Simultaneous Topography-Guided Photorefractive Keratectomy and Accelerated Corneal Collagen Cross-Linking for Keratoconus

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**Purpose:** To study the evolution of visual and refractive outcomes through the first year after simultaneous topography-guided photorefractive keratectomy (t-PRK) and corneal collagen cross-linking (CXL) in keratoconus.

**Methods:** This retrospective case series included 85 eyes of 66 patients with a mean age of 26.3 ± 5.7 years, which underwent simultaneous t-PRK with accelerated CXL. Patients were examined for uncorrected distance visual acuity and corrected distance visual acuity (CDVA), flat and steep keratometry readings, and manifest refraction spherical equivalent at 1, 3, 6, and 12 months.

**Results:** At 12 months, all study parameters demonstrated a statistically significant improvement with uncorrected distance visual acuity 0.46 ± 0.49 logMAR (vs. 0.86 ± 0.39 logMAR preoperatively), CDVA 0.11 ± 0.12 logMAR (vs. 0.41 ± 0.27 logMAR preoperatively), manifest refraction spherical equivalent −2.80 ± 4.47 D (vs. −4.51 ± 4.68 D preoperatively), flat keratometry 43.84 ± 3.24 D (vs. 44.61 ± 3.12 D preoperatively), and steep keratometry 46.05 ± 3.94 D (vs. 48.10 ± 3.68 D preoperatively). Although 90.6% eyes gained 1 or more lines of CDVA, no eyes lost any lines of CDVA. In all, 37.6% of the eyes demonstrated an improvement of 4 or more lines of CDVA with a maximum improvement of 11 lines of CDVA in 1 eye.

**Conclusions:** Simultaneous t-PRK with accelerated CXL improved the spherocylindrical refraction and visual function of keratoconus eyes, and the outcomes were stable through 12 months’ follow-up. Future studies with longer follow-up and larger data set are necessary to validate the results of the current study and evaluate the long-term safety and efficacy.

**Key Words:** topography-guided photorefractive keratectomy, corneal collagen cross-linking, t-PRK with CXL, keratoconus management

*Keratoconus is a bilateral, nonsymmetric, noninflammatory progressive corneal dystrophy that results in biomechanical weakening and progressive steepening. As keratoconus advances to a stage where contact lenses are not tolerated, surgical intervention is warranted to gain useful vision. Two major aspects that must be considered in the treatment of keratoconus are irregular astigmatism and corneal biomechanical instability. Therefore, the keratoconus surgical procedures may be classified as corneal regularization and corneal stabilization techniques. Corneal regularization may be further categorized as subtractive (eg, excimer laser ablation) or additive techniques [eg, lamellar keratooplasty, intracorneal ring segments (ICRS)] depending on if tissue is removed or added to the cornea, respectively.

Although the subtractive corneal regularization techniques such as excimer laser surface ablation were attempted more than a decade ago, these did not gain acceptance as tissue removal was associated with an increased risk of progression of keratoconus. Unlike standard photorefractive keratectomy, a recent development of a surface ablation protocol, topography-guided photorefractive keratectomy (t-PRK) targets to regularize the cornea based on topography measurements. Although the conventional refractive components of sphere and cylinder may be simultaneously incorporated into the treatment profile, in the treatment of keratoconus, tissue sparing is the prime consideration, and therefore, t-PRK typically limits the maximum depth of tissue ablation to less than 50 μm.

Separately, the corneal stabilization technique of corneal collagen cross-linking (CXL) has been demonstrated to successfully retard or eliminate the progression of keratoconus. There is a potential to combine the corneal regularization technique like t-PRK with CXL to achieve regularization of the corneal shape together with strengthening, thereby addressing the deficiencies of a subtractive technique.

Preliminary studies on the combined procedure have demonstrated that t-PRK with or without partial refractive correction can reduce irregular astigmatism and refractive error on one hand and increase biomechanical strength on the other hand, probably allowing long-term visual rehabilitation. Conventional CXL is a time-consuming procedure, lasting more than 60 minutes. Accelerated CXL has recently been proposed as an alternative means of speeding up the procedure by delivering higher irradiance to the cornea thus reducing the required light exposure time. In the current
study, we systematically examined the evolution of the visual and refractive changes through the first year of follow-up (1, 3, 6, and 12 months) after simultaneous t-PRK with partial correction of refraction followed by accelerated CXL in patients with keratoconus.

METHODS

Eighty-five eyes of 66 patients with mean age of 26.3 ± 5.7 years (range: 15–41 years), who underwent simultaneous t-PRK with CXL between January 2012 and April 2012 and completed 1 year follow-up, were included in this retrospective, interventional, noncontrolled study. All patients were operated by one surgeon (H.S.) at Ebsaar Eye Surgery Centre, Dubai, United Arab Emirates. All patients were informed about the aims, nature, and expected results of this procedure and signed an appropriate consent form. The study was approved by the local ethics committee. The presence of keratoconus was determined by the posterior and anterior elevation and pachymetric and keratometric parameters, as reported by Mihaltz et al.11 Inclusion criteria were the presence of keratoconus, as determined by topography (Allegro Oculyzer, Pentacam; WaveLight Laser Technologie AG, Erlangen, Germany),11 contact lens intolerance, and the expected residual corneal stromal bed thickness >350 μm (without including the epithelium thickness) after maximum ablation of 50 μm at the corneal centre. Exclusion criteria were patients with a history of delayed epithelial healing, history of laser-assisted in situ keratomileusis, and pregnancy or lactation during the course of the study. The patients with very thin corneas, below 400 μm, corneal scarring, or very poor corrected distance visual acuity (CDVA) <0.05 were not included in the study. Contact lens wearers were instructed to discontinue contact lens use for a minimum of 2 weeks before the preoperative eye examination for soft contact lenses and 1 month for hard contact lenses.

Surgical Technique

Under topical anesthesia, the central 9-mm of the epithelium was removed using an Amoils brush (Amoils Epithelial scrubber; Innovative Excimer Solvers, Inc, Toronto, Canada). All t-PRK procedures were performed using the T-CAT software from Wavelight Allegretto eye Q 400 laser system (WaveLight Laser Technologie AG) followed by accelerated collagen CXL with the corneal CXL system Peschke GmbH CCL-365-18 (Peschke Meditrade GmbH, Huenenberg, Switzerland). Partial t-PRK was performed with a 5.5-mm optical zone. The transition zone was 1.5 mm. Partial t-PRK refers to the correction of up to 70% of astigmatism and some of the sphere component without exceeding 50-μm ablation in planned stromal removal. Mitomycin C 0.2 mg/mL was applied for 20 seconds and washed with 40 mL of balanced salt solution (Alcon Laboratories, Fort Worth, TX). Accelerated CXL was performed by soaking the exposed stroma with isotonic riboflavin 0.1% in 20% dextran (Medio Cross Isotonic Solution; Medio-Haus Medizinprodukte GmbH, Kiel, Germany) for 5 minutes. Additionally, in corneas with mean preoperative pachymetry (with epithelium) of less than 450 μm (18 eyes), we also administered 0.1% hypotonic riboflavin (Medio Cross Hypotonic solution; Medio-Haus Medizinprodukte GmbH) every 2 seconds for 2 minutes just before exposure to the ultraviolet light. Riboflavin absorption throughout the corneal stroma and anterior chamber was confirmed by slit-lamp examination. Accelerated CXL was performed using 5 minutes exposure of continuous ultraviolet A (UVA) 365-nm light (Peschke GmbH CCL-365-18; Peschke Meditrade GmbH) at an irradiance of 18.0 mW/cm² (5.4 J/cm² fluence). During UVA exposure, the cornea was kept wet with a drop of distilled water for injection every minute and riboflavin was not applied during the 5-minute treatment time. All patients were treated postoperatively with topical moxifloxacin 0.5% (Vigamox, Alcon Laboratories) for 1 week and prednisolone acetate 1% (Pred Forte; Allergan Pharmaceuticals Ltd.) for 1 month. A bandage soft contact lens (Cooper Vision, Scottsville, NY) was placed. The contact lens was removed after the epithelial defect had closed (3–5 days postoperatively).

Outcome Measures

Patients were followed for 12 months postoperatively and had complete examinations at 1, 3, 6, and 12 months. Study parameters included uncorrected distance visual acuity (UDVA), CDVA, manifest refraction spherical equivalent (MRSE) and keratometry [flat keratometry (flat K) and steep keratometry (steep K)] measured at baseline and postoperatively at 1, 3, 6, and 12 months. Visual acuity was recorded using a Snellen chart and converted to logMAR values for analysis. The flat and steep K values were recorded from the topography data (Allegro Oculyzer, Pentacam; WaveLight Laser Technologie AG).

Statistical analysis

Statistical analysis was performed using SPSS software (IBM Corp, Somers, NY). Repeated-measures analysis of variance (Bonferroni corrected post hoc testing and descriptive statistics) were used to analyze the change from baseline values (preprocedure levels) to 1-, 3-, 6-, and 12-month values and other successive time intervals, that is, 1 to 3 months, 3 to 6 months, and 6 to 12 months. A statistically significant difference was based on the level α = 0.05.

RESULTS

Significant improvements in UDVA and CDVA from preoperative levels were observed at all time points postoperatively (Figs. 1A, B). There was a statistically significant improvement in all the parameters between 1 and 3 months; however, from 3 to 6 months, there was significant improvement only in UDVA, CDVA, MRSE, and flat K (Figs. 1–3). The improvement in refractive and keratometric parameters was found to plateau after 6 months; however, UDVA and CDVA continued to improve significantly from 6 to 12 months (Figs. 1–3).
All parameters demonstrated a statistically significant improvement at 12 months from baseline. At the last follow-up visit (12 months), the UDVA was $0.46 \pm 0.49$ logMAR (vs. $0.86 \pm 0.39$ logMAR preoperatively), CDVA was $0.11 \pm 0.12$ logMAR (vs. $0.41 \pm 0.27$ logMAR preoperatively), MRSE was $-2.80 \pm 4.47$ D (vs. $-4.51 \pm 4.68$ D preoperatively), flat K was $43.84 \pm 3.24$ D (vs. $44.61 \pm 3.12$ D preoperatively), and steep K was $46.05 \pm 3.94$ D (vs. $48.10 \pm 3.68$ D preoperatively) (Figs. 1–3). Minimal haze was observed at the 1-month visit that gradually diminished at the 3- and 6-month visits with no haze observed at 12 months.

At postoperative 12 months, nearly 66% of the eyes had UDVA of 20/50 (Fig. 4). Analysis of change in lines of CDVA revealed that 90.6% of eyes gained 1 or more lines of CDVA and 9.4% of eyes maintained their preoperative CDVA; no eye lost any lines of CDVA. Additionally, 37.6% of the eyes demonstrated an improvement of 4 or more lines of CDVA (Fig. 5) with a maximum improvement of 11 lines of CDVA in 1 eye.

**DISCUSSION**

Corneal collagen CXL increases the degree of interfibrillar linkages, thereby improving the biomechanical strength of the cornea. Several publications have documented the successful cessation of progression of keratoconus after CXL. However, it may or may not improve the refractive status of the eye. In fact, CXL, in itself, is believed to freeze the nonideal shape of keratoconic corneas.
It is, therefore, logical to improve the refractive status of the eye before locking in. Because the newer techniques of t-PRK attempt to decrease the surface irregularity, thereby effectively minimizing the irregular astigmatism of keratoconus, it is logical to combine it with CXL to address both the irregular corneal shape and structural collagen weakening of progressive keratoconus. Previous studies have reported that the combined use of t-PRK and CXL is safe and effective and provides good functional vision in eyes with keratoconus.

Initial investigations by Kanellopoulos and Kymionis to ascertain the best timings to combine the 2 procedures revealed that simultaneous treatment, that is, t-PRK followed immediately by CXL, produces superior outcomes when compared with sequential treatment. In a comparative study of sequential versus simultaneous t-PRK and CXL in 325 keratoconus eyes with a mean follow-up of 36 months, Kanellopoulos found improvement in UDVA and CDVA, a greater mean reduction in MRSE and keratometry, and less corneal haze in a simultaneous group as compared with a sequential group. Similarly, Kymionis et al in 2011 reported encouraging results in 26 patients (31 eyes) with simultaneous t-PRK and CXL for keratoconus. The combined treatment reduced refractive error and keratometry readings, yielding improvements in UDVA and CDVA that remained stable at a mean follow-up of nearly 20 months. Even in post-laser-assisted in situ keratomileusis corneal ectasia, the procedure has been demonstrated to result in significant clinical improvement and apparent stability of the ectasia in 5 cases with follow-up ranging from 11 to 37 months.

The aim of the present study was to systematically examine the evolution of the visual and refractive changes through the first year of follow-up (1, 3, 6, and 12 months) after simultaneous t-PRK and CXL. At postoperative 1 month, steep K decreased from 48.10 ± 3.68 D preoperatively to 47.33 ± 4.50 D; however, there was a slight increase in flat K (Figs. 3A, B). Although t-PRK attempts to regularize the cornea and flatten steep K with minimal effect on flat K, the worsening of flat K in the early postoperative period was potentially because of the initial corneal remodeling effect of CXL. As the CXL-associated steepening decreased in the following 5 to 6 months, we observed a statistically significant decrease in flat K from 1 to 3 months and 3 to 6 months with no statistically significant changes at 12 months (Fig. 3A). CXL-associated initial steepening may also have been responsible for the statistically insignificant improvement in MRSE at 1 month. As the CXL-associated steepening decreased in the following 5 to 6 months, we observed a statistically significant decrease in MRSE from 1 to 3 months and 3 to 6 months with stabilization observed at 12 months. In contrast to MRSE and keratometry, UDVA and CDVA improved significantly at 1 month, possibly because of a decrease in irregular astigmatism, and continued to improve further at each follow-up visit until the last follow-up visit at 12 months (Figs. 1A, B). We believe that this improvement in CDVA observed at each consecutive visit until 12 months was possibly because of continuing decrease in the haze or continuing effect of CXL.

The observations about the presence of haze in our study correspond with the previously reported publications on the occurrence and natural course of haze after CXL; it has been reported that the postoperative haze after CXL increases initially up to 1 month and gradually diminishes between 3 and 12 months. Overall, haze was minimal, which concurs with the previous reports of simultaneous t-PRK and CXL. Compared with UDVA and CDVA, that continued to improve further between 6 and 12 months, the improvement was not statistically significant for MRSE and keratometry (both steep and flat K) indicating plateauing and stabilization of refractive and keratometric outcomes after 6 months (Figs. 1–3).

In the past decade, there has been a gradual shift in the timing of administration of surgical intervention for keratoconus—from late-stage corneal transplantation to ICRS implantation when patients lose contact lens tolerance—to an early-stage CXL at the diagnosis of progression. Because keratoconus deteriorates the quality of life even in its initial stages, the ultimate aim of keratoconus treatment should be to treat the keratoconus early on so that the disease does not worsen from the time of diagnosis. Subject to the successful outcomes in the long-term follow-up, simultaneous t-PRK and CXL may emerge as a reasonable option to treat keratoconus eyes early on.
In the current study, the patients’ age ranged from 15 to 41 years. Although the progression of keratoconus has been known to arrest in the third or fourth decade of life, there are reports of the recommencement of progression even after remaining in cessation for several years.10 Because t-PRK is a subtractive procedure and tends to weaken the cornea, it was decided to perform simultaneous CXL in all cases, irrespective of the age or the cessation of progression.

In the current study, we did not perform the corneal endothelial cell density measurements that could be used to evaluate the possibility of corneal damage and endothelial cell toxicity from UVA irradiation after ablation. Additionally, the retrospective study design and lack of documentation of progression of keratoconus before intervention are other possible limitations of the current study. Future prospective studies with longer follow-up and a larger data set are necessary to evaluate the outcomes of this combined procedure.

To summarize, simultaneous t-PRK and CXL is a promising surgical alternative for keratoconus. After 12 months, the combined procedure improved the spherocylindrical refraction and visual function in eyes with keratoconus. Future studies with larger cohorts of patients and longer follow-up periods are needed to determine that the safety and efficacy are maintained, as the keratoconus patient ages.

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REFERENCES