Intraocular pressure measurements after corneal collagen crosslinking with riboflavin and ultraviolet A in eyes with keratoconus

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PURPOSE: To determine the possible effect of corneal collagen crosslinking (CXL) with riboflavin and ultraviolet A (UVA) on intraocular pressure (IOP) measurements by Goldmann applanation tonometry (GAT).

SETTING: Institute of Vision and Optics, Faculty of Medicine, University of Crete, Heraklion, Crete, Greece.

DESIGN: Prospective case series.

METHODS: This noncomparative study measured IOP by GAT before CXL and 6 months and 12 months after CXL.

RESULTS: The study evaluated 55 eyes (55 patients). There was a statistically significant increase in the measured IOP 6 months and 12 months after CXL (both $P<.001$). The mean measured IOP was 9.95 mm Hg $\pm$ 3.01 (SD) before CXL, 11.40 $\pm$ 2.89 mm Hg at 6 months, and 11.35 $\pm$ 3.38 mm Hg at 12 months. The change in IOP measurements at both postoperative examinations was not correlated with patient age, preoperative pachymetry, or preoperative keratometry readings.

CONCLUSION: After riboflavin–UVA CXL in eyes with keratoconus, there was a significant increase in IOP measured by GAT that was probably caused by an increase in corneal rigidity.

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Keratoconus is a bilateral noninflammatory disease characterized by progressive corneal thinning and bulging. The cornea assumes a conical shape, which leads to irregular astigmatism and to a decrease in visual acuity.[1] Treatment of keratoconus consists of spectacles, contact lenses, intrastromal corneal ring segments,[2] and when these treatment options are no longer effective, lamellar or penetrating keratoplasty.[3]

A new surgical treatment used to strengthen the corneal tissue in keratoconus is corneal collagen crosslinking (CXL) with riboflavin and ultraviolet A (UVA).[4] This technique increases corneal stiffness by using riboflavin and UVA to induce the formation of chemical bonds between the collagen fibrils.[5]

Results in several studies[4–7] indicate that CXL results in corneal stiffening. A recent in vitro study of human corneas[8] found an overestimation of true IOP as a result of CXL induced by riboflavin and UVA. To our knowledge, there are no clinical studies in the literature that directly evaluate the effect of CXL with riboflavin and UVA on IOP measurements by Goldmann applanation tonometry (GAT). In this study, we evaluated the effect of

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riboflavin–UVA CXL on GAT readings in patients with keratoconus.

PATIENTS AND METHODS

Study Group and Protocol

This prospective clinical study enrolled patients with keratoconus who had corneal CXL induced by riboflavin and UVA in 1 eye. The clinical diagnosis of keratoconus was based mainly on corneal topography data and clinical signs, such as Fleischer rings, Vogt striae, stromal thinning, and conical protrusion. An institutional review board approved the study. After being appropriately informed before their participation in the study, all patients gave written informed consent in accordance with the institutional guidelines in the Declaration of Helsinki.

Data obtained from the patient records included age and sex, preoperative and postoperative IOP measurements by GAT, keratometry (K) readings by videokeratoscopy (C-Scan, Technomed GmbH), central corneal thickness (CCT) by ultrasonic corneal pachymetry (Corneo-Gage Plus, Sonogage), slitlamp biomicroscopy, and fundus examination findings.

Surgical Technique

Corneal CXL was performed under sterile conditions. The patient's eye was anesthetized with proxymetacaine hydrochloride 0.5% eyedrops (Alcaine). A 7.5 to 8.0 mm diameter section of corneal epithelium was mechanically removed with a rotating brush, and riboflavin 0.1% solution was instilled every 2 to 3 minutes for approximately 30 minutes. Ultraviolet-A irradiation was performed using a commercially available UVA system (UV-X, Peschke Meditrade GmbH). Irradiance was performed for 30 minutes, corresponding to a dose of 5.4 J/cm^2. During treatment, riboflavin solution was applied every 3 to 5 minutes to saturate the cornea. At the end of the procedure, a silicone–hydrogel bandage contact lens (Lotrafilcon B, Air Optix, Ciba Vision; 14.0 mm diameter, 8.6 base curvature, Dk 140 barrers) was applied until full reepithelialization, typically after 4 days.

Measurements and Devices

Tonometry measurements were performed by GAT using a sodium fluorescein solution. The same tonometer (Haag-Streit AG) was used throughout the study. Tonometry measurements were taken at the center of the cornea; the median of 3 consecutive measurements was used for analysis. Measurements with a difference greater than 4.0 mm Hg were excluded.[9,10] Ultrasonic pachymetry measurements were taken at the center of the cornea by a masked observer, and the thinnest of 3 consecutive measurements was chosen. Corneal topography was taken using the same videokeratoscope as the K readings. The K measurements were actual K readings in the flat axis and steep axis. The GAT, CCT, and K measurements before surgery and at the 6-month and 12-month postoperative visits were included in the statistical analysis.

Statistical Analysis

The study was a 2-stage design. The pilot comprised 10 patients who had corneal CXL with a 3-month postoperative follow-up; the mean IOP was 9.22 ± 2.59 mm Hg preoperatively and 11.44 ± 3.28 mm Hg postoperatively. An a priori 2-tail paired *t* test power calculation showed a total sample size of at least 25 patients was required to achieve a power of 0.95.

Results are presented as means ± standard deviation. Analysis of variance (ANOVA) was used to compare IOP, K, and CCT measurements before and after CXL. Correlation analysis was used to test the influence of continuous variables (eg, patient age, preoperative corneal pachymetry, preoperative K readings) on the changes in IOP measurement. A P value less than 0.05 was considered statistically significant. A 1-way Kolmogorov-Smirnov test was used to examine the normality of the data.

RESULTS

The study enrolled 55 patients with a mean age of 24.4 ± 4.1 years (range 18 to 36 years). The apices of the patients' cones were mostly inferior (44 eyes); the rest (11 eyes) were central.

No intraoperative or postoperative complications occurred. There was a statistically significant increase in IOP measurements 6 months and 12 months after treatment (both $P<.001$). The mean IOP measurement was 9.95 ± 3.01 mm Hg (range 5 to 19 mm Hg) before CXL, 11.40 ± 2.89 mm Hg (range 7 to 19 mm Hg) 6 months postoperatively, and 11.35 ± 3.38 mm Hg (range 6 to 25 mm Hg) at 12 months. Between the 6-month and 12 -month postoperative measurements, there was no statistically significant change in IOP measurements (mean change 0.055 ± 2.305 mm Hg) ($P = .861$). The change in IOP readings at 6 months and 12 months was not correlated with patient age ($P = .323$ and $P = .231$, respectively), preoperative pachymetry ($P = .113$ and $P = .522$, respectively), or K readings ($P = .061$ and $P = .324$, respectively).

The ANOVA did not show statistical differences between the preoperative and the postoperative mean K readings ($P = .604$, 12-month postoperative) or CCT ($P = .154$, 12-month postoperative).

DISCUSSION

Collagen crosslinking with riboflavin and UVA is a new surgical technique used in the treatment of keratoconus.[4] The treatment is based on the activation of the photosensitizer riboflavin by UVA, which produces oxygen radicals that induce the formation of strong chemical bonds between the collagen fibrils and therefore increase corneal stiffness.[5]

Several studies[4–7] report corneal stiffening after riboflavin–UVA CXL to treat keratoconus. The corneal stiffening might be correlated with an increase in corneal and ocular rigidity. Ocular rigidity is a measurable physical parameter of the eye that expresses the elastic properties of the globe. In 1937,

Friedenwald[11] described the coefficient of ocular rigidity as a "measure of the resistance, which the eye exerts to distending forces."

Results in a recent in vitro study[8] indicate riboflavin–UVA CXL in human corneas results in overestimation of true IOP, in the range of 1.8 to 3.1 mm Hg depending on the tonometer type (GAT, dynamic contour tonometry, Tono-Pen XL). Nevertheless, this overestimation was considerably smaller than the magnitude of overestimation expected from theoretic calculations,[12] despite a reported increase in corneal rigidity after CXL in human corneas of up to 330%.[13] This result might be because CXL has the maximum stiffening effect in the anterior corneal stroma.[13,14] Another recent study[15] found that CXL with a dialdehyde agent in human corneas led to significant increases in wave velocity and transcorneal IOP measurements, despite a constant intravitreal pressure.

In our study, there was a statistically significant increase in measured IOP by GAT after CXL with riboflavin and UVA 6 months and 12 months postoperatively. Biomechanical alterations and corneal rigidity increments are probably related to IOP changes after CXL. The change in IOP readings at 6 months and 12 months was not correlated with patient age, preoperative pachymetry, or preoperative K readings. Ehlers et al.[16] report that applanation tonometry provided accurate IOP measurements only when the CCT was 520 μm, while thinner and thicker corneas gave falsely lower readings and higher readings, respectively. Nevertheless, in our study, neither CCT nor K readings changed after CXL.

Even though we believe that alterations in corneal rigidity and elasticity by CXL may induce an overestimation of IOP, we cannot exclude the possibility that the "true" IOP increased after CXL. This possibility could be verified through real-time measurement of the IOP using an invasive method.[17] Either the increase in measured IOP is an overestimation, an increase in true IOP, or both; in addition, it is possible that the etiology of this process is multifactorial. Thus, the preoperative IOP levels (used as baseline IOP) should be taken into account in patients treated by CXL, especially if glaucoma is suspected.

There are several limitations to this study. The change in IOP may have been a response to aqueous humor dynamics to the surgery (decrease in outflow from the effect on the trabecular meshwork), or the CXL procedure may have had an unknown effect on IOP readings. Other factors, such as patient cooperation, should also be considered. Another limitation is the lack of CCT measurements by optical coherence tomography technology. Moreover, this was a noncomparative study with no control group. Finally, the IOP measurements were by GAT only, without the use of other tonometer devices (eg, dynamic contour).

In conclusion, after CXL with riboflavin and UVA for keratoconus, there was a significant increase in IOP measured by GAT. The increase was probably the result of an increase in corneal rigidity.

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