Orthokeratology and riboflavin-UVA corneal collagen cross-linking in Keratoconus

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PURPOSE: A prospective study was designed to answer two questions: Is it possible to improve the quality of vision of keratoconus patients with overnight orthokeratology? Is it possible to stabilize the effect of corneal reshaping through collagen cross-linking?

METHOD: We developed a molding reverse geometry contact lens, specifically designed to be fitted in keratoconus. The lens was in siloxy-fluoro-methacrylate Dk 100 gas-permeable material (Boston XO, hexafocon-A). We selected a group of 5 eyes from 4 patients (3 females, 1 male) aged 22 to 43 years with clinical and topographical diagnosis of keratoconus. All patients were suffering from visual symptoms, intolerant to conventional CL, with corneal pachimetry > 400 µm. Patients underwent overnight orthokeratology (OK) for three months, then collagen cross-linking (CXL) was performed with riboflavin + UVA following the Siena group protocol. After a one-month gap for healing process, overnight orthokeratology was resumed with piggy-back (RGP + silicone-hydrogel CL) for three weeks, and with RGP lenses only for two further months. All kinds of CL were discontinued thereafter.

RESULTS: Data were collected at base line, at three months after OK, at four months after cross-linking (one month after OK interruption), and at one year after cross-linking. In all cases, corneal topography showed an improvement in corneal shape after overnight orthokeratology, with a significant reduction of corneal aberration. One month after OK interruption, corneal topography and corneal wave-front error returned at baseline level and remained stable at one-year follow-up. Uncorrected visual acuity (UCVA) and best spectacle corrected visual acuity (BSCVA) improved after orthokeratology; this improvement was reduced one month after OK lens interruption (4 months post CXL), but did not return to baseline level. No adverse reactions were observed during the three months of OK. After cross-linking, one eye showed an epithelial defect with asymptomatic iritis-like reaction. This complication resolved after a month of topical steroid therapy, so the treatment was continued. No relevant adverse events were observed at 4 months and one year after cross-linking.

CONCLUSION: Overnight orthokeratology may reshape the keratoconic cornea without significant adverse reactions. Riboflavin-UVA corneal collagen cross-linking is quite safe, but it is not able to stabilize the OK molding effect. Nevertheless, UCVA and BSCVA improved as compared to baseline level. At present, we are not able to explain this discrepancy.

KEYWORDS: keratoconus, overnight orthokeratology (OK), corneal collagen cross-linking (CXL).

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INTRODUCTION

Keratoconus is a degenerative noninflammatory disease of the cornea with onset generally at puberty. The course of the disease varies from slight irregular astigmatism to severe visual impairment due to increasing protrusion and subepithelial scarring. Because of the young age of the patients, keratoconus often has a significant negative effect on quality of life. Currently, available conservative and surgical therapeutical options such as glasses, contact lenses, intracorneal rings, epikeratoplasty, thermal keratoplasty, can temporarily correct the refractive effect but do not stop the progression of keratoconus. In the long term, about 20% of cases require corneal transplantation and can be treated by lamellar or perforating keratoplasty, although potential intraoperative and postoperative complications (eg, rejection, transplant failure, second-
ary cataract, secondary glaucoma, recurrence of keratoconus in the transplanted cornea) might limit good long-term results.

At present keratoconus is not curable. However, cross-linking can stop its progression. As we can successfully mold the cornea of normal eyes to correct myopia, and sometime hyperopia and astigmatism by means of overnight orthokeratology (OK) with minimal invasivity, we asked ourselves if it is possible to improve the quality of vision of keratoconus patients as well, and if it is possible to stabilize the effect of this corneal reshaping through collagen cross-linking (CXL). To answer our questions, we designed a prospective non-randomized pilot study.

MATERIALS AND METHODS

We selected a group of 5 eyes from 4 patients (3 females, 1 male) aged 22 to 43 years with clinical and topographical diagnosis of keratoconus. All patients were suffering from visual symptoms, intolerant to conventional contact lenses (CL), with corneal pachimetry >400 micron. Following the Helsinki Declaration, all patients gave informed consent after the risks, benefits, and alternative treatment methods were described. We developed a molding reverse geometry contact lens, specifically designed to be fitted in keratoconus (ESA per Cono) (Figure 1). The lens was in siloxy-fluoro-methacrylate Dk 100 gas-permeable material (Boston XO, hexafocon-A). Patients underwent overnight orthokeratology for three months, then collagen cross-linking was performed with riboflavin + UVA following the Siena group protocol: pilocarpin 1% drops 30 minutes before, topical anesthesia with lidocaine 4% drops 15 minutes before irradiation, mechanical scraping of epithelium (9 mm-diameter area), preirradiation soaking for 10 minutes in riboflavin solution 0.1% (Ricrolin, Sooft, Italy) applied every 2.5 minutes for 30 minutes, 30 minutes exposure to solid-state UVA illuminator (CBM X-linker, CSO, Italy), 8-mm-diameter irradiated area, energy delivered 3 mW/cm².

After a one-month gap for healing process, overnight orthokeratology was resumed with piggy-back (RGP + silicone-hydrogel CL) for three weeks, and with RGP lenses only for two further months. All kinds of CL were discontinued thereafter.

Before treatment, and during the follow-up all the patients had biomicroscope examination, assessment of uncorrected visual acuity (UCVA) and best spectacle-corrected visual acuity (BSCVA), corneal topography and corneal wave-front analysis (Eye Top CSO), and ultrasound pachymetry (Allergan Humphrey 850). Data were collected at base line, at three months after OK, at four months after cross-linking (one month after OK interruption), and at one year after cross-linking. Graph 1 shows the timeline of the study.

RESULTS

In all the cases, corneal topography showed an improvement in corneal shape after overnight orthokeratology, with an important reduction of corneal aberration. One month after OK interruption, corneal topography and corneal wave-front error returned at baseline level.

Figure 2 shows topographic results of patient #1. In the upper row, we can see axial curvature; in the lower one we can see instantaneous curvature. His pretreatment UCVA was 0.05 (20/400), after OK treatment...
UCVA was 0.5 (20/40), and one month after OK interruption UCVA was 0.3 (20/70).

In figure 3 we can see we can see the corneal wave-front error maps and the convolutions for patients #1. Corneal wave-front error maps correspond to a 5 mm pupil. Convolutions represent the simulation of the vision of the patient, based on his measured corneal wave-front error. At baseline, his RMS was 1.75 µm, after OK treatment it was 1.64 µm and one month after OK interruption it was 1.95 µm.

In figure 4 we can see topographic results of patient #2. His pretreatment UCVA was 0.4 (20/50), after OK treatment UCVA was 0.8 (20/25), and one month after OK interruption UCVA was 0.3 (20/70).

In figure 5 we can see the corneal wave-front error maps and the convolutions for patients #2. At baseline, his RMS was 1.75 µm, after OK treatment it was 1.64 µm and one month after OK interruption it was 1.95 µm.

In figure 6 we can see topographic results of patient #3. His pretreatment UCVA was 0.03 (20/700), after OK treatment UCVA was 0.15 (20/125) and one month after OK interruption UCVA was 0.05 (20/400).

In figure 7 we can see we can see the corneal wave-front error maps and the convolutions for patients #3. At baseline, his RMS was 3.04 µm, after OK treatment it was 1.92 µm and one month after OK interruption it was 3.11 µm.

In figure 8 we can see topographic results of patient #4. His pretreatment UCVA was 0.05 (20/400), after...
OK treatment UCVA was 0.5 (20/40), and one month after OK interruption UCVA was 0.1 (20/200).

In figure 9 we can see we can see the corneal wave-front error maps and the convolutions for patients #4. At baseline, his RMS was 1.99 µm, after OK treatment it was 1.75 µm and one month after OK interruption it was 2.33 µm.

In figure 10 we can see topographic results of patient #5. His pretreatment UCVA was 0.1 (20/200), after OK treatment UCVA was 0.5 (20/40), and one month after OK interruption UCVA was 0.3 (20/70).

In figure 11 we can see we can see the corneal wave-front error maps and the convolutions for patients #5. At baseline his RMS was 2.35 µm, after OK treatment it was 1.50 µm and one month after OK interruption it was 1.74 µm.

**REFRACTION AND VISUAL ACUITY**

Refraction at different stages is summarized in graph 2. After orthokeratology we observed an important reduction both of the spherical and the cylinder component that regress after OK interruption. One year after CXL the spherical component went back to the base line level, while the astigmatism was still reduced. Given to the small sample size, we cannot perform a statistical analysis to test the significance of mean difference. As summarized in graph 2, uncorrected visual acuity (UCVA) and best spectacle corrected visual acuity (BSCVA) improved after orthokeratology; this improvement was reduced one month after OK
lens interruption (4 months post CXL), but did not return to baseline level. After one year we did not observe further significant changes.

COMPLICATIONS

No adverse reactions were observed during the three months of overnight orthokeratology. After cross-linking, one eye showed an epithelial defect with asymptomatic iritis-like reaction. This complication resolved after a month of topical steroid therapy, so the treatment was continued. No relevant adverse events were observed at four months and one year after cross-linking.

DISCUSSION

The idea to use a conservative approach to treat keratoconus with a parasurgical therapy by riboflavin-UVA induced cross-linking of corneal collagen was conceived in Germany in the 1990s by a research group at Dresden Technical University. The aim was to slow or arrest progression to delay or avoid recourse to perforating keratoplasty. Nowadays, several works report that collagen cross-linking by the photosensitizer riboflavin and ultraviolet A-light is an effective means for stabilizing the cornea in keratoconus. Neverthless, CXL is not able to reduce the noteworthy high order aberration of the cornea. Clinically, ultraviolet cross-linking treatment appears to be able to halt progression of corneal ectasia in keratoconus patients, with additional evidence of slight flattening of the cornea and increasing uncorrected and best-corrected acuity with a trend towards increasing corneal symmetry. Since this treatment alone does not normalize corneal curvature, attempts have been made to combine it with other surgical modalities with procedures such as intracorneal ring implantation, topography-guided photorefractive keratectomy, and thermal keratoplasty.

Orthokeratology is a clinical technique that uses specially designed and fitted rigid contact lenses to reshape the corneal contour to temporarily modify or eliminate refractive error. OK is not a new procedure, but it has undergone a resurgence of clinical and research interest in the last decade, due to the availability of new technology. Nowadays, OK is widely used around the world for the temporary correction of low to moderate ametropia, using reverse-geometry contact lenses in high oxygen-permeability materials in an overnight lens-wearing modality. Orthokeratology contact lenses induce a temporary reduction of ocular refractive error by changing the shape of the cornea, taking advantage from corneal plasticity. If the amount of corneal molding is properly controlled, it is possible to bring the eye into correct focus to compensate the refractive error. With overnight wear of modern contact lenses for orthokeratology, usually changes are very rapid and retained throughout the day, with most change after the first night of lens wear and stability of refractive change after one to two weeks. Retainer lenses must be worn during sleep only. This treatment is reversible and, if the patient stops wearing the lenses completely, the refractive state of the eye will regress to the pre-treatment level. It is now recognized that orthokeratology is an effective treatment for low to moderate myopia. Treatment of astigmatism is achievable in selected cases as well. In our experience, treatment of hyperopia and presbyopia through corneal steepening is also promising. As we can successfully mold the cornea of normal eyes to correct myopia, and sometime hyperopia and astigmatism by means of overnight orthokeratology with minimal invasivity, we have tried to improve the quality of vision of keratoconus patients as well, and to stabilize the effect of this corneal reshaping through collagen cross-linking.
Our results show that overnight orthokeratology may reshape the keratoconic cornea without significant adverse reactions. Nevertheless, on the contrary of normal eyes\textsuperscript{11,12}, the molding effect on keratoconus persists only for a short time. Riboflavin-UVA corneal collagen cross-linking is quite safe, but it is not able to stabilize the OK molding effect. Nevertheless, UCVA and BSCVA improved as compared to baseline level. At present, we are not able to explain this discrepancy.

REFERENCES