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Assessment of two-year clinical outcomes after keratoconus treatment using two different crosslinking protocols

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Abstract. – OBJECTIVE: This study aims to compare the long-term outcomes of standard corneal collagen crosslinking with accelerated corneal collagen crosslinking (CXL) for progressive keratoconus.

PATIENTS AND METHODS: This prospective, comparative study included 79 eyes with progressive keratoconus, which were randomly assigned: 42 eyes received a standard CXL procedure, and 37 eyes were treated with the accelerated CXL protocol. We evaluated the following parameters, before the procedure and 1 month, 6 months, 12 months and 24 months postoperatively: best corrected visual acuity (BCVA), manifest refraction spherical equivalent (MRSE), cylindrical values, corneal dioptric powers on the steepest meridian (Kmax), central corneal thickness (CCT); demarcation line depth (DLD) preoperatively and 1 month after the CXL procedure.

RESULTS: The BCVA, MRSE, cylindrical values, Kmax, CCT improved significantly, after both the accelerated and the standard CXL procedure. Throughout the 24-months follow-up, BCVA improvement was achieved sooner in the accelerated group (after 1 month, *vs.* after 3 months). However, there were no statistically significant differences between the two groups in these aspects. The DLD-to-CCT was significantly greater in the standard group (66% *vs.* 62%, $p = 0.02$).

CONCLUSIONS: Standard and accelerated CXL are effective in stabilizing keratoconus progression in the long term. In clinical practice, the accelerated protocol has the added benefit of a faster visual recovery, in addition to the known reduced treatment time and increased comfort.

Key Words:
Corneal collagen crosslinking, Keratoconus, Keratometry, Demarcation line.

Introduction

Keratoconus is a corneal ectasia characterized by progressive corneal thinning and corneal scars in advanced stages, which lead to decreased visual acuity[1]. It is one of the main indications for penetrating keratoplasty. Initially, treatment options were based on optical correction with glasses or contact lenses, especially rigid ones, but these treatments do not prevent disease progression. Furthermore, corneal infections, corneal pannus, along with other complications caused by the improper use of contact lenses were not uncommon. Corneal transplant constitutes the first line of treatment in advanced cases but presents the risk of corneal allograft rejection and failure. Thus, it was essential to develop new ways of keratoconus treatment, safer and more effective[2,3].

Corneal collagen crosslinking has been developed as an efficient method of halting the disease progression. In 2003, Wollensaket al[4,5]introduced corneal crosslinking for the first time. The protocol they used is now considered the standard procedure which consists of removal of the corneal epithelium, stromal loading with riboflavin and exposure to ultraviolet A (UVA) light with a wavelength of 370 nm and an intensity of 3.0 mW/cm^2 for 30 minutes.

Although more and more clinical trials have demonstrated the efficacy and safety of corneal crosslinking, complications caused by epithelial removal and long-term exposure to ultraviolet radiation, such as postoperative eye pain, subepithelial edema, sterile infiltrates or infectious keratitis, could not be completely avoided. Taking into

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account the risk profile, attempts have been made to modify the standard protocol to avoid these complications. Thus, transepithelial crosslinking has been studied in order to preserve the corneal epithelium, and to, subsequently, reduce the rate of complications and postoperative pain[4-6].

Since the standard procedure requires a long treatment time of about an hour, accelerated protocols have been proposed to shorten treatment time, while improving patient comfort[7].

Various accelerated crosslinking protocols were tested, reporting similar effects to the standard procedure on porcine corneal biomechanical properties. However, there are *ex vivo* studies that have shown a low efficacy of accelerated procedures compared to the standard protocol[8].

Recent clinical trials have reported promising results in corneal crosslinking using the accelerated protocol compared to the standard protocol, having the advantage of a shorter exposure time to ultraviolet light and an increased comfort for the patient[9,10].

The reported results regarding accelerated crosslinking are not completely concordant. A retrospective study led by Brittingham concludes that the accelerated protocol is less effective in stopping the progression of keratoconus compared to standard protocol, in patients followed for a period of 1 year[11].

In the present study, the clinical outcomes of standard CXL (3.0 mW/cm^2 for 30 minutes) and accelerated CXL (9.0 mW/cm^2 for 10 minutes) were evaluated in a series of 79 eyes with progressive keratoconus, from 62 patients, over a 24-months follow-up period.

Patients and Methods

Patients

We conducted a prospective, comparative study which included keratoconus patients who underwent corneal crosslinking treatment, either with the standard epi-off or accelerated protocol at Oftaclinic Ophthalmology Clinic (Bucharest, Romania) between May 2016 and June 2018.

Before treatment we obtained informed consent from all participants. The study was performed in adherence to the Declaration of Helsinki and was approved by the Ethics Committee of the Carol Davila University of Medicine and Pharmacy Bucharest.

The inclusion criteria were as follows: age over 18 years old, progressive keratoconus and no previous ocular surgery. Keratoconus was considered progressive if, during a 12-months follow-up, there was an increase in simulated maximum keratometry by at least 1 D, documented by repeated corneal topographies, a deterioration of visual acuity (loss of at least 1 line on the Snellen chart) or an increase in astigmatism by at least 1.0 D, with subjective deterioration in vision.

Exclusion criteria included history of herpetic keratitis or recurrent infections, any corneal endothelial pathology, as well as immune system disorders and pregnancy or breastfeeding.

After applying the inclusion and exclusion criteria, the study included a number of 79 eyes from 62 patients, with a minimum of 2 years of follow-up for each patient. The patients were randomly assigned to the standard or accelerated protocol – 42 eyes from 32 patients were treated with standard CXL and 37 eyes from 30 patients were treated with the accelerated protocol.

All procedures were performed by a single surgeon. Cases were classified into four stages based on corneal power, astigmatism and corneal thickness, according to the classification of Amsler-Krumeich.

Data Collection

Each patient underwent a complete ophthalmologic examination, preoperatively and at 1 month, 6-months, 12 months and 24 months postoperatively. The examination included measurement of manifest refraction, uncorrected and best corrected visual acuity, slit lamp and fundus examination, corneal topography with Topcon CA-200F Corneal Analyser (Topcon Medical Systems), ultrasound pachymetry (Alcon®OcuScan®RxP Ophthalmic Ultrasound System), anterior segment imaging using optical coherence tomography (OCT, Optical coherence tomography 3D OCT 2000 series).

The parameters we evaluated were the best corrected visual acuity (BCVA), manifest refraction spherical equivalent (MRSE), cylindrical values, corneal dioptric powers on the steepest meridian (Kmax), central corneal thickness and demarcation line depth (DLD).

Anterior segment OCT using the Spectralis anterior segment module was performed preoperatively and then 1 month after the CXL procedure. The demarcation line depth was measured at the centre of the cornea from the corneal epithelium to the detectable hyper-refractive line within the corneal stroma. Measuring the DLD centrally, we determined the absolute depth and related to the total central corneal thickness – the depth/central corneal thickness (CCT) ratio.

CXL Treatment

Standard Procedure

Patients were treated with UVA-riboflavin CXL in the operating room under sterile conditions and topical anesthesia with oxybuprocaine hydrochloride 0.4% (Benoxi, Unimed Pharma Ltd). Collagen crosslinking was performed according to the classical methodology, with corneal epithelial mechanical debridement in a 9.0 mm diameter area. The epithelial tissue was removed with a blunt spatula to ensure penetration of riboflavin in the corneal stroma. Iso-osmolar riboflavin solution 0.1% in dextran 500 20% (Peschke D, PeschkeMeditrade GmbH, Switzerland) was applied to the cornea for 30 min every 3 min. After that, the cornea was exposed to UVA light, 365 nm wavelength, for 30 min at an irradiance of 3.0 mW/cm^2. During the 30 min of irradiation the riboflavin administration was continued every 5 minutes. At the end of surgery, topical treatment with an antibiotic (moxifloxacin) and a nonsteroidal anti-inflammatory agent (pranoprofen 1mg/ml) was administered, and a soft bandage contact lens was applied until corneal epithelium healing was completed.

Accelerated CXL Procedure

The steps of the intervention were the same with those in the standard procedure, with the mention that the exposure to 370 nm UVA light was performed with an intensity of 9.0 mW/cm^2, for 10 minutes.

Statistical Analysis

Statistical analysis was performed using statistical software – IBM SPSS Statistics, version 20 (Armonk, Ny, USA) and Microsoft Office Excel 2007 (12.0.4518.1014). The Kolmogorov-Smirnov test was used to check for a normal distribution of quantitative data. A paired *t*-test was used to evaluate postoperative changes. If the data were not distributed normally, the Wilcoxon test was performed. In order to analyze the difference in outcomes between the two groups, an independent sample *t*-test was performed, while the Mann-Whitney test was performed when data were not distributed normally. Correlation analysis of the demarcation line depth and the topographic keratometric values were performed with Pearson correlation test. Continuous variables are presented as mean ± standard deviation. A *p*-value of <0.05 has been chosen as the threshold of statistical significance.

Results

Baseline Characteristics

A total of 79 eyes (from 62 patients) were analyzed in this study (42 eyes after conventional CXL and 37 eyes after accelerated CXL). All patients included in the treatment protocol completed the 24-month follow-up.A comparison of baseline demographics, including age, gender, CCT, K readings, MRSE, cylindrical values, and BCVA was performed, and no significant differences were noted between the two groups (Table I).

Visual Acuity Change and Refractive Outcome

At the 24-month follow up, BCVA showed a statistically significant improvement of 0.09 ± 0.22 (p=0.008) and 0.16 ± 0.23 (p=0.0001) in the standard CXL and accelerated CXL groups, respectively. Although both groups exhibited statistically significant improvement in BCVA values, no significant differences were noted between them (p=0.117).

Table I. Baseline demographic, clinical and topographic parameters of the conventional and accelerated crosslinking groups.

	Standard CXL	Accelerated CXL	*p*-value
Gender, n (%)			
Men	31 (73.8%)	26 (70.3%)	0.730
Female	11 (26.2%)	11 (29.7%)	
Age, years	23.3 ± 6.40	25.6 ± 5.63	0.091
BCVA, decimal	0.51 ± 0.20	0.47 ± 0.12	0.263
MRSE values, D	-3.7 ± 2.86	-2.8 ± 2.42	0.123
Cylindrical values, D	-4.6 ± 2.49	-3.6 ± 2.13	0.065
Steepest K reading, D	52.7 ± 4.93	51.63 ± 4.81	0.334
CCT, µm	455.38 ± 41.42	460.51 ± 42.56	0.589

BCVA, best corrected visual acuity; MRSE, manifest refraction spherical equivalent; K steep, keratometry in steep meridian; CCT, central corneal thickness.

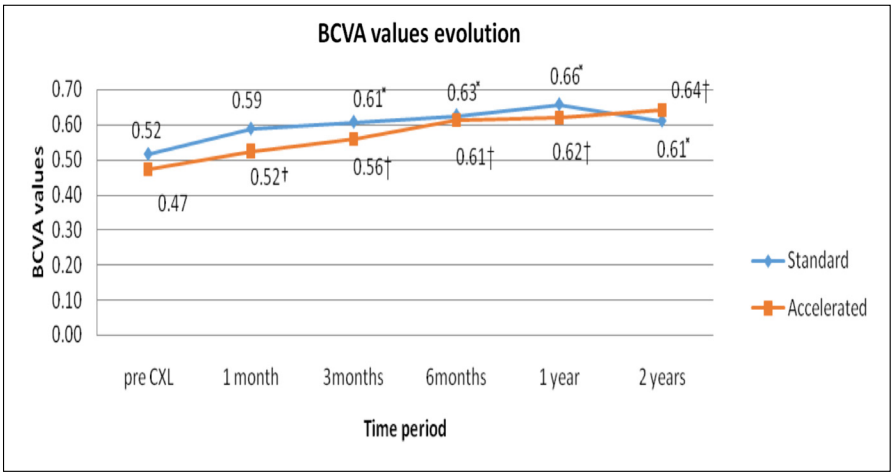

Figure 1. Trend of change in BCVA values after standard and accelerated CXL. x statistically significant improvement, compared to preoperative BCVA in standard CXL group (p<0.05); † statistically significant improvement, compared to preoperative BCVA in accelerated CXL group (p<0.05).

Best corrected visual acuity improved significantly in both groups, starting with the 1 month visit in the accelerated group and with the 3 months visit in the standard group and continued to improve throughout the follow-up period, with no statistically significant differences between the two groups (Figure 1).

At final follow-up, 27.03% of accelerated CXL-treated eyes gained more than one line of BCVA, in comparison to 14.3% of conventional CXL-treated eyes.

Both mean MRSE and mean cylindrical values showed a clinical improvement that became statistically significant by the third month. In the standard CXL group, MRSE was reduced by a mean of 0.63 ± 1.44 (p=0.007), whereas in the accelerated group MRSE was reduced by 0.38 ± 1.03 (p = 0.048) at final follow-up. In the standard CXL group, cylindrical values were reduced by a mean of 0.95 ± 0.91 (p = 0.0001), whereas in the accelerated group cylindrical values decreased by 0.71 ± 0.71 (p=0.0001). Although both groups exhibited statistically significant reductions in MRSE and mean cylindrical values, no significant differences were noted between them (p=0.415, respectively p=0.358, Table II). The trend of change in MRSE and cylindrical values over time in both conventional and accelerated CXL groups are shown in Figures 2 and 3.

Corneal Curvature Change

Corneal curvature change evolved differently after crosslinking. In the group of patients treated with standard procedure, Kmax values began to decrease starting with 3 months postoperatively, whereas in the group treated with accelerated procedure, Kmax values began to decrease starting with 6 months postoperatively (Figure 4).

In the accelerated CXL group, Kmax was reduced by a mean of -0.96 ± 1.09 D (p = 0.0001), whereas in the standard group Kmax decreased by a mean of -1.13 ± 1.22 (p = 0.0001) at final follow-up. Although both groups exhibited statistically significant reductions in keratometry readings, no significant differences were noted between them (p = 0.520).

Table II. Change in parameters at final follow up compared with the baseline measurements.

	Standard CXL	Accelerated CXL	*p*-value
BCVA change, decimal	0.09 ± 0.22	0.16 ± 0.23	0.117
MRSE change, D	-0.63 ± 1.44	-0.38 ± 1.03	0.415
Cylindrical change, D	-0.95 ± 0.92	-0.71 ± 0.71	0.328
Steepest K reading change, D	-1.13 ± 1.22	-0.96 ± 1.09	0.520
CCT change, µm	7.69 ± 14.67	9.70 ± 10.53	0.491

BCVA, best corrected visual acuity; MRSE, manifest refraction spherical equivalent; K steep, keratometry reading in the steepest meridian; CCT, central corneal thickness.

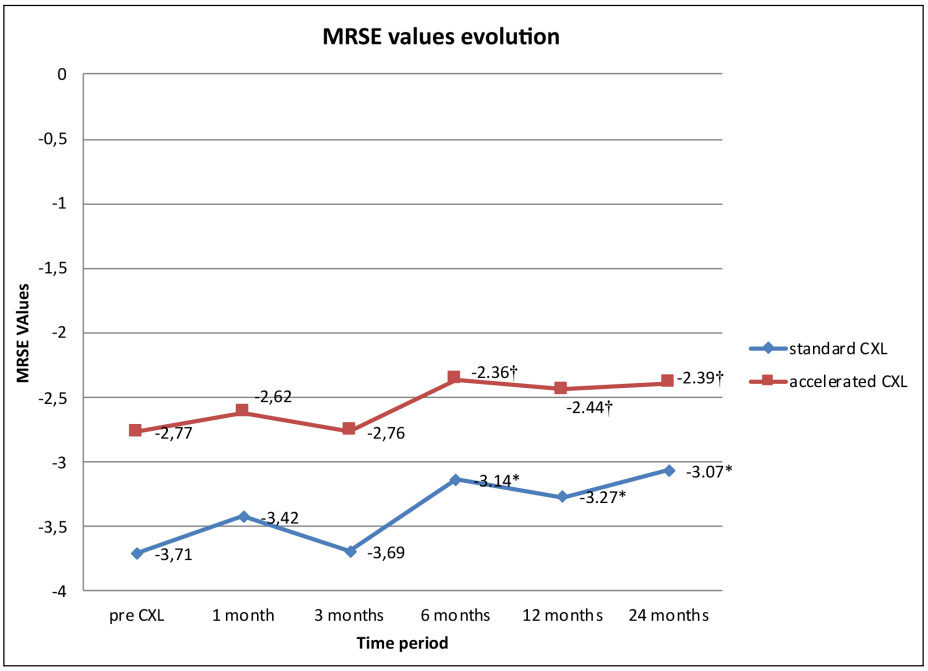

Figure 2. Trend of change in MRSE values after standard and accelerated CXL. x statistically significant improvement, compared to preoperative MRSE in standard CXL group ($p<0.05$); † statistically significant improvement, compared to preoperative MRSE in accelerated CXL group ($p<0.05$).

Demarcation Line

In the standard CXL group, the demarcation line was identified in 90% of patients with an average depth of 301.34 ± 27.02 µm. In the accelerated CXL group, it was identified in 89% of patients, but with a lower mean depth than in the standard group, of 286.18 ± 37.85 µm. This difference did not reach the statistical significance threshold.

A similar report was obtained for the depth of the demarcation line in relation to the total thickness of the cornea in the standard group compared to the group treated with the accelerated protocol. The ratio of DLD to corneal thickness was 66% in the standard CXL group and 62% in the accelerated CXL group, the difference being statistically significant ($p = 0.02$).

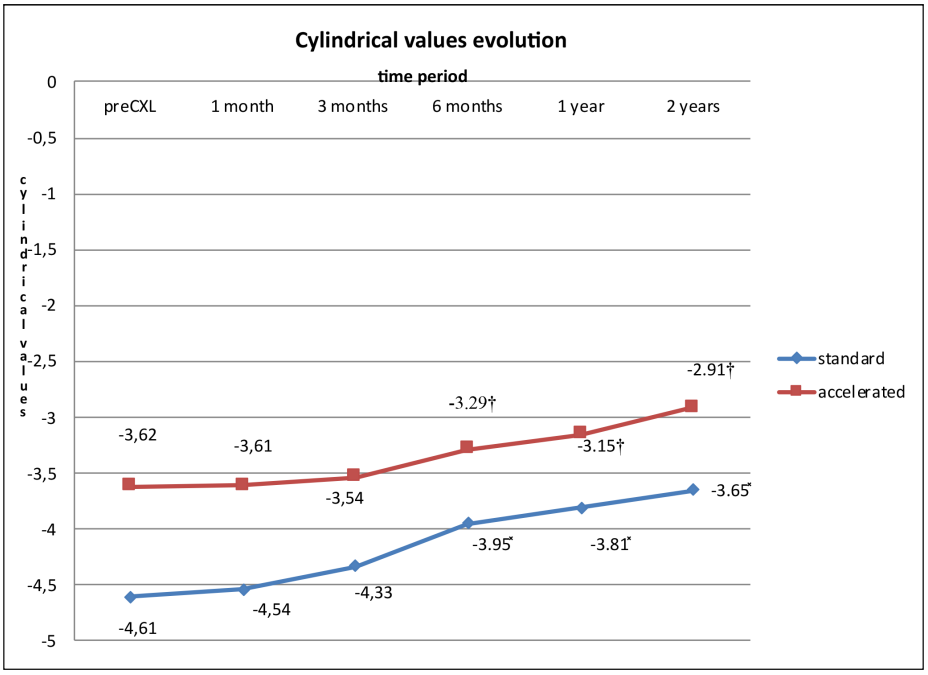

Figure 3. Trend of change in cylindrical values after standard and accelerated CXL. x statistically significant improvement, compared to preoperative cylindrical values in standard CXL group ($p<0.05$); † statistically significant improvement, compared to preoperative cylindrical values in accelerated CXL group ($p<0.05$).

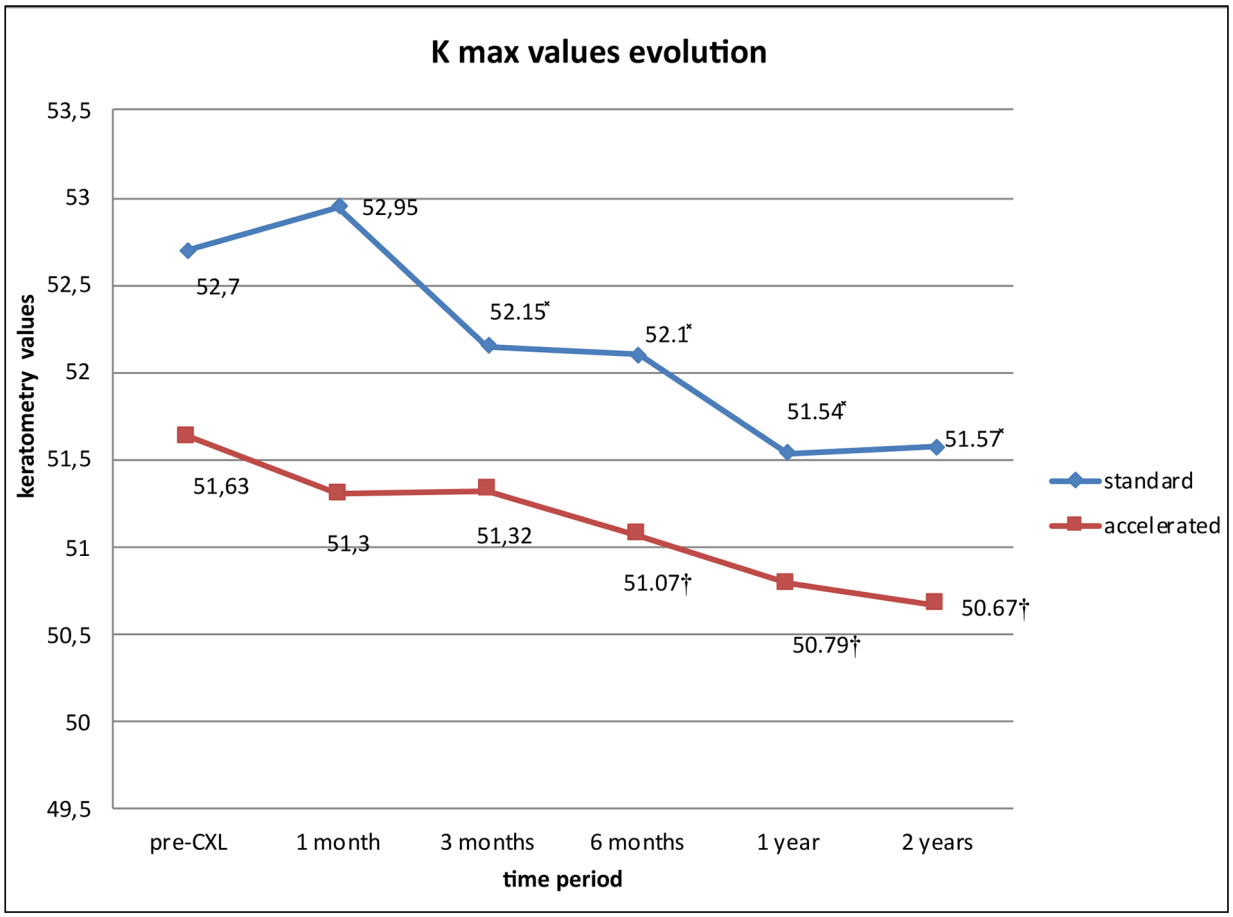

Figure 4. Maximum keratometry values prior to and following the standard and accelerated CXL procedures. x statistically significant improvement, compared to preoperative maximum keratometry values in standard CXL group ($p<0.05$); † statistically significant improvement, compared to preoperative maximum keratometry values in accelerated CXL group ($p<0.05$).

Post-hoc statistical analysis of experimental data shows the absence of statistically significant correlations between the steepest keratometry reading and the ratio of DLD to corneal thickness in the standard group (Pearson's r of -0.120, p = 0.474) and in the accelerated group (Pearson's r of -0.248, p = 0.163).

Changes of Corneal Topography vs. DLD

Changes of corneal topography were compared to demarcation line depth for both treatment groups. At 24 months postoperatively, the comparison of cases with a superficial demarcation line depth (<60%) with those with a greater demarcation line depth (≥ 60%) did not show a significant difference in change of maximal keratometry (DLD ≤ 60%: ΔKmax: -1.27 [SD ± 0.56] *vs.* DLD > 60%: ΔKmax: -1.35 [± 0.89]; p=0.716) (Figure 5).

Corneal Thickness Change

In the standard group, corneal pachymetry decreased significantly at 1 month and at 3 months postoperatively, compared to the initial moment. Subsequently, at 6 months, the pachymetry values returned to those prior to the intervention. At 12 months and 24 months, the statistical significant increase was observed in corneal thickness.

In the accelerated group, the corneal thickness decreased significantly compared to the initial moment at both 1 month and 3 months postoperatively. Subsequently, it began to increase at 6 months postoperatively, the growth continuing throughout the follow-up (Figure 6). There were no statistically significant differences in pachymetry changes between the two groups.

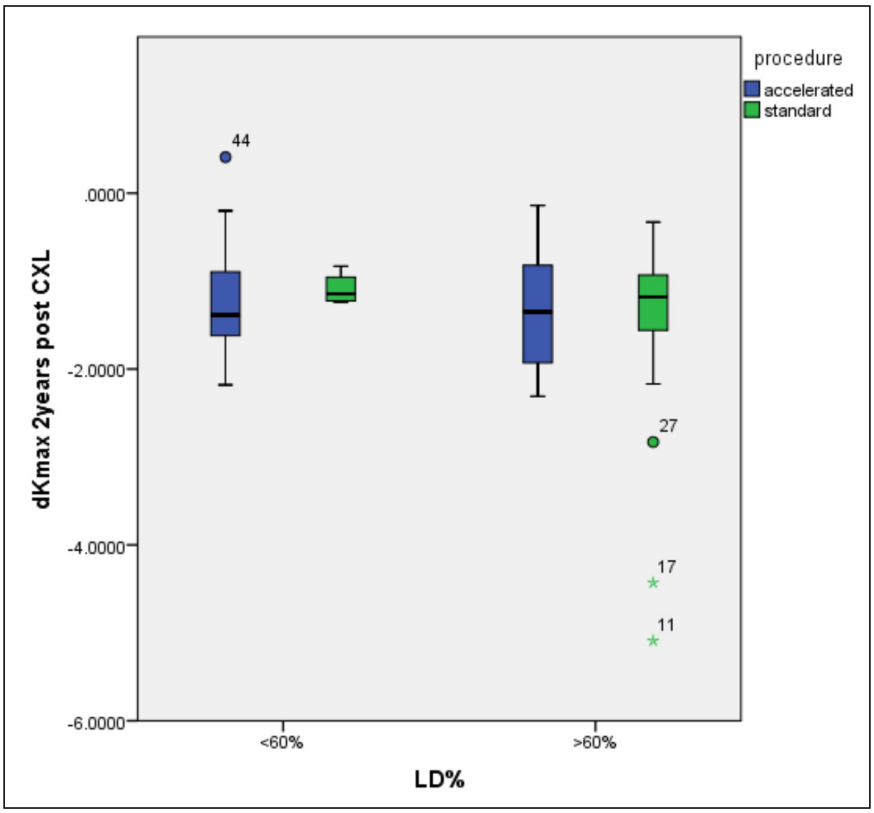

Figure 5. Box plots showing difference in the change of corneal topography, 24 months postoperatively, between corneas with superficial DL (depth < 60% of CCT) and deep DL (depth > 60% of CCT) for both treatment protocols.

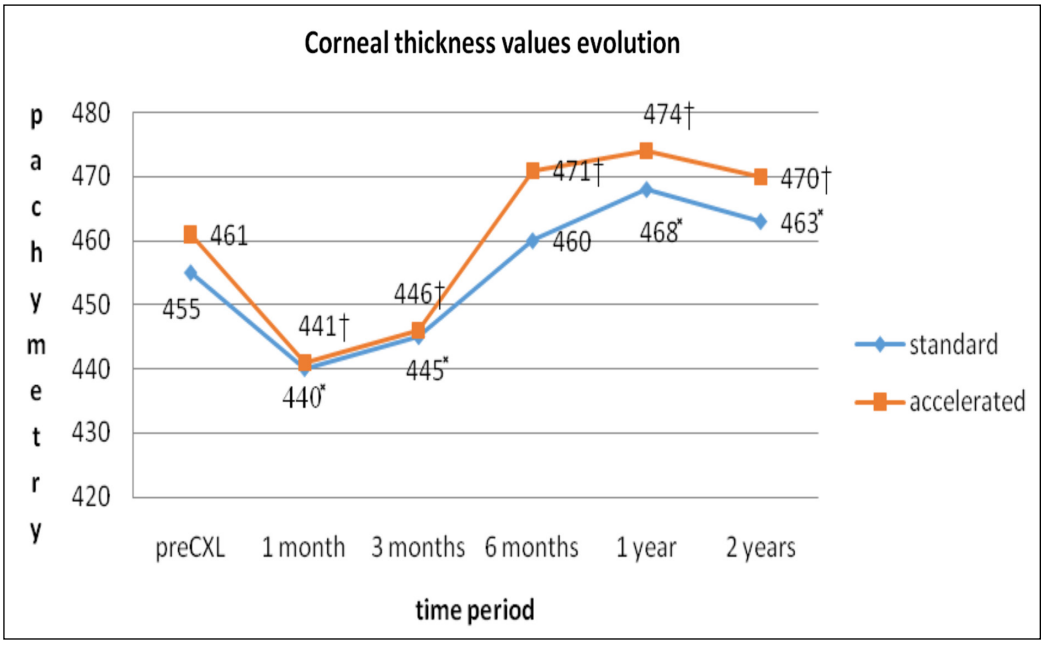

Figure 6. Corneal thickness values prior to and following the standard and accelerated CXL procedures. x statistically significant improvement, compared to preoperative central corneal thickness in standard CXL group (p<0.05); † statistically significant improvement, compared to preoperative central corneal thickness in accelerated CXL group (p<0.05).

Discussion

Many studies[12-15] in recent years have proven the efficiency of the standard Dresden protocol in stopping keratoconus progression. However, this protocol is time consuming, so the efforts of reducing the total treatment duration have already led to the introduction of the so-called "accelerated crosslinking protocols".

Previous clinical trials have demonstrated the efficacy and safety of accelerated crosslinking in stopping the progression of keratoconus[16,17].

In the present study we reported the long-term results of corneal crosslinking using standard protocol compared to corneal crosslinking using the accelerated procedure in the treatment of progressive keratoconus.

Immediately and over 24 months of follow-up after crosslinking, using both standard and accelerated protocols, none of the patients included in the study showed delayed corneal reepithelization, corneal melting, permanent scars, or sterile infiltrates corneal infections. However, 6 eyes (14.28%) in the standard CXL group and 4 eyes (10.81%) in the accelerated CXL group presented corneal haze, which was remitted between 3 and 12 months after the intervention. After performing corneal crosslinking, the corneal haze is a temporary and common complication, which can be present in 10 to 90% of the treated eyes18. Corneal haze can be caused by structural and physiological changes involved in the healing processes, such as fibroblast hyperplasia in the corneal stroma, after performing photooxidative crosslinking.

In the present study, the incidence of haze was higher in the standard CXL group compared to the accelerated CXL group. This could be explained by the longer exposure time in the former.

Our study demonstrated a faster recovery of visual acuity in the accelerated CXL group compared to the standard CXL group. This may be due to the reduced corneal edema, lower keratocyte loss, and a limited impairment of the subepithelial nervous plexus in the case of the accelerated protocol, due to shorter UVA exposure. These changes can be objectified by postoperative analysis of *in vivo* confocal microscopy. We were unable to perform this investigation, its absence being one of the limitations of the present study. However, 1 and 2 years postoperatively, there was no statistically significant difference between the two groups in terms of visual acuity. These results are consistent with those obtained by other studies[19,20].

Refractive parameters improved after both crosslinking procedures. Both the spherical equivalent and the manifest cylinder did not change in either group in the first 3 months postoperatively. They began to have a statistically significant decrease at 6 months postoperatively, which continued throughout the study. During the 24 months of follow-up, there were no statistically significant differences between the two treatment groups. Our results are partially consistent with those obtained from other studies that have shown stabilization or improvement in refractive parameters values[20-22].

The variation of keratometry values over time, measured using corneal topography, indicates favorable effects in both procedures. These results are consistent with those published by other authors. For instance, Tomita et al[22] showed that there were no significant statistical differences between the maximum keratometry values measured at 12 months postoperatively in the standard treatment *vs*. accelerated group using an energy of 30 mW/cm^2 for 3 minutes. A randomized study investigating the effects of crosslinking in progressive keratoconus in 41 eyes reported a reduction in Kmax of 1.03 D14 after 36 months of follow-up. In a study by Caporossi et al[23], the maximum keratometry regression was 1.96 D one year after the intervention.

Our study presents similar results to those mentioned above, regarding the variation of the maximum keratometry. More explicitly, a decrease of the maximum keratometry values was observed in both groups. In the standard group, Kmax began to decrease starting with 3 months postoperatively, and in the accelerated group it started decreasing 6 months after the intervention. The regression of the steepest K reading continued throughout the follow-up, without statistically significant differences between the two groups. A faster regression of the maximum keratometry values in the standard group can be explained by the longer exposure time to UVA, which could cause a faster corneal flattening effect. Our results showed a regression of Kmax by 1.13 D for the standard group and by 0.96 D for the accelerated group, which indicates the presence of corneal flattening. Therefore, the accelerated procedure seems to be as efficient as the standard one. On the other hand, these results differ from those presented by other authors. Brittingham et al[11] obtained a reduction of the maximum keratometry by 0.76 D following the standard procedure, and an increase of 0.72 D in patients treated with the accelerated procedure. Also, Ki et al[24] reported a decrease in Kmax by 1.8 D in

the standard group and by 0.3 D in the accelerated group, with a statistically significant difference between the 2 groups.

Corneal pachymetry values decreased in both groups in the first month postoperatively. After that, they returned to normal and started to improve with 6 months postoperatively, without statistically significant differences between the two groups.

A number of studies have reported changes in corneal thickness after performing photooxidative crosslinking. The results of our study are comparable to those reported in the literature, which showed a decrease in pachymetry values in the first 3 months postoperatively, followed by a normalisation of this parameter[23,25,26].

Decrease in corneal thickness at the first postoperative evaluation may be due to removal of the corneal epithelium, which causes an increase in the rate of water evaporation from the corneal stroma, as it does not benefit from the protective effect of the epithelium. Alternatively, decrease in corneal thickness postoperatively can be explained by increased endothelial pump activity[25,27].

At 1 month postoperatively, all patients included in the study underwent optical coherence tomography of the anterior segment to identify the demarcation line - which was found, on average, at a greater depth in the standard CXL group, compared to the accelerated CXL group. We may conclude that both the visibility of the demarcation line and its depth in absolute value were comparable in the two groups studied. Our results are similar to data in the literature. Namely, Shetty et al[9] have identified a demarcation line with an average depth of 280 ± 47 μm in the standard group, respectively 292 ± 73 μm in the accelerated group. Also, Kymioniset al[28] measured a demarcation line with an average depth of 337 ± 46.46 μm in the standard group, respectively 322.91 ± 48.28 μm in the accelerated group.

However, the reporting of the demarcation line to the corneal thickness revealed that the DLD is lower in the accelerated group (62%) compared to the standard group (66%), the difference being statistically significant. A possible explanation can be the existence of a limited diffusion rate of riboflavin with dextran in the treated corneas for a short time in the case of the accelerated protocol.

Our results are partially in line with those reported by Brittingham and collaborators, who, using the same protocols, identified a greater depth of the demarcation line in the standard group CXL, expressed both as absolute value and relative value[11].

As mentioned above, the regression of the maximum keratometry values was observed in both groups, without a statistically significant difference. These results are consistent with the comparable absolute values of the demarcation line observed.

However, using the accelerated protocol, the average depth of the demarcation line was measured at less than 300 μm (corresponding to 50% of the central corneal thickness).

Previous studies have reported that the treatment of photooxidative crosslinking is effective if a demarcation line with a depth of at least 300 μm is identified (60% of central corneal thickness)[29].

Taking this into account, and analyzing the corneal topography at the same time, we noted that there is no significant difference in diopter change on the most refractive meridian among the patients with shallow demarcation line (<60%) and the patients with a high depth of the demarcation line (>60%). Because there was no significant change in Kmax for those two groups, the predictability of a large depth of the demarcation line as a marker for crosslinking efficiency may be limited.

Post-hoc statistical analysis of experimental data shows the absence of statistically significant correlations between the demarcation line and the diopter on the most refractive meridian in both treatment groups at 24 months postoperatively. This data is in line with the results reported by previous studies[24].

Different treatment protocols seem to induce different depths of the stromal demarcation line. The eyes that were treated according to the standard Dresden protocol showed a deeper demarcation line, expressed as a percentage of central corneal thickness, and a significant flattening of cornea postoperatively. Even taking this into account, the value of the stromal demarcation line depth as a procedure efficacy parameter is uncertain, as a significant association between the depth of the demarcation line and the reduction of Kmax was not found in any of the groups in the present study.

The limitations of the study are related to the low number of patients and to the absence of confocal microscopy and topographic morphological indices analysis. However, we do not consider that these factors influence the final results of the study.

We also did not measure the demarcation line at the cone, which could explain the lack of correlation between the demarcation line and the Kmax change, since the dioptric power on the most refractive meridian is often not located in the center of the keratoconic cornea, where the demarcation line was measured in our study.

Conclusions

Our study demonstrates that both the standard and accelerated crosslinking procedures provide improvements in visual, refractive and topographic parameters at the end of the 24 months follow-up. We have also identified a faster improvement in visual acuity after the accelerated protocol, which is an important advantage because it allows a faster recovery and earlier reintegration into employment.

As a practical consideration, we should take into account the advantages of the accelerated protocol, not only due to reduced treatment time and increased comfort for the patient, but also due to the faster recovery of visual acuity and the existence of a lower postoperative corneal "haze" on biomicroscopic examination compared to the Dresden standard protocol.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare no conflicts of interest.

Author's Contributions

All authors have equal contribution to and participation in this paper.

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