Accelerated Corneal Collagen Crosslinking for the treatment of Keratoconus

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ABSTRACT

Corneal Collagen Crosslinking (CXL) is a method that has been established as the treatment of choice for keratoconus. Corneal strengthening is achieved with the use of riboflavin (vitamin B2) in combination with ultraviolet radiation UV-A. According to clinical trials conducted in the last years and based on the latest publications, this technique has advanced. The time needed for the procedure has been drastically decreased, and this is achieved by increasing the energy of the UV-A radiation. This constitutes a safe method with encouraging clinical results. The method's success is based on its safety, the improvement in visual acuity, as well as the arrest of the progression of keratoconus, as can be seen by the improvement of the keratometric parameters.

Key words: keratoconus, corneal collagen crosslinking, CXL, accelerated CXL

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Introduction

Keratoconus is a progressive, non-inflammatory disorder of the cornea, characterized by ectasia of its stromal collagen fibrils. This procedure leads to irregular corneal thinning, loss of elasticity and loss of shear strength, thus the cornea assumes a bulging, conical shape (Figure 1). Keratoconus causes irregular astigmatism, which in turn decreases the patient's visual acuity. Corneal stromal thinning has been shown to have the most predominant effect on the development of the cornea's conical shape.[1]

Figure 1: Keratoconus

Corneal Collagen Crosslinking, also known as CXL, is an interventional method for the treatment of keratoconus and other disorders with similar pathophysiologic background, first experimentally described on porcine eyes by Spörl et al in 1997[2]. The procedure (Figure 2.) begins with the application of a topical anesthetic, followed by scraping of the central portion of the corneal epithelium (8-9 mm diameter), so as to facilitate the riboflavin's subsequent infiltration into the corneal stroma. Afterwards, the riboflavin solution will be instilled on the cornea, followed by application of UV-A radiation. The radiation induces a high-energy state on the riboflavin molecules, which in turn cause the formation of free radicals. This process induces the polymerization and crosslinking of monomeric collagen fibrils into strongly tensile polymeric collagen fibers, thus strengthening the cornea and putting a halt to the progression of keratoconic ectasia[3]. Using the classic "Dresden Protocol", described by Wollensak et al[4], the de-epithelized cornea is instilled with a solution of 0.1% riboflavin 5-phosphate and 20% dextran every 5 minutes for 30 minutes, followed by exposure to UV-A radiation on 370 nm wavelength, 3 mW/cm^2 for 30 more minutes. This entails a total procedure length of more than one hour.

Figure 2: Cross-linking Procedure

It has been assumed that the same corneal strengthening can be achieved by applying more UV-A radiation energy in less time, namely 10 mW/cm^2 for 9 minutes[5]. This technique is named "Accelerated Corneal Collagen Crosslinking", or A-CXL. Reducing the operational time frame from one hour to about forty minutes encompasses the advantages of reducing the difficulty and time of the procedure for the clinician, as well as reducing the stress put on the patient, who has to lie still for less time. The main question that has to be answered is whether A-CXL indeed has the same or even better results than the classic method.

Efficacy comparison

A number of animal studies have been conducted in order to investigate the results of using high-energy, short-duration UV-A radiation on keratoconic corneas, after instilling riboflavin solutions. Wernli et al studied a total of 100 porcine eyes, divided into ten groups to receive different protocols of UV-A radiation. These included a spectrum of low-energy with long duration, up to high-energy with short duration protocols, always with the same total energy dose of 5.4 J/cm^2. The study's results showed that increasing the radiation energy succeeds in achieving greater results up to a maximum point of 50 mW/cm^2. Increasing the energy over this level produces inferior results in strengthening the cornea and halting keratoconus progression6 Although this is a result in animal studies, it raises the question of which the limits are in increasing UV-A energy output in human patients, so as to achieve better results.

Human clinical trials are also underway, aiming at correlating the two methods: the Accelerated Corneal Collagen Crosslinking A-CXL and the classic Corneal Collagen Crosslinking CXL, so as to compare the safety and efficacy of A-CXL to those of the classic CXL.

A clinical study of 42 eyes in 21 patients by Kanellopoulos[7] compares the two methods: the classic CXL using UV-A radiation of 3 mW/cm^2 for 30 minutes, and the A-CXL using 7 mW/cm^2 for 15 minutes. The study ascertains that the two studies have similar safety and efficacy. Specifically, the mean Best Corrected Visual Acuity, BCVA, increased from 20/30 to 20/25 in both groups of patients. The keratometric parameters also showed similar results using CXL and A-CXL. The mean spherical equivalent decreased by 2.5 and 2.1 diopters respectively, while the mean refractive cylinder was reduced by 2.9 and 2.5 diopters, showing no statistically significant difference between the two methods. Kmax decreased from 49.5 to 46.1 D in the A-CXL group and from 48.7 to 45.8 D in the CXL group. Four cases in the CXL and five cases in the A-CXL group had delayed re-epithelization that healed by the ninth post-operative day. Patient follow-up lasted a mean of 46 months.

A novel A-CXL technique that uses UV-A radiation of 9 mW/cm^2 for 10 minutes was used in a series of 23 patients, showing the efficacy of the method in stabilizing the progression of the keratoconic ectasia and inducing regression of the pathologic keratometric values. 23 eyes of 23 keratoconic patients were treated with A-CXL and their visual acu-

ity and keratometric parameters were evaluated preoperatively as well as the postoperative months 1, 3 and 6. On the sixth postoperative month, mean BCVA had improved from 0.49 to 0.34 logMAR (or 20/62 to 20/44 in Snellen charts). Keratometric parameters also improved, namely mean sphericity decreased from -4.47 to -3.79 diopters, mean cylinder was also found reduced from -5.60 to -4.55 D and mean Spherical Equivalent (SE) decreased from -7.22 to -6.36 D. Kmax was also significantly decreased8. This shows that A-CXL and the 9 mW/cm^2 Protocol in particular can be used as an effective treatment for keratoconus.

Tomita et al compared the two techniques, A-CXL and CXL in 48 eyes of 39 patients, finding no statistically significant difference between the two groups in a postoperative period of 1 year. 30 eyes received A-CXL (KXL system, 30 mW/cm^2, for 3 minutes, after 15 minutes instilling of riboflavin), while 18 eyes received the classic CXL protocol (CCL-365 Vario system, 3 mW/cm^2 for 30 minutes, after 15 minutes instilling of riboflavin). The patients were subjected to follow-up for one year. The study did not detect any statistically significant differences between the two protocols in the postoperative visual acuity and keratometric values, showing the similarity in efficacy of A-CXL and CXL. Furthermore, the study did not find any significant difference in postoperative Endothelial Cell Density (ECD) between the CXL and the A-CXL method of 30 mW/cm^2, concluding that the two methods are also equal in safety.[9]

In a larger study of 138 keratoconic eyes, a number of different protocols of UV-A radiation were used on patients that were followed-up for a postoperative period of one year. It was shown that the most efficacious protocols were the classic CXL (Dresden Protocol) as well as the A-CXL protocols of 9 mW/cm^2 and 18 mW/cm^2. The patients were divided into four groups. Group 1 received classic CXL (36 patients, 3 mW/cm^2, 30 minutes), while the rest of the patients received A - CXL: Group 2 (36 patients, 9 mW/cm^2, 10 minutes), Group 3 (33 patients, 18 mW/cm^2, 5 minutes) and Group 4 (33 patients, 30 mW/cm^2, 3 minutes). The results show that the mean Corrected Distance Visual Acuity, CDVA and the Spherical Equivalent, SE were significantly improved in all groups but Group 4 that showed no improvement. Of these groups, Group 3 had the best results. The keratometric parameters Kmax, Kmin were significantly improved in groups 1 and 2. Corneal Pachymetry and Specular Microscopy did not show any significant differences among the groups. This is to be noted, as other studies, such as that of Cingü et al[10] resulted in transient endothelial changes after use of A-CXL with more than 18 mW/cm^2, which was not observed in this study. Finally, Groups 1 and 2 showed a deeper corneal stromal demarcation line than the rest of the groups. No endothelial damage was noted in any of these groups[11]. The same group has shown in a previous study that UV-A radiation intensities of up to 30 mW/cm^2 are safe on experimental cultures of limbal endothelial cells[12]. This study demonstrates in human subjects that the efficacy of the A-CXL method correlates to the energy of radiation used. It seems that the classic Dresden Protocol as well as the novel A-CXL 9 mW/cm^2 and 18 mW/cm^2 Protocols are better in efficacy than the rest of the protocols considered.

In a prospective study of 62 eyes, A-CXL (18 mW/cm^2 for 5 minutes, 31 patients) was compared to the classic CXL (3 mW/cm^2 for 30 minutes, 31 patients). The patients were evaluated preoperatively and the postoperative months 1, 3 and 6. No statistically significant differences were detected between the two methods concerning the improvements in visual acuity, both Uncorrected Distance Visual Acuity (UDVA), and Corrected Distance Visual Acuity (CDVA). Keratometric Values also showed similar results between the two methods, with no significant differences in the Spherical Equivalent, Kmax and Kmin. Corneal Asphericity and the Corneal Spherical Aberration were also similar, as were corneal hysteresis and the corneal resistance factor. These parameters show small differences between the two methods, which are judged to be equally efficacious in halting keratoconic progression. However, the central thickness of the cornea postoperatively was found to be greater in the CXL group than the A-CXL group[13].

The mean corneal stromal demarcation line depth was measured using Confocal Microscopy and Anterior Segment Optical Coherence Tomography (AS OCT) in 18 eyes that underwent classic CXL. No statistically significant difference was detected between the two methods in measuring the demarcation line depth[14]. Using the AS OCT method, the corneal stromal demarcation line was measured in 21 eyes of 16 patients that received either CXL with the Dresden Protocol (3 mW/cm^2, 30 minutes, 9 eyes) or A-CXL with the 9 mW/cm2 Protocol (9 mW/cm^2, 10 minutes, 12 eyes) and was compared between the two groups. The study showed that the demarcation line was deeper in the Dresden Protocol patients (350.78 μm) than in the 9 mW/cm^2 Protocol patients (288.46 μm)[15]. The difference in demarcation line depth correlates with the infiltration of the therapy through the cornea[16].

A pilot study was conducted to investigate the results of using microwave keratoplasty after A-CXL for treating keratoconus. 6 eyes of 4 patients were prospectively investigated without randomization and followed up for six months. UDVA was found to be significantly improved from 0.92 to 0.47 logMAR (20/166 to 20/59 in Snellen charts), however no significant improvement was detected in CDVA. The keratometric parameters improved significantly. Kmean was reduced more than 7.00 D. Higher order aberration was reduced from 1.89 preoperatively to 1.51 μm and corneal

primary coma aberration was reduced from 1.45 μm to 0.84 μm. No statistically significant differences were found in biomechanical parameters. However, despite the good immediate postoperative results, a serious regression of the effects was detected in keratometry in the end of the 6-month follow-up.[17]

Safety comparison

Preoperative patient characteristics were studied in 96 eyes as prognostic factors for procedure success. These patients received the Dresden Protocol classic CXL and were followed up for one year. All patients had significant postoperative improvement in mean CDVA and Kmax. It was shown that patients with worse preoperative CDVA (20/40 and lower or higher than 0.3 logMAR), had better visual improvement postoperatively after CXL treatment. On the other hand, age of more than 30 years and corneal thickness less than 450 μm correlated with greater Kmax flattening. Gender, preoperative Kmax and the topographic location of the keratoconus did not show any statistically significant correlation to prognosis.[18]

Three groups of patients (24 in total) received CXL, A-CXL and trans-epithelial CXL, in which the corneal epithelium is not scraped off before instilling the riboflavin solution. The patients were evaluated preoperatively, and in the postoperative months 1, 3 and 6, using in vivo confocal microscopy to measure the postoperative changes in the anterior segment of the cornea. It was shown that A-CXL caused greater changes in the corneal epithelium than the classic CXL method. The trans-epithelial method did not cause any epithelial changes, as is its purpose. The corneal epithelial apoptosis healed by the third postoperative day after both the classic CXL and the A-CXL methods, without any significant differences between the two. The sub-basal nervous plexus on the corneal surface had not returned to its normal, preoperative status 6 months postoperatively in either one of the methods CXL and A-CXL. The middle and posterior segments of the cornea did not show any postoperative changes after any of the three protocols used.[19]

Cingü et al showed that there can be transient corneal endothelial changes in keratoconic eyes that receive A-CXL treatment with excessively high energy and short duration (five minutes), which will regress in three to six months postoperatively. For this reason, guidelines are to be set concerning the A-CXL technique so as to minimize its toxic effects on the endothelium. This study consisted of 36 patients with keratoconus that received A-CXL (18 mW/cm2 for 5 minutes) and were followed up on the postoperative months 1, 3 and 6 with corneal specular microscopy. Statistically significant changes were discovered in endothelial cell density, hexagonality percentages and the coefficient of variation of endothelial cell area in the first week and the first month postoperatively compared to the preoperative values, which delineates the damage that the corneal endothelium suffered from the five-minute A-CXL technique. Cell density was found to return to its preoperative value on the sixth postoperative month, while the rest of the parameters returned on the third month10. Notably, the endothelial damage sustained after A-CXL Protocols is a matter of controversy in the literature, where some articles.

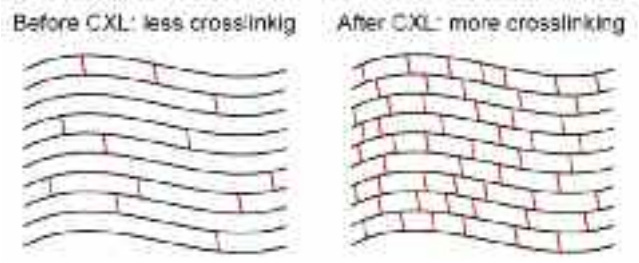

Figure 3: CXL increases the amount of Crosslinking in the corneal collagen fibers.

Η ΔΙΑΣΥΝΔΕΣΗ ΤΟΥ ΚΟΛΛΑΓΟΝΟΥ ΤΟΥ ΚΕΡΑΤΟΕΙΔΟΥΣ ΣΤΗ ΘΕΡΑΠΕΙΑ ΤΟΥ ΚΕΡΑΤΟΚΩΝΟΥ

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ΠΕΡΙΛΗΨΗ

Η διασύνδεση του κολλαγόνου του κερατοειδούς είναι μια μέθοδος η οποία έχει καθιερωθεί για την αντιμετώπιση του κερατοκώνου. Η τεχνική της ενίσχυσης του κερατοειδούς επιτυγχάνεται με τη χρήση της ριβοφλαβίνης σε συνδυασμό με την υπεριώδη ακτινοβολία UV-A. Σύμφωνα με τις κλινικές μελέτες που έχουν διεξαχθεί τα τελευταία χρόνια και με βάση τις πιο πρόσφατες δημοσιεύσεις η τεχνική αυτή έχει εξελιχθεί. Ο χρόνος που απαιτείται έχει μειωθεί και αυτό επιτυγχάνεται με την αύξηση της ενέργειας της UV-A. Αποτελεί μια ασφαλή μέθοδο με θετικά κλινικά αποτελέσματα.

Η αποτελεσματικότητα της έγκειται στην ασφάλεια της, στην βελτίωση της οπτικής οξύτητας, καθώς και στην αναστολή της εξέλιξης του κερατοκώνου, όπως φαίνεται από τη βελτίωση των κερατομετρικών παραμέτρων.

Λέξεις κλειδιά: κερατόκωνος, διασύνδεση του κολλαγόνου του κερατοειδούς, επιταχυνόμενη διασύνδεση του κολλαγόνου του κερατοειδούς.

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