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Magdy Ezzat Khallaf
Department of Ophthalmology, Faculty of Medicine for boys, Al-Azhar University, Cairo, Egypt

Ehab Abd Elsamea Elshiekh
Department of Ophthalmology, Faculty of Medicine for boys, Al-Azhar University, Cairo, Egypt

Mohamed Amr Mohamed Elmadbouh
Department of Ophthalmology, Faculty of Medicine for boys, Al-Azhar University, Cairo, Egypt, elmadboh@gmail.com

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ORIGINAL ARTICLE

Corneal Stromal Depth of the Demarcation Line After Accelerated Versus Conventional Cross-Linking

Magdy Ezzat Khallaf, Ehab Abd Elsamea Elshiekh, Mohamed Amr Mohamed Elmadbouh*

Department of Ophthalmology, Faculty of Medicine for Boys, Al-Azhar University, Cairo, Egypt

Abstract

Background: **Keratoconus is one of ectatic corneal disease which is marked by central corneal scarring, apical corneal thinning, visual impairment, and corneal steepening. Its exact etiology is unknown.**

Aim and objectives: **To assess the depth of the corneal stromal demarcation line (A measure of the depth of the cross-linking therapy into the stroma is thought to exist in the transition zone between the treated anterior corneal stroma and the untreated posterior corneal stroma) [6] after conventional crosslinking versus accelerated crosslinking after one and three months postoperative.**

Subjects and methods: **In Cairo, Egypt's Kobri El Qobba Military Specialized Eye Hospital, this prospective, randomized, comparative, cross-sectional research was carried out. The 40 eyes with progressive keratoconus used in this research were split into two groups, each of which had 20 eyes: group 1: 20 eyes had accelerated cross-linking, and group 2: 20 eyes had conventional (standard) cross-linking.**

Results: **The demarcation line and K_{max} at 1-month and 3-months postoperative showed no statistically substantial variation between the two study groups.**

Conclusion: **A safe and effective therapy for advancing keratoconus is cross-linking. At all times, rapid CXL was equivalent to traditional CXL, and both types of CXL considerably increased CCT and demarcation line depth.**

Keywords: Conventional cross-linking, Corneal stromal depth, Demarcation line

1. Introduction

Keratoconus is one of ectatic corneal disease which is marked by central corneal scarring, apical corneal thinning, visual impairment, and corneal steepening.[1] Its exact etiology is unknown.[2]

New corneal collagen cross-links form as a result of the operation. The collagen fibrils shorten and thicken as a result of those cross-links, resulting in a stiffer, stronger cornea. Cross-linking of the cornea is an outpatient treatment.[3]

The typical cxl consists of 30 min of 3.0 mv/cm^2 UVA irradiation with a total surface dose of 5.4 j/cm^2.

The accelerated CXL has been criticized as a competing method for accelerating the treatment by increasing corneal irradiation and cutting the necessary light exposure time to a few minutes. **Mita *et al.*,**[4] which calls for a total surface dosage of 5.4 J/cm^2 after 10 min of (UVA) irradiation at 9.0 mv/cm^2.

An area of honeycomb-lacunar edema and keratocyte apoptosis may be detected in the anterior stroma zone with high reflectivity, which is the transition between cross-linked and non-cross-linked tissue, when using a slit light to view the tissue. Conofocal microscopy can also show this transition up to a depth of about 300 μm.[5]

The demarcation line (DL), a zone of transition between the cured anterior corneal stroma and the untreated posterior corneal stroma, is regarded to represent a gauge of the depth of cross-linking treatment into the stroma.[6]

And in this investigation, we used anterior segment optical coherence tomography (AS-OCT) to assess and evaluate the depth of the corneal

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* Corresponding author at: Resident of Ophthalmology at Kobri Al-koba Military Specialized Eye Centre, 11765, Egypt. Fax: +2 01092844720.
E-mail address: elmadboh@gmail.com (M.A.M. Elmadbouh).

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stromal DL after two distinct cross-linking techniques (standard and expedited).

The goal of the research was to compare the depth of the corneal stromal DL between accelerated and traditional crosslinking at one- and three-months following surgery.

2. Materials and methods

This research was conducted in the Kobri El Qobba Military Specialized Eye Hospital in Cairo, Egypt. It was prospective, randomized, comparative, and cross-sectional. (Jan 2022) to (June 2022).

2.1. Sampling method

Convenience sampling: As soon as they arrived at the ophthalmology department, the first patients with keratoconus signed an informed consent form.

2.2. Sample size

Forty progressing keratoconus eyes were split into two groups, each consisting of twenty eyes: Group 1: twenty eyes underwent accelerated cross linking (9 mw/cm^2/10 min) with epi_ off (epithelium off) after applying isotonic riboflavin for 30 min (one drop every 5 min). **Group 2:** twenty eyes underwent conventional (standard) cross linking (3 mw/cm^2/ 30 min) with epi_ off after applying isotonic riboflavin for 30 min (one drop every 5 min).

2.2.1. Inclusion criteria

Patients with age between 10 and 40 years, patients with thinnest location>400 μm, patients with Kmax≤60, patients with BCVA≥0.4 with snellen chart.

2.2.2. Exclusion criteria

Patients with age>40 or <10, people with a history of anterior section surgery, those who have ocular surface issues, those who have had herpetic keratitis in the past, those who have a current ophthalmic infection, and those who have any central or paracentral corneal scars.

2.3. Operational design

All patients had thorough eye exams, which included the following: History: Patients' demographic data (age, gender, invasion, and residence), any chronic diseases (such as diabetes and HTN), surgical ophthalmic history, uncorrected visual acuity (UCVA), corrected visual acuity (CDVA), slit-lamp evaluation, and fundus evaluation, as well as central corneal thickness at the thinnest point (t-CCT) by corneal topography, were recorded prior to surgery and at the conclusion of the first and third months following surgery. At the 1st and 3rd months' ends, all patients underwent AS-OCT postoperatively under identical lighting conditions.

2.3.1. Follow up

Best-corrected visual acuity (BCVA) USING LOGMAR chart. CCT after 1 month and 3 months postoperative and depth of DL of stroma using AS-OCT for each patient were examined 1 month, and 3 months postoperatively.

2.3.2. Technique: conventional corneal crosslinking

Includes a total surface dosage of 5.4 J/cm^2 for 30 min of UVA radiation at 3.0 mv/cm^2.

2.3.3. Accelerated corneal crosslinking

The same technique except irradiance of 9 mw/ cm^2 UVA for 10 min instead of 3 mw/cm^2.

2.3.4. Data analysis

The data collected in the study was processed, coded and entered into a personal computer. Microsoft SPSS (Statistical Package for Social Sciences) will be used for data analyzing. Data was illustrated in the form of tables and figures by EXCEL program.

2.3.5. Ethical considerations

Before starting the interviews, all research participants gave their informed permission. The patient has the freedom to join or leave the study at any moment. The patient had a right to complete disclosure of the trial. Only the researchers were given access to all patient data and identities in the trial.

3. Results

Table 1.

This study was conducted on 40 patients, there were 57.5% women and 42.5% men with median age of the study group was 25.35 ± 3.93 years ranged from 17 to 34 years (Tables 2–10).

Table 1. Demographic data for the study group.

	Mean/*N* (SD/%)	Median (IQR)	Range
Age	25.35 (3.93)	24 (23–28)	(17–34)
Sex			
Males	17 (42.5%)		
Females	23 (57.5%)		
Eye side			
OD	21 (52.5%)		
OS	19 (47.5%)		

Table 2. Visual acuity for the study group.

	Mean	SD	Median (IQR)	Range
UCVA Pre	0.5	0.2	0.5 (0.3–0.7)	(0.2–1)
BCVA Pre	0.7	0.2	0.7 (0.55–0.8)	(0.3–1)
BCVA Post	0.7	0.2	0.7 (0.6–0.85)	(0.3–1)

4. Discussion

A corneal illness called keratoconus is characterized by regional stromal thinning and subsequent ectasia.[7] Myopia and abnormal astigmatism grow over time as a consequence, which lowers quality of life and causes progressive vision loss.[8] It is one of the most frequent corneal conditions, affecting 1 in 375 people on average and affecting people of all races.[9]

In Cairo, Egypt's Kobri El Qobba Military Specialized Eye Hospital, this prospective, randomized, comparative, cross-sectional research was carried out. The 40 eyes with progressive keratoconus used in this research were split into two groups, each with 20 eyes: group 1: 20 eyes had accelerated cross-linking, and group 2: 20 eyes had conventional (standard) cross-linking.

Regarding the demographic data for the studied 40 patients, 42.5% were men and 57.5% were women with the average age of the study group was 25.35 ± 3.93 years ranging from 17 to 34 years. There were 52.5% had OD and 47.5% had OS. Comparison between the studied groups showed that Age, sex, and eye side did not substantially vary amongst the groups under study.

The present study was supported by **Kandel *et al.*,**[10] sought to contrast the effectiveness and safety of conventional (UV power: 3 mW/cm^2, period: 30 min) and accelerated (UV power: 9 mW/cm^2, period: 10 min) corneal crosslinking (CXL) for maintaining keratoconus. 684 eyes (555 patients; median age, 25.0 7.9 years; women, 30.6%) having epithelium-off CXL for keratoconus were recruited in the research from 24 foreign locations. 418 eyes (327 patients) underwent accelerated CXL, whereas 266 eyes (228 patients) underwent normal CXL. Age, sex, visual acuity, Kmax, K2, and MCT were all found to be comparable amongst the groups at baseline (preoperative; all $P > 0.05$) in the research.

Table 3. CCT at TL for the study group.

	Mean	SD	Median (IQR)	Range
CCT at TL preoperative (Micron)	464.5	40.8	456 (444.5–483)	(417–584)
CCT at TL after 1 month (Micron)	448.1	44.9	451 (419–470)	(370–568)
CCT at TL after 3 month (Micron)	450.9	44.3	450 (425–471.5)	(375–568)

Table 4. Demarcation line for the study group.

	Mean	SD	Median (IQR)	Range
Demarcation line after 1 month (Micron)	348.0	42.2	340 (327–376)	(200–405)
Demarcation line after 3 month (Micron)	356.8	43.9	360.5 (340–387.5)	(200–408)
K max (Diopter)	49.9	4.7	49.8 (47.15–51.95)	(40.5–62.4)

Also, in agreement with the current study **Eissa & Yassin,**[11] compared the results of two distinct cross-linking (CXL) procedures in keratoconus eyes. The research included 68 eyes from 34 children, aged 9 to 16, who received CXL and were split into two groups. After 30 min of exposure to UVA radiation at a dose of 3 mW/cm^2, Group A reflects standard riboflavin-UVA-induced CXL. Group B denotes enhanced cross-linking under continuous UVA irradiation for five minutes at an intensity of 18 mW/cm^2. According to the research, there was no substantial variation in the investigated groups' ages.

As well, **Woo *et al.*,**[12] the visual, refractive, topography, and biomechanical outcomes in patients with advanced keratoconus treated with either conventional or rapid crosslinking at a one-year follow-up. Both traditional cross linking (CXL; 3 mW/cm^2 for 30 min) and accelerated cross linking (KXL; 30 mW/cm^2 for 4 min) were administered to 76 individuals with progressing keratoconus. According to the research, there were no discernible differences in the investigated groups' ages or sexes.

In line with the current study **Nicula *et al.*,**[13] Compare the efficacy and safety of epi-off traditional and accelerated CXL for the treatment of progressive keratoconus in individuals up to 4 years following therapy.37 eyes (S-CXL group) underwent conventional (normal) CXL epi-off procedure, while 27 eyes had accelerated CXL (A-CXL group). According to the research, there were no discernible differences in the investigated groups' ages or sexes.

In the present study regarding the Visual acuity between techniques of CXL, our results showed that Regarding preoperative UCVA and BCVA as well as postoperative BCVA, there was no statistically substantial variation between the analyzed groups.

In agreement with the current study **Woo *et al.*,**[12] showed that Regarding preoperative UCVA and BCVA as well as postoperative BCVA, there was no statistically substantial variation between the analyzed groups.

Similarly, **Nicula *et al.*,**[13] showed that Regarding preoperative UCVA and BCVA as well as postoperative BCVA, there was no statistically substantial variation between the analyzed groups.

Table 5. Visual acuity between techniques of CXL.

	Group (technique of CXL)		Student *t*-test		
	Conventional	Accelerated			
	Mean ± SD	Mean ± SD	t	*P* Value	Sig.
UCVA PRE	0.53 ± 0.27	0.53 ± 0.2	−0.066	0.948	NS
BCVA PRE	0.68 ± 0.19	0.65 ± 0.21	0.476	0.637	NS
BCVA POST	0.7 ± 0.17	0.68 ± 0.23	0.311	0.757	NS

However, **Eissa & Yassin,**[11] showed that Preoperative UCVA and CDVA did not substantially vary between the examined groups, however postoperative UCVA and CDVA in the ACXL group did differ statistically substantially ($P < 0.05$) from group A at all time periods.

In the current work regarding the CCT at TL between techniques of CXL, we found that the Preoperative CCT, 1- and 3-month postoperative CCT results of the examined groups did not substantially vary from one another.

In agreement with the present study **Eissa & Yassin,**[11] showed that Regarding preoperative CCT and 12-, 24-, and 36-month postoperative CCT, there was no substantial variation between the examined groups.

As well, in agreement with our results **Ng *et al.*,**[14] showed that CCT was comparable between the studied groups pre and postoperatively.

The recent meta-analysis by **Li *et al.*,**[15] showed that Central corneal thickness (CCT): The declining quantities of CCT in both groups were no substantial variation at short-term (6 and 12 months) and long-term (24 and 36 months) follow-ups ($P = 0.27$, 0.37, 0.62, and 0.93, respectively).

Also, in agreement with our results the meta-analysis by **Kobashi & Tsubota,**[16] planned to synthesize randomized controlled studies utilizing a meta-analysis in order to evaluate the clinical outcomes of ACXL to SCXL in progressive keratoconus. According to the research, identical outcomes were discovered when analyzing the CCT. After a year of follow-up, there was no variation between the two groups ($P = 0.06$; WMD = 7.41; 95% CI, 20.29−15.11).

In agreement with our results **Dervenis *et al.*,**[17] compared the thickness of the DL that developed in the cornea after using the conventional Dresden technique and rapid, pulsed, epithelium-off CXL, and discovered that the following surgery DL was deeper in the conventional group than the accelerated group, but without statistical significance. Kmax was also found to not substantially distinguish between the investigated groups.

Table 7. Best-corrected visual acuity pre and post within accelerated group.

Accelerated	Pre	Post	Paired *t*-test		
	Mean ± SD	Mean ± SD	t	*P* Value	Sig.
BCVA	0.65 ± 0.21	0.68 ± 0.23	−1.552	0.137	NS

In contrast to our results, **Eissa & Yassin,**[11] reported that Pentacam measurements of Kmax at the last follow-up visit 36 months after CXL revealed a statistically substantial variation ($P < 0.05$) between the two groups, with the ACXL group having a statistically substantial decline in steepest K. The statistically substantial variation in baseline narrowest corneal pachymetry between the two groups may be to blame for this.

The present study was supported by **Kandel *et al.*,**[10] who reported that The median Kmax and K2 decreased in both CXL groups, and habitual visual acuity increased in both. Additionally, they found that the MCT significantly decreased in the first three months, more so in the regular CXL group, and that the corneal thickness thereafter steadily rose.

As well, **Ng *et al.*,**[14] reported that The CDVA considerably increased in the traditional CXL group ($P = 0.021$). Kmax and Kmedian both showed a substantial decline ($P = 0.003$ and $P = 0.002$, respectively). No substantial increases in CDVA ($P = 0.395$), Kmax ($P = 0.388$), or Kmedian ($P = 0.952$) were seen postoperatively in the accelerated CXL group.

In addition, **Iqbal *et al.*,**[18] reported that At all postoperative evaluations, the standard group showed UDVA and CDVA improvements that were statistically substantial ($P < 0.0001$). A considerable proportion of eyes, 64 eyes (70.3%), had a decrease in Kmax>1 D ($P < 0.0001$), while 27 (29.7%) demonstrated essentially stable Kmax during the course of the 24-month follow-up. At the conclusion of the follow-up period, the corneal thickness was substantially decreased to 8.9 14.95 lm ($P = 0.003$). At months 6 ($P = 0.01$ and $P = 0.03$,

Table 6. Thinnest location pre and postoperative 3 months within conventional group.

Conventional	Pre	After 3 months	Paired *t*-test		
	Mean ± SD	Mean ± SD	t	*P* Value	Sig.
CCT at TL	475.3 ± 45.4	442.9 ± 53.48	4.168	0.001	S

Table 8. Thinnest location pre and postoperative 3 months within accelerated group.

Accelerated	Pre	After 3 months	Paired *t*-test		
	Mean ± SD	Mean ± SD	t	*P* Value	Sig.
CCT at TL	453.7 ± 33.35	458.9 ± 32.09	−9.363	<0.001	S

Table 9. CCT at TL between techniques of CXL.

	Group (technique of CXL)		Student *t*-test		
	Conventional	Accelerated			
	Mean ± SD	Mean ± SD	t	*P* Value	Sig.
CCT at TL preoperative (Micron)	475.3 ± 45.4	453.7 ± 33.35	1.715	0.095	NS
CCT at TL after 1 month (Micron)	435.8 ± 52.86	460.3 ± 32.06	−1.772	0.086	NS
CCT at TL after 3 month (Micron)	442.9 ± 53.48	458.9 ± 32.09	−1.147	0.260	NS

Table 10. Demarcation line and K max between techniques of CXL.

	Group (technique of CXL)		Student *t*-test		
	Conventional	Accelerated			
	Mean ± SD	Mean ± SD	t	*P* Value	Sig.
Demarcation line after 1 month (Micron)	358.95 ± 37.25	337.05 ± 44.84	1.680	0.101	NS
Demarcation line after 3 month (Micron)	366.8 ± 37.75	346.85 ± 48.1	1.459	0.153	NS
K max (Diopter)	50.8 ± 5.2	48.98 ± 4.16	1.218	0.231	NS

respectively) and 12 ($P = 0.007$ and $P = 0.01$), the mean UDVA and CDVA in the accelerated group showed a substantial increase, but by month 24 ($P = 0.009$ and $P = 0.01$), there had been a substantial regression. However, despite substantial increases at postoperative months 6 and 12 ($P = 0.03$ and $P = 0.01$, respectively), the ultimate increase at 2 years was not substantial ($P = 1.00$). The median postoperative Kmax likewise remained unchanged. At month 12, 47 eyes (51.1%) in this group improved in Kmax readings up to 1 D, but only 28 eyes (30.4%) continued to do so at month 24. At the conclusion of the follow-up period, the postoperative changes in corneal thickness were not substantial ($P = 1.00$).

4.1. Conclusion

Our investigation has added further support to the argument that cross-linking is a secure and effective therapy for progressive keratoconus. Both conventional and accelerated CXL considerably enhance CCT and Demarcation line depth, and accelerated CXL was equivalent to conventional CXL at all points in time. To verify the long-term safety and effectiveness of accelerated crosslinking, larger prospective randomized controlled studies with extended follow-up are required.

Authorship

All authors have a substantial contribution to the article.

Conflicts of interest

There are no conflicts of interest. The authors have no financial interest to declare in relation to the content of this article.

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