Corneal collagen crosslinking in progressive keratoconus: Changes in corneal irregularity indices and correlation with the best spectacle-corrected visual acuity

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PURPOSE: To report the mean refractive and topographic changes in progressive keratoconus (KC) patients post corneal collagen crosslinking (CXL) to assess the progression of corneal irregularity indices and their relationship with best spectacle-corrected visual acuity (BSCVA).

SETTING: Ocular Microsurgery Institute (IMO) of Barcelona, Spain.

METHODS: This is a retrospective uncontrolled study in eyes with progressive KC. In all 62 eyes from 48 patients, BSCVA, mean K, corneal irregularity at 3 mm and 5 mm were measured before CXL, at six months, and then annually until the last visit. For data analysis, patients were divided into three groups according to their mean preoperative K: group 1 included 12 patients with mean K value less than 43.9 D, group 2 included 41 patients with mean K value between 44-47.9 D, and group 3 included 10 patients with mean K value greater than 48 D.

RESULTS: All patients showed an improvement in BSCVA from 0.13 to 0.06 (p < 0.001) and a statistically significant decrease in maximum keratometry (Kmax) from 48.22 to 47.25 D (p < 0.001) and minimum keratometry (Kmin) from 45.7 to 44.89 D (p < 0.001). Measurement of corneal irregularity also showed a statistically significant decrease at 3 mm from 4.71 to 4.25 (p < 0.001) and at 5 mm from 4.87 to 4.51 (p < 0.007). No statistically significant results were found according to study group.

CONCLUSION: The improvement in ocular surface regularity indices was statistically significant in all patients studied, with a possible association between changes in corneal irregularity, corneal flattening and other topographic changes and the improvement in vision observed in KC patients undergoing CXL.

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corneal collagen fibers due to photochemical crosslinking with a combination of stromal inhibition with riboflavin and UVA light, increasing the rigidity of the cornea and stabilizing the ectatic disorder, thus reducing or eliminating the future need for keratoplasty. The long-term effects of CXL have been well documented in several publications, consisting mainly in halting progression of the disease and decreasing corneal curvature and flattening the steepest meridian by 1.3-2.4 diopters (D) (mean). In many cases, this results in an improvement in patients’ keratometric and visual outcomes.6-17.

Computer-assisted corneal topography has become indispensable for the diagnosis of subclinical KC and for evaluating clinical progression.18-20 Corneal irregularity indices measured at 3 mm and 5 mm reflect optical surface irregularities which are calculated automatically, for example, by the Orbscan II (Bausch & Lomb Surgical Inc., California, USA) software. Several studies have found that these indices are significantly higher in corneas with suspected or clinical KC.21 Choi and Kim22 and Souza et al.23 demonstrated that irregularity indices measured at 3 and 5 mm were significant predictors of KC detection and progression.

The purpose of this study was to report the mean refractive and topographic changes measured in patients with progressive KC treated with CXL and no other ocular surgery or using CLs in our institute from 2008 to 2012, and to assess the progression of corneal irregularity indices and their relationship with BSCVA.

PATIENTS AND METHODS

Patients with progressive KC were enrolled in this retrospective, nonrandomized study at the Instituto de Microcirugía Ocular (IMO) of Barcelona. Inclusion criteria were confirmed KC, central corneal thickness (CCT) greater than 400 microns on Orbscan II topography, agreed disease progression criteria proven by the loss of more than one line of corrected distance visual acuity (CDVA) in one year or topographic keratometry increasing more than 1.0 D in six months or 2.0 D in 12 months. Informed consent was obtained from all patients. Exclusion criteria were central corneal opacities, CCT less than 400 microns on topography, follow-up less than six months after the treatment, any other previous or subsequent ocular surgery (i.e. intra corneal segment rings, phakic lens), patients that continue wearing contact lenses after CXL, patients with abnormalities in lens or retina on biomicroscopic examination, patients who were pregnant or breastfeeding. The preoperative and postoperative evaluation included BSCVA, elevation topography data and endothelial cell count. For data analysis, patients were divided into three groups according to their preoperative mean K: group 1 included patients with mean K value less than 43.9 D, group 2 included patients with mean K value between 44-47.9 D, and group 3 included patients with mean K value greater than 48 D.

Visual Acuity

Visual acuity was evaluated using the logMAR chart at a 6-meter testing distance with the ambient room lighting remaining constant on all evaluations. Progressive cases were defined as those losing at least one line of BCVA in six months.

Elevation Topography

Scanning-slit anterior topography was used. Preoperative topographies were compared with corneal topographies obtained from the examination at least six month postoperatively. Progressive cases were defined by an increase of more than 1.0 D in central maximum keratometry (Kmax) at six months equal to or greater than 2.0 D in 12 months.

Crosslinking Surgical Technique

CXL was performed under topical anesthesia, after instilling one drop of 2% pilocarpine. A 7.0 mm diameter portion of central epithelium was removed using a smooth spatula. Then, intrastromal soaking via instillation of 0.1% isosmotic riboflavin at one drop per minute (Medio-cross®, Medio-Haus Medizinprodukte GmbH, Kiel, Germany) was performed for 20 minutes using a round silicone cup centered in the cornea and filled with riboflavin. Six 5-minute sequences of UVA (330 nm) exposure were performed. After treatment, a bandage soft CL was applied for three to five days until complete reepithelization. Postoperative treatment consisted of tobramycin and dexamethasone eyedrops and ofloxacin eyedrops every eight hours, and sodium hyaluronate eyedrops every hour during CL use, followed by tobramycin and dexamethasone eyedrops every six hours, 0.5% timolol eyedrops every 12 hours and chloramphenicol and dexamethasone ointment at bedtime for three weeks. After this, fluorometholone eyedrops were applied every eight hours for three weeks, every 12 hours for three weeks, and every 24 hours for three weeks. Post-treatment visits were scheduled at 1 and 7 days, 1, 3, 6, and 12 months, and at annual intervals thereafter.

Statistical Analysis

Statistical analysis was performed with SPSS version 20.0 software (SPSS Inc., Chicago IL, USA.). Preoperative and postoperative data were compared using Student’s t test or the Wilcoxon matched paired test according to the distribution. Pearson’s correlation coefficient was used to
assess the level of dependence between changes in corneal irregularity indices and BSCVA postoperatively. P-values less than 0.05 were considered statistically significant.

RESULTS

Sixty-two eyes from 48 consecutive patients fulfilled the recruitment criteria for this study. The mean age of the 33 men (68.75%) and 15 women (31.25%) was 25.42 years (16-45). Mean follow-up was 18.55, standard deviation (SD) 10.5 months.

Visual Acuity Results

The mean preoperative BSCVA on the logMAR was 0.13, and the last follow-up BSCVA improved to 0.06. This difference was statistically significant (p < 0.001).

Topographical Results

The preoperative Kmax was 48.22 D and 47.25 D at the last visit (p < 0.001). The preoperative mean K was 45.70 D and the last follow-up mean K was 44.89 D (p < 0.001). Mean preoperative 3 mm irregularity was 4.71 and the last follow-up value was 4.25 (p < 0.001). Mean preoperative 5 mm irregularity was 4.87 and the last follow-up value was 4.51 (p = 0.007). In all these measurements, the difference was statistically significant. There was no statistically significant correlation between visual acuity impairment and topographic changes induced after surgery when BSCVA with mean K (p = 0.075) 3 mm irregularity (p = 0.731) and 5 mm irregularity (p = 0.399) were compared. Figures 1 and 2 illustrate corneal topography of one patient before CXL and two years later. Figures 3 and 4 show slit-lamp photographs where progressive epithelization after CXL can be observed.

Total results and results per group are shown in Table 1. Patients were divided into three groups according to age: less than 19 years, 20-29 years, and over 30 years, with no significant result in any group other than that previously mentioned.

DISCUSSION

Currently, the only treatment that has proven effective in stopping the progression of KC is CXL, achieving an anatomical and functional improvement in most patients undergoing this therapy, and with proven results in multiple clinical studies worldwide. Corneal topography devices are a useful tool for classifying and measuring KC progression\(^{19,20}\), and thus determine...
therapeutic strategies aimed at stopping progression and improving the visual quality of these patients, avoiding as far as possible the need for penetrating keratoplasty. Corneal curvature is the clinical variable most commonly used to grade the severity of KC, while keratometry values and irregularity indices can be used to determine astigmatism and irregularities in the eye in order to diagnosis corneal ectatic conditions and assess their progression. The use of Orbscan for measuring corneal ectatic changes is highly valid and reliable for the assessment of anterior corneal variables. Irregularity indices are calculated automatically by the Orbscan software, based on a statistical combination of the standard deviations of the mean and toric curvatures. Although these indices are not considered an important factor in surgical screening, patients with higher levels of corneal irregularity experience more visual discomfort than those with lower levels. Improved visual acuity is expected after CXL because of the improvements in definable measures of corneal topographic regularity.
However, to date, it has been difficult to capture the correlation between clinical and topographic changes of the cornea and improvements in the visual acuity. In our study, keratometric changes tended to be slightly lower than those reported in most studies worldwide, which reported Kmax decreases of 1.45-2.57 D. However, corneal flattening was statistically significant (p < 0.001) and only eight eyes (12.9%) experienced a small increase in maximum keratometric value. In addition, there was an improvement in visual acuity with correction. The average visual improvement was 1.5 lines, but some patients improved visual acuity up to four Snellen lines. In contrast, only 13 patients had a decrease in VA, never less than 1.5 Snellen lines.

Irregularity indices measured at 3 and 5 mm reflect optical surface irregularities, which are proportional to the spherical defect of the axis-independent surface curvature. According to previous reports, mean corneal irregularity varies from 1.0-1.25 D in the central 3 mm zone, and from 2.05-2.44 D in the central 5 mm zone in the normal population, but in patients with suspected KC, mean irregularity reported is 2.44/2.61, and in patients with progressive KC mean irregularity can reach 6.60, 6.80 D in the 3.5 mm zone, respectively. To our knowledge, no one had yet tried to describe the changes experienced in corneal surface irregularity indices in patients with progressive KC undergoing CXL, and correlate these changes with visual improvement experienced in these patients. Improvements in the regularity of the ocular surface was statistically significant in all patients we studied. Accordingly, future studies with larger numbers of patients should seek a possible association between changes in corneal irregularity, corneal flattening and other topographic changes, and improved vision observed in KC patients undergoing CXL.

In conclusion, longer follow-up of these patients is necessary to determine the stability of clinical and optical outcomes. Patients with progressive KC appear to have improvements in most of the anterior surface topography measures, suggesting an overall improvement of the optical contour of the cornea that apparently results in improved visual acuity.

REFERENCES


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