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Research Article

The Sensitivity and Specificity of Schiøtz Tonometry for Distinguishing between Cross-Linked and Keratoconus Cases

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Received: July 03, 2020; **Published:** November 28, 2020

Abstract

Purpose: To determine if indenting Schiøtz tonometer weights can be used to effectively differentiate between keratoconus (K) cases that have been treated by cross-linking (CXL) and those that have not.

Methods: Two operators (1 and 2) independently used a Schiøtz tonometer to indent the corneas of post-CXL and keratoconus patients using 5.5g, 7.5g, 10g and 15g weights and record the corresponding scale readings. The post-CXL cases were checked > 28 days after routine cross-linking treatment (epi-off, 3.0 mW/cm2, 30 minutes). Data from each operator were used to determine the significance of intergroup differences for each weight. If significant differences were found then the corresponding ROC curves, the sensitivity and specificity of the procedure for distinguishing between post-CXL and keratoconus cases would be estimated.

Results: Operator 1 examined 45/55 post-CXL/keratoconus cases. The equivalent numbers or Operator 2 examined 41/48. Reporting key significant findings ($p < 0.05$). The mean (± sd, 95% CI) scale results for the post-CXL and keratoconus were, Operator 1 (10g) 11.6 (2.0, 11.0 - 12.2), 12.2 (1.9, 11.8 - 12.7), Operator 2 (5.5g) 5.2 (1.7, 4.7 - 5.7) 5.9 (2.1, 5.4 - 6.5). The sensitivity and specificity values were, Operator 1 70.7% and 48.3% (10g, cut-off scale reading of 12) and Operator 2 62.2% and 50.9% (5.5g, cut-off scale reading of 5).

Conclusion: Under certain circumstances, Schiøtz tonometer weights can statistically differentiate between post-CXL and keratoconus. The procedure, and sensitivity and specificity values, are operator dependent. The corresponding ROC curves were not sufficiently skewed in favour of recommending the Schiøtz tonometer as an ideal instrument for distinguishing between post-CXL and keratoconus.

Keywords: *Cornea; Keratoconus; Cross-Linking; Schiøtz Tonometer; Sensitivity and Specificity*

Introduction

The management of keratoconus was revolutionized by the advent of corneal cross-linking (CXL). The treatment increases resistance to deformation and flattens the anterior surface of the cornea [1-4]. To date, there is no universally accepted standard procedure for

quantifying corneal rigidity after CXL. Attempts with non-invasive systems, such as the Ocular Response Analyser (ORA), have met with limited success and conflicting conclusions [5-17]. The cost of such instruments, coupled with the expense of maintaining and providing CXL, may not be regarded as financially viable by some ophthalmologists. Cut-backs, financial restraints and limitations of space may prevent busy clinics from investing in some sophisticated technologies. A simple technique for detecting the CXL patient would be valuable in such circumstances.

Freidenwald's technique, based on the Schiøtz indentation tonometer, for estimating of the coefficient of ocular rigidity (Ko), has been useful in revealing the attenuation of Ko these various conditions such as keratoconus and myopia compared with norms [18-26]. The original process, associated with Freidenwald's technique, required taking at least two measurements with different tonometer weights, marking the measurements on a pre-printed chart provided with the tonometer, connect the markings by drawing a line and finally reading off the Ko value associated with the slope of the line. This is laborious and time consuming even though an app can be written to estimate Ko. Could a single weight Schiøtz indentation tonometer be used for screening purposes, to effectively distinguish between a keratoconus and CXL treated keratoconus? If so, what is the sensitivity and specificity of such a procedure?

Aim of the Study

The aim of this study was to provide answers by asking two trained observers to perform Schiøtz indentation tonometry on two groups of patients: post-CXL and keratoconus.

Materials and Methods

Schiøtz tonometer

A single factory calibrated Schiøtz tonometer (Gulden Ophthalmics Elkins Park, PA) was used on all occasions. The tonometer was cleaned and sterilised by soaking for at least 5 minutes in 3% hydrogen peroxide then rinsing thoroughly with sterile saline followed by soaking for at least 5 minutes in 70% ethanol then rinsing and dipping into sterile saline and finally air dried.

With the patient in the supine position, following topical anaesthesia with proparacaine hydrochloride 0.5% drops, the operator digitally kept the eyelids apart and placed the Schiøtz tonometer at the centre of the cornea and the scale reading was recorded immediately (5.5g plunger weight). The tonometer was kept steady on the cornea and the scale readings were recorded after sequentially increasing the plunger weights to 7.5, 10.0 and 15.0g. The corresponding scalar readings were entered into a spread sheet by another member of the investigative team, the tonometer was removed, the subject was asked to relax, remain in the supine position for 5 minutes and the procedure was performed on the left eye. The total time for taking a series of readings on one eye was about 20 seconds. The approximate centre of the scale reading was recorded when there was some oscillation of the pointer.

Study design of clinical investigation

This was a prospective, consecutive, case-by-case, randomized, masked observational study approved by the local Ethics Board and followed the tenets of the Declaration of Helsinki. All patients signed consent forms, agreeing that data obtained during the study could be used for inclusion, after the aims and procedures of the study were fully explained. Data were obtained from two groups, keratoconus and those that had undergone cross-linking (post-CXL) without complications. Where appropriate, patients were asked to discontinue wearing any rigid contact lenses for at least three weeks (one week for soft lenses) before acquisition of any study data. All subjects underwent non-contact pachymetry, topography (Orbscan II version 3.2 [Bausch and Lomb™, Rochester, NY] set at an acoustic equivalent correction

of 0.92) and Goldmann tonometry before application of the Schiøtz tonometer. The post-CXL cases consisted of patients attending for routine follow up checks. Measurements were taken from each subject on a consecutive, case-by-case, basis. The investigation was in three parts as noted below. None of the patients enrolled presented with any other complications that could have affected characteristics of the cornea.

Acquisition of data

Two operators (MS and OH labelled 1 and 2) underwent a period of training in the use a Schiøtz tonometer. Each operator was asked to perform Schiøtz tonometry on patients presented to them for assessment during routine clinical sessions.

The patients were either keratoconus cases attending for routine clinical checks or keratoconus that had previously undergone routine corneal cross-linking without any complications. Measurements were taken from the right eye then the left eye after a break of approximately 5 minutes. Where applicable measurements, were taken from the treated eye in CXL cases and untreated eye in keratoconus subjects. The operators remained unaware if the patient had, or had not been, treated by cross-linking.

Description of cross-linking procedure and postoperative treatment

Corneal cross-linking (epi-off, 3.0 mW/cm^{2,} 30 min) had been performed by one surgeon (LT). Topical anaesthesia was made possible with proparacaine hydrochloride 0.5% drops. The corneal epithelium was stripped off the central 8 mm zone after soaking with 20% alcohol for 30 sec followed by instillation of riboflavin 0.1% with 20% dextran onto the cornea every 2 min for a total of 30 min. When the pachymetry (measured by using Axis II PR Ultrasound A mode and Pachymeter, Quantel Medical) at this point was 400 µm or more, the cornea was exposed to UVA radiation at a wavelength of near 370 nm and an irradiance of 3.0 mW/cm^2 and concurrent instillation of riboflavin 0.1% with 20% dextran every 2 min for a total of 30 mins. If the pachymetry before irradiation was < 400 µm, the cornea was hydrated with hypotonic riboflavin until the pachymetry reached minimum of ≥ 400 µm. Soft bandage contact lens was placed over the cornea at the end of procedure and remained on the patient's eye until re-epithelization had been completed. Postoperative treatment included drops of levofloxacin, dexamethasone and dexpanthenol gel 5 times a day each with a gradual tapering off and a preservative-free combination of trehalose and hyaluronic acid 3 times a day.

Data analysis

The data were stored on an Excel spread sheet (Microsoft, Redmond, WA) and analysed as follows. Firstly, to check if data were normally distributed (Kolomogorov-Smirov test of normality). Secondly, to determine the significance of any apparent differences in the tonometer scale readings between keratoconic and post-CXL cases for each weight (unpaired t-test or Mann-Whitney U test). Thirdly, on condition that a significant difference between keratoconic and post-CXL cases was found, the sensitivity and specificity of the procedure to correctly identify CXL cases. The significance level was set at $p < .05$.

Results

There were no significant differences in age or intra-ocular pressure between the two groups of the subjects examined by Operator 1 or Operator 2 ($p > .05$). The chief results are shown in table 1 and 2 and figure 1 and 2.

Operator 1 obtained measurements from 36 keratoconus patients (58 eyes of 9 females and 27 males age range 15 - 47 years) and 32 patients that had previously undergone CXL (41 eyes of 9 females and 23 males age range 17 - 43 years). Operator 2 obtained measurements from 37 keratoconus patients (55 eyes of 10 females and 27 males age range 15 - 47 years) and 31 patients that had previously undergone CXL (45 eyes of 10 females and 21 males age range 17 - 43 years).

Wt	Operator 1		Operator 2	
	K (n = 55)	Post - CXL (n = 45)	K (n = 58)	Post - CXL (n = 41)
5.5	6.8 (1.8, 6.3 - 7.2)	6.2 (2.1, 5.6 - 6.8)	5.9 (2.1, 5.4 - 6.5)	5.2 (1.7, 4.7 - 5.7)*
7.5	9.4 (1.9, 8.9 - 9.9)	8.7 (2.2, 8.0 - 9.4)	8.5 (2.2, 7.9 - 9.1)	7.8 (1.8, 7.3 - 8.4)
10.0	12.2 (1.9, 11.8 - 12.7)	11.6 (2.0, 11.0 - 12.2)*	11.5 (2.2, 10.9 - 12.1)	11.1 (1.7, 10.7 - 11.7)
15.0	14.2 (1.8, 13.8 - 14.7)	13.8 (2.0, 13.2 - 14.4)	13.5 (2.2, 12.9 - 14.1)	13.1 (1.9, 12.7 - 13.8)

Table 1: *Summary of Schiøtz scale readings. Mean (± s.d, 95% confidence limits) scale readings are shown for keratoconus (K) and cases that received cross-linking treatment (Post-CXL) for each of the four tonometer weights (Wt, units g). The number of eyes per group is noted in parenthesis after the group abbreviation (K, Post-CXL). An * denotes statistically significant differences between K and Post-CXL mean scores ($p < 0.05$).*

	Operator 1 (10.0g)			Operator 2 (5.5g)		
Scale setting	10	11	12	4	5	6
Sensitivity	34.1	36.6	70.7	28.9	62.2	84.4
Specificity	75.9	63.8	48.3	70.9	50.9	36.4
Likelihood Ratio	1.42	1.01	1.37	1.62	1.52	1.24

Table 2: *Sensitivity and specificity values for detecting the post-CXL. Values (%) for a range of scale settings are noted for the two operators. For both operators, the selected weight and arbitrary scale settings correspond with the significant findings noted in table 1.*

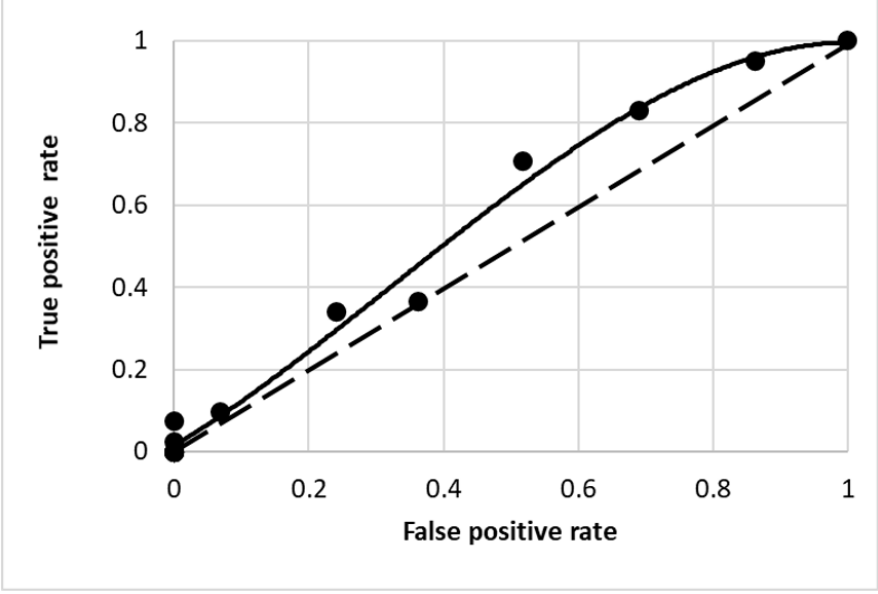

Figure 1: *The ROC curve for operator 1 using the 10.0g weight. The true and false positive values are noted in decimal format. The equation of the least squares best fit ogive (solid line) is, y = 1.008x + 0.919x2 - 0.945x3 (n = 15, r = 0.996, p < 0.001). --- is the 1:1 line.*

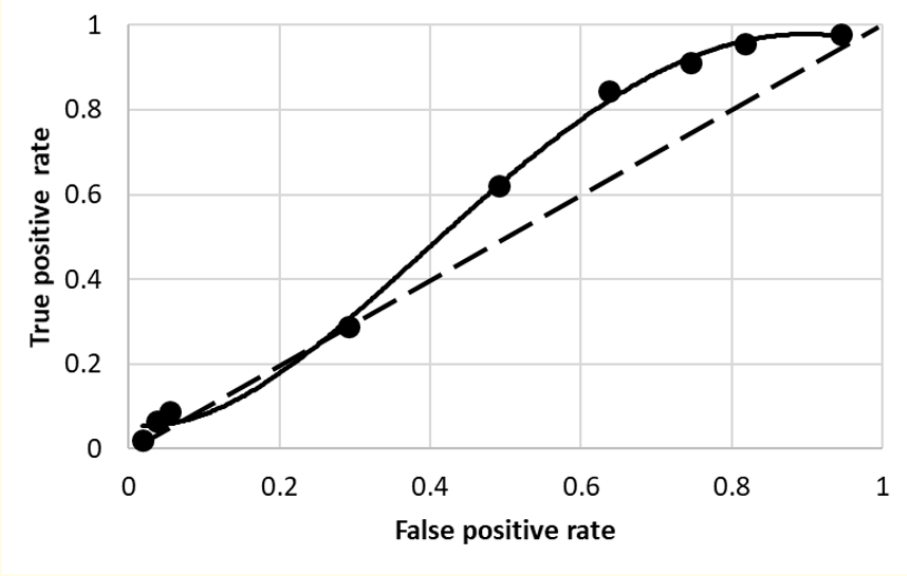

Figure 2: *The ROC curve for operator 2 using the 5.5g weight. The true and false positive values are noted in decimal format. The equation of the least squares best fit ogive (solid line) is, y = 0.210x + 3.160x2 - 2.482x3 (n = 15, r = 0.999, p < 0.001). --- is the 1:1 line.*

The distribution of results obtained, from both groups for each of the four weights, did not differ significantly from the normal distribution (Kolomogorov-Smirov test, $p > 0.05$). Hence, the data were subjected to parametric statistical tests.

There were no significant differences between the mean results of the two groups in 3 of the 4 weight conditions. These key findings are shown in table 1.

The results obtained by Operator 1 revealed significant differences in mean Schiøtz scale values between keratoconus and post-CXL except when the 10.0 g weight was used ($t = 1.68$, $p = 0.048$). For Operator 2, a significant difference was revealed only when using the 5.5 g weight ($t = 1.95$, $p = 0.027$). The corresponding receiver-operator characteristic curves (ROC) for these two weights, 10.0 g for Operator 1 and 5.5 g for Operator 2, are shown in figure 1 and 2. The sensitivity and specificity values for Operator 1 using 10.0 g weight and adopting a scale reading of 12 as the cut-off point was 70.7% and 48.3%. For Operator 2, the sensitivity and specificity values using 5.5 g weight and adopting a scale reading of 12 as the cut-off point was 62.2% and 50.9%. The sensitivity and specificity values for other cut-off values are shown in table 2. Furthermore, the corresponding likelihood ratios [Sensitivity/(1- Specificity)] are also noted in table 2. This ratio indicates how likely is it for a subject to be classified as being a CXL patient compared with one who is classified as not being a CXL patient when the test is used as outlined.

Discussion

Table 1 shows the mean, ± s.d and 95% confidence limits of the results obtained using the Schiøtz tonometer. Each one of the two operators found no significant differences between keratoconus and post-CXL in three of four different conditions. Cross-linking improves the resistance of the corneal stroma to stretch forces acting over the plane of its' surface but not along its' depth [27-30]. The forces between stromal lamellae are reckoned to remain unchanged after CXL [30]. This maintains the property of the lamellae to move against each other when the cornea is indented and estimates of some corneal biomechanical properties should remain unaffected after CXL. This is a reasonable explanation accounting for the negative outcomes uncovered by some studies after CXL [11,31-34] and some statistical outcomes noted in table 1.

However, significant differences between the keratoconus and post-CXL groups for weights of 10\g, according to the results obtained by operator 1 and 5.5g, according to the results obtained by operator 2 were found. This implies There is a tendency for the results according to operator 1 to be higher than those according to operator 2 and for the mean values in keratoconus to be higher compared with corresponding values in post-CXL. A statistical analysis to assess the significance of inter-operator differences cannot be made because the two operators did not apply the test on identical groups of keratoconus and post-CXL patients. However, it is interesting to note the consistent differences between the keratoconus and post-CXL patients. Compared with the keratoconus cases, the mean score in post-CXL was always lower. The chances of achieving such a result by a single operator is 1 in 16. The odds for two operators to achieve such a result is 4 in 1000. Therefore, it is reasonable to accept that on average post-CXL case are more resistant to Schiøtz induced corneal deformation when compared to keratoconus. Most in vivo studies, where the corneal biomechanics were assessed by non-contact means, concluded that CXL increases the corneal resistance to deformation along the direction of its' thickness [33,35-39]. These findings support our assertions.

The ROC curves are shown in figure 1 and 2. Both curves are above the 1:1 line indicating that, on the whole, the true positive rate for detecting a post-CXL case exceeds the false positive rate for each of the two operators using a Schiøtz tonometer. Ideally, each curve should be ogival with the steep slope skewed to the right and a plateau commencing at co-ordinates (x, y) close to (0.1, 0.9). The ROC curves in figure 1 and 2 fell short of the implying that the accuracy of the Schiøtz tonometer to differentiate between keratoconus and post-CXL cases was poor. Fontes., *et al*. [10] subjected results obtained from keratoconus and normal corneas, of similar thickness, to ROC analysis. They used the ocular response analyser (ORA), to quantify differences in corneal biomechanical properties, and concluded ORA did not sufficiently accurate to predict differences between the two groups.

Turning to the sensitivity and specificity values noted in table 2, for operator 1 the sensitivity value of 70.7% is promising but the relatively low specificity value further calls into question the value of using the Schiøtz tonometer to screen for CXL cases. A fall in specificity with rising sensitivity is, by definition, not a surprise. In theory, increasing the resolution of the tonometer scale could balance out the sensitivity and specificity values, but these are not likely to extend beyond 60%. For operator 2, the sensitivity and specificity values for a cut-off of 5 indicates a 62% chance of correctly identifying a post-CXL case and 51% chance of correctly identifying a keratoconus case, but the likelihood ratio is poor.

Conclusion

The Schiøtz tonometer was, under certain circumstances, capable of detecting differences between keratoconus and CXL when certain weights are used. The results appear to be operator dependant. ROC analysis, coupled with sensitivity and specificity values, question the value of using the Schiøtz tonometer to accurately differentiate CXL from keratoconus.

Declaration

None of the authors have any financial interest in any of the products or procedures mentioned in this paper. The study was self-financed.

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Volume 11 Issue 12 December 2020