Cross-linking treatment for better visual acuity

Griševi, Senad; Gilevska, Fanka; Biščević, Alma; Ahmedbegović- Pjano, Melisa; Pidro, Ajla; Patel, Sudi; Bohač, Maja

Source / Izvornik: **Medicinski glasnik Ljekarske komore Zeničko- dobojskog kantona, 2020, 17, 123 - 128**

Journal article, Published version
Rad u časopisu, Objavljena verzija rada (izdavačev PDF)

https://doi.org/10.17392/1071-20

Permanent link / Trajna poveznica: https://urn.nsk.hr/urn:nbn:hr:184:935288

ORIGINAL ARTICLE

Cross-linking treatment for better visual acuity

Senad Grišević[1], Fanka Gilevska[2], Alma Biščević[1,3], Melisa Ahmedbegović-Pjano[1], Ajla Pidro[1], Sudi Patel[4], Maja Bohač[3]

[1]Eye Clinic Svjetlost Sarajevo, Bosnia and Herzegovina; [2]Ophthalmology Clinic "Sistina Ophthalmology", Skopje, North Macedonia; [3]University Eye Hospital ''Svjetlost'' Zagreb, School of Medicine University of Rijeka, Croatia; [4]NHS National Services Scotland, Edinburgh, UK

ABSTRACT

Aim To correlate the maximum anterior sagittal curvature (Kmax) changes and uncorrected (UDVA) and corrected distance visual acuity (CDVA) in keratoconus patients after the cross-linking (CXL) procedure.

Methods Forty-four eyes of 34 patients with keratoconus were analysed after the standard Dresden protocol CXL procedure had been performed. All patients underwent complete preoperative examination with a follow-up of 12 months with focus on UDVA, CDVA and Oculus Pentacam (Scheimpflug technology) analysis. We analysed and correlated K_{max} changes in the postoperative period of 12 months together with visual acuity changes.

Results Visual acuity improved significantly in the first 3 months after the procedure and even more significantly until the end of the first year. Even K_{max} is the most relevant and most followed parameter for progression and regression of keratoconus, its lowering was not directly correlated with the visual acuity improvement (both uncorrected and corrected) in the first 6 months after corneal CXL procedure. K_{max} was changed significantly in the period of 12 months post cross linking, but not in the first 6 months.

Conclusion Corneal CXL should be considered as a procedure not just for corneal stiffening and stabilization, but also for visual acuity improvement in keratoconus patients.

Key words: corneal stroma, keratoconus, refractive errors, tomography

Corresponding author:
Ajla Pidro,
Eye Clinic ''Svjetlost''
dr. Mustafe Pintola 23, Sarajevo,
Bosnia and Herzegovina
Phone: +387 33 762 772;
Fax: +387 33 762 771;
E-mail: ajla@svjetlost-sarajevo.ba
Senad Grišević ORCID ID: 0000-0001-7703-7563

Original submission:
19 August 2019;
Revised submission:
26 September 2019;
Accepted:
12 November 2019
doi: 10.17392/1071-20

Med Glas (Zenica) 2020; 17(1):123-128

INTRODUCTION

Keratoconus is a chronic, bilateral and non-inflammatory disorder characterized by progressive steepening, thinning and apical scarring of the cornea. For a long time, the most cited annual incidence has been 2 per 100,000 with a prevalence of 0.054% (1). Recent data from a large study carried out in the Netherlands revealed different epidemiological results. Today, the annual incidence of keratoconus is 13.3 cases per 100 000 and estimated prevalence in general population is 0.26%. These values are 5 to 10 times higher than previously reported values in population studies, excluding keratoconus from the community of rare diseases (2). Keratoconus is known to affect all ethnicities, but its incidence exhibits geographical variability due to *forme fruste* or subclinical forms of the disease, differences in diagnostic methods and criteria and differences in genetic variations (3). Although keratoconus affects both genders, most of the studies suggest its higher incidence in men than in women (4). Clinical onset of keratoconus occurs typically in early adolescence, and it progresses during the third and fourth decade (4).

Earlier there had been just radical surgical methods in keratoconus treatment, like penetrant keratoplasty and RGP lenses without any influence on the disease progression. However, everything has changed since 2004, when Wollesak et al. published first clinical study of new invasive pharmacological approach on the cornea (5). Introduction of corneal cross-linking (CXL) marked a new era for treatment of keratoconus and other ectatic diseases (6). The CXL is a less invasive method than anterior keratoplasty and it enables better improvement of the corneal shape, biomechanical properties and stability, as well as better visual acuity. The CXL is a therapy method using vitamin B2 (riboflavin) and UV light, which enables to firm the collagen and stabilize the cornea, stops the thinning and bulging of the cornea and stops progression of keratoconus in that manner (6). The interaction of riboflavin and UVA enhances the formation of reactive oxygen species, which leads to the formation of additional covalent bonds between adjacent collagen molecules in the stroma, with consequent biomechanical stiffening of the cornea (6). As a result, the cornea is more firm, rigid and stable. The effect of CXL is localized in the front part of the cornea (7). A few years later Seiler and Hafezi found slit-lamp visible demarcation line two weeks after the procedure (8), in the depth at approximately 300 microns (μ), (60%) of the corneal stroma. Demarcation line raises the question about changed refraction index and refraction properties in the cornea. A large number of previous studies has shown significant changes in biomechanical parameters of the cornea in patients with keratoconus undergoing CXL protocol (9-11). Majority of these studies outline that CXL is a very effective protocol for keratoconus treatment delaying or reducing the need for corneal transplantation (10,11).

The aim of this study was to analyse changes of uncorrected distance visual acuity (UDVA), corrected distance visual acuity (CDVA) and maximum anterior sagittal curvature (K_{max}) in patients with keratoconus before and after the CXL procedure. In Bosnia and Herzegovina and the region, there has been no similar research reported.

PATIENTS AND METHODS

Patients and study design

Forty-four eyes of 34 patients with manifest keratoconus were included in this study. This was a prospective study, which enrolled patients who had been treated at the Eye Clinic "Svjetlost" Sarajevo from January 2017 to January 2018. Twenty-four of them had monocular procedure, while 10 patients had binocular treatments. Inclusion criteria were: patients diagnosed with keratoconus and progression of steepest meridian of 1 dioptre (D) or more within a year (but no more than 60 D), CDVA ≤0.8, aged 15–40 years and pachymetry values ≥400 μ.

Every patient underwent complete preoperative ophthalmological examination prior to deciding if the patient met the criteria for inclusion into the study. Ophthalmological examinations included UDVA, CDVA, manifest and cycloplegic refraction, corneal topography, tonometry, slit-lamp and dilated funduscopic examination. Visual acuity was measured using a standard Snellen charts and it was presented in the decimal format. The patients were asked to discontinue the use of contact lenses up to 4 weeks prior to all examinations, depending on the type of lenses they were using.

Patients who met the inclusion criteria were interviewed and gave written informed consents prior to participation in the study. All procedures and examinations were approved by the Ethics Committee of the Eye Clinic "Svjetlost" Sarajevo. The study was in compliance with the Declaration of Helsinki.

Methods

Topography measurements were derived from a rotating Scheimpflug topography instrument Pentacam (Pentacam HR, Oculus Optikgeräte GmbH, Wetzlar, Germany). K_{max} changes over the 12-month period (baseline, 3, 6, and 12 months) were assessed. In addition to establishing postoperative trends in keratometry, these data were also used to explore potential relationships between the keratometry changes across all visits and the final visual and keratometry outcomes at 12 months. The UDVA-and CDVA were measured over the period of 12 months (baseline, 3, 6, and 12 months) and they were measured on a digital screen (Clear Chart 4 Digital Acuity, Reichert Technologies, Buffalo, New York, USA). For testing, Snellen chart was used. Visual acuity was expressed as a decimal number that is equal to the numeric value of the Snellen fraction or to the reciprocal value of the visual angle in minutes. Tonometry was performed using non-contact tonometer (Auto Non-Contact Tonometer, Reichert Inc., Buffalo, NY, USA).

Collagen crosslinking therapy protocol was performed using the model of Dresden protocol (12-14). Before the surgery, treated eye was cleaned with povidone iodide, speculum was placed on the eyelids and anaesthetic and pupil constriction drops were instilled to protect inner part of the eye from UVA radiation. By using a spatula, mechanical debridement of 8–9 mm of corneal epithelium was performed under local anaesthesia. After that, application of topical riboflavin 0.1% solution (Riboflavin, Ricrolin, Peschke Meditrade, Germany) was used every 2 minutes during the first 30 minutes in combination with balanced salt solution (BSS). Then UVA radiation started. Before radiation, ultrasonic pachymetry was necessary to confirm that the thinnest part of the stroma is not less than 400 microns. If pachymetry was less than that, hypotonic riboflavin (0.1 % in sterile solution, Medio Cross hypotonic) was used at intervals of 10 seconds. This was repeated until the pachymetry was at least 400 microns. This last diameter has been shown in the literature to keep the posterior structures protected from UVA radiation. The wavelength of UVA was arranged at 365 nm (UVX system), with energy intensity of 3 mW/cm^2. UVA radiation treatment lasted for 30 minutes, and during the treatment riboflavin drops and BSS were used in the same way as mentioned before.

After the surgery antibiotic and corticosteroid eye drops were applied, and bandage contact lens was inserted. This lens was removed 3-5 days after the treatment, depending on epithelium healing. Eye drops were used during the first postoperative month. Patients' follow-ups were in first 3 days in a row, then 1 week, 1 month, 3 months, 6 months and 12 months after the procedure.

Statistical analysis

Descriptive statistical methods were used for the description of the frequency distribution for all analysed variables. Continuous variables were expressed as mean ± standard deviation, while the values of categorical variables were expressed as N (%). Student's t-test was used to compare continuous variables between the groups. The odds ratios, the confidence intervals and the significance levels were examined to evaluate the individual predictor variables. The level of statistical significance was set at $p<0.05$.

RESULTS

Twenty-four patients had monocular intervention and 10 of them had binocular treatment, which means that 34 patients (44 eyes) were treated. At the time of the surgery, the average age of patients was 22±5 years; the youngest examinee was 16 and the oldest one was 33 years old. Regarding the gender distribution 36 (82%) eyes were from male patients and 8 (18%) were from female patients.

K_{max} after 3 months was not statistically significant ($p=0.144$). Preoperatively average K_{max} was 58.05 ± 6.98 D, and 3 months postoperatively was 58.75 ± 6.11 D. After 6 months values were also not statistically significant ($p=0.221$), but a small decrease was noted, 57.51 ± 6.40 D. After 12 months differences in keratometries were statistically significant ($p=0.007$). One year after the surgery a decrease in keratometry values occurred, and it was 56.87 ± 6.44 D. In the first 3 months K_{max} insignificantly steepened, followed by insignificant

flattening in the 3 – 6 months period. $K_{max,}$ as a topographic indicator, decreased by average of 1.17 D in the period 6 -12 months (Table 1).

Table 1. Comparison of maximum anterior sagittal curvature (K_{max}) preoperatively and 3, 6 and 12 months (M) postoperatively

Period	Paired differences			p
	Mean	95% CI		
		Lower	Upper	
Preoperatively - 3 M after CXL	-.69545	-1.64732	0.25641	0.144
Preoperatively - 6 M after CXL	.53636	-.34875	1.42148	0.221
Preoperatively - 3 M after CXL	1.17727	.35928	1.99527	0.007

CI, Confidence Interval

There was statistically significant difference in average values of UDVA preoperatively and during 12 months postoperatively (p=0.0001). After 3 months the difference in average values was statistically significant (p=0.04). Preoperative UDVA was 0.26±0.18, while in 3 months of postoperative period it increased to 0.32±0.18. After 6 months the difference in values was statistically significant, 0.36±0.18 (p=0.002). After 12 months the difference in values was statistically much higher and significant, 0.42±0.22 (p<0.001). UDVA was significantly improved 3 months (p= 0.04), 6 months (p=0.002) and 12 months (p<0.001) after CXL (Table 2).

Table 2. Differences in corrected distance visual acuity (UDVA) preoperatively and 3, 6 and 12 months (M) postoperatively

Period	UDVAMean	p
Preoperatively	0.2636	
3 M after CXL	0.324	p= 0.04
Preoperatively	0.2636	
6 M after CXL	0.3636	p=0.002
Preoperatively	0.2636	
12 M after CXL	0.419	p<0.001

The CDVA was significantly improved 6 months (p<0.001) and 12 months (p<0.001) after CXL, while 3 months postoperatively it was higher but without statistical significance (p=0.193). Preoperative CDVA was 0.42±0.17, while 3 months postoperatively it increased to 0.47±0.18. After 6 months it increased to 0.50±0.18, and 12 months postoperatively it increased to 0.60±0.20 (Table 3).

Table 3. Differences in corrected distance visual acuity (CDVA) preoperatively and 3, 6 and 12 months (M) postoperatively

Period	CDVA Mean	p
Preoperatively	0.420	
3 M after CXL	0.4705	p=0.193
Preoperatively	0.420	
6 M after CXL	0.555	p<0.001
Preoperatively	0.420	
12 M after CXL	0.6068	p<0.001

DISCUSSION

Keratoconus gender predisposition is very different in literature. Most of the studies show male predisposition (15). In a study of Tan et al. it is even 2.6 times more frequent disease in men than women (16). High male dominance also found in our study can be a result of gender differences in reporting ocular problems, due to lifestyle and everyday activities (17). Corneal CXL is an already established treatment for keratoconus in the meaning of halting the ectasia progression, but anatomical flattening of the cornea by lower keratometry values also achieves better visual acuity (18). The most commonly used progression parameter of keratoconus is an increase in K_{max} of 1 D or more. An abnormal anterior surface of keratoconus cornea with an elevated K_{max} already implies some degree of visual compromise (19). A further increase in K_{max} is typically associated with a further reduction in visual function (19). Lombardo et al. reported that two years after the standard CXL the mean maximum K flattened by 1.51±0.89 D (20). Sedaghat et al. observed that keratometry values in the steepest and flattest axes (21), and also mean keratometry in both anterior and posterior surface decreased postoperatively. Reduced corneal steepening and astigmatism may contribute to improved visual acuity in postoperative follow-ups in these patients. As observed during the course of postoperative keratometry responses in the cohort study of Hersh et al. (22), we also recorded a trend of significant K_{max} steepening at 1 month. The trend of K_{max} flattening between 6 and 12 months appeared to plateau and did not reach statistical significance. In our study in the first 3 months K_{max} insignificantly steepened, followed by insignificant flattening in the 3 – 6 months period. A study by Toprak and Yildirim illustrated the effect of CXL on K_{max} and UDVA (23). They reported that mean UDVA and K_{max} after CXL improved significantly. In our study, the difference for UDVA and K_{max} was also significant.

The Snellen-based charts are universally accepted tools for testing visual acuity despite its poor reliability and reproducibility (24). Visual acuity in this study is the only tool used to evaluate the effect of CXL on presenting vision. The mechanism by which CLX improves or alters vision is not known completely. It might be due to

decrease in refractive error, corneal steepness and astigmatism, and also because of improvement in definable topographic indices (19,20). Lombardo et al. reported results that show that the mean UDVA and CDVA improved significantly 6 and 12 months after CXL (20). Results of our study showed a statistically significant trend in the increase of CDVA and UDVA in a time period of one year postoperatively. Our results are in accordance to a large number of previous other studies that had the same or a longer follow-up period (20-25). This improvement in UDVA and CDVA was parallel with the improvement in subjective and cycloplegic spherical and cylindrical refractions; furthermore, spherical equivalent in our research decreased 6 months after CXL and remained stable till 1-year follow-up. Chang et al. (27) reported that mean CDVA gained slightly more than 1 Snellen line at 12 months, which is similar to our results.

Changes in visual outcome were carefully documented over time because a comprehensive understanding of postoperative time course in visual responses will greatly help physicians in setting realistic patient expectations after CXL (25,26). Our study showed a significant improvement in topographic corneal changes and UDVA results in patients with keratoconus after the CXL illustrating the efficacy and usage of CXL for keratoconus among patients with progressive keratoconus. Based on the positive results obtained in various studies conducted on the efficacy of this method (19-25), including the current study, CXL presents an important strategy to halt the progress of keratoconus and improve it, while it can also play an effective role in limiting vision loss. More research should be done to find which indices are mostly correlated with the visual acuity, both preoperatively and postoperatively in order to predict the outcomes for best patient satisfaction.

FUNDING

No specific funding was received for this study.

TRANSPARENCY DECLARATION

Competing interests: None to declare.

REFERENCES

1. Gordon-Shaag A, Millodot M, Shneor E, Liu Y. The genetic and environmental factors for keratoconus. Biomed Res Int 2015; 2015:795738.
2. Godefrooij DA, de Wit GA, Uiterwaal CS, Imhof CA, Wisse RPL. Age-specific incidence and prevalence of keratoconus: a nationwide registration study. Am J Ophthalmol 2017; 175:169-72.
3. Bialasiewicz A, Edward DP. Corneal ectasias: study cohorts and epidemiology. Middle East Afr J Ophthalmol 2013; 20:3-4.
4. Wollensak G, Spoerl E, Seiler T. Riboflavin/ultraviolet-a-induced collagen crosslinking for the treatment of keratoconus. Am J Ophthalmol 2003; 135:620-7.
5. Wollensak G, Spoerl E, Seiler T. Stress-strain measurements of human and porcine corneas after riboflavin-ultraviolet-A-induced cross-linking. J Cataract Refract Surg 2003; 29:1780-5.
6. Balparda K, Maldonado MJ. Corneal collagen cross-linking. A review of its clinical applications. Arch Soc Esp Oftalmol 2017; 92:166-74.
7. Badawi AE, Abou Samra WA, El Ghafar AA. Clinical study predictive factors of the standard cross-linking outcomes in adult keratoconus: one-year follow-up. J Ophthalmol 2017; 2017:4109208.
8. Mazzotta C, Wollensak G, Raiskup F, Pandolfi AM, Spoerl E. The meaning of the demarcation line after riboflavin UVA corneal collagen crosslinking, Expert Rev Ophtalmol 2019; 14:115-31.
9. Aixinjueluo W, Usui T, Miyai T, Toyono T, Sakisaka T, Yamagami S. Accelerated transepithelial corneal cross-linking for progressive keratoconus: a prospective study of 12 months. Br J Ophthalmol 2017; 101: 1244-9.
10. Subasinghe SK, Ogbuehi KC, Dias GJ. Current perspectives on corneal collagen crosslinking (CXL). Graefes Arch Clin Exp Ophthalmol 2018; 256:1363-84.
11. Mazzotta C, Traversi C, Baiocchi S, Bagaglia S, Caporossi O, Villano A, Caporossi A. Corneal collagen cross-linking with riboflavin and ultraviolet A light for pediatric keratoconus: ten-year results. Cornea 2018; 37:560-6.
12. Wittig-Silva C, Chan E, Islam FM, Wu T, Whiting M, Snibson GR. A randomized, controlled trial of corneal collagen cross-linking in progressive keratoconus: three-year results. Ophthalmology 2014; 121:812–21.
13. Uysal BS, Sarac O, Yaman D, Akcay E, Cagil N. Optical performance of the cornea one year following keratoconus treatment with corneal collagen cross-linking. Curr Eye Res 2018; 43:1415-21.
14. Epstein RL, Chiu Y, Epstein GL. Pentacam HR criteria for curvature change in keratoconus and postoperative LASIK ectasia. J Refract Surg 2012; 28:890–4.
15. Prabhu PB, Prasannkumary C, Jyothi PT, Babitha V. Correlation between topographic color patterns, keratometric indices, and clinical features among young adults with keratoconus. Kerala J Ophthalmol 2018; 30:193-7.
16. Tan JCK, Nguyen V, Fenwick E, Ferdi A, Dinh A, Watson SL. Vision-related quality of life in keratoconus: a save sight keratoconus registry study. Cornea 2019; 38:600-4.
17. Fink BA, Wagner H, Steger MK, Rosenstiel C, Roediger T, McMahon TT, Gordon MO, Zadnik K. Differences in keratoconus as a function of gender. Am J Ophthalmol 2005; 140:459-68.

18. Lamy RI, Netto CF, Reis RG, Procopio B, Porco TC, Stewart JM, Dantas AM, Moraes HV Jr. Effects of corneal cross-linking on contrast sensitivity, visual acuity, and corneal topography in patients with keratoconus. Cornea 2013; 32:591-6.
19. Saffarian L, Khakshoor H, Zarei GM, Esmaily H. Corneal crosslinking for keratoconus in iranian patients: outcomes at 1 year following treatment. Middle East Afr J Ophthalmol 2010; 17:365-8.
20. Lombardo M, Serrao S, Lombardo G, Schiano LD. Two-year outcomes of a randomized controlled trial of transepithelial corneal crosslinking with iontophoresis for keratoconus. J Cataract Refract Surg 2019; 45:997-1000.
21. Sedaghat M, Bagheri M, Ghavami S, Bamdad S. Changes in corneal topography and biomechanical properties after collagen cross linking for keratoconus: 1-year results. Middle East Afr J Ophthalmol 2015; 22:212-9.
22. Hersh PS, Greenstein SA, Fry KL. Corneal collagen crosslinking for keratoconus and corneal ectasia: one-year results. J Cataract Refract Surg 2011; 37:149-60.
23. Toprak I, Yildirim C. Effects of corneal collagen cross-linking on corneal topographic indices in patients with keratoconus. Eye Contact Lens 2013; 39:385-7.
24. Hussain B, Saleh GM, Sivaprasad S, Hammond CJ. Changing from snellen to logMAR: debate or delay? Clin Exp Ophthalmol 2006; 34:6-8.
25. Asri D, Touboul D, Fournié P, Malet F, Garra C, Gallois A, Malecaze F. Colin J. Corneal collagen crosslinking in progressive keratoconus: multicenter results from the French national reference center for keratoconus. J Cataract Refract Surg 2011; 37:2137-43.
26. Greenstein SA, Fry KL, Hersh PS. Corneal topography indices after corneal collagen crosslinking for keratoconus and corneal ectasia: one-year results. J Cataract Refract Surg 2011; 37:1282-90.
27. Chang YC, Hersh SP. Corneal collagen cross-linking: a review of 1-year outcomes. Eye Contact Lens 2014; 40:335-45.