregular astigmatism and subsequent decrease in visual acuity. It typically commences at puberty and progresses to the mid 30s at which time progression slows and often stops.1–4 The reported prevalence varies significantly from 8.8 to 54.4 per 100 000 and both sexes are equally affected.4 Keratoconus may occur in one eye initially but commonly affects both eyes, with one eye being more severely affected than the other. Visual loss occurs primarily from irregular astigmatism and myopia and secondarily from corneal scarring.5,6 Ultimately about 12–20% of the affected individuals may require a corneal transplantation1–6 at a relatively young age.7

The main goal of treatment of keratoconus has changed over the last few years from that focused mainly on improvement of visual acuity to an array of newer modalities focused on the prevention of progression of the disease. Based on the current literature and array of treatment modalities available, we have devised a treatment algorithm for management of cases of keratoconus (figure 1).

CONTACT LENSES

The management of keratoconus depends on the state of progression of the disease. In the very early stages, spectacles lenses are an option, especially for patients who achieve 20/40 or better vision with spectacles. However, spectacles do not correct irregular astigmatism, and rigid gas permeable contact lenses provide better correction in such cases. Contact lenses represent the treatment of choice in 90% of patients of keratoconus.

The type of contact lenses used varies depending on the stage of keratoconus. Early in the disease, soft lenses with toric design may be adequate to correct myopia and regular astigmatism. As the disease progresses, rigid gas permeable lenses are used. A proportion of patients who elect to undergo keratoplasty return to contact lenses after successful keratoplasty in order to achieve their best corrected visual acuity. Smiddy et al have shown that approximately 70% patients who present for surgical consideration with keratoplasty for keratoconus can be maintained successfully on contact lenses.8

Keratoconus lens options

Polymethyl methacrylate (PMMA) was the original contact lens material used in all contact lenses from the 1940s. Rigid gas-permeable contact lens materials have been available since 1970s. The most commonly used lens design in patients with keratoconus is a single spherical base curve in rigid gas-permeable material. For patients with moderately advanced keratoconus who are unsuccessful with single-base curve lenses, multi-curve lenses can be successfully used. The Rose K lens is a relatively new system of multiple curves in the periphery to vary edge lift (figure 2).9,10

In severe keratoconus with irregular anterior corneal surface it may be difficult to achieve reasonable lens centration with corneal lenses. In this group of patients scleral contact lenses have been found to be useful with satisfactory outcomes.11,12 It is imperative to understand that many keratoconus patients depend on contact lenses for most of their daily activities. Appropriate case selection and proper contact lens fitting may delay the requirement of a definitive treatment such as corneal transplantation in these patients.

CORNEAL COLLAGEN CROSS-LINKING

Collagen cross-linking (CXL) is relatively new treatment option for keratoconus. In the last few years various studies have shown that CXL may offer some promise in slowing the progression of disease.13–25 The procedure involves epithelial debridement, application of topical riboflavin drops and ultraviolet-A exposure at 370 nm for approximately 50 min.

The first clinical study on the cross-linking treatment of keratoconus was performed by Wollensak et al.24 Twenty-two patients with progressive keratoconus were treated over a 3-year period. In all treated eyes, the progression of keratoconus was at least stopped, with a slight reversal and flattening of the keratoconus by 2 D in 70% of eyes. The results were substantiated with the 5-year follow-up study. There have been a few trials in the following years that have reconfirmed
the usefulness of the cross-linking procedure in cases of progressive keratoconus (table 1). Recently the US Food and Drug Administration (FDA) have also approved recruitment for the clinical trials around the world.

The studies on use of CXL that have been reported in the literature, shown in table 1, have not reported any serious adverse effects of the procedure itself. Most of the problems encountered occur during the early postoperative period and are related to the use of bandage contact lens for epithelial healing. Currently, CXL is being used in many parts of the world for the management of progressive keratoconus. Although it provides a less invasive approach to stop the progression of keratoconus, long-term results and safety are yet to be evaluated. More prospective randomised controlled trails in future would provide the corneal surgeons with objective guidelines for the optimal use of this novel therapy.

**Intracorneal ring segments**

Intracorneal rings are PMMA segments that were initially approved by the US FDA and the Communauté Européene for management of myopia and astigmatism.25–28 Recent studies have reported their effective use for the treatment of keratoconus and to stabilise ectasia resulting from keratorefractive surgery.29 Treatment with intrastromal rings does not eliminate the progression of keratoconus, but it may delay a corneal transplant procedure. There are three models of PMMA intracorneal rings available for the correction of myopia: (1) Ferrara intracorneal ring (Mediphacos Inc, Belo Horizonte, Brazil); (2) Bisantis segments (Opticon 2000 SpA and Soleko SpA, Rome, Italy); (3) intrastromal rings, with the most commonly used known as Intacs (Addition Technology, Fremont, California, USA). Recent designs include semicircular segments, intrastromal corneal ring segments and Intacs microthin prescription inserts.

Keratoconus patients with clear central corneas and corneal thickness of ≥400 μm at the point of insertion of intrastromal segments are suitable for this treatment. Colin et al performed the first implantation of Intacs for keratoconus in 199730 and published the 1 year follow-up data in 2001.31 Alió et al reported that Intacs insertion provided better visual acuity in eyes with keratoconus with relatively low mean K-values (≤55.0 D) and a relatively low spherical equivalent.32 Boxer Wachler et al showed greater improvement in visual acuity and astigmatism after intrastromal ring implantation in keratoconic corneas with scarring compared with those without scarring.33

The channels for the Intacs can be created mechanically or with the help of femtosecond laser. Previous studies have reported good visual outcomes with the use of mechanical dissection.34–35 However, the mechanical technique of tunnel creation can cause epithelial defects at the keratotomy site, anterior and posterior perforations, shallow or uneven placement of the segments, introduction of the epithelial cells into the channel, stromal thinning and corneal stromal oedema.36 The femtosecond laser potentially reduces these complications due to more precise localisation of the channel.37 Piñero et al found significant differences between mechanical and femtosecond group for primary spherical aberration, coma and other higher-order aberrations, favouring the femtosecond group.38 Coskunseven et al have reported the occurrence of incomplete channel creation and segment migration using femtosecond laser for channel creation.39 Besides these complications, infection following implantation of intracorneal rings is a serious complication and can occur many months after the initial procedure.40–42

Most of the earlier studies have advocated the use of two segments during the surgery.30 31 33 Boxer Wachler et al found that asymmetric Intacs implantation can improve uncorrected and best corrected visual acuity (BCVA) and reduce irregular astigmatism.35 Rabinowitz et al reported no statistically significant differences between the visual outcomes in one and two Intacs implantation.44

Chan et al have shown that combining riboflavin with Intacs augmented the flattening effects of Intacs.45 Although cross-linking can potentially be used in conjunction with Intacs insertion to attain stability in cases with progressive keratoconus, further trials are needed to validate long-term results of this combination treatment.

**TORIC AND PHAKIC INTRAOCULAR LENSES**

There have been recent reports regarding the successful use of toric as well as phakic intraocular lenses in patients with keratoconus. Venter assessed the refractive outcome of implanting Ophtec Artisan phakic intraocular lenses Ophtec BV, Groningen, The Netherlands in patients with non-progressive keratoconus.44 Kamiya et al have reported good results after implantation of phakic toric Implantable Collamer Lenses (toric ICL; STAAR Surgical, Nidau, Switzerland) for correction of myopic astigmatism in stable keratoconic eyes.45

The major issue with the use of phakic IOLs is that is these patients would probably need another procedure if they develop cataract in future. More recently, Navas and Suárez have reported toric intraocular lens implantation in two cases with forme fruste keratoconus.46

The use of special intraocular lens in patients with non-progressive keratoconus is a recent development. More studies with greater number of carefully selected participants and longer follow-up are awaited.
and worse in 1% of the cases. Similar results have been visual acuity to be better after surgery in 96%, unchanged in 3%, and 89% at 5 and 10 years, respectively, after corneal transplantation in cases with keratoconus.

Australian Corneal Graft Registry reports graft survivals of 95% and 95% at 7 years after epikeratophakia for keratoconus.65

Despite the inherent advantages of the technique, including reversibility and low risk, epikeratophakia for keratoconus became less popular over the years due to the availability of better surgical techniques.

**CORNEAL TRANSPLANTATION FOR KERATOCONUS**

**Penetrating keratoplasty**

Penetrating corneal transplantation has been the mainstay of treatment for keratoconus since many decades, as reported by the data from the USA, the New Zealand National Eye Bank, and individual reports from countries such as Iran, Saudi Arabia, and Ireland. The Australian Corneal Graft Registry reports graft survivals of 95% and 89% at 5 and 10 years, respectively, after corneal transplantation in cases with keratoconus.

**Sizing of the donor during keratoplasty**

The use of oversize donor trephines in penetrating keratoplasty (PKP) for keratoconus has been reported to produce an increase in corneal curvature, resulting in postoperative refractive outcomes that are more myopic than when same-size donor trephines are used. In a large retrospective study Jaycock et al evaluated the results of PKP in patients with keratoconus using same-size donor and recipient trephines. The authors found a significantly higher incidence of postoperative wound leaks in the same-size group.

**Long-term results after PKP**

Paglen et al reviewed the long-term results of PKP performed by a single surgeon in 326 eyes grafted for keratoconus. The mean follow-up was 11.3 years, during which 90% of grafts remained clear and 73% of the eyes achieved 0.5 or better vision. In a 9-year follow-up study, Sayegh et al found the postoperative visual acuity to be better after surgery in 96%, unchanged in 3%, and worse in 1% of the cases. Similar results have been reported by other authors.

The visual rehabilitation is often slow after PKP and is influenced by high degrees of postoperative astigmatism and significant anisometropia. Despite these negative influences, the importance of PKP for advanced cases of keratoconus, especially with healed corneal hydrops, cannot be underestimated. The ongoing development of techniques such as femtosecond-assisted keratoplasty is expected to further improve the outcomes of corneal grafting in cases with keratoconus.

**Epikeratophakia for keratoconus**

Epikeratophakia was first introduced by Kaufmann and Werblin in 1982 for the treatment of keratoconus. It is an onlay lamellar keratoplasty that utilises acellular, freeze-dried corneal stromal lenticules prepared from donor corneas that are sutured to a peripheral trephine groove in the patient’s cornea. Vajpayee and Sharma followed up 10 cases with keratoconus for 4 years after epikeratophakia, with 80% of cases achieving a visual acuity of ≥0.5. Spitznas et al showed a decrease in astigmatism and mean refractive power and an increase in BCVA at the end of 7 years after epikeratophakia for keratoconus.

Despite the inherent advantages of the technique, including reversibility and low risk, epikeratophakia for keratoconus became less popular over the years due to the availability of better surgical techniques.

**LAMELLAR KERATOPLASTY**

Over the last few years there has been a move from PKP towards lamellar keratoplasty for keratoconus in cases without significant corneal scarring or corneal hydrops. The deep lamellar keratoplasty (DALK) technique aims to remove all or near total corneal stroma down to Descemet’s membrane, as in the air/saline-assisted dissection Melles technique, the ‘big-bubble’ technique, or variations of the big-bubble technique.

The benefits of DALK are that it is mostly an extra-ocular procedure, and it preserves the host Descemet’s membrane and endothelium so that there is no risk of endothelial rejection.

In the UK, the percentage of transplants for keratoconus in which DALK was used increased from 10% in 1999–2000 to 35% in 2007–2008. Some of the complications associated with DALK are likely to be different from PKP, in particular the risk of intraoperative perforation of Descemet’s membrane.

**DALK using intrastromal air injection**

Air-assisted lamellar keratoplasty involves injection of air into the corneal stroma followed by corneal trephination and dissection as close as possible to Descemet’s membrane. Once the Descemet’s membrane is reached, viscoelastic can be injected to promote its separation from the stroma, which is then excised in order to bare the Descemet’s membrane. In a randomised controlled trial comparing air-assisted DLKP with PKP for the management of keratoconus, Shimazaki et al found that the PKP group showed faster recovery in visual acuity than the DLKP group.

**DALK using Melles technique**

The concept of DALK and baring of Descemet’s membrane was introduced by Melles et al. The technique involves injection of air into the anterior chamber initially in order to highlight the air-to-endothelium interface. This is followed by injection of viscoelastic into deep corneal stroma using the interface as a guide.

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**Table 1** Outcomes of corneal collagen cross-linking for keratoconus

<table>
<thead>
<tr>
<th>Authors</th>
<th>Type of study</th>
<th>Number of participants</th>
<th>Follow-up period</th>
<th>Results</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caporossi et al</td>
<td>Prospective, non-randomised</td>
<td>10 eyes of 10 patients</td>
<td>6 months</td>
<td>Increased UCVA, mean Km reduction of 2.1±0.13 D</td>
<td>None reported</td>
</tr>
<tr>
<td>Wittig-Silva et al</td>
<td>Prospective, randomised</td>
<td>66 eyes of 49 patients</td>
<td>12 months (9 patients)</td>
<td>Reduction of Km max by an mean of 1.45 D</td>
<td>No serious adverse effects reported</td>
</tr>
<tr>
<td>Hoyer et al</td>
<td>Retrospective</td>
<td>153 eyes of 111 patients</td>
<td>12 months (minimum)</td>
<td>Km readings decreased in the third year by 4.34 D</td>
<td>One case of keratitis, resolved and retreated successfully</td>
</tr>
<tr>
<td>Raisikup-Wolf et al</td>
<td>Retrospective</td>
<td>480 eyes of 272 patients</td>
<td>6 months (minimum)</td>
<td>Km values decreased by 4.84 D in the third year</td>
<td>None</td>
</tr>
<tr>
<td>Jankov et al</td>
<td>Prospective, non-randomised</td>
<td>25 eyes of 20 patients</td>
<td>4–7 months</td>
<td>Km max decreased by more than 2 D</td>
<td>None</td>
</tr>
<tr>
<td>Vinciguerra et al</td>
<td>Prospective, non-randomised</td>
<td>28 eyes of 28 patients</td>
<td>12 months</td>
<td>Mean average simulated Km decreased by 6.07 D</td>
<td>None reported</td>
</tr>
<tr>
<td>Grewal et al</td>
<td>Prospective, non-randomized</td>
<td>102 patients</td>
<td>12 months</td>
<td>No significant change in visual acuity and corneal curvature</td>
<td>None reported</td>
</tr>
<tr>
<td>Agrawal et al</td>
<td>Retrospective</td>
<td>37 eyes of 25 patients</td>
<td>12 months (minimum)</td>
<td>Km max value decreased by a mean of 2.47 D in 54% of eyes</td>
<td>None reported</td>
</tr>
</tbody>
</table>

Km, keratometry; UCVA, uncorrected visual acuity.

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Watson et al retrospectively compared the visual outcomes of DLKP using Melles technique and PKP in keratoconic patients. The median final BCVA of patients in the DLKP group was 6/9 and in the PKP group 6/6, with similar complication rates in both groups. Funnell et al found that although astigmatism was significantly higher in patients undergoing PKP compared with DLKP, patients in the PKP group were more likely to achieve 6/6 at 1 year.

**DALK using the big-bubble technique**

The big-bubble technique was introduced by Anwar and Teichmann in patients with keratoconus. In this surgical technique, 60–80% deep corneal trephination is followed by injection of air using a 27- or 30-gauge needle. The authors have reported complete baring of Descemet’s membrane in majority of the cases with excellent results. Al-Torbak et al have reported a BCVA of ≥20/50 in 75% of eyes using the big-bubble technique. Similar results have been reported from other case series of big-bubble DALK technique for keratoconus (table 2) (figure 3).

In a retrospective cohort study, Han et al compared the outcomes after PKP and two techniques of deep anterior lamellar keratoplasty in patients with keratoconus. At 12 months there was no significant difference in the mean spherical equivalent and astigmatism between the PKP and DALK groups. In a recent study from the UK, Jones et al compared the outcomes after PKP and DALK for keratoconus. The risk of graft failure for DALK was almost twice that for PKP. Mean BCVA was similar for the two procedures, but overall 53% of patients who underwent PKP achieved a BCVA of ≥6/6 at 2 years compared with only 22% of those who underwent DALK.

**FEMTOSECOND-ASSISTED KERATOPLASTY**

Femtosecond laser allows the surgeon to create a desired incision shape and to easily match donor and recipient dimensions. 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. Clinical trials to use femtosecond lasers to perform deeper lamellar ablations in lamellar as well as full-thickness surgery are now ongoing, and early results are encouraging.

**‘TUCK IN’ LAMELLAR KERATOPLASTY FOR KERATOCONUS**

Certain special techniques of corneal transplantation are useful in cases that are usually not amenable to routine corneal transplantation procedures. ‘Tuck in’ keratoplasty (TILK) involves a central lamellar keratoplasty with intrastromal tucking of the peripheral flange. Kaushal et al reported TILK in cases with combined keratoconus and pellucid marginal degeneration as well as extreme corneal ectasias. The authors reported improved visual acuity, and decreased keratometry and refractive astigmatism after TILK.

**MICROKERATOME-ASSISTED LAMELLAR KERATOPLASTY**

The major disadvantage of earlier techniques of lamellar keratoplasty is that the manual dissection may result in irregular interface and suboptimal visual results. The semi-automated procedure of automated lamellar therapeutic keratectomy (ALTK; Moria S.A., Antony, France) uses a gas-turbine-driven microkeratome to perform both the recipient bed dissection and lamellar dissection of the donor button with the use of an artificial chamber maintainer.

In cases of keratoconus with corneal thickness ≥380 μm, microkeratome-assisted keratoplasty achieves satisfactory results (figure 4). The surgery involves shaving off the superficial 250 μm of the keratoconic cornea with the help of a microkeratome. The 350 μm donor lenticule is sutured on to the recipient bed. The advantages of microkeratome-assisted keratoplasty include a smooth graft-host interface and a technically easy procedure compared with DALK.

Busin and Scorcia have presented a modification of the technique that involves partial trephination of the recipient bed before suturing the graft. The authors propose that collapse of the cone by full-thickness trephination of the recipient bed in conjunction with lamellar keratoplasty makes the corneal shape regular (video abstract ‘Microkeratome-assisted PKP without

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**Table 2** Summary of results from various big-bubble DALK studies

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Number of eyes</th>
<th>Indication</th>
<th>BCVA ≥20/40 (%)</th>
<th>Perforation rate (%)</th>
<th>Rejection (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anwar and Teichmann</td>
<td>2002</td>
<td>181</td>
<td>Keratoconus</td>
<td>Not reported</td>
<td>9</td>
<td>None reported</td>
</tr>
<tr>
<td>Al-Torbak et al</td>
<td>2006</td>
<td>127</td>
<td>Keratoconus</td>
<td>75</td>
<td>13</td>
<td>3</td>
</tr>
<tr>
<td>Fogla et al</td>
<td>2006</td>
<td>13</td>
<td>Keratoconus</td>
<td>100</td>
<td>15</td>
<td>None</td>
</tr>
<tr>
<td>Bahar et al</td>
<td>2008</td>
<td>17</td>
<td>Keratoconus</td>
<td>100</td>
<td>7.6</td>
<td>7.6</td>
</tr>
<tr>
<td>Fontana et al</td>
<td>2007</td>
<td>81</td>
<td>Keratoconus</td>
<td>100</td>
<td>13</td>
<td>2</td>
</tr>
<tr>
<td>Feizi et al</td>
<td>2010</td>
<td>129</td>
<td>Keratoconus</td>
<td>78</td>
<td>4</td>
<td>14.3</td>
</tr>
</tbody>
</table>

BCVA, best-corrected visual acuity; DALK, deep lamellar keratoplasty.

Tan et al have described a two-stage procedure ALTK procedure, combining it with a Hanna trephine system (Moria S.A.).93

EXCIMER LASER SURGERY FOR KERATOCONUS
Buratto et al have described excimer laser lamellar keratoplasty of augmented thickness in which a deep plano excimer laser ablation is done on the host cornea and a donor lamellar button is sutured onto the recipient bed.94 As well as these techniques, several other groups have evaluated the role of phototherapeutic keratectomy,95 photoastigmatic refractive keratectomy,96 photorefractive keratectomy (PRK),97 topography-guided surface ablation98 and circular keratotomy99 in cases of keratoconus, with variable results.

The main drawback associated with the use of excimer laser is that the ablation of a large amount of corneal tissue requires high energy levels, possibly inducing endothelial damage. In addition, high costs are involved and there may be risk of contamination and other intra-operative complications.

COMBINED TREATMENT OPTIONS
In addition to the combination treatment option of using Intacs with CXL described earlier, a few studies have reported the use of CXL along with topography-guided PRK in order to provide better visual rehabilitation in patients with keratoconus.99–102 Kymionis et al101 presented the results after simultaneous PRK followed by corneal CXL in 14 eyes with progressive keratoconus. The study found it to be a promising treatment for visual rehabilitation in patients with keratoconus. Kanellopoulos102 reported that same-day simultaneous topography-guided PRK and cross-linking are superior to sequential cross-linking and PRK in cases with progressive keratoconus. In his study, the simultaneous group did better (p<0.05) in all fields evaluated, with improvement in visual acuity, a greater mean reduction in spherical equivalent refraction and keratometry, and less corneal haze.

Combined Intacs and anterior or posterior chamber phakic intraocular lens have been described.103–106 If the corneal shape improves after Intacs implantation, the degree of myopia may be corrected to some extent using a phakic refractive intraocular lens. The use of toric phakic intra-ocular lens has been reported in eyes with high astigmatic refractive errors after Intacs implantation.104

Although combination treatment strategies have been reported to be effective with a potential to avoid or delay corneal transplantation surgery in selected cases of keratoconus, controlled randomised studies with longer follow-ups are needed to determine their safety, predictability and stability.

CONCLUSIONS
Keratoconus has long puzzled the corneal specialists with regard to the genetics, progression and management of the disease. Modern technology has certainly helped greatly in understanding the pathophysiology and diagnosis of keratoconus. In many cases a conservative approach with contact lenses can make a patient’s life more comfortable. The surgical options are growing, with the availability of new machines and femtosecond lasers. The shift from gold standard PKP to parasurgical treatment options is a significant attempt to change the treatment paradigm. Therapies such as corneal cross-linking might hold the key to the future with a promise to arrest the progression of keratoconus.

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Review

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