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Original research

# Multipoint assessment of demarcation line depth after standard and accelerated cross-linking in central and inferior keratoconus

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## Abstract

***Purpose***: To determine the changes in the depth of the demarcation line in the central to peripheral cornea following accelerated compared to standard corneal cross-linking (CXL).
***Methods***: In this prospective, non-randomized study, 60 eyes with progressive keratoconus underwent accelerated or standard CXL (30 in each group). Anterior segment optical coherence tomography (AS-OCT) was done one month later by two independent masked examiners to measure the depth of the demarcation line in the central cornea and on peripheral rings.
***Results***: The inter-examiner agreement (intra-class correlation coefficient) was >0.75 for all measured points, and average measurements were used in the analysis. The depth of the visualized demarcation line in the center was 223.4 ± 67.4 μm and 354.9 ± 79.0 μm in the accelerated and standard groups, respectively ($P < 0.001$). The depth significantly decreased from the center to the 7 mm ring in both groups (all $P < 0.05$). This change was 7.7–26.1% and 2.2%–11.1% in the accelerated and standard groups, respectively. In the accelerated group, the demarcation line was deeper in the central cone sub-group compared to the inferior cone sub-group, but in the standard group, the demarcation line was deeper in the inferior cone sub-group (all $P < 0.05$). Cases with an inferior cone showed greater inter-group differences in all studied points.
***Conclusions***: The depth of the demarcation line with accelerated CXL is less than the standard protocol and decreases from the center towards the periphery. Demarcation lines are more homogenized with standard CXL. In cases with an inferior cone, demarcation line depth varies throughout the cornea.


*Keywords:* Accelerated cross-linking; Standard cross-linking; Demarcation line; Peripheral cornea; Cone position

## Introduction

Corneal cross-linking (CXL) is a procedure that can halt the progression of keratoconus by creating new covalent bands in the corneal stroma and biomechanical corneal strengthening.[1] Short and long-term studies have shown the effectiveness of both the standard and accelerated protocols in stopping the

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destructive effect of the disease, improving vision, and reducing the corneal curvature.[2−5]

Another parameter assessed in the evaluation of CXL effectiveness is the corneal stromal demarcation line, which is the transition between the anterior treated stroma and the posterior untreated stroma.[6] The line should be deep enough to ensure efficacy, but not too deep to risk safety by causing injury to endothelial cells. Several studies have used confoscan or anterior segment optical coherence tomography (AS-OCT), and they have reported depths up to 300 μm after the 30 min standard protocol.[6−8] With the introduction of accelerated CXL protocols, studies began to address the line depth with this protocol. Some studies have reported a more superficial demarcation line after the 10-min, 9 mW/cm$^2$ protocol compared to standard CXL.[9,10] Some have studied it following 9-min[11] and 14-min[12] protocols, and Kymionis et al.[13] have reported almost 244.3, 322.9, and 233.0 μm after the 5-min approach.

The present study is designed to compare the 5- and 30-min CXL protocols in terms of 1) the visibility and depth of the demarcation line; 2) line homogeneity in the center and at 3, 5, and 7 mm from the center; and 3) line depth in two subgroups with central and inferior cones.

## Methods

In this non-randomized clinical trial, 60 eyes with progressive keratoconus were enrolled and underwent either standard (3 mW/cm$^2$, 30 min) or accelerated (18 mW/cm$^2$, 5 min) CXL (30 eyes in each group), consecutively. Enrollment was first completed for the accelerated group and then the standard group. Progression of keratoconus was defined as at least 1.0 diopter (D) increase in maximum keratometry (Kmax), manifest cylinder, or manifest refraction spherical equivalent (MRSE), or loss of two or more lines of corrected distance visual acuity (CDVA) over the previous 12 months. The inclusion criteria were age between 15 and 35 years, Kmax less than 55.0 D, and minimum central corneal thickness of 400 μm. Patients with a history of ocular surgery or other ocular disease were excluded from the study. The keratoconus cone was central (within the 3 mm zone) in 33.3% of cases and inferior in 66.7% (beyond the 3 mm zone). Posterior elevation map in Pentacam (Oculus Optikgeräte GmbH, Wetzlar, Germany) was used in the classification.

The study protocol was reviewed and approved by the local institutional review board, and it adhered to the tenets of the Declaration of Helsinki at all stages. All participants read and signed informed consents.

In the standard group, we used a method similar to that described by Wollensak et al.[14] After administering local anesthesia, the central 9 mm of the corneal epithelium was manually removed. Then the lid speculum was removed, and riboflavin 0.1% drops in dextran 20% (Streuli Pharma, Uznach, Switzerland) were instilled onto the corneal surface at 3 min intervals for 30 min. After anterior chamber saturation with riboflavin, the cornea was irradiated for 30 min with 370 nm UV-A and an intensity of 3 mW/cm$^2$ using the IROC UV-X System (Zürich, Switzerland) from a distance of 5 cm, and riboflavin instillation was repeated every 3 min. At the end of this stage, the corneal surface was rinsed with sterile balanced saline solution, one drop of levofloxacin was instilled, and a soft bandage contact lens (Night & Day, Ciba Vision, Duluth, GA, USA) was placed. The postoperative regimen included levofloxacin and betamethasone 0.1% eye drops four times daily and artificial tears (Hypromellose, preservative free) as needed. Patients were examined at one and three days after the procedure, and daily thereafter if necessary until complete epithelial healing was observed. When corneal re-epithelialization was complete, the bandage contact lens was removed, levofloxacin was discontinued, and betamethasone was continued 4 times daily for another week.

For the accelerated group, the same protocol was applied, but the cross-linking procedure was modified to a power of 18 mW/cm$^2$ and irradiation time of 5 min using the CCL 365 (PESCHKE Meditrade GmbH, Waldshut-Tiengen, Germany). The two devices are similar in terms of wavelength (365 nm), light emission (continuous wave), spot size (7−11 mm), and electric power (100−240 V).

All patients were examined with the Spectralis AS-OCT (Heidelberg Engineering GmbH, Heidelberg, Germany) at one week and one month after the procedure. Multiple images were acquired from each eye, and the one with the best line clarity was selected for depth measurement. To improve visualization, the reverse image was used during measurements, and line depth was measured from the back of the tear film to the front of the demarcation line. Line depth was measured at the corneal center and on 4 points on the superior, inferior, nasal, and temporal meridians at 3 mm, 5 mm, and 7 mm from the center. Measurements were done by two independent observers. The observers were masked to treatment groups. The agreement between their measurements was assessed using the Bland-Altman analysis. The averages of the two measurements were used in the main analyses. Statistical comparisons were made using the independent sample *t*-test. Considering the limited number of samples in the subgroups, we used the G*Power software 3.1.9.2 to run a power analysis where the *P*-value was not significant with the two-group independent sample *t*-test.

## Results

The mean age in the standard and accelerated groups was 25.2 ± 4.4 and 24.0 ± 4.5 years ($P = 0.467$), respectively. No complication was observed either during or after the procedures. The baseline topographic data were compared between groups in Table 1. At one week after the procedure, the demarcation line was not visible in either group.

In the Bland-Altman analysis, the inter-examiner difference± standard deviation (SD) in line depth measurement in the center and at 3, 5, and 7 mm rings was, respectively, 0.29 ± 2.1, 1.97 ± 2.6, 0.1 ± 4.3, and 1.1 ± 10.7 in the accelerated group and 7.4 ± 8.7, 0.3 ± 16.7, 3.5 ± 16.6, and 0.7 ± 6.7 μm in the standard group. Except for the center in the standard group ($P = 0.014$) and the 3 mm ring in the

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