Limitation of Collagen Cross-Linking With Hypoosmolar Riboflavin Solution: Failure in an Extremely Thin Cornea

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Purpose: We report a case of failure of corneal collagen cross-linking (CXL) for progressive keratoconus after preoperative stromal swelling with hypoosmolar riboflavin solution in an extremely thin cornea.

Methods: CXL was performed using the protocol established for the treatment of thin corneas. Preoperative minimal thickness after abrasion was 268 μm and increased to 406 μm after swelling with hypoosmolar riboflavin solution.

Results: Despite CXL, a distinct progression of up to 1.9 diopters was observed at 3 months after the procedure on the anterior corneal surface. At 6 months after CXL, progression had increased to 2.3 diopters. Although swelling with hypoosmolar riboflavin solution was effective and led to a preoperative thickness of more than 400 μm, the increase in biomechanical resistance was not sufficient to arrest the progression of the disease.

Conclusions: Little is known about the minimal stromal thickness required for effective CXL to occur. Although swelling with hypoosmolar riboflavin solution over 400 μm and safety of the procedure can be achieved in even thinner corneas, the outcome of this case suggests that a minimal preoperative stromal thickness of 330 μm needs to be respected for a successful CXL procedure.

Key Words: cornea, CXL, corneal, collagen cross-linking, riboflavin, hypoosmolar

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Keratoconus represents a disorder of the corneal stroma associated with decreased biomechanical strength, probably because of diminished intrafibrillar cross-links. Cross-linking (CXL) of corneal collagen with riboflavin and UV-A irradiation is a surgical technique that induces cross-links within and between collagen fibers.[1] CXL increases the corneal biomechanical and biochemical stability and is currently used to treat progressive primary (keratoconus)[2,3] and secondary (iatrogenic) keratectasia[4] as well as infectious corneal melting[5] and bullous keratopathy.[6]

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The currently used treatment parameters induce cross-links in the anterior 250–350 μm of the corneal stroma.[7] Thus, to protect the endothelium, CXL inclusion criteria require a minimal corneal thickness of 400 μm after removal of the epithelium.[7] In many cases of advanced progressive keratectasia, however, minimal stromal thickness is below 400 μm and represents the only parameter prohibiting safe CXL. We have recently modified the technique by applying hypoosmolar riboflavin solution to induce stromal swelling before UV-A irradiation; the thinnest cornea showed a minimal thickness of 320 μm after removal of the epithelium, which required a swelling of at least 80 additional μm to achieve the minimal corneal thickness of 400 μm required for safe CXL.[7]

Here, we report a case of an extremely thin cornea with a minimal thickness of 268 μm after removal of the epithelium. Although swelling with hypoosmolar riboflavin solution increased thickness to 406 μm and no adverse endothelial reaction was observed postoperatively, CXL could not stop the progression of keratoconus. This increase might indicate that there is a minimal and yet to be determined stromal thickness for effective CXL to occur.

CASE REPORT

A 48-year-old-man was referred to our department in July of 2007 because of bilateral progressive keratoconus. The initial slit-lamp examination revealed no direct signs of keratoconus in the right eye, whereas the left cornea showed numerous Vogt striae in the stroma and an apical scar. Scheimpflug analysis showed a distinct keratoconus in the right eye with K_{max} readings of up to 61.4 diopters (D) and a minimal corneal thickness of 342 μm, as measured by ultrasound pachymetry (SP 2000; Tomey GmbH, Erlangen, Germany). The left eye showed a more pronounced keratoconus (K_{max} readings of up to 67.5 D, ultrasound pachymetry 406 μm).

Over the following 2 years, the patient was followed regularly. In July 2009, Scheimpflug analysis showed a progression of K_{max} readings of more than 1.5 D in the right eye, whereas the left eye showed no progression. Manifest refraction in the right eye was −17.25 −5.75 × 44, and preoperative best spectacle–corrected visual acuity was 20/200. Corneal thickness, as measured by ultrasound pachymetry, was 306 μm.

In the face of a keratoplasty as the only valuable alternative, we discussed the possibility of a CXL procedure with the patient, although the cornea was distinctly thinner than any other cornea that we had treated before. We informed the patient that if preoperative swelling with hypoosmolar solution would not allow for a stromal thickness of more than 400 μm, CXL would not be performed. In this circumstance, the epithelium would be allowed to heal as described below.

After removal of the corneal epithelium and application of isoosmolar riboflavin solution for 30 minutes, the minimal stromal thickness was 268 μm, as measured by ultrasound pachymetry. We applied hypoosmolar riboflavin every 20 seconds for 5 minutes, and

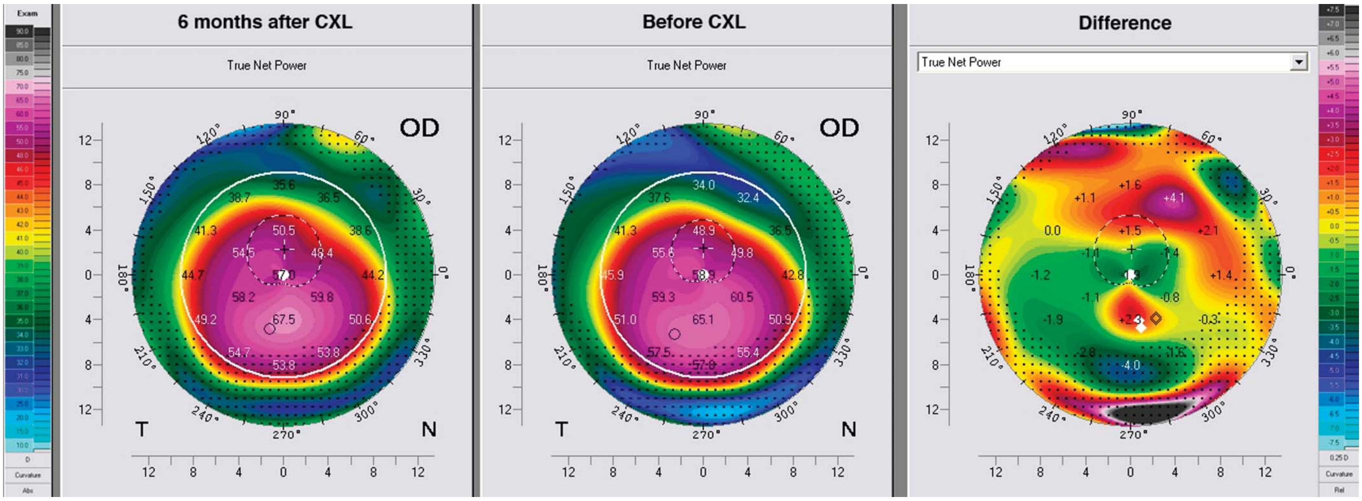

FIGURE 1. Scheimpflug analysis (true net power) of the anterior corneal surface before and after CXL. Left cornea before (A) and at 6 months after CXL (B). The difference image (C) shows a distinct increase of K_{max} readings of up to 2.3 D.

corneal thickness increased to 364 μm. After prolonged swelling for another 15 minutes, stromal thickness increased to 406 μm. The remaining part of the procedure was performed as described previously.[8] Because optical pachymetry does not provide reliable intraoperative data in swollen corneas because of the increased light scattering and absorption, all measurements (pre- and postoperative) were performed using ultrasound pachymetry.[9]

The early postoperative period was uneventful. Closure of the corneal epithelium was complete after 4 days, and the degree of postoperative haze reached a maximum of +1 at 6 weeks after CXL. The demarcation line was apparent at a depth of 60 μm of the stroma at 2 weeks after surgery.[10] Signs of endothelial reaction were absent at all postoperative time points. At 3 months after CXL, Scheimpflug analysis showed an increase of K_{max} values of the anterior surface of up to 1.9 D. At 6 months after CXL, progression of K_{max} readings was 2.3 D (Fig. 1). Accordingly, manifest refraction changed to -21.00 -7.5×31, and best spectacle–corrected visual acuity decreased to 20/400.

DISCUSSION

We recently modified the technique of CXL, so that corneas thinner than 400 μm after abrasion of the epithelium become eligible for treatment: the corneal stroma shows a swelling pressure of 50 to 60 mm Hg under physiological conditions. Irrigation of the corneal stroma with a solution that has a lower colloid osmotic pressure (hypoosmolar solution) leads to swelling of the stroma[11] up to double its normal thickness.[12] This characteristic behavior was used to increase corneal thickness before the CXL procedure.

In the case presented here, CXL in a cornea that was substantially thinner (268 μm) was not successful. This case raises the question about what the minimal stromal thickness for successful CXL might be. The following thoughts might help elucidate this question. The standard isoosmolaric CXL technique that has been used successfully in "common" keratoconus corneas (>400 μm) for the past 10 years[3] cross-links approximately 300 μm of the anterior stroma. This equals 75% of the total stromal thickness. A cornea with a stromal thickness of 268 μm, as exemplified, will thus present with a cross-linked part of 75% of 268 or 201 μm only, once it has returned to its normal thickness after the swelling. Such a limited amount of cross-linked cornea may not be sufficient to arrest an ectatic process. If we assume that we need a minimal (cross-linked) stromal thickness of 250 μm to prevent ectasia, similar to our guidelines for iatrogenic keratectasia, we need to respect a minimal preoperative thickness (X) of 250 = 75% times X. According to this equation, the minimal preoperative thickness should be at least 330 μm.

Accordingly, in our initial study on patients with progressive keratoconus and thin corneas, where we only included corneas with a minimal stromal thickness of 323 μm and more, we were able to arrest progression in all cases.[8] Current studies performed on the swelling behavior of the human cornea are based on the physiological response of the normal cornea, and little is known about the swelling properties of the keratoconus cornea.[11–14] In the case presented here, we achieved a minimal thickness of 406 μm after swelling, and no signs of endothelial damage were noted postoperatively. Based on the outcome in this case and the findings of the earlier study, the author suggests to perform CXL only in cases where stromal thickness is 330 μm or more before swelling with hypoosmolar riboflavin solution.

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