• Clinical Research •

Accelerated versus standard corneal cross linking in the treatment of ectasia post refractive surgery and penetrating keratoplasty: a medium term randomized trial

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Abstract

● AIM: To compare the clinical outcomes of the standard corneal cross linking (CXL) and the accelerated CXL in patients with progressive corneal ectasia post refractive surgery and penetrating keratoplasty.

● METHODS: Totally 120 eyes of 83 patients scheduled to receive either standard CXL (3 mW/cm^2 for a period of 30min) or accelerated CXL (18 mW/cm^2 for a period of 5min). The main outcomes for comparison were the change in: maximum-K reading (K-max), manifest refractive spherical equivalent (SE), central corneal thickness (CCT), and the best corrected distance visual acuity (CDVA).

● RESULTS: One hundred and eleven eyes completed the study. The main outcome measurement was the K-max reading. Both group showed significant improvement in the value postoperatively at 6 and 12mo. The mean change in the standard group was 1.21±0.11 D and in the accelerated group was 0.90±0.05 D at the end of 12mo postoperatively, with no statistically significant difference between the 2 groups. Similarly, CDVA improved significantly from their preoperative value in the standard group by 2.98±0.11 letters, and in the accelerated group by 2.20±0.06 letters, with no statistically significant difference between the two groups. Both of the SE, and CCT showed no statistically significant difference at the end of follow up period in each group.

● CONCLUSION: Both standard CXL and accelerated CXL are safe and effective treatment in halting ectasia after corneal refractive surgery. The accelerated CXL results are comparable to the standard CXL with short time exposure of the cornea to ultraviolet irradiation, leading to reduced operation time, reduced operative ocular discomfort, and corneal haze.

● KEYWORDS: corneal cross linking; accelerated; refractive surgery; penetrating keratoplasty; corneal ectasia

INTRODUCTION

Corneal cross-linking (CXL) has become a widely accepted treatment to halt the progression of corneal ectatic diseases especially after the United States Food and Drug Administration approval in 2016[1]. The standard Dresden CXL protocol (with a continuous irradiation of 3 mW/cm^2 for 30min) has been shown to be effective in halting the progression of ectasia. However, the procedure is time consuming lasting for almost an hour which results in long operation time, patient discomfort, and postoperative ocular pain[2-6]. Prolonged exposure to ultraviolet (UV) rays may increase the risk of complications such as sub epithelial haze, corneal infiltrate, and infectious keratitis[7-11]. Hence, the use of radiation of higher intensity and shorter duration (accelerated CXL) was introduced[12]. Variable accelerated CXL protocols were prescribed in the literature. The most common ones involved UVA irradiation of 9 mW/cm^2 for 10min, and 18 mW/cm^2 for 5min[13].

Pooled data from several comparative studies has been discussed in a recent Meta-analysis. It was found that the reduction in the maximum keratometry value (K-max) as well as in the spherical equivalent (SE) were significantly greater in standard than in accelerated protocol. However, comparative outcomes of best corrected distant visual acuity (BCVA), central corneal thickness (CCT) and endothelial cell density (ECD) indicated no significant differences between the two procedures[6,14-27].

The aim of this study was to compare the clinical outcomes of the standard CXL and the accelerated CXL in patients with progressive corneal ectasia post refractive surgery or penetrating keratoplasty.

SUBJECTS AND METHODS

Ethical Approval This prospective, randomized study

recruited patients from Menoufia University Hospitals and its satellite clinics (between January 2016 and June 2017). The study protocol was approved by the Ethical Committee of Menoufia Medical School (adhering to the tenets of the Declaration of Helsinki). Trial Registration Number: NCT03791684. The study protocol was explained to the patients and all patients provided a written informed consent.

The data used to support the findings of this study are restricted by the Ophthalmic Ethics Committee at Menoufia University Hospital, in order to protect patient privacy. Data are available from Mr Hany A. Khairy (khairyhany@hotmail.com), for researchers who meet the criteria for access to confidential data.

Inclusion and Exclusion Criteria Eligible patients were adults aged above 18y. They had been diagnosed clinically with progressive corneal ectasia following refractive surgery procedure [laser *in situ* keratomileusis (LASIK), photorefractive keratectomy (PRK), ReLex small incision lenticule extraction (SMILE)], or penetrating keratoplasty with CCT above 400 μm and the K-max>47.00 D (Table 1).

The diagnosis of recurrent ectasia was based on clinical findings, such as poor BCVA, pachymetric corneal thinning, Vogt striae, visible anterior bulge, and topographic irregular astigmatism.

Evidence of progression included: increase in keratometry readings (K-max) of greater than 1.00 D, increase in mean spherical refractive equivalent by 0.50 D, increase in astigmatism by 1.00 D, or a decrease of patient's visual acuity by 5 or more letters over a period of 6mo. Enrolled patients had the ability to understand and the willingness to follow study instructions and were likely able to complete all required visits.

The exclusion criteria involved: history of herpetic ocular diseases (including herpes simplex virus and varicella zoster virus) in the study eye; active or recurrent ocular disease in either eye (*e.g.*, uveitis, chronic moderate to severe blepharitis or severe dry eye) or sight-threatening diseases (*e.g.*, previous retinal or optic nerve diseases) that would interfere with the interpretation of the study data.

Data collected from patients included age, previous ocular and medical history, medications, and family history of ocular diseases. Patients had baseline assessment at their preoperative visit, including: BCVA in letters, refraction with auto-refractometer, intraocular pressure (IOP) measurement with applanation tonometry, dilated fundus examination with +78 D volk lens, and corneal tomography by Pentacam® (Oculus, Germany).

The randomization process used four opaque envelopes in two containers. One contained for standard CXL, and for accelerated CXL, and the other contained the name of two patients listed for CXL on that day. The two patients were randomized to one of the procedures by asking an independent person to choose one envelope from each container. For patients who were listed for both eyes, envelopes had right and left instead.

Surgical Procedure Patients were draped, after topical anesthesia (Benoxinate Hydrochloride 0.4% eye drops) application. After the debridement of the corneal surface (9 mm), riboflavin (Hypotonic riboflavin 0.1%, Mediocross TE®, Peschke Meditrade GmbH, Switzerland) every 2min for 10min before the start of irradiation and then every 5min during the irradiation time. Irradiation was started after the yellow flare of riboflavin was seen in the anterior chamber with slit-lamp examination. In the standard CXL group UVA radiation of 365 nm wavelength (CCL-365 vario, Peschke Meditrade GmbH, Switzerland), and an irradiance of 3 mW/cm^2 (spot size 7 mm), at a distance of 45 mm from the cornea, was applied for a period of 30min, delivering a dose of 5.4 J/cm^2. While in the accelerated CXL group, an irradiance of 18 mW/cm^2 was applied for 5min delivering the same dose as the standard group.

Postoperatively, Ofloxacin 0.3% drops were instilled as a prophylaxis and an eye bandage contact lens was left for 72h. Patients were asked to use dexamethasone 0.1% eye drops, and ofloxacin 0.3% eye drops four times daily for one week postoperatively and then reduce it to twice a day for another week.

Outcomes The main outcomes for comparison were the change in: K-max, manifest refractive SE, CCT, and the BCVA. Patients were followed up clinically at 1d, 1wk, 1, 6, and 12mo postoperatively but the topographic measurements were done only at the 6 and 12mo visits.

Statistical analysis was conducted using the SPSS (Version 15, 2006) for Windows statistical package. Data were presented as mean±SD. Results were analyzed using Mann-Whitney-Wilcoxon test. P<0.05 was considered statistically significant.

RESULTS

One hundred and twenty eyes of 83 patients were included in the study; 42 males and 36 females. Five patients (9 eyes) did not continue the follow up period and were excluded from the study. One hundred and eleven eyes were enrolled; 54 eyes had the standard CXL, and 57 had the accelerated CXL. Most eyes with post refractive surgery ectasia had LASIK, and the most common indication for penetrating keratoplasty was keratoconus (Table 1). Thirty three patients had both eyes treated; all of them had ectasia post refractive surgery. Twenty one patients had one eye treated for post refractive surgery ectasia, and 24 patients (24 eyes) had treatment for post penetrating keratoplasty ectasia. There was no statistically significant difference between the 2 groups in the K-max measurement, BCVA, manifest SE refraction, or CCT (Table 2).

Table 1 The distribution of surgery type in each group

Patients distribution	Type of refractive surgery				Indication for penetrating keratoplasty	
	LASIK	Femto-LASIK	SMILE	PRK	Keratokonus	Other
Accelerated CXL	36	5	2	2	9	3
Standard CXL	34	5	1	2	10	2

CXL: Corneal cross linking; LASIK: Laser *in situ* keratomileusis; SMILE: Small incision lenticule extraction; PRK: Photorefractive keratectomy.

Table 2 Comparison of the outcome parameters in each group and between the two groups mean±SD

Parameters	The standard CXL group			The accelerated CXL group			^1P	^2P
	Preoperatively	6mo postoperatively	12mo postoperatively	Preoperatively	6mo postoperatively	12mo postoperatively		
K-max (D)	52.19±1.88	51.10±1.78[a]	50.98±1.77[a]	52.17±1.81	51.41±1.74[a]	51.27±1.76[a]	0.36	0.38
BCVA	37.56±5.08	39.78±4.64[a]	40.54±4.97[a]	37.58±5.11	39.47±4.94[a]	39.78±5.17[a]	0.74	0.37
SE (D)	-3.55±1.29	-3.18±1.21[a]	-3.12±1.23[a]	-3.55±1.32	-3.14±1.37[a]	-3.15±1.27[a]	0.97	0.97
CCT (μm)	439.11±33.8	434.28±33.57[a]	432.57±33.54[a]	439.67±36.5	433.14±37.4[a]	433±35.9[a]	0.87	0.92

CXL: Corneal cross linking; K-max: Maximum keratometry value; BCVA: Best corrected distant visual acuity; SE: Spherical equivalent; CCT: Central corneal thickness. [a]P=0.001 *vs* preoperatively; [1]P: Comparing the parameters 6mo postoperatively between the two group; [2]P: Comparing the parameters 12mo postoperatively between the two group.

The main outcome measurement was the K-max reading. Both group showed significant improvement in its value postoperatively at 6 and 12mo. The mean change in the standard group was 1.21±0.11 D and in the accelerated group was 0.90±0.05 D at the end of 12 months postoperatively. There was no statistically significant difference between the 2 groups at all points of follow up (Table 2). There was no deterioration of BCVA in either group. Both groups showed significant improvement in the BCVA from their preoperative value. In the standard group they improved by 2.98±0.11 letters at 12mo postoperatively. In the accelerated group they improved by at 2.20±0.06 letters at 12mo postoperatively. There was no statistically significant difference between the 2 groups at all points of follow up (Table 2). The mean SE of manifest refraction showed no statistical difference at the end of follow up period in each group, with no statistical significant difference between the 2 groups at all points of follow up. The CCT showed no statistical difference at the end of follow up period in each group. There was no statistically significant difference between the 2 groups at all points of follow up.

Most of patients K-max improved, 80.5% (46/57) in the accelerated group, and 75.8% (41/54) in the standard group), by up to 2.00 D. There was a recorded progression of ectasia following treatment in 10.5% (6/57) of patients in the accelerated group, and in 9.2% (5/54) of patients in the standard group. However, the progression never exceeded 1.0 D in either group (Figure 1).

The success rate was similar in postrefractive surgery and post penetrating keratoplasty cases with progression of ectasia of around 10% in each group. There were no recorded serious complications as corneal infiltrate, stromal keratitis or corneal decompensation, postoperatively. Corneal haze (mild) was

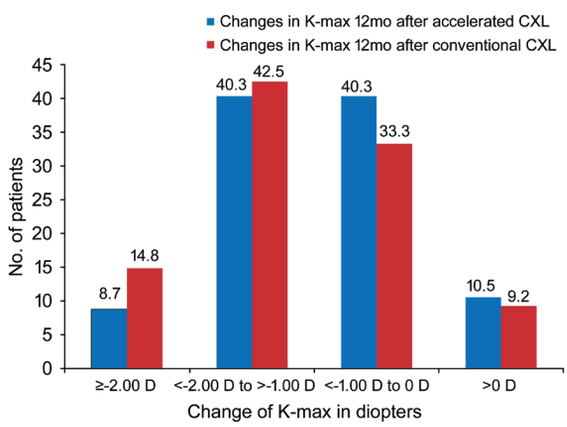

Figure 1 Distribution of the changes of the maximum keratometry (K-max) value between the two groups.

reported in 5 eyes in the standard group and 2 eyes in the accelerated group. All cases of corneal haze resolved at the 6mo visit apart from one case post refractive ectasia which resolved at the end of follow up period.

DISCUSSION

The risk factors and the course of development of corneal ectasia after corneal refractive procedure are still not well understood. However, similar to keratoconus, successful management of ectasia after refractive surgery particularly in cases with steep cornea includes early detection before the symptoms become more pronounced, careful monitoring, and prompt CXL treatment in progressive cases[28].

The efficacy of standard CXL in the prevention of keratoconus progression has been established now according to different clinical trials. However, studies about CXL for post refractive surgery ectasia were rare until Hersh *et al*[27] published his US phase 3 multicenter trial. The results of the trial showed statistically significant difference in the K-max value between the treatment group (decreased by 0.7 D) and the sham

group (progression of 0.6 D) after 12mo of follow up. They concluded that progressive ectasia has stabilized with some degree of improvement in CXL treated patients, while the control group continue to progress over the follow up period.

Wan *et al*[29] in a recent Meta-analysis reviewed the safety and stability of CXL for the treatment of post LASIK ectasia. In the 7 studies analyzed, the topographic parameters of the treated patients did not improve as reported in studies involving keratoconic eyes but it was successful in halting its progression. This indicated that post refractive surgery corneas treatment with CXL was less effective compared with keratoconic corneas, possibly due to of the post refractive surgery corneas flap formation and tissue ablation[2,30-35].

The standard Dresden CXL protocol used irradiation of 3 mW/cm^2 for 30min. However, the procedure is time consuming, with long exposure of the cornea to ultraviolet irradiation, leading to postoperative ocular pain, and corneal haze. Several modifications have been introduced to reduce these drawbacks, including: trans-epithelial CXL, using radiation of high intensity and shorter duration (accelerated CXL)[2], the use of accelerated epithelium on CXL, and the use of pulsed-light accelerated CXL[2].

There is no uniform protocol for the Accelerated CXL, and the evidences of its efficacy are not well understood. Accelerated CXL in the treatment of keratokonus has been compared to standard CXL in different clinical trials. In a recent Meta-analysis by Liu *et al*[6], they reported that the K-max reduction (pooled mean difference was 0.49) was significantly greater in the standard group. In addition, spherical equivalent decreased significantly (mean difference was 0.62) for the standard when compared to the accelerated group. However, corrected distant visual acuity, CCT, ECD indicated no significant difference between the two CXL regimes.

K-max remained the most important factor to evaluate the efficacy of treatment in post refractive surgery ectasia. In this study, the mean change in the standard group was 1.21±0.11 D and in the accelerated group was 0.90±0.05 D at the end of 12mo postoperatively. There was no statistically significant difference between the 2 groups at all points of follow up. Hersh *et al*[27] in their randomized controlled trial reported significant decrease in the mean K-max value (0.7±2.1 D) at the end of 12mo postoperatively. In 76 treated eyes, the K-max decreased by 2.00 D or more in 14 eyes (18%), and remained within 2 D in 59 eyes (78%). Despite of the initial increase of mean K-max by 1.0 D at month 1, it showed progressive decrease from 1.1 D between months 1 and 3, to 0.2 D between months 6 and 12.

Richoz *et al*[33] reported the long term effect of standard CXL in corneal ectasia after LASIK (23 eyes) and PRK (3 eyes). At the end of 2y follow up, the mean K-max after CXL (50.9±4.9 D) was significantly lower than the pretreatment measures (52.8±5.0 D). Other studies have reported similar outcomes but most of them were non-randomized with a small number of patients (21-35 patients)[30-35].

Marino *et al*[34] studied the effect of accelerated CXL on 40 eyes of 24 patients with post LASIK ectasia. Patients were treated with irradiation of 9 mW/cm^2. At the end of the 24mo follow up period, none of the studied eyes showed signs of progression, with more than 70% of patients with stable or better vision. Despite the long term follow up the stud was not controlled or randomized. The topographic results of the study by Choi *et al*[35] showed that despite the use of high irradiance exposure (30 mW/cm^2 for 3min and 40s), the effect of corneal flattening was less in the transepithelial accelerated CXL compared to the standard CXL. A previous study that compared 4 different protocols, including conventional (3 mW/cm^2 for 30min) and modified (9 mW/cm^2 for 10min, 18 mW/cm^2 for 5min, and 30 mW/cm^2 for 3min) methods, showed that the flattening effect of the steep and flat keratometry was reduced with higher irradiation and less time[25]. Aixnjueluo *et al*[36] in his study on Japanese patients with progressive keratoconus, reported statistically significant improvements in K-max and BCVA at the end one year post trans-epithelial accelerated CXL.

There is an agreement between investigators that the CXL treatment in post LASIK ectasia is successful in improving or at least stabilizing visual acuity. The improvement of the SE was statistically significant (decrease by 0.5 D) in the US multicenter trial[27] CXL treated group. In the crosslinking treatment group, there was a significant improvement of 5.0 letters of visual acuity at the end of follow up. In the control group, there was a loss of 0.3 letters. Hafezi *et al*[7] reported that CDVA increased by one more lines in 90% of the treated patients. Morino *et al*[34] in his study on accelerated CXL, reported that BCVA, uncorrected distance visual acuity was stable or improved in all patients after 2y, and Richoz *et al*[33] in their study on 26 eyes who has the standard CXL for post LASIK and PRK ectasia, reported that BCVA improved to a mean of 0.3 logMAR unit in 19 cases and remained stable in 7 patients.

The most common complications recorded by this procedure are ocular pain caused by epithelium stripping and long exposure to UV radiation, sub-epithelial haze, sterile infiltration, corneal decompensation and infectious keratitis. In the US trial[27] out of the 76 treated eyes, 5 had persistent corneal haze and one had corneal scar at the end of the 12mo period. There were no recorded serious complications in our study as corneal infiltrate, stromal keratitis or corneal decompensation, postoperatively. However, corneal haze was reported in 5 eyes in the standard group and 2 eyes in the accelerated group. All cases of corneal haze resolved at the end of follow up period.

To the best of our knowledge, there is no published studies comparing the standard and the accelerated technique in post refractive surgery or penetrating keratoplasty patient diagnosed with corneal ectasia. One advantage of this study was the good sample size despite the strict inclusion criteria. In contrast to the US trial by Hersh *et al*[27] who set the corneal thickness at 300 μm, we included only patients with CCT above 400 μm, as the local ethical guidelines do not allow the use of CXL in thickness less than 400 μm. In the US trial, they used hypotonic riboflavin (0.1% riboflavin, no dextran), 1 drop every 10s for 2min sessions, in cases with pachymetry less than 400 μm. It is not clear whether this modification had an effect on the results of treatment or not. Although they have not reported any case of corneal decompensation, there were no evidences of its effect on the ECD. Limitation of this study was the lack of studying the endothelial cell count by specular microscopy or the demarcation line by OCT. However, it is well established that the use of CXL is very unlikely to cause damage in corneas thicker than 400 μm.

The interpretation of this study results showed that both standard CXL and accelerated CXL are effective treatment in halting ectasia after corneal refractive surgery. The accelerated CXL results are comparable to the standard CXL with short time exposure of the cornea to UV irradiation and reduced operation time.

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