ORİJİNAL ARAŞTIRMA ORIGINAL RESEARCH

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The Comparison of Peripheral Corneal Stromal Demarcation Line Depth Percentages After Standard and Accelerated Collagen Crosslinking

Periferal Korneal Stromal Demarkasyon Hat Derinliği Yüzdelerinin Standard ve Hızlandırılmış Kollajen Çapraz Bağlama Sonrası Kıyaslanması

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ABSTRACT Objective: To assess the effectiveness of accelerated cross-linking (CXL) on cornea periphery by comparing stromal demarcation line (SDL) depths in accelerated CXL with conventional CXL. **Material and Methods:** Patients with progressive keratoconus who were applied conventional 30 minutes CXL with 3 mW/cm^2 (conventional group) or accelerated 10 minutes CXL with 9 mW/cm^2 (accelerated group) were involved in the study. The SDL was measured in central and 3 mm periphery at the postoperative first month by using anterior segment optical coherence tomography. The SDL in the periphery was calculated as the proportion of central for each group seperately (SDL in the periphery/SDL in the central*100). The proportions were compared between two groups. **Results:** The mean central SDL depths in conventional and standard group were 302±49 µm and 251±42 µm, respectively (p: 0.004). The mean SDL percentages at 3-mm periphery (superior, inferior, temporal, nazal) in conventional group were 84±14, 76±18, 77±12 ve 71±12, respectively. The same measurements in accelerated group were 74±12, 76±08, 70±12 and 70±12, respectively. Apart from the superior peripheral cornea there was no difference between two groups (p: 0.079). The SDL percentage at superior cornea was lower in accelerated group compared to conventional group (p: 0.044). **Conclusion:** The SDL percentage at superior cornea is lower in accelerated group compared to conventional group. It is a convenient advice to think again while deciding application of accelerated CXL in conditions effecting superior cornea.

Keywords: Collagen cross-linking;
stromal demarcation line;
anterior segment optical coherence tomography

ÖZET Amaç: Standard ve hızladırılmış protokol kollajen çapraz bağlama (KÇB) tedavisi sonrası santral ve periferik stromal demarkasyon hat (SDH) derinliğini kıyaslayıp hızlandırılmış protokolün kornea periferindeki etkinliğini değerlendirmek. **Gereç ve Yöntemler:** Otuz dakika boyunca 3 mW/cm^2 dozunda standard protokol (standard grup) veya 10 dakika boyunca 9 mW/cm^2 dozunda hızlandırılmış protokol (hızlandırılmış grup) KÇB uygulanmış ilerleyici keratokonus hastalığı olan kişiler çalışmaya dâhil edildi. SDH santral ve 3 mm periferden ön segment optik koherens tomografi kullanılarak postoperatif birinci ayda ölçüldü. Perifer SDH santralin yüzdesi şeklinde her grup için hesaplandı (perifer SDH/ santral SDH* 100). Yüzdeler iki grup arasında kıyaslandı. **Bulgular:** Çalışmaya 26 hastanın 42 gözü dâhil edildi, 38 gözde SDH gözlenebildi. (Bunlardan 18'i standard grup, 20'si hızlandırılmış gruptaydı). Standard ve hızlandırılmış grupta santral SDH derinliği sırasıyla 302±49 µm ve 251±42 µm idi (p=0,004). Üç mm periferden (üst, alt, temporal, nazal) ölçülen ortalama SDH yüzdeleri standard grupta sırasıyla 84±14, 76±18, 77±12 ve 71±12 idi. Aynı ölçümler hızlandırılmış grupta sırasıyla 74±12, 76±08, 70±12 ve 70±12 idi. Üst bölge hariç iki grup arasında fark yoktu (p>0,05). Üst korneada SDH yüzdesi hızlandırılmış grupta standard gruba kıyasla daha düşük bulundu (p= 0,044). **Sonuç:** Üst korneada SDH yüzdesel olarak hızlandırılmış grupta standard gruba kıyasla daha düşüktür. Klinik uygulamalarda korneanın üst bölgesini etkileyen durumlar için KÇB tedavisi yapılacak hastalarda hızlandırılmış protokol uygulama kararı alırken tekrar düşünülmesi yerinde olacaktır.

Anahtar Kelimeler: Kollajen çapraz bağlama;
stromal demarkasyon hattı;
ön segment optik koherens tomografi

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Collagen cross-linking (CXL) is a procedure that induces cross-linking in stromal collagen of cornea by exciting riboflavin molecules with ultraviolet A (UVA). This procedure changes corneal biomechanics by increasing corneal stiffness. CXL has become an accepted treatment modality effective in halting progression of keratoconus.

The standard "Dresden protocol" comprises the following steps: creating a 7- to 9-mm abrasion in the central cornea, applying riboflavin to the area at every 5 minutes for a total of 30 minutes, and then exposing it to a 370-nm wavelength UVA beam for 30 minutes.[1,2] However, that procedure disadvantageously requires a long period for the completion of surgery. Based on the Bunsen-Roscoe law of reciprocity, various high-intensity accelerated protocols have emerged to shorten the treatment duration and to reduce patient discomfort, while maintaining effectiveness of treatment as the conventional Dresden protocol.[3-7] There is still controversy about the effectiveness of these high intensity protocols in the literature.[8,9] Variety of accelerated protocols are described in the literature. The effectivity of accelerated protocols with regard to halting progression seems to be equivalent but some parameters such as stromal demarcation line (SDL) depth or amount of topographic flattening generally do not confirm equivalence of accelerated protocol with conventional protocol.[10-12]

The corneal SDL indicating the border between the anterior cross-linked and posterior untreated corneal stroma could be observed as early as 2 weeks after CXL.[13] It has been thought that the depth of this line is an indirect manifestation of cross-linking effectiveness.[9,14] The depth of SDL could be measured from central and peripheral cornea by using anterior segment optic coherence tomography (AS-OCT). The central corneal SDL depth has been found lower in accelerated protocols compared to standard protocols in several studies.[14,15] The SDL depth has been observed lower in all regions of peripheral cornea compared to central cornea.[16,17] To the best of our knowledge; there is only one study comparing the central and peripheral SDL depths between standard (3 mW/cm^2) and accelerated (9 mW/cm^2) protocols. In this study; the SDL depths were compared as numerical values and the SDL depths were found lower in accelerated protocol for all regions.[18] This result was not surprising because it was known that the central SDL depth was lower in accelerated protocol compared to standard protocol and SDL depth was shallower towards periphery.[19] The comparison of SDL depth percentages of peripheral cornea in comparison with central cornea between standard and accelerated protocols could give more reliable information about the efficiency of accelerated protocol on peripheral cornea.

The aim of this study was to assess the efficiency of accelerated CXL on cornea periphery by comparing the peripheral SDL depths percentages in accelerated CXL with those in conventional CXL.

MATERIAL AND METHODS

This study was conducted at Ophthalmology Department of Kayseri Training and Research Hospital. Fortytwo eyes of 26 keratoconus patients in whom progression was detected at the last three months were involved in the study. The progression was detected with repetitive corneal topography and optical pachymetry measurements. Progression criteria were as follows >1.00 diopter (D) increase in maximal keratometry, or >1.00 D increase in the manifest cylinder, or 5% decrease in average central corneal thickness over a period of 12 months. All patients undergoing CXL in the study were older than 18 years. Patients with a corneal pachymetry <450 μm were treated with hypoosmolar riboflavin.

Exclusion criteria for this study were corneal thickness <350 μm at the thinnest point, herpetic keratitis, severe dry eye, corneal infection, autoimmune disease and previous ocular surgery.

Contact lense use stopped before first measurements (1 week for soft contact lense, 3 weeks for rigid gas permeable lense). Informed consent was obtained from all subjects. The study was approved by Institutional Review Board of Erciyes University (02.12.2016-2016/614). The study was conducted according to the tenets of the Declaration of Helsinki.The patients were divided into two groups, 3.0 mW/cm^2 UVA was applied for 30 minutes in standard group and 9.0 mW/cm^2 UVA was applied for 10 minutes for in accelerated group following riboflavin

instillation for 30 minutes. Visual acuity, refractive error, corneal topography (Pentacam, Oculus, Germany) were measured for all patients following detailed ophthalmic examination.

All procedures were performed under topical anesthesia. The central 9-mm corneal epithelium was scraped off with a blunt knife. %20 dextran-%1 riboflavin solution (Ricrolin, Sooft, Montegiorgio, Italy) was applied to the deepithelialized cornea at every 3 minutes in standard group and at every 2 minutes in accelerated group for 30 minutes, followed by UVA irradiation (Apollon Crosslinking System, Meram Medicine, Turkey) for 30 minutes for standard group and 10 minutes for accelerated group, at a working distance of 45-50 mm. During irradiation, riboflavin application was continued at every 2 minutes for both groups A bandage contact lens was applied at the end of the procedure and 0.3% ofloxacin (Okacin, Novartis), 0.1% fluorometholone (Flarex, Alcon) and artificial tears were prescribed postoperatively. Corneal topography (Pentacam, Oculus, Germany) and the SDL depth measurements (AS-OCT) (Heidelberg, Dossenheim, Germany) were performed at postoperative first month. Measurement of the demarcation line was performed using postoperative AS-OCT by a single examiner (A.Ç.). Measurements were taken at the corneal center and at 3 mm superior, inferior, temporal, and nasal from the center. The SDL depth was measured from the corneal epithelium to the detectable hyperreflective line within the corneal stroma. The peripheral SDL depths were inferred as percentages by calculating ratio to the central SDL depth separately for both groups (peripheral SDL/central SDL*100).

Figure 1 and Figure 3 showed the measurement of SDL depth from central cornea in standard and accelerated groups, respectively. Figure 2 and Figure 4 showed the measurement of SDL depth from peripheral cornea in standard and accelerated groups, respectively.

Statistical analysis was performed using the SPSS software version 19.0 (IBM, Inc, Chicago, IL). Preoperative values of both groups were compared using the Mann-Whitney U test for continuous data and the Fisher exact test for categorical data. Comparison of the demarcation line depth between both groups was performed by the Mann–Whitney U test. The difference in SDL depth between the center and the periphery was compared with the Friedman test, followed by post hoc analysis with the Wilcoxon test in each group. A p value of <0.05 was regarded as statistically significant.

RESULTS

Fortytwo eyes of 26 keratoconus patients in whom progression has been detected were involved in the

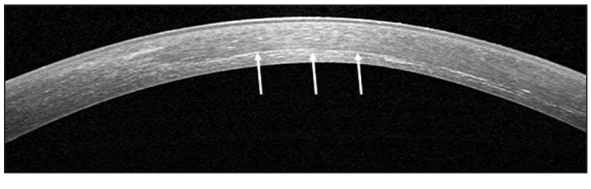

FIGURE 1: The measurement of SDL depth from central cornea in standard group.

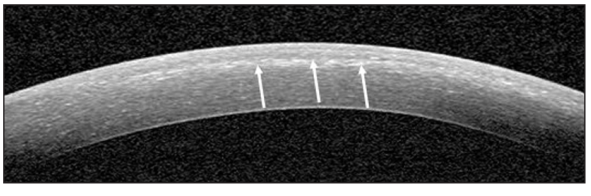

FIGURE 2: The measurement of SDL depth from peripheral cornea in standard group.

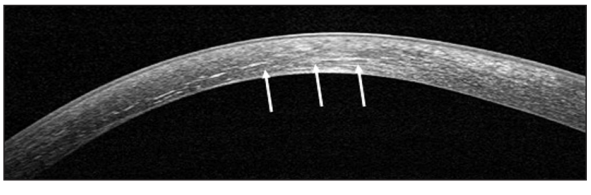

FIGURE 3: The measurement of SDL depth from central cornea in accelerated group.

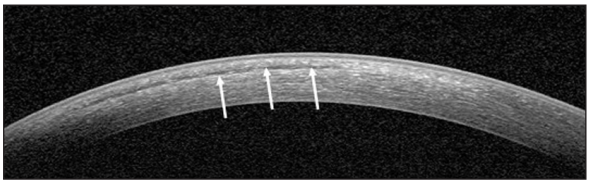

FIGURE 4: The measurement of SDL depth from peripheral cornea in accelerated group.

study. The SDL was visible in 38 eyes of 24 patients (standard group: %88; accelerated group: %90, p=0.659 Fisher's exact chi square test). Average measurement time following treatment was 5.05±1.35 weeks. Standard group was composed of 18 eyes of 13 patients; accelerated group was composed of 20 eyes of 11 patients.

There was no statistically significant difference in average age, preoperative astigmatism, corneal thickness at the thinnest region and maximal keratometry values between two groups (p=0.07) (Table 1). Average age was 19.5±3.72 years.

The SDL depths on central and peripheral cornea were shown in Table 2. The central SDL depths in standard and accelerated groups were 302 ± 49 and 251±42 µm, respectively (p=0.004). The peripheral SDL depths were statistically significantly lower at all regions in accelerated group compared to standard group (p=0.010). The SDL depth percentages from 3 mm periphery (superior, inferior, temporal, nasal) in standard group were 84±14µm, 76±18µm , 77±12 µm and 71±12 µm, respectively. The same measurements in accelerated group were 74±12 µm, 76±08 µm, 70±12 µm and 70±12 µm, respectively. There was no statistically significant difference except superior region between two groups (p>0.05) (Table 3). The SDL depth percentage at except superior region was lower in accelerated group compared to standard group (p=0.044).

The SDL depth was highest at central region and became shallower towards periphery (p<0.001, for both groups). In the post hoc analysis; the SDL depth

TABLE 1: The comparison of preoperative values between standard and accelerated groups.

	Standard Group	Accelerated Group	P*
Age	19.0±3.3	19.7±3.8	0.576
Astigmatism (D)	3.58±1.54	4.20±1.96	0.710
Maximal keratometry (D)	54.4±3.8	55.9±5.1	0.294
The thinnest pachymetry (µm)	464±30	446±26	0.074

TABLE 2: The stromal demarcation line depths at central and peripheral cornea (3 mm away from central at each quadrant).

	Standard Group N= 18	Accelerated Group N= 20	P*
Central (µm)	302±49	251±42	0.004
Superior (µm)	252±51	187±43	<0.001
Inferior (µm)	226±41	191±39	0.010
Temporal (µm)	232±54	175±38	<0.001
Nasal (µm)	211±33	175±36	0.002
Friedman test	0.000	0.000	

TABLE 3: The percentages of stromal demarcation line depths at peripheral cornea with proportion to central cornea.

	Standard Group N= 18	Accelerated Group N= 20	P*
Superior (%)	84±14	74±12	0.044
Inferior (%)	76±18	76±08	0.953
Temporal (%)	77±12	70±12	0.079
Nasal (%)	71±12	70±12	0.861

was lower at four peripheral regions compared to central region in both groups (Superior, inferior, temporal, nasal; respectively. Standard group p= 0.001, 0.001, <0.001, <0.001; accelerated group p=<0.001, <0.001, <0.001, <0.001).

DISCUSSION

In our study; we have observed that the SDL depth following accelerated CXL (9 mW/cm^2) was significantly lower than the SDL depth following standard CXL. This result was consistent with Kymionis' study in which the SDL following standard CXL was found significantly deeper.[9] In this study, the SDL depths were 351 µm and 288 µm in standard and accelerated (9 mW/cm^2) protocols, respectively. In another study; the SDL depth following standard CXL (303 µm) was measured deeper compared to the SDL following CXL performed with 30 mW/cm^2 UVA application for 3 minutes (212 µm).[15] Tomita et al. have not observed any difference in SDL depth between standard CXL and accelerated CXL (30 mW/cm^2).[20]

Kymionis et al. assessed the SDL depth from 3 mm nasal and 3 mm temporal periphery of cornea in their study and they measured 212 µm and 218 µm, respectively.[16] The SDL depths at these two regions were lower than the central SDL depth (311 µm). Also it has been shown that the SDL depth following standard CXL became shallower from central (305 µm) towards periphery (3 mm nasal: 214 µm; 3 mm temporal: 235 µm) in a study.[17] There is only one study evaluating the SDL depth following accelerated CXL (9 mW/cm^2). In this study, Ng et al. did not find any difference between the SDL depth measured at the corneal center and the SDL depths at its periphery (3 mm superior, inferior, temporal, nasal).[18] They suggested that this result could be related with different design of UV-X 2000 (IROC Innocross) machine used in accelerated CXL in their study. This machine had an optimized illumination beam profile and its design took into account the thickness distribution of the cornea and the differences in anterior and posterior corneal curvature. This theoretically could result in more homogeneous cross-linking treatment over the peripheral cornea. It has not been mentioned a design like this about the CXL machines used in other studies and also our machine has not this design. For this reason, we will assess the issue basing the machines with routine specialities in the remaining part. In our study, the SDL depths at the all peripheral regions were shallower compared to central in standard and accelerated group. This is congruent with the other studies evaluating central and peripheral SDL depth following CXL except the study mentioned above.[18] It has been thought that this was associated with the difference in exposed UVA density or the difference in beam plane between central and peripheral parts. Also the longer distance between the peripheral cornea and UVA source might be related. We have thought that inevitable eye movements of patients during procedure might cause peripheral cornea sometimes exit from UVA beam ray and this might result in less cross-linking area and shallow SDL. This hypothesis needs to be searched with the studies evaluating the correlation between patient adaptation and the SDL depth at the corneal periphery. Our another hypothesis is that the probable difference in the oxygenation of cornea between central and peripheral regions could result in shallower SDL at the periphery because cross-linking has been established as an oxygen dependent process.[20] The probable lower oxygen amount at the peripheral cornea could result in shallower SDL. This hypothesis also needs studies with large number to be confirmed.

To the best of our knowledge, the only study comparing the central and peripheral SDL depths (3 mm superior, inferior, temporal, nasal) between standard and accelerated CXL is the study explained above.[18] In this study, central and peripheral SDL depths were compared as numerical values and shallower SDL was found at all regions in accelerated group. This result could be foresaw by arithmetical calculations. Because the central SDL following accelerated CXL has been shallower compared to standard CXL and the SDL has become shallower from central towards periphery in all studies use routine UVA machines without added specialities. This result does not provide any beneficial information for the future of cross-linking therapy. We have thought that the comparison of SDL depth percentages at the peripheral regions between two groups was more suggestive. In this comparison; there was a statistically

significant difference in SDL percentages between two groups only at the superior region. The SDL proportion at superior region was lower in accelerated group compared to standard group. This difference observed only at the superior region incite us to think possible mechanisms other than the difference in exposed UVA density or the difference in beam plane between central and peripheral parts. Some factors existing only at superior cornea should explain this difference observed in the SDL percentage. In the etiology of this, probable lower oxygenation of superior cornea might have role. The eyelid cover superior cornea 2 mm from limbus at superior but it stays at the level of limbus in inferior. Cornea takes its oxygen supply from atmosphere in consequence of lack of vascular supply. Oxygen dissolves in tear then it diffuses to cornea.[21] Atmospheric oxygen pressure is 155 mm Hg, oxygen pressure in palpebral conjunctiva is almost 55-60 mm Hg.[22] It has been shown in a study that closed eyelids throughout the night decreased oxygen level in cornea to the level in palpebral conjunctiva.[23] The 2 mm covering of superior cornea could decrease oxygenation at this region and it could affect cross-linking process. As a result; shallower SDL proportion could be observed. Of course this is only a hypothesis and needs to be confirmed. According to our experiences; the patients move their eyes most frequently upwards during CXL procedure. This means that superior cornea exits from UVA beam ray more frequently than other corneal peripheral regions. Also this might explain the lower SDL proportion at the superior cornea. The investigation of pathophysiology of this difference observed at superior cornea could be guiding for new modifications in CXL treatment by explaining the mechanism of shallower SDL at all regions in accelerated CXL (9 mW/cm^2). To the best of our knowledge, our study is the only study comparing the SDL depths both as numerical and proportional values between standard and accelerated CXL (9 mW/cm^2) in the literature.

There were a few factors limiting our study. First of them was low number of subjects. But we have found significant difference in SDL between two groups at the statistical analysis. Secondly, all AS-OCT measurements were performed by a single examiner. The correlation between examiners was found high for the measurement of SDL depth in the literature.[24,25] Finally, the accuracy of SDL depth measurements was limited by hyperreflective appearance of corneal stroma following CXL.

CONCLUSION

In conclusion, the SDL depth following accelerated CXL (9 mW/cm^2) was lower as numerical values at central and peripheral cornea compared to the SDL depth following standard CXL. In the comparison of peripheral SDL depths as percentages (in proportion to central), the SDL depth percentage was lower in accelerated group only at superior region compared to standard group. This result could be explained with probable difference in oxygenation at superior cornea. It is a convenient advice to think again while deciding application of accelerated CXL in conditions affecting superior cornea. There is need for larger studies researching the effectiveness of accelerated CXL on superior cornea.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Ayşe Çiçek, Mustafa Ataş;* ***Design:*** *Ayşe Çiçek, Mustafa Ataş;* ***Control/Supervision:*** *Ayşe Çiçek, Mustafa Ataş, Süleyman Demircan, Necati Duru;* ***Data Collection and/or Processing:*** *Ayşe Çiçek, Döndü Melek Ulusoy;* ***Analysis and/or Interpretation:*** *Ayşe Çiçek, Mustafa Ataş, Necati Duru;* ***Literature Review:*** *Ayşe Çiçek, Döndü Melek Ulusoy;* ***Writing the Article:*** *Ayşe Çiçek, Mustafa Ataş, Necati Duru;* ***Critical Review:*** *Ayşe Çiçek, Mustafa Ataş, Necati Duru;* ***References and Fundings:*** *Ayşe Çiçek, Mustafa Ataş, Döndü Melek Ulusoy;* ***Materials:*** *Ayşe Çiçek, Mustafa Ataş, Döndü Melek Ulusoy.*

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