HAYDARPAŞA NUMUNE MEDICAL JOURNAL

DOI: 10.14744/hnhj.2021.93798
Haydarpasa Numune Med J 2021;61(4):412–416

hnhtipdergisi.com

ORIGINAL ARTICLE

Comparison of Accelerated Corneal Collagen Cross-Linking Methods

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Abstract

Introduction: Our aim in this study was to compare the results of accelerated collagen cross-linking (CXL) treatments on visual acuity and topographic parameters in cases with progressive keratoconus.

Methods: The cases with the diagnosis of progressive keratoconus between January 2015 and January 2018, who underwent accelerated CXL, were analyzed retrospectively. Subjects who received 9 mW/cm^2 ultraviolet A (UV-A) treatment for 10 min and were treated with 18 mW/cm^2 UV-A for 5 min were included in the study. Uncorrected visual acuity (UCVA), Uncorrected visual acuity (BCVA), refractive value changes (spherical, cylindrical values), and corneal topography values obtained using the Sirius device at preoperative and postoperative 1st, 3rd, 6th and 12th months (K1, K2, Kmaximum, anterior elevation, posterior elevation) were compared statistically.

Results: A total of 80 eyes of 80 cases; 40 eyes treated with UV-A for 10 min and 40 eyes treated with UV-A for 5 min were included in the study. There was no difference between the two groups in terms of age and gender. There was a statistically significant increase in UCVA and BCVA (logMAR) values for both groups at the 6th and 12th months post-operatively when we compared the values before surgery ($p<0.05$) There was no significant difference between the two groups in terms of refractive changes and topographic changes (K1, K2, K maximum, anterior elevation, posterior elevation) after surgery compared with before surgery ($p>0.05$).

Discussion and Conclusion: In cases of progressive keratoconus, 10-min 9 mW/cm^2 and 5-min 18 mW/cm^2 accelerated CXL methods showed similar results at the end of 1-year follow-up in terms of visual acuity improvement and topographic changes. Both methods seem to be effective in preventing keratoconus progression.

Keywords: Accelerated; collagen crosslinking; keratoconus.

Keratoconus is characterized by progressive corneal thinning and steepening which can show bilateral but asymmetrical course between the eyes[1-3]. Conventional corneal collagen cross-linking (CXL) method has been shown to stop the progression[2]. In this method, the cornea is saturated with riboflavin drops for 30 min and then 3 mW/cm^2 ultraviolet A (UV-A) is applied for 30 min. Cross-links occur between riboflavin and UV-A and corneal collagens[2]. These bonds cause an increase in corneal rigidity, which is thought to play a role in preventing progression[2]. According to the Bunsen-Roscoe law, which is used to explain photochemical reactions such as CXL treatment, the UV-A energy absorbed by the cornea shows its effectiveness in the tissue according to the total dose amount. According to this rule, the intensity of the applied energy and the application time can be arranged so

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Submitted Date (Başvuru Tarihi): 13.06.2021 **Accepted Date (Kabul Tarihi):** 04.08.2021

that the total amount of applied energy does not change. Therefore, based on the equal dose physical principle, 9 mW/cm^2 in 10 min, 18 mW/cm^2 in 5 min, 30 mW/cm^2 in 3 min, and 45 mW/cm^2 in 2 min, corresponding to 5.4 J/cm^2 energy doses, is predicted to be as effective as the conventional CXL treatment with the Dresden protocol[4]. Based on this law, accelerated methods have become more preffrable in order to increase patient comfort, since the total time in conventional CXL is 1 h. Accelerated methods have been shown to have similar efficacy and reliability with conventional methods[3]. The number of studies comparing accelerated methods with each other in the literature are quite limited[1]. Instead, more publications are present in the literaure comparing accelerated methods with the conventional method[5-10].

Our aim in this study is to compare the results of accelerated collagen CXL treatments applied at different times (10 min 9 mW/cm^2 and 5 min 18 mW/cm^2) in patients with progressive keratoconus on visual acuity and topographic parameters at the end of 1 year follow-up.

Materials and Methods

For this study, cases with progressive keratoconus disease who underwent accelerated CXL between January 2015 and January 2018 were retrospectively analyzed. Cases that received 9 mW/cm^2 UV-A treatment for 10 min and who were treated with 18 mW/cm2 UV-A for 5 min with a follow-up period of at least 1 year were included in the study. The study was approved by the ethical committee of Health Sciences University Okmeydanı Training and Research Hospital (Istanbul, Turkey) according to the principles of the Declaration of Helsinki. The written informed consent was obtained from each patient before the procedure.

Those who were under the age of 18 and over the age of 40, those with a thin corneal thickness of <400 microns (µm), patients with scars or opacities in the cornea, patients who had eye surgery before, those who had a systemic disease or who had eye pathology except keratoconus, those who were on pregnancy or lactation at that time and cases with a follow-up period of <12 months were excluded from the study. Uncorrected visual acuity (UCVA), best-corrected visual acuity (BCVA), refractive value changes (spherical and cylindrical values), and parameters (K1, K2, K maximum, anterior elevation, posterior elevation) obtained from corneal tomography device Sirius® (Scheimpflug tomography system-CSO Inc) at preoperative and postoperative 1st, 3rd, 6th, and 12th months were statistically compared.

Surgical Technique

Accelerated CXL treatment was administered under topical anesthesia (0.5% proparacaine hydrochloride (Alcaine®, Alcon Laboratories, Inc., Hünnenberg, Switzerland) under sterile conditions). After debridement of the epithelial layer with a diameter of 8–9 mm in the central cornea, riboflavin drops (MedioCROSS® M Kiel, Germany) containing 0.1% riboflavin and 1.1% hydroxypropyl methylcellulose were applied every 2 min for 20 min. Afterward, an UVA beam with a diameter of 9 mm (370 nm) was applied from a distance of 5 cm perpendicular to the corneal apex with the help of a device (Peschke Vario 365, Huenenberg, Switzerland). UVA duration was 10 min (9 mW/cm^2, total 5.4 J/cm^2) in group 1, and 5 min (18 mW/cm^2, total 5.4 J/cm^2) in group 2 cases. A bandage contact lens was placed after the eye was washed with BSS (20 ml balanced salt solution) solution.

Statistical Analysis

While evaluating the findings obtained in the study, IBM Statistical Package for Social Sciences Statistics 23.0 (IBM SPSS, Turkey) for windows statistical package program was used for statistical analysis. While evaluating the study data, the conformity of the parameters to the normal distribution was evaluated with the Shapiro Wilks test. While evaluating the study data, in addition to descriptive statistical methods (mean, standard deviation, frequency), Student's t-test was used for the comparison of normally distributed parameters between two groups, and Mann Whitney U test was used for comparisons of non-normally distributed parameters between the two groups. Paired Sampled t-test was used for in-group comparisons of normally distributed quantitative data, and Wilcoxon Signed Ranks test was used for in-group comparisons of non-normally/qualitatively distributed parameters. Chi-square test, Fisher's Exact test, Continuity (Yates) Correction was used to compare qualitative data. Pearson correlation analysis was used to examine the relationships between parameters. Significance was evaluated at the $p<0.05$ level.

Results

The study was conducted with 80 eyes of 80 subjects, 50 (62.5%) male and 30 (37.5%) female subjects. The mean age of the cases was calculated as 25.56±6.47 years (range 18–45).

Table 1 shows the age and gender distribution of the cases according to the groups. There was no statistically significant difference between the two treatment groups in terms of age and gender ($p>0.05$).

Table 1. Evaluation of demographic characteristics among treatment time groups

Variable	5 min A-CXL	10 min A-CXL	p
Age (Mean±SD)	26.87±6.58	24.25±6.15	[1]0.069
Sex			
Male	21 (52.5%)	29 (72.5%)	[2]0.106
Female	19 (47.5%)	11 (27.5%)	

[1]Student t-test; [2]Continuity (yates) correction. CXL: Cross-linking.

In terms of UCVA; in the group treated with UV-A for 10 min; while there was no significant change in the 1st and 3rd month values after the treatment compared to the pre-treatment (p>0.05), the increase rates observed in the 6th and 12th month values were statistically significant (p<0.05). In the group treated with UV-A for 5 min; while there was no significant change in the 1st month values after the treatment compared to the pre-treatment (p>0.05), the increase rates observed in the 3rd, 6th, and 12th month values were statistically significant (p<0.05).

In terms of BCVA (logMAR); while there was no significant change in the 1st and 3rd month values after the treatment (p>0.05), the increases in the 6th and 12th month values were statistically significant compared with pre-treatment (p<0.05) in the group treated with 10 min of UV-A. In the group treated with UV-A for 5 min; The increases in the 1st, 3rd, 6th, and 12th months after treatment were statistically significant (p<0.05).

Preoperative BCVA and BCVA at 1st, 3rd, 6th, and 12th months after the surgery is shown in Figure 1 by groups. There was no statistically significant difference between the groups treated with 5 min and 10 min of CXL in terms of BCVA (logMAR) values for all visits (before surgery and after the surgery) (p>0.05).

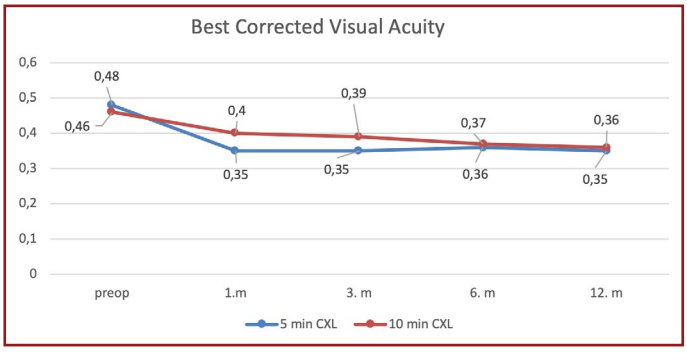

Figure 1. Best-corrected visual acuity levels: Before surgery and after surgery 1st month, 3rd month, 6th month, and 12th month (logmar). CXL: Cross-linking, min (m): min.

Table 2 shows the UCVA and BCVA and refractive changes at the examination before the surgery and 1, 3, 6, 12 months after the surgery. Among the groups treated with UV-A for 5 min and 10 min; there was no statistically significant difference in terms of UCVA, BCVA, spherical value, and cylindrical value changes at 1st, 3rd, 6th, and 12th months after the surgery compared to the values before the surgery (p>0.05).

Table 3 shows flat keratometry (K1), steep keratometry (K2), maximum keratometry (Kmax), anterior elevation (KVf), and posterior elevation (KVb) values for before the surgery and 1, 3, 6, and 12 months after the surgery. There was no statistically significant difference between groups (5 min and 10 min) in terms of the amount of change in f K1, K2, Kmax, KVf, and KVb values preoperatively and at the postoperative 1st, 3rd, 6th, and 12th months (p>0.05).

Discussion

Since the treatment time is lengthy in the standard corneal collagen crosslinking protocol, the irradiation time can be reduced by maintaining the total treatment dose in the ac-

Table 2. Evaluation of the changes values in refractive data between the groups at the 1st, 3rd, 6th, and 12th months after surgery compared to before surgery

	Processing time		p
	5 min A-CXL Mean±SD	10 min A-CXL Mean±SD	
UCVA			
Preop-1.m	−0.05±0.25	−0.07±0.34	10.536
Preop-3.m	−0.11±0.25	0.09±1.08	10.598
Preop-6.m	−0.13±0.28	−0.15±0.48	10.243
Preop-12.m	−0.11±0.29	−0.15±0.43	10.084
BCVA			
Preop-1.m	−0.12±0.22	−0.06±0.26	10.177
Preop-3.m	−0.12±0.21	−0.07±0.2	10.223
Preop-6.m	−0.12±0.19	−0.09±0.21	10.422
Preop-12.m	−0.13±0.2	−0.11±0.22	10.521
Spherical refractive value			
Preop-1.m	−0.31±1.73	−0.51±1.97	10.119
Preop-3.m	−0.43±2.06	−0.28±1.57	10.582
Preop-6.m	−0.19±1.86	−0.33±1.48	10.229
Preop-12.m	−0.21±1.97	−0.14±1.3	10.329
Cylindrical refractive value			
Preop-1.m	−1.01±1.66	1.57±12.51	20.200
Preop-3.m	−0.77±1.65	−0.34±1.77	20.270
Preop-6.m	−0.86±1.57	−0.31±1.86	20.157
Preop-12.m	−0.8±1.61	−0.31±1.87	20.210

[1]Mann whitney U test; [2]Student t-test. CXL: Cross-linking; UCVA: Uncorrected visual acuity; BCVA: Best corrected visual acuity.

Table 3. Evaluation of the changes in topographic measurements between the treatment duration groups at the 1st, 3rd, 6th, and 12th months after surgery compared to pre–operative status

	5 min A–CXL Mean±SD	10 min A–CXL Mean±SD	p
K1			
Preop-1.m	0.06±2.1	−0.13±1.04	0.599
Preop-3.m	0.02±1.94	−0.23±1.04	0.478
Preop-6.m	0.14±1.96	−0.23±1.03	0.294
Preop-12.m	0.1±1.94	−0.26±0.99	0.305
K2			
Preop-1.m	−0.5±2.72	0.02±1.03	0.261
Preop-3.m	−0.28±1.46	−0.1±1.11	0.534
Preop-6.m	−0.11±1.8	−0.12±1.12	0.988
Preop-12.m	−0.18±1.84	−0.32±1.11	0.688
Kmax			
Preop-1.m	1.5±2.72	1.62±3.5	0.872
Preop-3.m	1.75±3.86	0.44±2.8	0.087
Preop-6.m	1.45±3.71	0.63±2.81	0.270
Preop-12.m	1.31±3.67	0.11±2.12	0.081
KVb			
Preop-1.m	−0.73±10.7	−4.1±16.95	0.291
Preop-3.m	−1.53±14.34	1.43±15.56	0.381
Preop-6.m	−0.35±13.55	4.35±15.18	0.148
Preop-12.m	0.58±10.38	1.88±13.66	0.633
KVf			
Preop-1.m	2.9±7.74	−0.98±7.39	0.025*
Preop-3.m	−0.13±2.88	−1.35±8.62	0.398
Preop-6.m	−0.1±3.05	−1.15±8.23	0.452
Preop-12.m	−0.68±3.59	−1.73±8.7	0.483

SD: Standart deviation; Student t-test; *: p<0.05; CXL: Cross-linking; K1: Flat keratometer; K2: Steep keratometer; Kmax: Maximum keratometer; KVb: Keratoconus vertex back; KVf: Keratoconus vertex front.

celerated method applied as an alternative[4]. Shortening the treatment time is most important for patient comfort. For the accelerated corneal crosslinking method, there are different protocols including 3 min, 5 min, 10 min, and 15 min application options. In the literature, there are studies comparing accelerated procedures with the conventional technique[5-9]. However, there are very few studies comparing accelerated techniques with each other[10].

In this study, we aimed to compare the accelerated techniques applied in different times (5 min of UV-A and 10 min of UV-A) in terms of visual acuity and corneal tomography results.

In the literature, in two different studies that prospectively compared the results of cases treated with accelerated CXL (5-min and 10-min) with the conventional method, there was no significant difference between the two groups in terms of visual acuity values according to the results of postoperative 6th month[5-7]. In our study, we compared the cases with accelerated corneal crosslinking (5 and 10 min UV-A) among themselves, and we did not find any difference in terms of visual acuity improvement in the 6th month results, and the 1st year results were also similar. In the study of Shetty et al.,[10] in which the 1st year results were examined prospectively, the results of 5 min, 10 min, and 30 min were compared and no significant difference was found between the groups in terms of visual acuity improvement. In the study of Kirgiz et al.,[1] the results of CXL with 5 min and 10 min UV-A application were compared with each other and the results were similar at the end of 1st year in terms of visual acuity improvement.

In the literature, it has been reported in cases with accelerated corneal crosslinking that spherical and cylindrical values remained stable after treatment and even decreased in some studies[9,11]. When the spherical and cylindrical changes were evaluated in our study, the absence of a significant increase after the surgery can be interpreted in favor of the prevention of keratoconus progression. At the same time, no difference was found between the two groups in terms of spherical and cylindrical refractive changes in our study. Similar to the results of our study, no difference was found between the groups in terms of spherical and cylindrical changes in studies comparing accelerated CXL treatments both with each other and with the conventional method[9,10].

In our study, the fact that there was no significant difference in K1, K2 values postoperatively compared to the preoperative values in both groups suggests that no progression was observed in the 1st year follow-up of keratoconus. In a prospective randomized study by Shetty et al.[10] in which 138 eyes were included with 1-year follow-up, while it was reported that there was no significant difference in K1 and K2 values in the group with 5 min UV-A application, they reported in the same study that they found a significant decrease in both K1 and K2 levels in the patients with 10 min UV-A application. Another study that applied UV-A for 10 min reported a decrease in K1 and K2 levels[11]. In our study, we did not find a significant difference between the two groups in terms of change in K1 and K2 values. This may be due to the limited number of patients included in our study.

There was no difference in the postoperative Kmax values between the two groups compared to the preoperative period, and we did not find any difference when the two groups were compared. Among the studies in which CXL was applied with 10 min of UV-A as in our study, there are several studies that did not detect a significant change

in Kmax in the 1st year results,[12] as well as studies that published 1 year results and found a significant decrease in Kmax[3,13]. The same results are valid for the studies in which CXL was applied with 5 min of UV-A. That is, among the studies reporting 1-year results, there are several publications with no significant change in Kmax[7-9], similar to our study, and there are also publications with a significant decrease in Kmax[11]. The presence of different results for Kmax change in the accelerated CXL cases indicates the need for prospective studies with a larger number of cases comparing accelerated CXL applications.

In our study, although a statistically insignificant decrease was found in the mean corneal anterior elevation value for both groups after the treatment, no significant difference was found in the mean corneal posterior elevation values. There was no difference between the two groups in terms of the mean change in both anterior and posterior elevation. The anterior and posterior elevation values were evaluated in the study of Koç et al.[3] with the accelerated procedure (10 min), and they found a decrease in the mean amount of anterior elevation at the postoperative 6th month. It can be thought that the decrease in anterior elevation may be due to flattening of the anterior corneal surface and epithelial remodeling. In the same study, they did not detect a significant change in posterior elevation, similar to our study.

The fact that this study was retrospective, the number of cases was low, and the follow-up was limited to 1 year may have had limited the results of the study.

Conclusion

No difference was found between A-CXL procedures which were applied with 5 and 10 min of UV-A in terms of visual acuity, refractive power values, keratometric values, and corneal elevation values in the 1st year after the treatment. R2-1 The results of the accelerated CXL (5 min and 10 min) procedures are similar. Both methods seem to be effective in preventing keratoconus progression.

Ethics Committee Approval: The study was approved by the ethical committee of Health Sciences University Okmeydanı Training and Research Hospital (Istanbul, Turkey) according to the principles of the Declaration of Helsinki.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Concept: M.E.; Design: S.Y.O.; Data Collection or Processing: F.Ö.A.; Analysis or Interpretation: S.Y.O.; Literature Search: F.Ö.A.; Writing: F.Ö.A.

Conflict of Interest: None declared.

Financial Disclosure: The authors declared that this study received no financial support.

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