

Alterations In The Measured Intraocular Pressure Following Corneal Collagen Cross Linking

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ABSTRACT:

Purpose: To evaluate the effect of corneal collagen crosslinking on measured intraocular pressure with indentation tonometry.

Setting: Department of ophthalmology and visual sciences, Medical College of Wisconsin, Milwaukee, Wisconsin; Department of ophthalmology, University of Messina, Italy.

Design: Retrospective chart review

Methods: A total of 60 keratoconic eyes who underwent corneal collagen cross linking (CXL) were included. Indentation (Tonopen) tonometry was used to evaluate intraocular pressure (IOP) preoperatively and at one, three, and six-month postoperative follow-up visits.

Results: The average preoperative IOP was 14.1 +/- 2.1. See Table 1. The average IOP at the 1-month, 3-month, and 6-month follow-up were 17.1 +/- 2.7, 15.8 +/- 2.3, and 16.8 +/- 1.8 respectively. Relative to the preoperative IOP, the IOP at the 1-month, 3-month, and 6-month follow-up were statistically higher.

Conclusion: A statistically significant increase was noted in measured IOP with a Tonopen after CXL for keratoconus, which is likely due to an increase in corneal rigidity after CXL.

Keratoconus is a bilateral, asymmetric ectatic disorder of the cornea characterized by progressive thinning and weakening of the anterior central cornea.^{1,2} Affecting roughly 1 in 2000 individuals, the typical onset is in the 2nd decade of life, most commonly presenting as a refractive error with significant astigmatism, and subsequent corneal steepening with irregular astigmatism can result in worsening visual acuity.²⁻⁴ Progression usually occurs over the course of 10-15 years, followed by stabilization.² There are a multitude of treatment modalities for keratoconus, including spectacle correction, hard and soft contact lens use, intrastromal corneal ring segments,

and corneal transplants, each depending on the severity of ectasia and progression.⁴ Historically about twenty percent of patients required penetrating keratoplasty due to significant keratoectatic progression.⁵ The advent of riboflavin with ultraviolet-A-induced corneal collagen cross linking (CXL) offered an intervention to decelerate and potentially halt the progression of keratoconus through photopolymerization of corneal stroma fibers.^{3,5}

We hypothesized that measured intraocular pressure (IOP) would increase after CXL secondary to increased corneal rigidity, as has been previously suggested.^{6,7} However, of the few human and animal studies and meta-analyses that have been conducted on the effects of CXL on measured IOP, the results have been varied.^{1,3-8}

The purpose of this study was to evaluate the measured IOP in keratoconus patients before and after CXL using indentation tonometry, specifically by Tonopen.

METHODS

This was a retrospective chart review study of patients from the Medical College of Wisconsin Froedtert Eye Institute and the University of Messina Department of Ophthalmology, who underwent CXL for keratoconus, according to the Dresden protocol between July 2018 and May 2019.⁵ As is standard, only the central 9 mm of the cornea were exposed to the U/V illumination. Inclusion criteria included a diagnosis of keratoconus based on clinical examination and corneal topography, and an age ranging from 14 to 90 years old. Exclusion criteria included subjects with a history of glaucoma, other corneal pathology, and a previous history of undergoing CXL. Data collected included the subject's age, sex, pre-operative corneal pachymetry, IOP, and keratometry. IOP was record-

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ed with a Tonopen (Reichert Technologies, Buffalo, NY). Ultrasonic corneal pachymetry measurements were obtained using a DGH Pachmate 2 Handheld Pachymeter (DGH Technology Inc, Exton, PA). Measurements were obtained in the central cornea after administration of topical anesthetic drops (Proparacaine hydrochloride 0.5%) and prior to any contact of the corneal surface with other devices or lenses. The primary outcomes measured were IOP at the preoperative examination, and postoperative one, three, and six month visits. Data was collected following the tenants of the Declaration of Helsinki, was in accord with the Health Insurance Portability and Accountability Act of 1996, and was approved by the Institutional Review Boards at the Medical College of Wisconsin and University of Messina.

RESULTS

Results are detailed in Table 1. Sixty nine eyes from 69 subjects were identified in the chart review process as having a clinical diagnosis of progressive keratoconus and having undergone CXL. Initially, one subject was excluded for having an IOP measured by Goldmann applanation tonometry (GAT), and two subjects were excluded for not having available corneal topography data. Four additional subjects were excluded for having missed post-operative one-month visits. Six subjects (8.7%) were excluded due to requiring topical steroid drops at one month, which could affect the IOP measurements. Fifty six of the 60 subjects (93%) followed up at one month, 38 of 60 subjects (63%) followed up at three months, and 30 of 60 subjects (50%) followed up at six months. The average preoperative measured IOP was 14.1 +/- 2.1. The average measured IOP at the one-month, three-month, and six-month follow-up were 17.1 +/- 2.7, 15.8 +/- 2.3, and 16.8 +/- 1.8 respectively (Figure 1). Relative to the preoperative IOP, the IOP at the one-month, three-month, and six-month follow-up were statistically significantly higher, with paired t-test values of <0.001 for all 3 groups.

Table 1 demonstrates the mean IOP, standard deviation and P-value, for the pre CXL IOP compared to the post-CXL measurements at 1, 3 and 6 months. There was a statistically significant increase between all post-CXL IOP measurements compared to the pre-CXL IOP measurement.

	Pre-op	Post-op 1 month	Post-op 3 month	Post-op 6 month
Subjects	69	56	38	30
Mean IOP	14.1	17.1	15.8	16.8
Std Dev	2.1	2.7	2.3	1.8
P-value (vs Pre-op)		<0.001	<0.001	<0.001

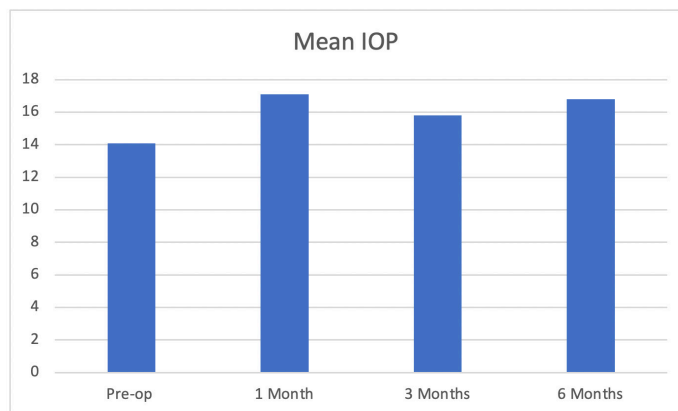


Figure 1 represents a bar graph with the mean pre-treatment IOP and the IOP measure after CXL at 1, 3 and 6 months. The IOP after CXL was significantly higher than the pre-treatment IOP.

DISCUSSION

Our study showed that IOP measurements with indentation tonometry were elevated following CXL. To the best of our knowledge, no other study has been published with as robust a sample size, length of follow-up, and consistency of modality of measuring IOP following CXL. Since the advent of CXL, several studies have secondarily assessed effects on measured IOP, though most have had small sample sizes or inconsistent methods of measuring or tracking IOP, and the results were varied.^{1,3,4,6} In Wollensak’s original 2003 study on riboflavin with ultraviolet-A-induced collagen cross linking, he did not find statistically significant changes in measured IOP with GAT.⁵

We know that the methods with which we measure IOP have inherent variability.⁹ An ex vivo study from Zurich, Switzerland compared measured IOP with GAT, dynamic contour tonometry (DCT), and indentation tonometry (i.e. Tonopen) with an IOP transducer in an artificial anterior chamber with 10 ex-vivo corneas before and after CXL.⁷ Results of the study showed a statistically significant increase in measured IOP by all three modalities relative to the IOP transducer.⁷ However the study did not utilize keratoconic eyes and were well out of a normal range of expected pachymetry.⁷ In a rabbit study comparing Tonopen readings to an *in vivo* IOP transducer in a matched CXL versus control trial, the cross linked corneas had significantly higher Tonopen-measured IOP compared to both the non-cross linked corneas and the IOP measured with a transducer in both sets of eyes.⁸ However, a study involving 10 non-keratoectatic rabbits found no significant changes in measured IOP with Tonopen after CXL.¹⁰

There are few *in vivo* human studies of measured IOP after CXL. In a large meta-analysis of CXL in keratocornus patients, only ten of the thirty studies reviewed in the

analysis evaluated measured IOP.¹ Three studies took into account corneal hysteresis and found that the corneal-compensated IOP was increased at one month, five studies evaluating measured IOP with GAT found increased measured IOP at twelve months, and two studies found no effect on measured IOP.¹ In a safety and efficacy study for CXL from Italy, no significant changes in measured IOP with Tonopen were noted in a group of 10 subjects at one and three month follow-up.³ Kasumovic et al in Bosnia found in their study of 30 keratoconic eyes that the measured IOP with GAT was significantly increased after CXL, however, they noted significant variability in the measured IOP with GAT.⁶ A study by Kymionis, et al at the University of Greece also looked at measured IOP after CXL using GAT.⁴ In their larger, 55-subject cohort, they noted a statistically significant increase in measured IOP at six and twelve months after CXL.⁴

Studies hypothesized that the increase in measured IOP after CXL was related to alterations in corneal biomechanics from cross linking, leading to increased corneal rigidity and a change in hysteresis.^{4,6,11} Because the CXL treatment does not extend beyond the central 9mm of the cornea and does not include the limbus, it is unlikely that angle structures are affected by the treatment.

Falsely elevated IOP measurements from CXL could make the diagnosis, management, and treatment of diseases such as ocular hypertension and glaucoma difficult. The same argument has been made concerning the effect of central corneal thickness (CCT) and measured IOP in patients with thinner and thicker corneas. Numerous studies have shown that CCT is correlated with measured IOP.^{12,13} While the Ocular Hypertension Treatment Study (OHTS) looked at the benefits of treating patients with ocular hypertension to prevent progression to glaucoma, it did not specifically comment on the role the CCT or corneal rigidity might have on measured IOP.¹⁴ Conversely, in a subsequent analysis of the OHTS trial, CCT was assessed, and showed no significant correlation between baseline IOP and CCT in the patients with ocular hypertension.¹⁵ However, the authors of that study postulated that the lack of significant correlation between measured IOP and CCT was likely due to the strict high IOP ranges adhered to in the inclusion criteria of the OHTS trial.¹⁵

Our study has limitations. Indentation tonometry with Tonopen has some degree of inherent variability, and we only used one measurement at each visit, rather than averaging measurements. Additionally, even with a large sample size of nearly 70 participants, we were unable to uniformly achieve the anticipated six-month of follow-up. Finally, our study only included central pachymetry values prior to cross linking, and did not evaluate pachymetry at post-operative visits.

In conclusion, this study shows that measured IOP with indentation tonometry increases following CXL, which is likely due to increased corneal rigidity, and that this should be strongly considered in patients with a history of CXL and a new increase in IOP.

REFERENCES

- 1 Meiri, Z., Keren, S., Rosenblatt, A., Sarig, T., Shenhav, L., & Varssano, D. (2016). Efficacy of Corneal Collagen Cross-Linking for the Treatment of Keratoconus. *Cornea*, 35(3), 417–428.
- 2 Jiménez, J. L. O., Jurado, J. C. G., Rodríguez, F. J. B., & Laborda, D. S. (1997). Keratoconus: Age of Onset and Natural History. *Optometry and Vision Science*, 74(3), 147–151.
- 3 Caporossi, A., Baiocchi, S., Mazzotta, C., Traversi, C., & Caporossi, T. (2006). Paracrosslinking therapy for keratoconus by riboflavin-ultraviolet type A rays induced cross-linking of corneal collagen. *Journal of Cataract & Refractive Surgery*, 32(5), 837–845.
- 4 Kymionis, G. D., Grentzelos, M. A., Kounis, G. A., Portaliou, D. M., Detorakis, E. T., Magarakis, M., ... Pallikaris, I. G. (2010). Intraocular pressure measurements after corneal collagen cross linking with riboflavin and ultraviolet A in eyes with keratoconus. *Journal of Cataract & Refractive Surgery*, 36(10), 1724–1727.
- 5 Wollensak, G., Spoerl, E., & Seiler, T. (2003). Riboflavin/ultraviolet-a-induced collagen crosslinking for the treatment of keratoconus. *American Journal of Ophthalmology*, 135(5), 620–627.
- 6 Kasumovic, S., Mavija, M., Kasumovic, A., Lepara, O., Duriccolic, B., Cabric, E., ... Jankov, M. (2015). Intraocular Pressure Measurements Referring to the Corneal Thickness in Keratoconic Eyes After Corneal Crosslinking with Riboflavin and Ultraviolet A. *Medical Archives*, 69(5), 334.
- 7 Romppainen, T., Bachmann, L. M., Kaufmann, C., Kniestedt, C., Mrochen, M., & Thiel, M. A. (2007). Effect of Riboflavin-UVA-Induced Collagen Cross-linking on Intraocular Pressure Measurement. *Investigative Ophthalmology & Visual Science*, 48(12), 5494.
- 8 Livny, E., Kaiserman, I., Hammel, N., Livnat, T., Zadok, D., Israel, K., & Bahar, I. (2012). The effect of riboflavin-ultraviolet A-induced collagen cross-linking on intraocular pressure measurement: an experimental study. *British Journal of Ophthalmology*, 96(7), 1029–1033.
- 9 Berk, T. A., Yang, P. T., & Chan, C. C. (2016). Prospective Comparative Analysis of 4 Different Intraocular Pressure Measurement Techniques and Their Effects on Pressure Readings. *Journal of Glaucoma*, 25(10).
- 10 Kozobolis, V., Gkika, M., Sideroudi, H., Tsaragli, E., Lydataki, S., Naoumidi, I., ... Labiris, G. (2016). Effect of Riboflavin/UVA Collagen Cross-linking on Central Cornea, Limbus and Intraocular Pressure. Experimental Study in Rabbit Eyes. *Acta Medica (Hradec Kralove, Czech Republic)*, 59(3), 91–96.
- 11 Rehnman, J. B., Behndig, A., Hallberg, P., & Lindén, C. (2014). Increased Corneal Hysteresis After Corneal Collagen Crosslinking. *JAMA Ophthalmology*, 132(12), 1426.
- 12 Doughty, M. J., & Zaman, M. L. (2000). Human Corneal Thickness and Its Impact on Intraocular Pressure Measures. *Survey of Ophthalmology*, 44(5), 367–408.
- 13 Foster, P., Baasanhu, J., & Alsbirk, P. (1998). Central corneal thickness and intraocular pressure in a Mongolian population. *Ophthalmology*, 105(6), 969–973.
- 14 Kass, M. A., Heuer, D. K., Higginbotham, E. J., Johnson, C. A., Keltner, J. L., Miller, J. P., ... Gordon, M. O. (2002). The Ocular Hypertension Treatment Study. *Archives of Ophthalmology*, 120(6), 701.
- 15 Brandt, J. D., Beiser, J. A., Kass, M. A., & Gordon, M. O. (2001). Central corneal thickness in the ocular hypertension treatment study (OHTS). *Ophthalmology*, 108(10), 1779–1788.