Abstract

Keratoconus is a common ectatic disorder occurring in more than 1 in 1000 individuals. The condition typically starts in adolescence and early adulthood. It is a disease with an uncertain cause and its progression is unpredictable, but in extreme cases, vision deteriorates and can require corneal transplant surgery. Corneal collagen cross-linking with Riboflavin (C3R) is a new treatment in North America that can enhance the rigidity of the cornea and prevent disease progression. Other surgical options for keratoconus will be discussed herein, including intracorneal rings, photorefractive keratectomy, and phakic implants.

Background

The cornea consists of layers of collagen fibers that are connected by cross-links. These cross-links are the natural “anchors” within the cornea. If the collagen cross-links are reduced, as in keratoconus, there is risk of progressive ectasia characterized by corneal steepening and thinning. Forward bulging of the front and/or back of the cornea results in irregular astigmatism that can be difficult to correct with glasses or soft contact lenses.

Risk Factors for Keratoconus

Although the cause of keratoconus is unknown, it is believed that risk factors include: eye rubbing, a family history of keratoconus, or certain systemic disorders such as Down’s syndrome, eczema, and connective tissue disease (e.g. Ehlers-Danlos and Marfan syndromes).

Most cases have no familial history of keratoconus, but pedigrees with autosomal dominant and recessive inheritance have been described. It affects men and women in equal proportions and is bilateral in 90% of patients.

Signs and Symptoms

During the early stages, the symptoms of keratoconus may be similar to having the need for spectacle correction. As the disease progresses, the vision deteriorates. Keratoconus can cause substantial distortion of vision, with multiple images and glare, especially at night. The disease can progress very quickly during the late teens and twenties.

Diagnosis

The diagnosis of keratoconus is based on a variety of clinical signs. These signs vary from early to late disease stages (see Figure 1). Early keratoconus can often be overlooked with a standard eye evaluation, as keratoconus in its mild form rarely shows any identifiable signs. Advanced corneal imaging with a Pentacam or
Orbscan can usually confirm the absence or presence of the disease (see Figure 2). One of the earliest corneal signs is forward bulging of the posterior cornea. The anterior curvature and elevation may be normal at this early stage. Changes to the epithelial thickness occur to smooth the anterior corneal surface. Thickening usually occurs around the base of the cone, while thinning occurs over the apex of the cone. This often results in normal anterior topography. With further progression of the disease, changes occur to the anterior topography. This results in asymmetric or irregular astigmatism.

**Progress**

In 10-20% of keratoconus patients, the cornea may become extremely steep and the correction of vision with contact lenses will not be sufficient. These patients will require a corneal graft for visual restoration. It is ideal to halt the progression of keratoconus at an early stage. A corneal transplant has a long healing period and unpredictable refractive error.

**Contact Lenses**

Contact Lenses are the most popular nonsurgical treatment for symptoms related to keratoconus. Contact lenses can provide good vision in early to mid stages of keratoconus by correcting the refractive error, but lens tolerance and good quality vision can be difficult to maintain as the condition progresses. Although contact lenses can aid vision, they do not slow the rate of corneal deterioration.

Many specialized types of contact lenses have been developed for keratoconus. Traditionally, contact lenses for keratoconus have been the ‘hard’ or rigid gas-permeable variety, although manufacturers have also produced specialized ‘soft’ or hydrophilic contact lenses. Some patients find good vision correction and comfort with a “piggyback” contact lens combination, in which gas permeable rigid contact lenses are worn over soft contact lenses, providing clarity of vision and comfort.

Promising new surgical treatments are currently available for the treatment and management of keratoconus.

**Corneal Cross-linking with Riboflavin – C3-R**

A new treatment for keratoconus in North America is Corneal Collagen Cross-linking with Riboflavin (C3-R) and Ultraviolet A. C3-R was developed by Theo Seiler and Eberhard Spoerl of Germany. The basic research was performed from 1993 to 1997 and the first patients were treated in 1998. Today there are over 300 centres performing C3-R in Europe. The Bochner Eye Institute became the first centre in Canada to perform C3-R in January of 2008.

The riboflavin, when activated by UV-A light, augments the collagen cross-links within the stroma and so recovers some of the cornea’s mechanical strength or rigidity. Collagen cross-linking utilizes the photosensitizer riboflavin (vitamin B2), which, when exposed to longer wavelength ultraviolet light (370 nm UVA), will induce chemical reactions in the corneal stroma and ultimately result in the formation of covalent bonds between the collagen molecules, fibers, and microfibrils.

Long-term studies have shown the procedure to arrest the progression of keratoconus. In addition, there is usually some improvement in UCVA with corneal flattening occurring over time. The procedure has the potential to become the standard treatment for keratoconus. The earlier that C3-R is offered, the better the prognosis for quality of vision. Keratoconus patients as young as 14 years old are being treated in Europe.

The technique of cross-linking is not new. The procedure has been used in the field of polymer material science for over 70 years. This process is required to transform silicone oil into a rubber ball. Dentists have used cross-linking for over 25 years (see Figure 3). The normal aging of connective tissue involves cross-linking. This probably accounts for why keratoconus tends to slow down with age.

The goal of C3-R is to create additional chemical bonds between collagen fibers by means of photopolymerization (see Figure 4 and Figure 5).

**The Procedure**

The patient is in a supine position for approximately one hour if one eye is treated or two hours if both eyes are treated. The pupil is constricted preoperatively with pilocarpine drops. The energy level of the UV-A laser is verified (see Figure 6). Treatment is performed under topical anesthesia (e.g. proparacaine or tetracaine drops). The central corneal epithelium of approximately 8 x 8 mm area is removed. It is common to use the Amoils Rotary brush to remove the epithelial cells.
Riboflavin (0.1%) eye drops are applied every minute for 30 minutes (see Figure 7). The eye is then exposed to UV-A light (low-intensity) with an energy of 370 nm for 30 minutes (see Figure 8). After the treatment, antibiotic eye drops are applied and a bandage contact lens is inserted. The contact lens is removed once the epithelium is intact, typically at day five. Protective eye-wear is recommended for a few days until complete healing takes place.

Corneas treated with riboflavin/UVA without previous deepithelization have been shown to have a diminished cross-linking effect compared with those that had the epithelium removed. Riboflavin has a molecular weight of 376.37 g/mol and is water soluble, therefore a hydrophobic structure such as the epithelium would not permit the complete diffusion of this drug.

Safety

The safety of C3-R to the intraocular structures has been extensively evaluated. Keratocytes are depleted to the 300 um level (see Figure 9). These cells regenerate by 6 months. The corneal endothelium, the crystalline lens, and the retina are preserved as long as a minimum corneal thickness of 400 um is respected.

Candidates for the Procedure

Corneal collagen cross-linking is not a cure for keratoconus, rather, it aims to arrest the progression of the disease and thereby prevent the need for corneal transplantation. Patients will usually need to continue to wear spectacles or contact lenses, although a change in
the prescription is usually required.

A 5-year study involving 48 eyes in 60 treated patients showed no patient had further progression of keratoconus. A postoperative regression of 2.87 diopters was noted and best-corrected visual acuity improved by 1.4 lines.\(^6\)

A long-term study on the results of C3-R in keratoconus involving 241 eyes with follow-up from 6 months to 6 years showed that no patient lost lines of best-corrected visual acuity.\(^7\) Corneal flattening was 2.68 diopters at 12 months and 4.84 diopters at 24 months. Only 2 patients had progression of keratoconus and required repeat treatments. Both of these patients had systemic conditions and were on oral prednisone that was felt to interfere with the results of C3-R.

In addition to the treatment of keratoconus, C3-R has been shown to be effective in the management of progressive hyperopia after radial keratotomy.\(^9\) Another disease application is Fuchs corneal dystrophy or bullous keratopathy. C3-R has been shown to result in compactness of the collagen fibers and a decrease in corneal thickness. In patients with early disease or those that are not candidates for a corneal graft, C3-R can lead to enhanced comfort by reducing epithelial edema.

C3-R treatments at the Bochner Eye Institute in Toronto on the first 100 eyes are shown in Figure 10, with 88 eyes having keratoconus, 6 having ectasia following LASIK, and 6 after radial keratotomy. Epithelium was intact by 5 days in 99/100 eyes. Return of BCSVA occurred from 1 to 6 weeks. There were no cases of persistent corneal edema, infiltrates, ulcers, lens, or macular changes.

Risks and consequences

Very few potential risks associated with this treatment have been reported to date. The ultraviolet light dose is designed to prevent damage to the corneal endothelium or the other structures within the eye. No cataracts have been attributed to this treatment in European trials. Postoperatively, there is some light sensitivity and mild discomfort during the first week – not unlike photorefractive keratectomy (PRK).

Other consequences of the procedure include an inability to wear contact lenses for several weeks after the treatment. Also, corneal shape changes necessitate the refitting of contact lenses or changes in spectacle correction.

As with many treatments, there may also be long-term risks that have not yet been identified. The increased corneal rigidity resulting from the procedure may wear off over time and further periodic treatments may be required.
Intracorneal Rings

Intracorneal rings (ICR) are clear thin inserts placed in the mid-periphery of the corneal stroma to flatten the cornea (see Figure 11 and Figure 12). The rings were initially developed over 10 years ago to correct low degrees of myopia. The procedure, although effective, was unsuccessful in competing against PRK in the refractive arena. In recent years there has been a resurgence of interest in ICR to flatten the cornea and reduce irregular astigmatism in the treatment of keratoconus.\(^{10,11}\) The procedure has the potential to improve uncorrected visual acuity (UCVA) and enhance contact lens wear. It is important to note that unlike C3-R, the ICR procedure does not prevent the progression of keratoconus. Therefore, ICR can be most effective following the C3-R procedure.

ICR reshapes the curvature of the cornea from within, to enhance vision via the resultant corneal flattening and reduced irregular astigmatism. Because no tissue is removed, the ICR does not weaken the cornea.

In the past, the channel made in the cornea prior to the placement of the rings was made with a mechanical dissector. With this surgical technique, it was somewhat difficult to achieve a consistent depth. Today, the Intralase Laser can be used to accurately create the corneal channels. The anterior micro-incision is placed on the steep corneal meridian. One or two corneal rings (see Figure 11 and Figure 12) are then inserted through this incision and a temporary suture is used to close the wound. The rings cause the cornea to flatten which can help improve the fit and comfort of contact lens wear. The procedure is performed under topical anesthesia. The ICR can be exchanged or removed if needed. The corneal suture is removed after 6 to 8 weeks.

An example of a single ring (450 um segment) is shown in Figure 13. Preoperatively the patient had an UCVA of 20/70 and best-corrected spectacle visual acuity (BCSVA) of 20/30 with \(-1.00\) - \(2.75\) \(\times\) 63. Postoperatively UCVA improved to 20/25 and BCSVA improved to 20/20 with \(-0.25\) - \(0.75\) \(\times\) 25.

An example of 2 rings (300 um segments) is shown in Figure 14. Preoperatively UCVA was 20/50 and BCSVA was 20/30 with \(-1.25\) - \(1.25\) \(\times\) 155. Postoperatively UCVA was 20/25 and BCSVA was 20/20 with \(-0.50\) - \(0.50\) \(\times\) 160.

Another example of advanced keratoconus with contact lens intolerance is shown in Figure 15. With the insertion of one ring (450 um segment) the patient was able to wear a rigid-gas permeable lens.

Refractive Surgery Options

Once the keratoconus disease is halted using C3-R, and irregular astigmatism is reduced with the ICR, refractive surgery can be offered if the patient is not satisfied with glasses or contact lens wear. Refractive surgery options included PRK or a phakic implant such as the Implantable Contact Lens.

PRK

PRK is a proven laser vision correction treatment for myopia, hyperopia, and astigmatism. PRK is a reasonable treatment option for patient’s who correct well with spectacles or soft contact lenses and who do not demonstrate significant corneal thinning.

PRK can be performed when the cornea shows some refractive stability after C3-R or after C3-R and Intacs. It typically takes 4 to 6 months for the maturation of the
epithelium after C3-R or biomechanical stability after ICR. Typically, only a portion of the prescription is treated as further flattening from the C3-R procedure can occur over a number of years. Usually only low prescriptions are treated with PRK so as not to potentially weaken a cornea.

PRK ablation options include a standard treatment, wavefront-optimized, wavefront-guided, or topographically-linked. The latter two treatments allow for the reduction of higher-order aberrations, especially coma, commonly seen in keratoconus eyes.

Phakic Intraocular Lens

Phakic implants can be used in the refractive treatment of patients with keratoconus. A phakic intraocular lens is the preferred refractive treatment for patients with moderate to high refractive errors and/or thin corneas. Similar to PRK, a phakic implant is recommended for patients who have satisfactory vision with glasses or a soft toric contact lens. Refractive errors of myopia, hyperopia, and astigmatism can be treated.

The two most popular phakic implants are the implantable contact lens (ICL) (see Figure 16A, B) or Verisyse implant (see Figure 17). Both of these implants can be used for vision correction following C3-R and/or ICR. The phakic implants are custom-ordered based on the patient’s prescription and other eye measurements. Contraindications include a pupil size greater than 7 mm or a central anterior chamber depth of less than 2.8 mm. Prior to the insertion of the ICL, two superior peripheral iridotomies are performed to prevent pupil-lary-block glaucoma. If there is residual refractive error after a phakic implant, then a PRK enhancement can be performed.

Summary

Corneal collagen cross-linking with riboflavin and UVA is one of the most exciting new therapeutic treatments in ophthalmology. For the first time in North America, a treatment is available to prevent progression of keratoconus. Advances in corneal imaging now allow for the early detection of disease. C3-R treatment performed at an early disease stage results in a better visual prognosis. Following C3-R treatment, a reduction in irregular astigmatism can be achieved with the intracorneal ring procedure. Once the ectatic disease is halted and irregular astigmatism reduced, the patient may function well with glasses or contact lenses. If further improvement in uncorrected vision is desired the surgical options of PRK or a phakic implant can be offered.

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