Outcomes of corneal crosslinking for the treatment of keratoconus at a tertiary South African hospital.

By

Dr Jozef Kriek III

Student nr. KRKJOZ001

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Supervisor: **Prof Nagib du Toit, Division Ophthalmology**
University of Cape Town

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Acknowledgements and contributions

My supervisor, Prof Nagib du Toit, guided me throughout this research degree. He will be co-author on the published paper and his contributions were as follows:

- Conceptualization of research
- Assistance with structure of proposed research
- Review and editing of manuscripts

The second author, Dr Myles Potter, made the following contributions:

- Assistance in the gathering of data

The third author, Prof Christopher Tinley also made significant contributions:

- Review and editing of manuscripts

My contributions, as the candidate submitting this work for an MMed (Ophthalmology) were:

- Gathering of data
- Analysis of data
- Writeup of manuscripts

For this reason, I am the first author when the paper is to be published.

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Outcomes of corneal crosslinking for the treatment of keratoconus at a tertiary South African hospital.

Jozef Kriek III[1], Myles Potter[2], Christopher Tinley[1], Nagib du Toit[1]

1 Division of Ophthalmology, Groote Schuur Hospital, University of Cape Town, South Africa
2 Faculty of Medicine, King's College, London, England

Abstract

Objectives. To describe and analyse the effectiveness of using accelerated epithelium-off corneal crosslinking (A-CXL), in a cohort of patients with progressive keratoconus (KC), presenting to Groote Schuur Hospital, South Africa. *Methods.* A retrospective review of patients who underwent A-CXL, using 6.4 mW/cm^2 ultraviolet-A irradiation for 15 min, for progressive KC between 1 May 2017 and 1 June 2018. All patients completed 6 months minimum follow-up (Mean 9months, range 6-15). The diagnosis of keratoconus was based on corneal tomography and its clinical signs. Keratometry values and visual acuities were measured to ascertain if there was improvement in acuity or corneal curvature at 6 months post-procedure. *Results.* Nineteen eyes of 17 patients were included. The group consisted of 6 (32%) males and 13 (68%) females, with a mean age of 22.17 years (SD = 5.8). Zero eyes showed mild keratoconus, 8(42%) showed moderate keratoconus and 11(58%) showed severe keratoconus. At 6 months follow-up, results revealed that UCDVA improved from logMAR 0.96 to 0.83 (p = 0.068) and BCVA improved from logMAR 0.40 to 0.34 (p = 0.073). The mean UCDVA and BCVA Snellen line gain was 0.43 and 0.94. Overall the change in UCDVA and BCVA trended towards being statistically significant. The median Kmax value decreased from 57.7D to 55.9D. The mean Kmax value decreased from 59.46D to 58.85D (p = 0.137). The mean Kmean anterior increased from 50.26D to 50.86D (p = 0.139), the mean Kmean posterior from -7.48D to -7.67D (p = 0.026). There was a statistically significant change in Kmean post, but not so for Kmean ant and Kmax. Both severity groups showed a decrease in thinnest point corneal pachymetry from mean 445 micrometer(μm) to mean 422 μm (Moderate: p = 0.009; Severe: p = 0.003). KC progression was stopped or stabilised in 13 eyes (68%); 6 eyes (32%) showed progression. No complications were found. *Conclusions.* Our results show the effectiveness of 15-minute A-CXL (irradiance of 6.4 mW/cm^2) in maintaining both corneal stability and visual acuity in our patient population at 6 months

follow-up. In future, a larger study with prolonged follow-up would be required to elucidate this finding.

Introduction

Keratoconus (KC) is the most common of the corneal ectasias.[1] With KC often being the most common indication for corneal transplantation in the developing world, its timely identification and management is paramount.[2,3] Though the pathophysiology is not completely understood, KC is well recognised as a multifactorial disease with biomechanical, biochemical, environmental and genetic components - culminating in structural instability of the corneal collagen matrix (CCM).[4] If left unchecked, this leads to progressive corneal thinning, conical shape distortion and eventual profound vision loss due to irregular astigmatism and corneal scarring.[5] Young patients, especially those diagnosed before adulthood, are at an especially high risk of KC progression and therefore also at increased probability of needing corneal transplantation later in life.[6] It is therefore the young that stand to benefit most from interventions that could halt disease progression. [7]

The clinical introduction of CXL has revolutionised the conservative and non-invasive treatment of progressive KC[11]. It slows or stops the disease progression in its early stages, reducing the need for more invasive surgical treatment down the line.[12] The CXL procedure addresses corneal structural instability via a complex photochemical interaction between vitamin B2/riboflavin as photosensitiser, Ultraviolet A (UVA) light and oxygen.[13] The conversion of UVA light energy into biochemical energy releases reactive oxygen species, which through protein oxidation, increases the number of intra- and interfibrillar cross-links/bonds between individual collagens fibres in the CCM. These new photochemically induced cross-links increases the corneal tensile strength, rigidity and resistance to enzymatic degradation.[13,14,15] The standard non-accelerated Dresden CXL (S-CXL) protocol has been in worldwide clinical use for more than 15 years.[11] Though S-CXL is considered by many to be the gold standard, CXL protocol design and application has remained in continuous evolution.[16] More recently there has been an emergence of accelerated CXL (A-CXL) protocols with the aim of shortening treatment time. Based on the Bunsen–Roscoe law of reciprocity, A-CXL, when compared to S-CXL, uses greater irradiation energy for a shorter amount of time.[17] This allows A-CXL to achieve similar photochemical treatment effect as S-

CXL in less time, with positive implications on not only patient comfort, but throughput and cost effectiveness.[18,19] The conventional S-CXL protocol takes one hour per eye. Utilising A-CXL in our clinical setting has reduced treatment time by 25% per eye, allowing us to cross-link more patients with available resources.

Multiple first world studies, including systematic review and meta-analysis, have demonstrated safety and efficacy of A-CXL protocols for the management of KC. [20,21,22] This study aims to determine if using A-CXL, in a resource limited setting, was successful in halting KC progression in a cohort of patients with mild, moderate and severe KC, presenting to Groote Schuur Hospital, South Africa.

Patients and Methods

A retrospective review was conducted on patients with a diagnosis of progressive keratoconus, who underwent A-CXL (6.4mW/cm^2 for 15 minutes) at Groote Schuur Hospital, Cape Town, South Africa, between 1 May 2017 and 1 June 2018, with at least 6 months documented follow-up. The study was performed in accordance with the tenets of the Declaration of Helsinki and with the approval of the University of Cape Town research ethics committee. Patients were consented for the CXL procedure only after being counselled on keratoconus progression, its management options and the risks and benefits of CXL. Progression was defined as being one or more of the following changes seen over two consecutive visits as measured with Pentacam® HR imaging: 1. more than 1.50 dioptre (D) increase in the maximum curvature of the cornea (Kmax), 2. 2% decrease in corneal thickness, 3. 0.50 D increase in refractive astigmatism,[23,24] 4. 1 line drop in BCVA. Patients with a history of corneal surgery, pachymetry of less than 400 μm after epithelial removal, current pregnancy, lactation, severe dry eye, ocular infection, or any inflammatory eye surface problems that could potentially delay epithelial healing were excluded.[25] Patients who did not return for follow-up for a minimum of 6 months post-procedure and who did not have tomographic data at 6 months post procedure, were also excluded.

Outcome Measures

Along with visual acuity, change in Kmax is the most crucial parameter used to track success or failure of CXL. Endpoints of interest were changes in the following outcomes: Uncorrected distance visual acuity (UCDVA), Best corrected distance visual acuity with pinhole (BCVA), Maximum keratometry in the steepest meridian of corneal curvature (Kmax), Mean anterior keratometry (Kmean ant), Mean posterior keratometry (Kmean post), Corneal pachymetry / Thinnest point of corneal thickness (CT), Complications (Persistent epithelial defect, sterile corneal infiltrates, persistent corneal haze, endothelial decompensation, corneal oedema or infective keratitis).

Statistical Analysis

Descriptive statistics are presented as means and standard deviations for continuous variables and proportions for categorical variables. The level of significance for all analyses was set at $p = 0.05$. Repeated measures t-tests were used to compare pre-and-post operative (a) UCDVA, (b) BVCA, (c) Kmax, (d) Kmean ant, (e) Kmean post. Separate repeated measures t-tests were also used to compare pre-and-post operative (f) CT, for patients with moderate and severe keratoconus.

Pre and Postoperative Evaluation

Patients underwent complete ophthalmic examinations before and after A-CXL. Measurements included; pre and post A-CXL UCVA, pre and post A-CXL BCVA, corneal keratometry (Kmax, Kmean ant, Kmean post) and CT. Slit-lamp and dilated funduscopic examination was also performed. Visual acuity was measured using a standard Snellen acuity chart at 6 meters and captured. For purposes of statistical analysis, Snellen acuity was converted to Logarithm of the Minimum Angle of Resolution (LogMAR). Corneal keratometry and CT was measured with a rotating Scheimpflug camera (Pentacam HR, Oculus, Optikgeräte GmbH, Wetzlar, Germany, v 1.22r05). Keratometry was captured in dioptres (D) and CT was captured in μm. Baseline KC severity was also graded and grouped, according to Kmax value, as Mild <48D, moderate 48-54D and severe >54D, using a system described in the Collaborative Longitudinal Evaluation of Keratoconus (CLEK) study.[26] Keratoconus progression was deemed stabilized if change in Kmax was <1.0D, progressive if Kmax increased by >=1.0D, and reduced if Kmax decreased by >1.0D. Treatment was deemed

successful with either stabilisation or reduction of Kmax at minimum 6 months post A-CXL. Treatment was deemed unsuccessful with progressive Kmax seen at minimum 6 months post A-CXL.

Surgical Procedure

Crosslinking was performed as an outpatient procedure, in a clinic based procedure room, in all but one patient who was too young to tolerate local anaesthetic and therefore cross-linked in theatre under general anaesthesia. Topical anaesthesia of the cornea was achieved using Oxybuprocaine drops (Minims®, Oxybuprocaine Hydrochloride 0.4%, Bausch & Lomb). The eye was then disinfected with 5% povidone iodine solution for two minutes and rinsed with balanced salt solution. After lid speculum insertion, the central 9mm diameter of corneal epithelium was removed by first devitalising it with 10% alcohol, applied within a well for 20 seconds. Care was taken not to allow any alcohol to come into contact with the limbus. The eye was then washed with balanced salt solution, followed by mechanical debridement of the epithelium. The cornea was subsequently soaked in Riboflavin 0.1% in a hydroxypropyl methylcellulose solution for 30 minutes, one drop every 5 minutes for 30 minutes. The central 8mm of the cornea was then exposed to 15 minutes of continuous 6.4 mW/cm^2 Ultraviolet A irradiation, using the Opto XLink-Corneal Crosslinking System (Opto Global Pty Ltd.). Light centration on the cornea was controlled by the surgeon. During irradiation, riboflavin 0.1% drops were applied at intervals of 2-3 minutes. At completion, the treated cornea was rinsed with BSS and a soft bandage contact lens (Purevision®, Bausch&Lomb) was then applied. Ofloxacin antibiotic and artificial tears were given 6 times a day until complete re-epithelialization of the cornea. Patient follow-up was planned for day 1, week 1, 1 month, 3 months, 6 months and 12 months after the procedure. The bandage contact lens was removed once the cornea was completely epithelialized and dexamethasone and artificial tear drops were then prescribed 4 times a day and tapered over the following 4 weeks.

Results

Nineteen eyes of 17 patients who underwent A-CXL were included in the study. See **{table I}** for baseline values. All patients completed 6 months follow-up, with the mean follow up being 9 months (range 6-15).

Age and gender

The group consisted of 6 (32%) males and 13 (68%) females with a mean age of 22.17 years (SD = 5.8), ranging from 10.13-to-35.44 years. Three (16%) patients were younger than 18 years.

Keratoconus groups based on keratometry readings

Of the 19 eyes graded into 3 severity groups according to the CLEK grading system; zero eyes showed mild keratoconus, 8(42%) showed moderate keratoconus and 11(58%) showed advanced keratoconus.

Visual outcome

Pre-operative mean UCDVA was 0.96 LogMAR (SD = 0.59) and at 6 months post-CXL was 0.83 LogMAR (SD = 0.63) [The mean UCDVA Snellen line gain was 0.43] The preoperative mean BCVA was 0.40 LogMAR (SD = 0.29) and at 6 months post-CXL was 0.34 (SD = 0.26) [The mean BCVA Snellen line gain was 0.94] ***{Figure 1}*** shows the distribution of the pre and post A-CXL BVCA by severity Group. ***{Figure 2}*** shows the percentage of patients with specific BCVA Snellen acuities pre and post A-CXL.

Corneal topographic outcomes

The mean pre A-CXL Kmax was 59.46D (SD = 13.08; range 47.8 – 106.9) and the median was 57.7D (outlier of 106.9D), whereas the mean post A-CXL Kmax was 58.85(SD = 12.42; range 47.2-100.7) and Median was 55.9D. The mean pre A-CXL Anterior Kmean was 50.26D (SD = 7.27; range 43.7-74.3) and the median was 47.8D, whereas the post A-CXL Anterior Kmean was 50.87D (SD = 7.37; range 42-74.7) and the median was 48.7D. The mean pre A-CXL Posterior Kmean was -7.48D (SD = 1.27; range -11 - -6.2) and the median was -7D, whereas the post A-CXL mean Posterior Kmean was -7.67D (SD = -7.4; range -11 - -6.3) and the median was -7.4D. After A-CXL of the 19 total eyes, 10 (52%) eyes had shown reduction in Kmax with a mean flattening of corneal curvature of 3.23D (SD = 1.63). Three (16%) eyes stabilised with mean Kmax increase of 0.57D (SD = 0.42). The remaining 6 (32%) eyes showed progressive steepening of Kmax, mean 4.12D (SD = 2.59) at 6 months review. See **{table II}** for changes in keratometry.

Pachymetry

Both severity groups showed decrease in CT from mean 445 μm to mean 422 μm, at 6 months follow-up, post A-CXL. ***{Figure 3}***

Discussion

Corneal cross-linking is an effective treatment for progressive KC, with long term stabilization of the condition resulting in many socioeconomic benefits.[27,28] A recent study of S-CXL, with 3 year follow-up of 156 eyes, showed that S-CXL was successful in stopping progression of KC in 120 (76.92%) eyes. On the other hand, it was unsuccessful in stopping progression in 31 (19.87%) eyes.[29] A study by Males et al. which compared the long-term (mean 20 months) outcomes of S-CXL and A-CXL (9 mW/cm^2 for 10 minutes), found A-CXL to be equivalent to S-CXL in managing progressive KC.[21] Moreover, several studies using different A-CXL protocols, have also demonstrated the procedure to be safe and effective in stopping keratoconus progression.[30,31,32]

In our study, at 6 months follow-up post A-CXL, the majority of eyes maintained or improved both UCDVA and BCVA. The average visual improvement of 0.43 Snellen lines in UCDVA and 0.94 Snellen lines in BCVA are in keeping with other studies showing improvement in visual acuity following A-CXL.[21,33] Improvement in visual acuity can be explained through the work of Caporossi et al.[34] They showed, through topo-aberometric analysis, the cornea assuming a more regular shape post CXL. Their study found a trend towards increased corneal morphological symmetry through a significant reduction in asymmetry between vertical hemi meridians - this results in overall reduction in higher order aberrations. Notwithstanding the above, the overall change in UCDVA and BCVA in our study was statistically nonsignificant ($p = 0.068$ and $p = 0.073$).

Several studies have shown that Kmax, a primary topographic indicator of CXL success, decreased significantly after S-CXL.[11] Our results show that A-CXL was successful in 13 of 19 eyes (68%) treated, showing either reduction or stabilisation in Kmax values at mean 9 months follow-up. On the other hand we found A-CXL unsuccessful in stopping progression in 6 of 19 eyes treated (32%). This failure rate is in keeping with the expected failure rate of

8.1-33%, as shown by Shalchi et al. in a systematic review.[35] At the same time it is notably higher than the 1 % failure rate reported by Raiskup-Wolf et al.[27] Our higher failure rate can be explained by the findings of Koller et al. who showed that eyes with severe keratoconus, at time of CXL, are at increased risk of treatment failure.[36] This is in keeping with our findings, where 4 of 6 (67%) eyes which progressed had severe keratoconus. Analysis of keratometry showed a statistically significant increase for Posterior Kmean (p = 0.026) but did not show a statistically significant change in Anterior Kmean(p = 0.139) and Kmax (p = 0.137), evaluated pre-CXL and post-CXL after mean 9 months follow-up. The increase in posterior corneal elevation may likely be due to continued ectactic changes in the posterior cornea post-CXL. This could be explained by the biomechanical stiffening effect of CXL not penetrating full thickness into the posterior stroma. Cross-linking treatment parameters are designed to avoid potential UVA damage to corneal endothelium and the effective treatment depth is typically only in the anterior 300 to 400 μm of corneal stroma.[11,34,37]

A systematic review and meta-analysis by Meiri et al confirms post-CXL corneal thinning to be expected.[38] The cornea thins initially and then recovers towards baseline thickness over time. They found that corneal thickness was reduced by 10 to 20 micron in the year following CXL, but not beyond 24 months. Multiple factors have been implicated in this thinning, but the exact causal relationship still needs to be determined.[39] The pachymetric findings of our study are in keeping with this, showing statistically significant decrease in mean CT, from 445.37 μm to 422 μm, across both severity groups at 6 months post-CXL (Moderate: p = 0.009; Severe: p = 0.003).

No complications occurred in our study. Transient clinical or subclinical anterior stromal haze can be expected post-CXL as it induces anterior stromal keratocyte apoptosis.[40] In contrast to the more persistent myofibroblast induced haze found post-PRK, post-CXL haze is typically transient in nature and is related to corneal fibroblast generation in response to keratocyte apoptosis.[41] Kim et al. found that greater haze could be expected in advanced keratoconus.[42] One of 19 eyes still had some mild stromal haze at 13 months follow-up. This eye had severe keratoconus with pre A-CXL Kmax of 57.8D. Alnawaiseh et al. showed that in the first month after CXL, haze formation reduced corneal transparency as measured with scheimpflug densometry. Haze then started to decrease after 3-6 months and improved with

time. So much so, that at 24-36 months after CXL, corneal transparency could reach untreated physiological levels.[43]

Shortcomings of this study include it's retrospective nature, limited size of the study population, relative short term follow-up and non-attendance of appointments. Only 25 of 36 patients, or 29 of 40 eyes attended their cross-linking procedure appointments. Of these 29 crosslinked eyes, 10 eyes defaulted follow-up before 6 months and were unreachable at time of data collection and subsequently excluded. Poor follow-up remains a problem in the public health setting as previously also reported by du Toit et al.[44] This poor follow-up is likely due to the socioeconomic circumstances in South Africa, with financial and transport constraints hampering patients' ability to fully and timeously utilise the medical services available to them.

CONCLUSION

Our findings agree with previously published studies that demonstrated the safety and efficacy of A-CXL for the management of progressive KC.[21, 30,31,32] The future will no doubt hold many more treatment options, allowing the management of corneal ectasias to be ever more tailored to the specific patient and eye. To confirm long term stability of findings presented here, any future study should include a larger number of patients with extended follow-up.

Table I. Baseline measurements

Pre A-CXL	Mean	SD	Minimum	Maximum
Visual Acuity in LogMAR				
UCDVA	0.96	0.59	0.18	1.88
BCVA	0.40	0.29	0	0.78
Keratometry/ Curvature in Diopter (D)				
Kmax	59.46D	13.08D	47.8D	106.9D
Kmean anterior	50.26D	7.27D	43.7D	74.3D
Kmean posterior	-7.48D	1.27D	-11D	-6.2D
*Pachymetry in micrometres (*µm*)*				
Thinnest point of corneal thickness	445.37 µm	37.56 µm	381 µm	508 µm

Table II. Pre and post A-CXL – Keratometry

	Pre A-CXL	Post A-CXL
Kmax – mean	59.46D	58.85D
Kmax – median	57.7D	55.9D
Kmean anterior – mean	50.26D	50.87D
Kmean anterior – median	47.8D	48.7D
Kmean posterior - mean	-7.48D	-7.67D
Kmean posterior - median	-7D	-7.4D
Thinnest point pachymetry	445.37	508

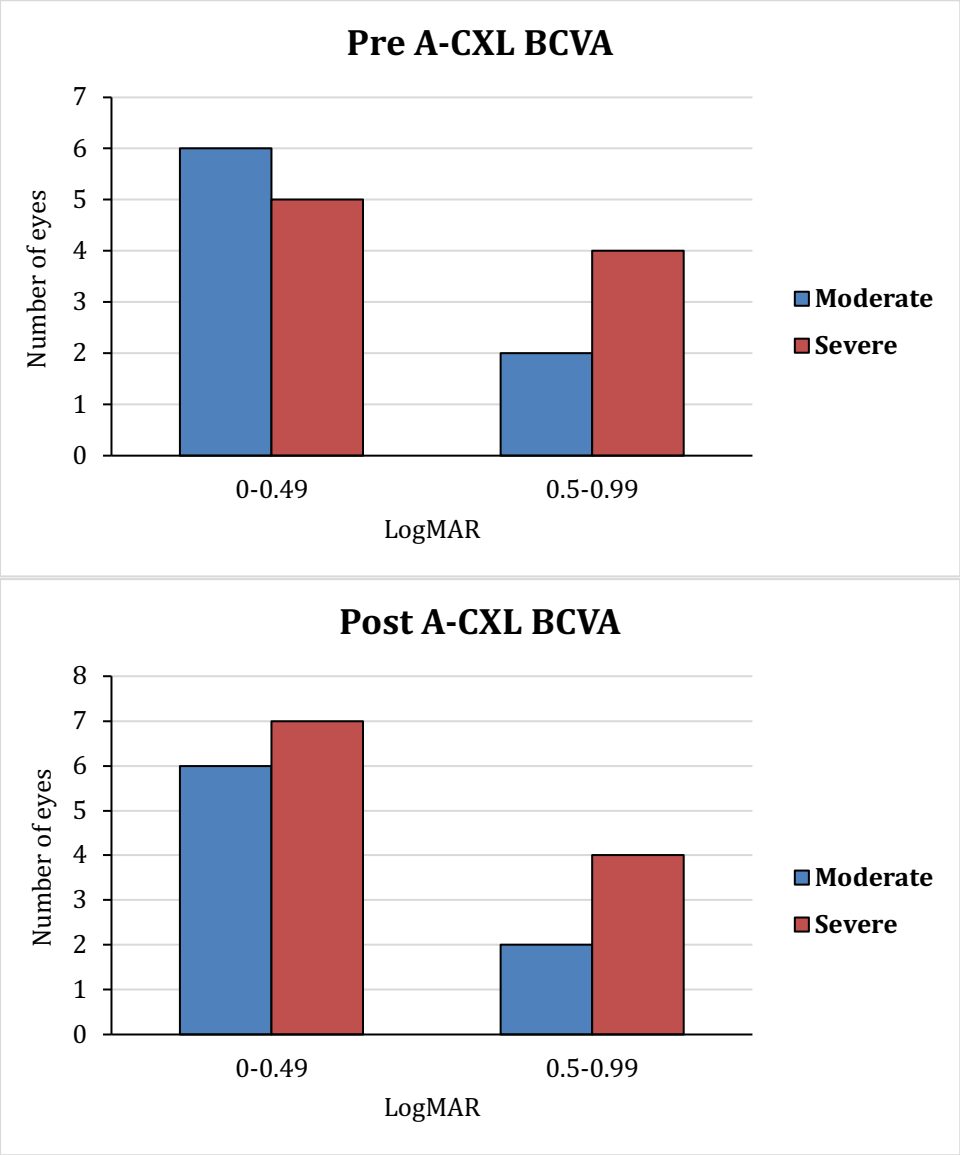

Figure 1. Distribution of the preoperative and postoperative BCVA by severity group.

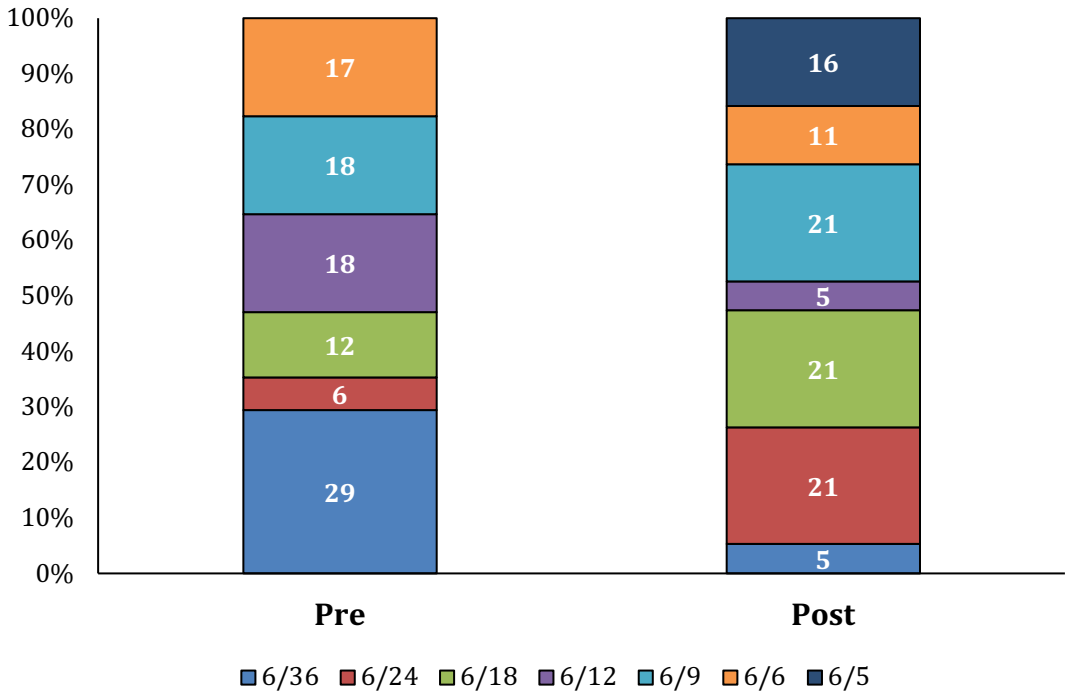

Figure 2. Percentage of patients with specific BCVA Snellen Visual Acuities – pre and post A-CXL.

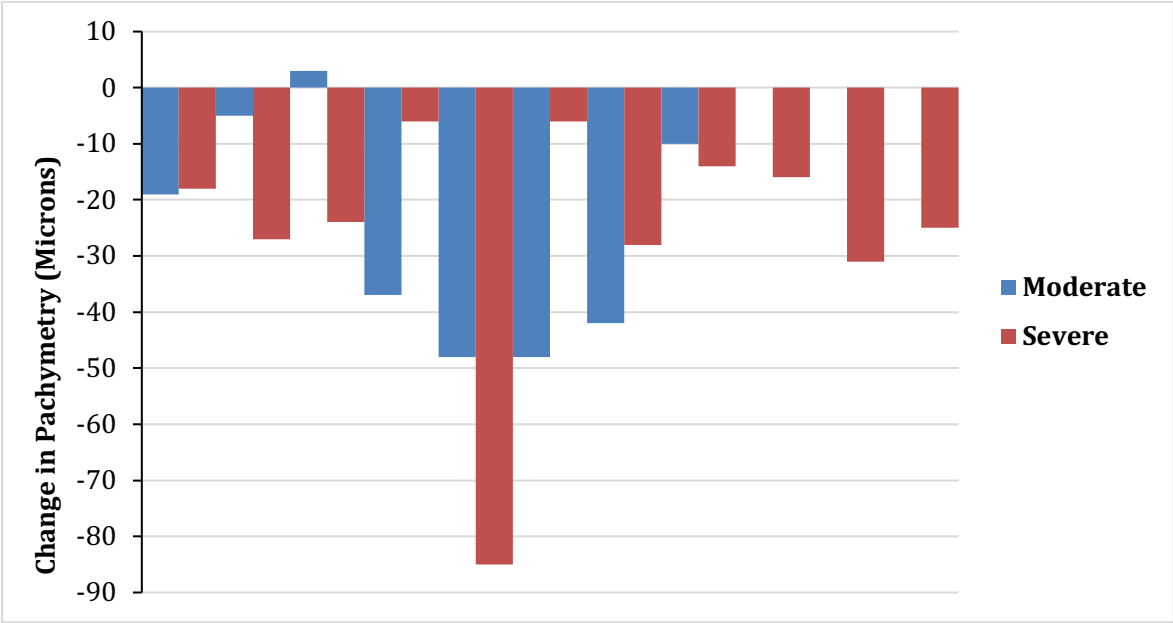

Figure 3. *Change in corneal thickness at thinnest point,* for both severity groups, post A-CXL.

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