SPECIFIC CORNEAL PARAMETERS AND VISUAL ACUITY CHANGES AFTER CORNEAL CROSSLINKING TREATMENT FOR PROGRESSIVE KERATOCONUS

Veselý P.[1,3], Veselý Ľ.[2], Combová V.[1], Žukovič M.[4]

[1] VESELY, eye clinic– Bratislava, Refractive and laser eye surgery teaching facility of Medical Faculty, Comenius University, Bratislava, Slovakia
[2]Department of Ophthalmology, Královské Vinohrady University Hospital, Prague, Czech Republic
[3]Department of Ophthalmology, Medical Faculty of Comenius University, Bratislava, Slovakia
[4]Risk Intelligence Analytics, Dell Technologies, Prague, Czech Republic

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MUDr. Pavol Veselý
VESELY, očná klinika
Karadžičova 16
821 08 Bratislava
E-mail: palo.vesely@veselyok.com

SUMMARY

Aim: To evaluate the effect of crosslinking (CXL) therapy on the change in the quality of visual acuity and the change in the topographic properties of the cornea – curvature, pachymetry, and change of astigmatism, coma abberation and CLMIaa (Cone Localisation and Magnitude Index).
Methods: A retrospective analytical study included 29 eyes of 24 patients who had progressed in the last 12 months and were suitable candidates for CXL surgery. The monitored parameters were the steepest, flatest and mean anterior instantaneous curvature (AIC_S, AIC_F, AIC_M) and the steepest, flatest and mean posterior instantaneous curvature (PIC_S, PIC_F, PICM) of the cornea, corneal thickness in the centre of the cornea ($PACH_C$) and in the thinnest point of the cornea ($PACH_T$), corneal astigmatism (ASTIG). coma (COMA), Cone Localization and Magnitude Index (CLMIaa) and uncorrected distance visual acuity (UDVA) with corrected distance visual acuity (CDVA). Data were analysed before surgery and 12 months after surgery. The AIC, COMA, CLMIaa and ASTIG parameters were analysed by paired t test. As the parameters of UDVA, CDVA, PIC and PACH did not meet the conditions of normal distribution, the Wilcoxon test was used to investigate the change in these parameters after CXL.
Results: Twelve months after the procedure, we recorded an improvement in UDVA ($p = 0.371$) and CDVA ($p = 0.825$), an increase in PIC_S, PIC_F and PIC_M ($p = 0.902$; $p = 0.87$ and $p = 0.555$), a decrease in $PACHC_C$ ($p = 0.294$) and a decrease in CLMIaa ($p = 0.113$) that did not reach statistical significance. The decrease in $PACH_T$ ($p = 0.027$), decrease in COMA ($p = 0.037$) and decrease in anterior corneal curvature of AIC_S, AIC_F and AIC_M were statistically significant ($p = 0.019$; $p = 0.010$ and $p = 0.005$). The decrease in the value of astigmatism did not show statistical significance, as $p = 0.297$.
Conclusion: CXL corneal therapy has been shown to be an effective method to stabilize the cornea in progressive keratoconus, and to improve the higher order of coma. This contributes to the possible improvement of UDVA and CDVA.
Key words: cornea, ectasia, CXL, pachymetry, anterior instantaneous curvature, posterior instantaneous curvature, coma, CLMIaa

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INTRODUCTION

Keratoconus is an ectatic corneal pathology, which is probably an inherited disease with incomplete gene penetrance [1]. A characteristic of keratoconus is alteration in the biomechanical properties of the cornea. Changes in the elastic components cause the cornea to lose its almost "hemispherical" shape and its centre to protrude anteriorly [2]. This process results in thinning of the cornea, the development of irregular astigmatism and myopia, and deterioration of visual acuity, which is difficult to correct with optical aids. In the final stages of the disease, corneal scarring can be observed. The disease most often begins at puberty and progresses into the third or fourth decade of life. The most severe stages of the disease appear between 20-40 years of age [3,4].

Until recently, the only available treatment was the application of a hard contact lens. However, this therapy has only a corrective effect and not a therapeutic one. Corneal transplantation was the only causative

treatment. New technologies and therapeutic procedures – intrastromal ring implantation and corneal cross-linking (CXL) have brought a change in the treatment of keratoconus. While transplantation requires the replacement of the damaged cornea with an allogeneic cornea, the later mentioned procedures preserve the original corneal tissue. Corneal cross-linking has long been considered the only minimally invasive method that can halt the progression of the pathology and provide stabilisation of corneal biomechanical properties. This is achieved by applying UV-A radiation to the cornea, which has been saturated with a riboflavin solution, resulting in the formation of additional bonds between the collagen fibers and the reinforcement of the corneal stroma [5]. The aim of this study is to assess the change in anterior and posterior corneal surface curvature, corneal thickness, astigmatism, higher order coma aberration and Cone Localisation and Magnitude Index (CLMIaa) after CXL procedure and their effect on visual acuity quality after a minimum of 12 months of observation.

PATIENTS AND METHODS

Patients who were diagnosed with progressive keratoconus were recruited in this retrospective study. All the patients were examined and subsequently underwent the procedure at VESELY eye clinic. All preoperative examinations were performed by a single physician and using a Galilei G6 anterior segment analyser (Ziemer Ophthalmic System, Port, Switzerland). Subsequently, all the procedures were also performed by the same doctor. We did not seek approval from the Ethics Committee as this was a retrospective analysis of the results. However, all the patients signed an informed consent form before the examination and before the procedure they were informed about the course of the examinations and the procedure.

The study population consisted of 29 eyes of 24 patients who were diagnosed with keratoconus and were eligible for CXL treatment.

The admission criteria were as follows-maximal keratometry < 50.0 Dpt, pachymetry > 400 µm, age > 20 years, keratoconus confirmed on topographic map, and change in at least one of the following parameters: increase in steepest keratometry of more than 1.0 Dpt in the 12 months prior to the procedure, increase in astigmatic correction of more than 1.0 Dcyl in the 12 months prior to the procedure, or increase in spherical equivalent of 0.5 Dpt or more in the preceding 12 months. Patients with previous corneal surgery by perforating keratoplasty (PK), photorefractive keratectomy (PKR), Laser In Situ Keratomileusis (LASIK), radial keratotomy (RK), patients who had recovered from herpetic keratitis, with structural changes on the cornea (Vogt's striae, edema, epitheliopathy), suffering from dry eye syndrome or autoimmune disease were excluded from the study. All patients had stopped wearing contact lenses for at least two weeks prior to the examination. This was both before the examination and before the procedure.

The assessment of keratometry was not based on a standard axial map but on instantaneous curvature, referred to as anterior (AIC) or posterior (PIC), instantaneous curvature, i.e. the instantaneous curvature of the cornea at any one point of the cornea. This type of measurement is more accurate compared to the standard axial measurement and better renders the asymmetry of the corneal curvature [20]. Pentacam users know this type of corneal topography as a Tangential Map. We evaluated changes in the steepest, flattest, and mean anterior (AICS, AICF, AICM) and steepest, flattest, and mean posterior (PICS, PICF, PICM) instantaneous curvatures. Corneal thickness (pachymetry) was also assessed, both at the thinnest corneal PACHT and the centre of the cornea PACHC, as well as uncorrected distance (UDVA) and corrected visual acuity (CDVA), both before the procedure and 12 months after the procedure. The specific parameters monitored were higher order coma aberration (COMA) and Cone Localisation and Magnitude Index (CLMIaa). This index, unlike the AIC and PIC, works with the axial curvature of the cornea and compares two locations located 180° apart on a circle. It processes not only the location of the steepest anterior surface curvature, the region of the anterior surface with the highest elevation, but also the same parameters for the posterior surface, along with the thinnest pachymetry at the location [18].

All patients underwent a complete ocular examination prior to the procedure, which included examination of uncorrected and corrected visual acuity, intraocular pressure values, Ziemer Galilei G6 anterior segment analyser, biomicroscopic examination of the anterior and posterior segments of the eye, and Schirmer's test I. The anterior segment analyser examination with a double Scheimpflug camera provided accurate values of corneal parameters-anterior and posterior curvature and corneal thickness. Patients underwent the same examinations 12 months after the procedure.

The procedure

Corneal cross-linking was performed on all patients using a standardised and uniform procedure. In the operating room, the local anaesthetic 0.4% oxybuprocaine hydrochloride (Benoxi, UniMed Pharma s.r.o., Bratislava, Slovakia) was injected into the eye to be operated on four times before the procedure – 30 minutes, 20 minutes, 10 minutes, and 5 minutes. Subsequently, in the sterile environment of the operating room, after disinfection of the surrounding eye and the eye itself with povidone iodide solution (Betadine, Egis Pharmaceuticals PLC, Budapest, Hungary), corneal epithelial abrasion with a diameter of 10 mm was performed. After complete cleansing of epithelial debris from the ocular surface, isotonic riboflavin solution (MedioCROSS D, Medio-Haus Medizinprodukte GmbH, Kiel, Germany)

was applied to the corneal surface for 30 minutes, at intervals of every 2 minutes. Subsequently, the penetration of riboflavin into the corneal stroma and anterior chamber was checked biomicroscopically. The riboflavin-saturated cornea was then exposed to UV-A radiation for 10 minutes at an energy of 9 mW/cm^2. (Light-Med Corporation, New Taipei City, Taiwan). Riboflavin was also applied to the corneal surface every 2 minutes during UV-A irradiation.

After the end of radiation, a therapeutic contact lens was placed on the treated eye; this was removed from the eye on the fifth postoperative day. The prescribed postoperative therapy was moxifloxacin (Alcon Pharmaceuticals Ltd., Geneva, Switzerland) every two hours on the day of surgery and then five times daily for seven days after surgery. Also dexamethasone 0.1% (UniMed Pharma s.r.o., Bratislava. Slovakia) was administered every two hours on the day of surgery, followed by five times daily for the first postoperative month and three times daily for the second and third postoperative months.

Statistical methods

Individual parameters were analysed by two statistical methods. A Wilcoxon test was used to analyse the effect of the CXL procedure on PIC, PACH, UDVA and CDVA. The Wilcoxon test belongs to the group of nonparametric tests that are used when the data do not have a normal distribution. It is used to compare data from the same group of respondents under different conditions. Based on the null and alternative hypotheses, a critical value or p – value is calculated. If the calculated test criterion is less than the critical value, we reject the null hypothesis in favor of the alternative hypothesis.

A paired t – test was used to analyse the effect of the CXL intervention on AIC, COMA, CLMIaa, and ASTIG, because the available data for the AIC parameters satisfy the conditions of a normal distribution. Based on the null and alternative hypotheses, a critical value or p-value is calculated. If the calculated t0 statistic is greater than the critical value of t1-α (n - 1), we reject the null hypothesis in favour of the alternative hypothesis.

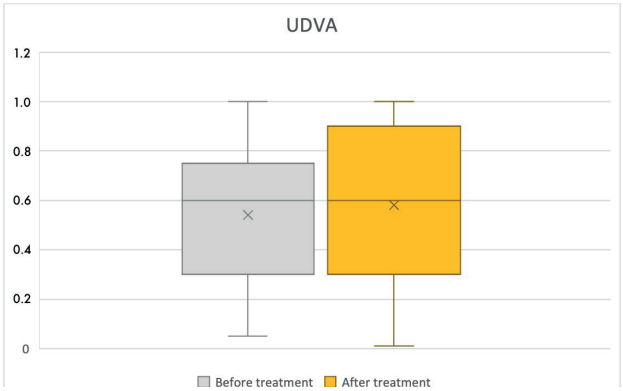
The change in the distribution of the observed parameters was recorded using so called Kernel plots. These show the change in the amount of a particular parameter with a given property with change over time in the group under study.

RESULTS

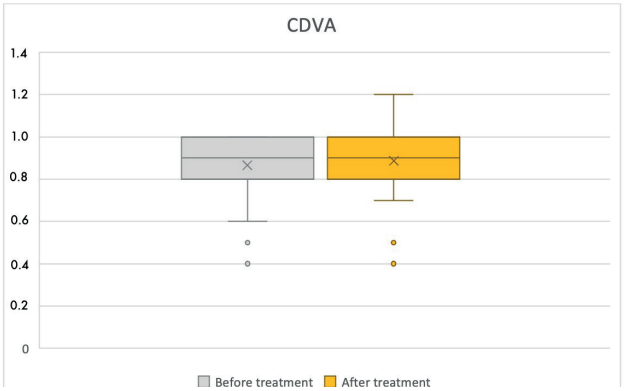
This is a retrospective study that included 29 eyes of 24 patients, ranging in age from 20 to 32 years. Twelve months after the procedure, all patients underwent a slit lamp examination and no structural changes were observed on the cornea in terms of opacities, scarring, or signs of infection.

The results report an UDVA change of 0.54 (Snellen) (0.267 logMAR) ±0.31 before the procedure and 0.58 (Snellen) (0.235 logMAR) ±0.34 after the procedure, thus with no statistical significance (p = 0.371) (Chart 1) and CDVA of 0.87 (Snellen) (0.06 logMAR) ±0.17 before the procedure and 0.89 (Snellen) (0.05 logMAR) ±0.18 after the procedure, also without statistical significance (p = 0.938) (Chart 2). Changes in anterior corneal surface curvature – AICS (before 45.95 Dpt ±1.51 after 45.67 Dpt ±1.43), AICF (before 43.81 ±1.47, after 43.48 Dpt ±1.53) and AICM (before 44.89 Dpt ±1.4, after 44.57 Dpt ±1.35) were also observed, which showed a statistically significant change in terms of reduction (p = 0.019; p = 0.010 and p = 0.005 respectively). Changes in posterior corneal surface curvature of PICS (before 6.99 Dpt ±0.58, after 7.04 Dpt ±0.54), PICF (before 6.26 Dpt ±0.35, after 6.27 Dpt ±0.33), and PICM (before 6.59 Dpt ±0.46, after 6.62 Dpt ±0.4) were statistically insignificant (p = 0.829; p = 0.563 and p = 0.54 respectively). The corneal thickness (pachymetry) parameter PACHT (before 471.79 µm ±46.94, after 463.41 µm ±37.19) showed a statistically significant change (p = 0.027) (Chart 3), while the PACHC parameter (before 507.69 µm ±34.95, after 502.59 µm ±29.18) did not show a statistically significant change (p = 0.078) (Chart 4).

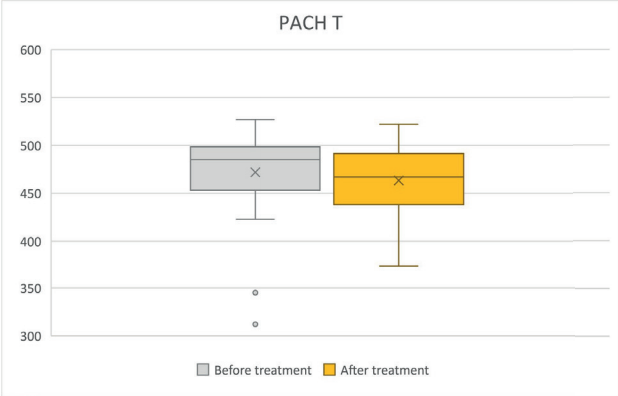
The change in corneal astigmatism values before the procedure of 2.51 Dcyl ±1.49 and after the procedure of 2.37 Dcyl ±1.49 also did not show statistical significance (p = 0.297). The reduction in COMA (1.1 µm ±0.56 before



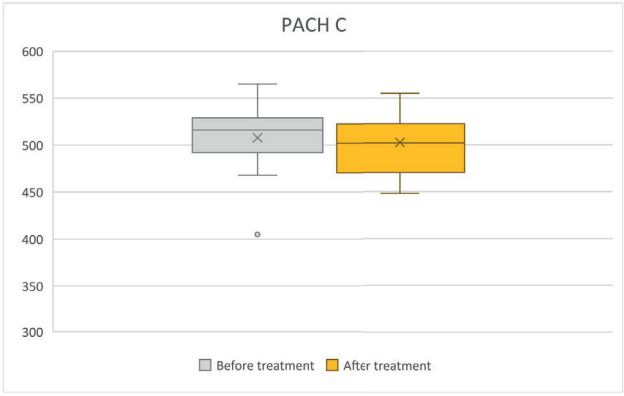
Graph 1. Change of UDVA before and after treatment
UDVA – best uncorrected distance visual acuity



Graph 2. Change of CDVA before and after treatment
CDVA – best corrected distance visual acuity



Graph 3. Change of corneal thickness at thinnest point before and after treatment PACHT – thinnest point corneal pachymetry



Graph 4. Change of central corneal thickness before and after treatment PACHC – central corneal pachymetry

CXL and 1.04 µm ±0.54 after CXL) was statistically significant (p = 0.037). By contrast, the change in CLMIaa did not show statistical significance, as p = 0.113 and the value of this index was 6.55 Dpt ±3.43 before and 6.03 Dpt ±2.75 after the procedure. The mean values of the individual corneal and UDVA parameters studied together with CDVA are summarised in Table 1.

DISCUSSION

Corneal cross-linking with CXL is a procedure used to halt the progression of keratoconus, with economic and psychosocial benefits [6]. Kapitanova states that this procedure expands the management options not only for keratoconus but also for other corneal ectasias [16]. Although the exact mechanism of action to improve visual acuity is not yet fully understood, it is thought to be due to a decrease in corneal steepness and astigmatism, a reduction in refractive error and specific corneal indices [7,8]. The results published by Sedaghat et al. show not only improvement in UDVA and CDVA both 6 and 12 months after CXL surgery, but also in subjective spherical and cycloplegic refraction [9]. Other studies also point to this fact [10,11]. A significant improvement in CDVA was also observed by Strmenova et al. [15] and in a study published in 2015 by Raiskup et al. [17].

UDVA results in our cohort of patients did not show a statistically significant change. The mean UDVA values changed from 0.54 (Snellen) (0.267 logMAR) ±0.31 before the procedure to 0.58 (Snellen) (0.235 logMAR) ±0.34 after

Table 1. Mean values and SD of followed parameters before and 12 months after the treatment

	Before treatment (mean ±SD)	After treatment (mean ±SD)	Mean difference (mean ±SD)	p	Number of eyes
UDVA	0.54 ±0.31	0.58 ±0.34	0.04 ±0.2	0.371	29
CDVA	0.87 ±0.17	0.89 ±0.18	0.02 ±0.16	0.938	29
AIC_S	45.95 ±1.51	45.67 ±1.43	0.28 ±0.68	0.019	27
AIC_F	43.81 ±1.47	43.48 ±1.53	0.32 ±0.69	0.010	27
AIC_M	44.89 ±1.4	44.57 ±1.35	0.32 ±0.6	0.005	27
PIC_S	6.99 ±0.58	7.04 ±0.54	0.05 ±0.42	0.829	28
PIC_F	6.26 ±0.35	6.27 ±0.33	0.01 ±0.32	0.563	28
PIC_M	6.59 ±0.46	6.62 ±0.4	0.04 ±0.41	0.54	28
$PACH_T$	471.79 ±46.94	463.41 ±37.19	8.38 ±33.7	0.027	29
$PACH_C$	507.69 ±34.95	502.59 ±29.18	5.10 ±23.61	0.078	29
ASTIG	2.51 ±1.49	2.37 ±1.49	-0.14 ±066	0.297	28
COMA	1.1 ±0.56	1.04 ±0.54	-0.06 ±0.17	0.037	29
CLMIaa	6.55 ±3.43	6.03 ±2.75	-0.52 ±2.2	0.113	29

BUDVA – best uncorrected distance visual acuity, BCDVA – best corrected distance visual acuity, AIC_S – steep anterior instantaneous curvature, AIC_F – flat anterior instantaneous curvature, AIC_M – mean anterior instantaneous curvature, PIC_S – steep posterior instantaneous curvature, PIC_F – flat posterior instantaneous curvature, PIC_M – mean posterior instantaneous curvature, $PACH_T$ – pachymetry at the thinnest point, $PACH_C$ – pachymetry in the center of the cornea, ASTIG – astigmatism, CLMIaa – conus location and magnitude index

the procedure (p = 0.371). Even CDVA in our case did not show a statistically significant change within 12 months of the CXL procedure, with a mean of 0.87 (Snellen) (0.06 logMAR) ±0.17 before the procedure and 0.89 (Snellen) (0.05 logMAR) ±0.18 at p = 0.825.

Wollensak et al. commented on the results of their pilot study that an indicator of a successfully performed CXL procedure is a significant decrease in maximal keratometry (Kmax) [12]. In addition to Kmax, postoperative reductions in curvature of the flat, steep, and mean keratometry of the anterior and posterior corneal surfaces were observed along with corneal astigmatism [9]. We observed a statistically significant reduction in all the parameters anterior of instantaneous curvature studied – steep (before 45.95 Dpt ±1.51, after 45.67 Dpt ±1.43), flat (before 43.81 ±1.47, after 43.48 Dpt ±1.53), and mean (before 44.89 Dpt ±1.4, after 44.57 Dpt ±1.35). However, we did not observe a statistically significant change in the posterior instantaneous curvature curvatures of steep (before 6.99 Dpt ±0.58, after 7.04 Dpt ±0.54), flat (before 6.26 Dpt ±0.35, after 6.27 Dpt ±0.33) or mean (before 6.59 Dpt ±0.46, after 6.62 Dpt ±0.4) keratometry, and neither in corneal astigmatism (before 2.51 Dcyl ±1.49 and after 2.37 Dcyl ±1.49).

Mean COMA decreased from 1.1 µm ±0.56 before the procedure to 1.04 µm ±0.54 after the procedure. This change was statistically significant (p = 0.037). Similar results were reported in an Italian study [11].

The change in the CLMIaa value did not show statistical significance, unlike COMA. Its values before the procedure were 6.55 Dpt ±3.43 and after the procedure were 6.03 Dpt ±2.75, at p = 0.113.

Since corneal thickness after CXL procedure at the apex has been studied repeatedly [9,21,22], we decided to focus on corneal thickness at two distinct points – the thinnest point of the cornea and the centre of the cornea. Smadja et al. showed a significant difference in corneal thickness between healthy corneas and those affected by keratoconus [20]. In both our cases, there was a decrease in corneal thickness. Greenstein et al. described a statistically significant reduction in corneal thickness at the thinnest point [13]. In our series, a statistically significant change in pachymetry at the thinnest point was also confirmed – before 471.79 µm ±46.94 and after 463.41 µm ±37.19 (p = 0.027). However, opposite results to ours have also been frequently observed [9,11,14]. Pachymetry in the centre of the cornea showed no statistically significant changes (before 507.69 µm ±34.95, after 502.59 µm ±29.18) at p = 0.078. Corneal thickness measurements were performed using a device with two Scheimpflug cameras; we therefore assume more accurate pachymetry measurements. This is mainly due to the shorter measurement time, which reduces the probability of an increase in error due to eye movement but double scanning of the measurement location at the time of measurement.

CONCLUSION

Our study showed a significant change in the topographic parameters of the anterior corneal surface after corneal cross-linking in patients affected by progressive keratoconus. This change in the anterior corneal surface, combined with a significant change in the higher order coma aberration implies a restoration of a more regular corneal shape and a change in the quality of visual acuity. The stabilisation and improvement of corneal parameters proves that corneal cross-linking by CXL method is an effective method for the treatment of keratoconus, bringing not only stabilisation and limitation of the progression of the disease, but also an improvement of visual acuity quality.

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