Combined intrastromal corneal rings (KeraRing) and corneal collagen cross-linking (UV-X) in patients with keratoconus – which is the right treatment sequence?

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INTRODUCTION

Keratoconus is relatively rare disease of the cornea with reported frequency approximately 1 in 2,000 in the general population. [1] It is an asymmetric, bilateral, progressive and non-inflammatory ectasia of the cornea due to a gradual biomechanical instability of the cornea. Usually, the condition starts at puberty and progresses until mid-thirties; up to 20% of the patients will have their cornea affected to such an extent that their best corrected visual acuity is severely decreased and not achievable with any optical means. [1]

Once the patient is not able to use rigid contact lenses, there are few surgical alternatives for correction. Expectations are limited, and consequences may be unpredictable, anatomically and functionally. [1] Apart from different lamellar and penetrating keratoplasty procedures, the introduction of intracorneal rings such as INTACS (Addition Technologies, Fremont, CA), Ferrara rings (Ferrara Ophthalmics, Validolid, Spain) or Kerarings (KeraRing, Mediphacos, Belo Horizonte, Brazil) have provided us with tools for managing keratoconus. [2]-[5],[18]-[36]

These vision-correcting methods attempt to regularize the front surface of the cornea, while maintaining the existing biomechanical status within the underlying stroma. In cases where the irregular astigmatism is progressive, such as keratoconus, pellucid marginal degeneration, or post-laser induced iatrogenic ectasia, the corneal stroma is structurally weakened, and some may worsen following tissue ablation procedures.

Corneal collagen cross-linking with riboflavin and UVA (UV-X) is a new technique of corneal tissue strengthening by using riboflavin as a photosensitizer and UVA to increase the formation of intra- and inter-fibrillar covalent bonds by photosensitized oxidation. [6] This technique is similar to photo-polymerization in polymers, where biomechanical stabilization of the cornea is achieved. To correct the irregular astigmatism due to a biomechanically unstable cornea, a primary intervention, such as collagen cross-linking should be considered to potentially stabilize the cornea.

CORNEAL COLLAGEN CROSS LINKING WITH RIBOFLAVIN AND UVA (UV-X)

The key indication for the use of UV-X is to inhibit the progression of corneal ectasias, such as keratoconus and pellucid marginal degeneration. [6]-[12] Collagen cross-linking may also be effective in the treatment and prophylaxis of iatrogenic keratectasia, resulting from laser in situ keratomileusis. [13] Beyond keratectasia, the new technique can also be used in treating corneal melting conditions or infectious keratitis because cross-linking would strengthen a collagenolytic cornea while UVA irradiation sterilizes the infectious agent. [14]

In vitro studies show that the UVA light arriving to an intact cornea is absorbed within its lamellae by approximately 30%, while an additional 50% of the UVA absorption occurs in the lens. [6] On the other hand, in the presence of riboflavin acting as a photo-sensitizer, the cornea absorbs a considerable amount of UV light. Thus, using the irradiance of 3 mW/cm^2 of UVA and 0.1% riboflavin, as much as 95% of UVA light will be absorbed within the cornea. This results in a twenty-fold reduction of the original irradiance from 3 mW/cm^2 of UVA (at the corneal surface) down to 0.15 mW/cm^2 (at the endothelial level), which is below the cytotoxic threshold for endothelium of 0.36 mW/cm^2. [15]-[17]

For the sake of comparison, the same UVA irradiance at the corneal surface as used in this study can be measured at noon during an average sunny summer day in the tropics (23 degree of latitude and 800 m above the sea level).

Even with the expected reduction of irradiance from the corneal surface towards deeper layers of corneal stroma, as described above, the irradiation levels still exceed the threshold all the way down to the depth of about 300 microns. Therefore, keratocyte apoptosis in the anterior segment of the corneal stroma has been described, and a demarcation line between the treated and untreated cornea has been clearly shown in in-vitro studies. [15]-[17] Confocal microscopy studies also show that repopulation of

keratocytes is already visible one month after the treatment, reaching its preoperative quantity and quality in the terms of functional morphology within six months after the treatment. [10]

Surgical technique

The treatment procedure IS conducted under sterile conditions in an operating theater. Topical anesthetic eyedrops is applied. After an abrasion of the corneal epithelium of 7 mm, 0.1% riboflavin solution in 20% dextran (Peshckemed, Huenenberg, Switzerland) is applied on the cornea every 3 minutes for 30 minutes. The saturation of the cornea with riboflavin and its presence in the anterior chamber is monitored closely by slit-lamp inspection prior to treatment. Riboflavin saturation ensures the formation of free radicals whereas riboflavin shielding ensures the protection of deeper ocular structures such as the corneal endothelium. Prior to treatment, ultrasound pachymetry is performed over the deepithelialized cornea at the thinnest point to ensure a minimal corneal thickness of 400 μm.

UVA irradiation is performed using an optical system (Koehler illumination) consisting of an array of 7 UVA diodes with a potentiometer in series to allow for regulation of voltage (UV-X, Peschkemed, Huenenberg, Switzerland) [Figure 1]. Prior to treatment, intended irradiance of 3 mW/cm2 surface irradiance (5.4 J/cm^2 surface dose) is calibrated using a UVA meter (LaserMate-Q; LASER 2000, Wessling, Germany) at a working distance of 6 cm. Irradiance is performed for 30 minutes using 3 mW/cm^2, corresponding to a surface dose of 5.4 J/cm^2. During treatment, riboflavin solution and topical anesthetic (oxybuprocaine 0.4%) is applied every two to three minutes to saturate the cornea with riboflavin and moisten it.

After the treatment, ofloxacin 0.3% (Exocine, Allergan, Irvine, CA) is applied and a bandage contact lens was then fitted to the corneal surface until re-epithelialization. Typically, the contact lens is removed on the third day. The patient is given topical

steroid dexamethasone phosphate 0.1% (Maxidex, Alcon-Couvreur, Belgium) four times daily, with gradual decrease of dosage over the following two months.

Clinical results

The first *in vivo* controlled clinical study by Wollensak et al that included 23 eyes with moderate or advanced progressive keratoconus showed that collagen cross-linking was effective in halting the progression of keratoconus over a period of up to four years [7]. In this study, a mean preoperative progression of keratometry (max K) by 1.42 D in 52% of eyes over a 6-month period immediately prior to the treatment was followed by a postoperative decrease in 70% of eyes. The statistics also revealed a reduction of max K by 2.01 D, while the postoperative SEQ was reduced by an average of 1.14 D. At the same time, 22% of the untreated fellow control eyes had a postoperative progression of keratectasia by and average of 1.48 D.

Results from other study by Coscunseven et al confirm the previous findings: the group treated with UV-X showed a similar mean decrease in SEQ by 1.03 +/- 2.22 (-5.25 to +3.75) D, in cylinder by 1.04 +/- 1.44 (-2.00 to +4.00) D, while max K decreased by 1.57 +/- 1.14 (0.00 to 3.90) D. [11] At the same time the non-treated group showed progression of all measured corneal parameters. In another study Jankov et al found that progression of keratoconus stopped in all patients, in contrast with ongoing progression in all of them in the six months period prior to the surgery. Max K decreased by more than 2 D (from 53.02 ± 8.42 to 50.88 ± 6.05 D), SEQ in less that 1 D (from -3.27 ± 4.08 to -2.68 ± 3.02 D), while refractive cylinder decreased by less 0.5 D (from -2.29 ± 1.77 to -1.86 ± 0.92 D). None of the eyes lost any line of BSCVA, 12 maintained the preoperative BSCVA, 7 gained one line, 5 gained two lines, and 1 patient gained three lines of BSCVA. [12]

Corneal cross-linking has also been used successfully in stopping the advancement of iatrogenic ectasia in eyes after excimer laser ablation. In a recently published study, UV-X was performed in ten patients with a formerly undiagnosed *forme fruste*

keratoconus or pellucid marginal corneal degeneration that underwent LASIK for myopic astigmatism and subsequently developed iatrogenic keratectasia. [13] UV-X led to an arrest and/or even a partial reversal of keratectasia over a postoperative follow-up period of up to 25 months as demonstrated by pre- and postoperative corneal topography and reduction of maximal K-readings.

When compared to other treatment methods for KC such as intracorneal rings, UV-X shows only a modest reduction in SEQ, cylinder and max K. However, one must not forget that UV-X method likely only *stops* or *slows down,* rather than revert the progression of the keratoconus. A small regression that occurred may be explained as an effect of the rearrangement of corneal lamellae and the surrounding matrix. [6] Due to an increased number of cross-linking sites within the collagen molecule after UV-X, stiffer fibrils and lamellae are likely generated. This process produces a rearrangement of corneal lamellae and the consequent relocation of the surrounding matrix, which, in turn, results in the reduction of the central corneal curvature.

Considering the collagen turnover in the cornea of several years, it is yet to be seen in the long-term studies whether the repeated treatment may be necessary.

Although UV-X resulted in a decrease of SEQ, astigmatism, and max K, UCVA and BSCVA increased only modestly up to one line. Other studies with alternative treatment methods, on the other hand, showed more than two-line increase in BCVA after the implantation of the intracorneal rings. [4]-[5][18]-[38]

This leads us to the following hypothesis: If the result of the treatment with UV-X was only to stop or slow the progression of the KC, while other methods can re-shape the cornea, a logical solution would be to combine the two treatment methods in order to synergize their effect. This way, a pre-treatment with an alternative method would significantly re-shape the cornea by flattening and regularizing it, which would be followed by UV-X in order stabilize the cornea in this newly achieved state. Alternatively, the UV-X procedure could be done first, followed by a reshaping procedure.

INTRACORNEAL RING SEGMENT IMPLANTATION

The implantation of intracorneal ring segments is a minimal invasive surgical procedure for keratoconic [18] or post-LASIK ectatic corneas. [19] Before the introduction of femtosecond laser technology, tunnel creation was accomplished manually using mechanical devices. [20]-[29] This step of the procedure related with a number of possible complications such as epithelial defects, anterior or posterior corneal perforations, infectious keratitis, asymmetric segment placement, corneal stromal edema around the incision, extension of the incision towards the central visual axis or the limbus and persistent incisional gapping. [20]-[24]

Recently, tunnel creation is performed using the femtosecond laser, which can deliver energy accurately to a precise depth in a programmed way. Studies indicate that ICR implantation using a femtosecond laser is a safe and effective procedure for treating keratoconic corneas.[30]-[38] The femtosecond laser minimizes procedure time and decrease the risk of inflammation or infection.

Intracorneal Ring Segments (INTACS, Addition Technolgy, Fremont, CA, USA) are originally designed to correct low myopia. [39] Refractive effect is achieved by adding tissue to the periphery, thus flattening the central corneal curvature and maintaining the clarity of the central optical zone. Its advantage is that it is reversible and tissue-saving technique. After the first result with corrections of low myopia, other reports showed its efficacy in the regularization of the irregular astigmatism due to keratoconus [18],[20]-[30],[32]-[38] and iatrogenic keratectasia post LASIK [19],[31].

There are several different types of intracorneal rings, with varying curvature, width and zone of implantation. INTACS inserts have a crescent-shaped arc of 150 degrees of length. Their inner diameter is 6.8 mm and the outer 8.1 mm, with a thickness which ranges form 0.25 to 0.45 mm in 0.05 increments. Last generation INTACS SK still have an arc length of 150 degrees but come only in 0.40 and 0.45 mm thicknesses. The

profile has now an elliptical, edgeless shape apparently providing a diffractive dsign to achieve reduced halo, glare and increased quality of vision at the 6.0 mm optical zone.

The KeraRing (Mediphacos, Belo Horizonte, Brazil) is a newly developed implantable intrastromal corneal ring segment made of PMMA and is characterized by a triangular cross section that induces a prismatic effect on the cornea. The KeraRing's apical diameter is 5 mm and the flat basis width is 0.6 mm with variable thickness (0.15 to 0.30 mm thickness with 0.5 mm steps) and arc lengths (90, 160 and 210 degree).

Surgical technique

The surgical procedure of implantation of the corneal rings is performed under sterile conditions and topical anesthetic drops in an operating theater. The Purkinje reflex is chosen as the central point and marked under the WaveLight Allegretto Biomicroscope. A 5-mm marker is used to locate the exact ring channel. Corneal thickness is measured intraoperatively using ultrasonic pachymetry (Sonogage, Cleveland, Ohio, USA) along the ring location markings. Tunnel depth is set at 80% of the thinnest corneal thickness on the tunnel location.

Arc length and thickness were chosen according to the manufacturer's nomogram. The IntraLase Femtosecond Laser (Advanced Medical Optics, Santa Ana, California, USA) is used and the channel's inner diameter is set to 4.4 mm, while the outer diameter is 5.6 mm. The entry cut thickness is 1 μm, and the ring energy used for channel creation is 1.30 μj. The entry cut energy is 1.30 μj and channel creation timing with the 60 kHz femtosecond laser is 15 seconds. The intracorneal ring segments is implanted immediately after channel creation, before the bubbles disappear, as they reveal the exact tunnel location. To avoid any injury to the incision area, the segment os directly implanted with the special KeraRing forceps.

Postoperatively antibiotic steroid eye drops are prescribed, taken 4 times daily for 2 weeks. The patients are instructed to avoid rubbing the eye and to use preservative-free

artificial tears frequently. On the first postoperative day, a slit-lamp biomicroscopic examination is performed. Corneal wound healing and migration of the segment is evaluated in each eye. At the last follow-up examination manifest refraction, UCVA and BSCVA, slit-lamp, and topographic examination are performed.

Clinical results

In 2001 Colin et al reported one-year results in 10 patients with keratoconus showing a significant improvement of BSCVA by two lines, reduction of SEQ and max K by more than 2.00 D and 4.00 D respectively after implantation of INTACS. [40] Miranda et al. reported in 2003 a higher reduction of SEQ and max K by more than 2.50 D and 6.00 D respectively using the Ferrara rings. Miranda's study included 26 eyes diagnosed with keratoconus grades 3 and 4. [5] The rings flattened the central and peripheral cornea, and thus displacing the corneal apex to its physiological position in front of the pupil by reducing the paracentral ectasia commonly seen in keratoconic corneas.

Other studies by Alio et al [25], Siganos et al [41] and Kymionis et al [18] show similar improvement in UCVA and BSCVA with a small number of eyes losing lines of BSCVA, while a majority enjoyed increase of BSCVA by up to 6 lines, as well as significant decrease of SEQ and manifest cylinder.

In the only comparative study regarding INTACS inserts using the femtosecond laser or a mechanical spreader of Rabinowitz et al reported no significant difference between the two groups regarding UCVA, BSCVA, SEQ, max K, surface irregularity index and surface asymmetry index. [20] However, considering the complication rate, femtosecond group showed fewer and less intense complications than the mechanical one.

COMBINED INTRASTROMAL CORNEAL RINGS (KERARING) AND CORNEAL COLLAGEN CROSS-LINKING (UV-X) IN PATIENTS WITH KERATOCONUS

The key indication for the use of UV-X is to inhibit the progression of corneal ectasias, such as keratoconus and pellucid marginal degeneration. On the other hand, the implantation of intracorneal ring segments is a minimal invasive surgical procedure for keratoconic corneas. While the former method stops or slows down the progression of the ectatic process without significantly changing its shape, the latter one considerably flattens and notably regularizes the cornea, though with no influence on the biomechanical properties of the cornea as the underlying cause of the ectasia. Thus, a logical solution would be to combine the two treatment methods in order to synergize their effect.

Questions rose about the correct treatment sequence: will the cornea already pre-treated with UV-X react to the ICR implantation the expected way or will its effect be lessened by being applied over now stiffer a cornea? Alternatively, will UV-X exercise the same effect over a cornea with ICR already in place?

Clinical results

Kamburoglu et al [40] reported a case with postoperative LASIK ectasia with best spectacle-corrected visual acuity (BSCVA) of 20/60 and 20/80 in the right and left eyes, respectively, was operated for Intacs SK implantation for both eyes. Spherical equivalent refraction and mean keratometric values in the right and left eyes were -14.50 diopters (D) and -10.50 D and 56.20 D and 50.70 D, respectively. Following bilateral Intacs SK implantation, UV-X was performed after 1 day in the left eye and 1 month in the right eye.

Eight months postoperatively, BSCVA was 20/25 and 20/25, manifest refractions were -1.50 x 170 and -1.25 x 50, and mean keratometric values were 47.20 and 44.20 D in the right and left eyes, respectively.

In 2007 Chan et al performed a retrospective nonrandomized comparative case series comprised 12 eyes of 9 patients who had inferior-segment INTACS placement without

UV-X and 13 eyes of 12 patients who had inferior-segment INTACS placement combined with UV-X. [41] Corneal collagen cross-linking with riboflavin was performed after the INTACS segments were inserted.

The INTACS with UV-X group had a significantly greater reduction in cylinder than the INTACS-only group, Max K were reduced significantly more in the INTACS with UV-X group. The conclusion was that the addition of UV-X to the INTACS procedure resulted in greater keratoconus improvements than INTACS insertion alone.

We conducted a prospective comparative study that comprised forty-eight eyes of forty-three patients and progressive keratoconus. In Group 1, UV-X corneal collagen cross-linking treatment was performed first, followed by intracorneal rings implantation. In group 2, intracorneal rings implantation was carried out first, followed by UV-X. Mean interval between the steps was 7 months, while mean follow-up after the second step was 6 months.

Our results in the group 1, where UV-X was applied on an intact cornea, expectedly show a similar results as in the literature for UV-X treatments only: increase in UVA and BSCVA of about one line and half a line respectively, and a decrease in SEQ, Cyl and mean K of 1.39 D, 0.44 D and 0.88 D respectively. In the group 2, where UV-X was applied to a cornea with ICR in place, the results show a similar increase in UVA, BSCVA, and a decrease in Cyl, while there was a statistically insignificantly smaller increase in SEQ and insignificantly higher decrease in max K.

Therefore, UV-X treatment showed a similar effect when applied over the cornea with ICR already in place as it had on an intact cornea, having a similar modest improvement in all the corneal parameters. It is yet to be seen after a longer follow-up if the biomechanical effect will also be present in the later postoperative period as it has been described in an intact one.

Compared to a modest reduction in SEQ, Cyl and max K after UV-X only, other treatment methods for KC such as intracorneal rings, show much more a significant improvement of the corneal parameters. Miranda et al. reported a reduction of SEQ and max K by more than 2.50 D and 6.00 D respectively using the Ferrara rings. Miranda's study included 26 eyes diagnosed with keratoconus grades 3 and 4. [5] The Ferrara rings flattened the central and peripheral cornea, and thus displacing the corneal apex to its physiological position in front of the pupil by reducing the paracentral ectasia commonly seen in keratoconic corneas.

Our results in the group 2, with implantation of ICR in an intact cornea, expectedly show the same results as in the literature for ICR only: increase in UVA and BSCVA of about two lines and three lines, and a decrease in SEQ, Cyl and mean K of 3.31 D, 2.05 D and 2.94 D respectively. In the group 1, where ICR were implanted after the previous treatment with UV-X, the results show a similar, however slightly smaller increase in UVA and mean K, while there was a statistically significantly smaller increase in BSCVA of one line, There was also a statistically significantly smaller decrease SEQ and Cyl by 2.76 D and 1.32 D respectively.

Therefore, ICR implantation showed a greater effect when applied over an intact cornea rather than on a cornea already treated with UV-X, although showing improvement in all the corneal parameters in either treatment sequence.

Considering the overall effect of joint treatments, the group 2 showed a higher overall increase in BSCVA and Cyl ($p<0.01$), as well as higher but insignificant overall increase in UVA and decrease in SEQ compared with the group 1. This finding suggests that, although each of the treatment steps demonstrates the improving effect on the cornea, a stiffer cornea already treated by UV-X holds back the flattening forces of ICR, thus restricting their effect and decreasing its maximal flattening potential. In order to achieve the maximal overall effect, ICR should be applied first, allowing them to reshape the cornea unrestrictedly, after which the additional UV-X treatment should be applied to additionally flatten the cornea and biomechanically stabilize it.

A small regression that occurred has been explained as an effect of the rearrangement of corneal lamellae and the surrounding matrix. [6] Due to an increased number of cross-linking sites within the collagen molecule after UV-X, stiffer fibrils and lamellae are likely generated. This process produces a rearrangement of corneal lamellae and the consequent relocation of the surrounding matrix, which, in turn, results in the reduction of the central corneal curvature. [11][12] We can therefore conclude that the same process occurred in the cornea with ICR in place, and assume that the biomechanical effect will also be present in the later postoperative period, which is yet to be seen after a longer follow-up.

More detailed both in-vitro and in-vivo studies of the corneas treated with combination o UV-X and ICR implanation would be of a greater interest in order to show the potential influence of the ICR on the distribution of the UV light, pharmacodynamics of the riboflavin, as well as a potential alteration in the cross-linking effect. Regarding safety issues when validating central corneal pachymetry, ECC and IOP, there was no significant change in either of the parameter in our study.

CONCLUSIONS

Combination of ICR implantation with UV/riboflavin mediated corneal collagen cross-linking procedure seems to have a synergic effect for reverting the progressive irregular astigmatism due to keratoconus or iatrogenic ectasia. Implantation of ICR followed by the UV-X resulted in greater keratoconus improvements than UV-X procedure followed by ICR implantation.

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FIGURE LEGENDS

Figure 1 – Treatment in progress with the cornea soaked with riboflavin (yellow) and irradiated by the UV lamp. In the upper-right corner the UV lamp from the patient's perspective can be seen.

Figure 2 – Slitlamp examinations three days after the UV-X treatment: one can observe a thin demarcation line between the anterior (treated) and the posterior (non-treated) portion of the cornea (left); three months after UV-X treatment the line almost completely disappears and the cornea returns anatomically and physiologically to its previous state. (Courtesy of prof dr dr T. Seiler, Switzerland)

Figure 3 – Slitlamp examination ? days after KeraRing implantation 6 months after the UV-X treatment: one can observe perfectly clear cornea and no signs of inflammation around the edges of the ring segments.