Standard cross-linking versus photorefractive keratectomy combined with accelerated cross-linking for keratoconus management: a comparative study

Mohammed Iqbal,1 Ahmed Elmassry,2 Ahmed Tawfik,3 Mervat Elgharieb,4 Khaled Nagy,5 Ashraf Soliman,5 Hisham Saad,5 Tarek Tawfik,7 Osama Ali,1 Ahmed Gad,1 Islam El Saman,1 Alaa Radwan,8 Hosam Elzembely,9 Amin Abou Ali1 and Omar Fawzy10

1Department of Ophthalmology, Faculty of Medicine, Sohag University, Sohag, Egypt
2Department of Ophthalmology, Faculty of Medicine, Alexandria University, Alexandria, Egypt
3Department of Ophthalmology, Faculty of Medicine, Zagazig University, Zagazig, Egypt
4Department of Ophthalmology, Faculty of Medicine, Suez Canal University, Suez, Egypt
5Department of Ophthalmology, Faculty of Medicine, Tanta University, Tanta, Egypt
6Department of Ophthalmology, Faculty of Medicine, Ain Shams University, Cairo, Egypt
7Department of Ophthalmology, Faculty of Medicine, Benha University, Benha, Egypt
8Department of Ophthalmology, International Eye Clinic, Cotoba EYE Center, Cairo, Egypt
9Department of Ophthalmology, Faculty of Medicine, Minia University, Minia, Egypt
10Department of Ophthalmology, Sohag Eye Hospital, Sohag, Egypt

ABSTRACT.
Purpose: To compare the safety and efficacy of standard 30 min epithelium-off cross-linking (CXL) versus photorefractive keratectomy (PRK) combined with accelerated epithelium-off cross-linking (AXL) for the treatment of progressive keratoconus (CXL-Plus).

Methods: This study was a prospective multicentre comparative clinical study. A total of 125 eyes of 75 patients with grade 1 keratoconus and documented progression were divided into two groups. Group A included 58 eyes treated with standard CXL. Group B included 67 eyes treated with combined PRK and AXL. The recorded data included UDVA, CDVA, subjective and objective refraction, keratometry and pachymetry using corneal topographies preoperatively and postoperatively at 3, 6, 12 and 24 months of follow-up.

Results: In group A, at 24 months of UDVA and CDVA were improved from 1.12±0.38 and 0.58±0.42 to 0.66±0.20 and 0.20±0.12 (LogMAR±SD). The spherical equivalent was reduced from 4.03±1.18 to 1.78±1.04 D. The cylinder reduction was 0.32±0.19 D. In group B, at 24 months of UDVA and CDVA were improved from 1.26±0.52 and 0.68±0.36 to 0.58±0.28 and 0.20±0.16 (LogMAR±SD). The spherical equivalent was reduced from 4.23±0.95 to 1.92±0.74 D. The cylinder reduction was ±1.76 D.

Conclusion: Surprisingly, standard CXL showed close results to CXL-Plus at the 24th follow-up month. Standard CXL acted as a stabilizing procedure associated with a late myopic component reduction. CXL-Plus acted as a refractive and stabilizing procedure with an early effect on both the myopic and the astigmatic component but no later improvements. Standard CXL seems to be more powerful than AXL in its long-term effect. Therefore, in the future, we want to test the combination of PRK with standard CXL.

Key words: CXL-Plus – ectasia – epithelium-off CXL – keratoconus – PRK – standard CXL

Introduction
Fifteen years ago, standard corneal cross-linking (CXL) was introduced as a successful treatment for the stop of corneal ectasia in progressive keratoconus by Wollensak et al. (2003) in Dresden, Germany. In the meantime, accelerated epithelium-off cross-linking (AXL) to reduce the treatment time has been developed and its combination with refractive procedures such as PRK and intracorneal ring segments (ICRS) to also reduce the refractive error of keratoconus has been promoted (Kanellopoulos & Binder 2007; Kanellopoulos 2009; Kanellopoulos & Asimellis 2014; Kymionis et al. 2014; Saleem et al. 2018). This combination is sometimes called cross-linking plus (CXL-Plus).

Over the last decade, the so-called Athens Protocol was used by many authors and surgeons as a documented protocol to treat progressive keratoconus. The Athens Protocol includes the use of both wavefront topography-guided PRK with epithelium-off AXL in the same session as a both therapeutic and refractive treatment of keratoconus. The protocol allows a maximum ablation of 50 μm of the stromal
corneal tissue to correct up to 2.5 D of the spherical equivalent. Furthermore, it was designed for the correction of anterior surface irregularities thus improving the overall postoperative refractive and topographic status. Cross-linking plus (CXL-Plus) describes the combination of CXL and a refractive procedure promoted (Kanellopoulos & Binder 2007; Kanellopoulos 2009; Kanellopoulos & Asimellis 2014).

The main purpose of the present study was to compare the efficacy in terms of refractive and visual outcomes of the standard CXL treatment of progressive keratoconus versus photorefractive keratectomy (PRK) combined with accelerated epithelium-off cross-linking (AXL).

**Patients and methods**

**Patients**

This study was designed as a prospective comparative multicenter clinical study. This study was carried out in five universities in Egypt including Sohag, Alexandria, Zagazig, Suez Canal and Ain Shams universities. This study gained the approval of the high ethical committee in Sohag University Hospital and followed the rules of the Declaration of Helsinki. The nature of the KC disease, the proposed surgical treatment and the possible postoperative complications were fully explained to all patients preoperatively. Furthermore, all patients signed written consents before surgery approving the surgical procedures and approving the use of their medical data in scientific research work. Only cases with documented keratoconus progression were treated (Galvis et al. 2017).

This study included 125 eyes of 75 patients (32 males and 43 females). All eyes included in this study had fulfilled the following inclusion criteria: all eyes with grade 1 (early KC) according to Amsler–Krumeich classification (the central corneal thickness at the thinnest location >400 μm, the spherical equivalent including both myopic and astigmatic KC components <5 D while the mean k readings <48 D), all eyes had documented active pathological progression of KC (by documenting 2 or more specific parameters including increase in the k_{max} more than 1 D, increase in the SE more than 0.5 D, decrease in the corneal thickness more than 2% and increase in the k readings on posterior corneal surface), all eyes were operated by one of the authors (M.I.) and completed 24 months of follow-up period.

**Preoperative and postoperative assessment**

The eyes included in this study were divided into two groups. Group A included 58 eyes of 33 patients (46.4% of the study eyes), and they were subjected to standard 30 min epithelium-off CXL (Wollensak et al. 2003). The age of the patients in group A ranged from 14 years to 27 years old with a mean age of 20.65 ± 6.24 (mean ± SD).

Group B included 67 eyes of 42 patients (53.6% of the study eyes), and they were subjected to CXL-Plus combining standard PRK with accelerated epithelium-off CXL (AXL). The age of the patients in group B ranged from 14 years to 28 years old with a mean age of 21.37 ± 6.92 (mean ± SD).

The main objectives of this study were to compare between the results of the standard CXL alone (‘Standard Dresden Protocol’) versus the results of combined standard PRK with AXL (‘Athens Protocol’). All keratoconic eyes were examined preoperatively and postoperatively to collect the preoperative data that recorded the visual status including both uncorrected distance visual acuity (UDVA) and corrected distance visual acuity (CDVA), refractive status mainly the subjective refraction including both myopic and astigmatic components and spherical equivalent, topographic status including central corneal thickness at the thinnest location, k readings on the anterior and posterior corneal surfaces and back surface elevation. The investigative device for the topographic and tomographic parameters was a CSO SIRIUS Topographer (CSO, Firenze, Italy).

**Surgical procedure**

The surgical devices used in this study included the Opto XLink-corneal cross-linking System (Opto Global Pty Ltd., Adelaide, Australia), the KXL Crosslinking System (Avedro Inc., Burlington, MA, USA) and the excimer laser VISX STAR S4 IR™ (Abbott Laboratories, Lake Bluff, IL, USA).

**Group A**

The surgical procedure in this group was performed according to the Standard Dresden Protocol (Wollensak et al. 2003) using the Opto XLink-Corneal Crosslinking System (Opto Global Pty Ltd.) with continuous irradiation mode. The first step in this procedure was to use an 8 mm zone marker to mark the corneal area to be de-epithelialized. Then, a blunt tip spatula was used to remove the corneal epithelium within the 8 mm marked zone. 0.1% riboflavin with dextran solution (RICROLIN®, Sooft Italia S.p.A., Montegiorgio FM, Italy) was applied every 3 min for 30 min thus allowing corneal saturation with the photosensitizer riboflavin before UVA irradiation. Adjustment of the parameters of the Opto XLink-corneal crosslinking system was performed including the following parameters: power 1.50 mW, UVA irradiance 2.984 mW/cm², UVA dose 5.371 J/cm² and the duration 30 min. The next step was the irradiation of the riboflavin-saturated cornea with UVA for 30 min with continued riboflavin installation every 3 min during the UV irradiation time. At the end of the procedure, a bandage contact lens (CooperVision, The Cooper Companies, Inc., Pleasanton, CA, USA) was placed onto the cornea. Finally, installation of topical antibiotic eye drops (Zymar, gatifloxacin 0.3%, Allergan, Inc, Jersey City, NJ, USA) and topical steroid eye drops (Pred Forte, prednisolone acetate 1%, Allergan, Inc.) was performed.

**Group B**

All eyes in group B were treated with CXL-Plus that included non-topography-guided PRK followed immediately by AXL in the same session. The Standard Nomogram (Maloney Vision Institute VISX S4) was used to perform PRK with a maximum tissue ablation of 50 μm. Figure 1 shows the steps of CXL-Plus in the right eye of one patient in group B: Centration of the reticle onto the pupil was performed and followed by epithelial removal of the central 6 mm zone via the trans-epithelial treatment mode (Fig. 1A). A hockey knife was used to remove additional corneal epithelium
to achieve an 8 mm de-epithelialized corneal zone (Fig. 1B). Corneal ablation of the stromal tissue via standard PRK was performed (Fig. 1C). After PRK, a disposable K-Sponge triangular spear (hydrocellulose sponge, Katena Products, New Jersey, USA) was soaked with 0.02% Mitomycin C solution (MMC, Cadila Healthcare Pharmaceutical, Mumbai, India) was placed onto the cornea, e: washing the corneal surface with careful MMC solution removal, F: Installation of 0.1% of riboflavin onto the cornea, G: Pulsed mode of the accelerated epithelium of CXL, H: Washing the corneal surface with BSS in between the UVA pulses, I: Applying of the bandage contact lens onto the cornea.

Fig. 1. The CXL-Plus steps (Group B); A: The reticle was centred over the pupillary entrance to be followed immediately by epithelial treatment that included epithelial removal within a 6 mm zone using the trans-epithelial ablation mode, B: Using a hockey knife to widen the de-epithelialized corneal zone to 8 mm, C: Standard PRK for ablation of the corneal stromal tissues, D: A K-Sponge triangular spear saturated with 0.02% MMC solution was applied onto the cornea, e: washing the corneal surface with careful MMC solution removal, F: Installation of 0.1% of riboflavin onto the cornea, G: Pulsed mode of the accelerated epithelium of CXL, H: Washing the corneal surface with BSS in between the UVA pulses, I: Applying of the bandage contact lens onto the cornea.
contact lens was applied onto the cornea (Fig. 1I) followed by installation of topical antibiotic and steroid eye drops (gatifloxacin 0.3% and prednisolone acetate 1%).

Postoperative treatment and follow-up
Both groups received the same postoperative treatment that continued till the end of the 4th postoperative week. Topical therapy included three types of eye drops, gatifloxacin 0.3%, prednisolone acetate 1% and sodium hyaluronate 0.15% eye drops (Hyabak, THEA laboratories, Clermont-Ferrand, France). The topical prednisolone acetate 1% and sodium hyaluronate 0.15% were installed five times daily in the first postoperative week and then tapered gradually.

All patients were examined at the second and fourth postoperative days to check for complete regeneration of the corneal epithelium after which the bandage contact lens was removed. Then the patient was followed up at the end of the first, second, third and fourth postoperative weeks. During the follow-up period, all patients were examined at 3, 6, 12 and 24 months postoperatively.

Regarding corneal haze, it was graded according to a scale from 0–4. Scale 0 means clear cornea, scale 0.5 means faint haze, scale 1 means mild haze seen only with tangential illumination, scale 2 means faint opacity seen with direct illumination, scale 3 means opacity obscuring iris details while scale 4 means opacity seen without slit-lamp (Kim et al. 2004).

Statistical analysis
The statistical package for social sciences software (ssrs version 22 for Windows, SPSS Inc., Chicago, IL, USA) was used for the analysis of the study data. Median, mean and standard deviation were used to describe the quantitative data. Qualitative data were presented as number and percentage. For non-normally distributed data, Wilcoxon test was used. For a normally distributed data, paired sample T-test was used. The postoperative data results were considered statistically significant if p value was <0.05.

Results
This study included surgical intervention in 125 keratoconic eyes of 75 patients. The study patients included 32 males and 43 females (ratio 1:1.34). Fifty eight eyes (46.4%) of 33 patients represented group A while 67 eyes (53.6%) of 42 patients represented group B.

Central corneal thickness
Regarding the corneal thickness at the thinnest location (CCT), both groups had different postoperative courses of corneal pachymetry pathway (Table 1). In group A, CCT showed a slowly progressive slight thinning from the preoperative CCT of 459.5 ± 29.7 μm to 407.4 ± 26.0 μm at 24 months. In group B, the CCT had a different postoperative pathway as it showed an immediate reduction in the CCT by the action of the PKR-induced stromal ablation effect after which CCT remained stable along the 2 years of follow-up period with only minor changes. The immediate postoperative reduction by PKR ablation was from 486.2 ± 33.5 μm preoperatively (range 437–503) to reach 421.2 ± 27.1 μm (range 392–481) at the end of the 1st postoperative month.

Topographic outcome analysis
Regarding the keratometry readings (k readings) on the anterior corneal surface, both groups showed different pathways in the postoperative reduction in the k readings (Tables 1 and 2, Fig. 2). The major difference between the postoperative courses in both groups was the nature of the postoperative improvement in relation to time. In group A, the improvement in k readings was both slow and progressive while in group B, the improvement in k readings was immediate and approximately stable over time in most cases.

In group A, the preoperative k1, k2, k average and k reading at the apex (kmax) were 46.43 ± 0.78, 48.43 ± 1.37, 47.27 ± 1.13 and 48.64 ± 1.34 D (mean ± SD), respectively. At the end of the 24-month follow-up period, the postoperative k1, k2, k average and kmax readings were significantly reduced to 44.43 ± 0.75, 46.01 ± 0.76, 45.15 ± 0.73 and 46.61 ± 1.11 D (mean ± SD), respectively (p value <0.001). The preoperative k2 and kmax ranges were 44.23–50.11 and 44.50–50.21 D, respectively, while the postoperative k2 and kmax ranges were 42.51–48.20 and 43.53–48.62 D, respectively, at the end of the 24 follow-up months.

In group B, the preoperative k1, k2, k average and kmax readings were 45.65 ± 1.16, 49.22 ± 0.39, 47.51 ± 0.78 and 49.30 ± 0.49 D (mean ± SD), respectively. At the end of the 24 months of follow-up period, the preoperative k1, k2, k average and kmax readings were reduced to 44.80 ± 0.52, 47.05 ± 0.41, 46.07 ± 0.59 and 47.07 ± 0.56 D (mean ± SD), respectively (p value <0.001). The preoperative k2 and kmax ranges were 47.91–50.24 and 46.31–50.25 D, respectively, while the postoperative k2 and kmax ranges were 46.15–48.72 and 45.13–48.32 D, respectively, at the end of the 24 follow-up months.

While in group B the reduction in kmax was present from the first month, it started at 6 months and continued to 24 months in group A (Fig. 2).

Refractive outcomes analysis
In group A, there was a statistically highly significant reduction in the myopic component that was reduced from 3.21 ± 1.09 to 1.17 ± 0.73 D (mean ± SD) postoperatively at the end of the 24th month of follow-up period (p value <0.001) (Tables 3 and 4). This excellent improvement in the myopic component in the keratoconic eyes in group A was attributed to the remarkable sphere reduction achieved by the standard CXL that was 1.97 ± 0.62 D at the 24th postoperative month (p value <0.001). The slight postoperative cylinder reduction of 0.32 ± 0.19 D at the end of the 24th postoperative month was statistically insignificant (p value <0.1). The postoperative spherical equivalent reduction in group A was by 2.15 ± 0.67 D at the end of the 24th postoperative month (p value <0.001).

In group B, both myopic and astigmatic components in group B showed a remarkable early postoperative improvement. The preoperative myopic component was reduced from 2.89 ± 1.05 to 1.38 ± 0.57 D postoperatively (p value <0.05). The preoperative astigmatic component showed a postoperative statistically highly significant reduction from 3.07 ± 1.26 to 1.43 ± 0.62 D (p value < 0.001). Remarkably there was a great reduction in the astigmatic component of KC more than the reduction in the
myopic component. The postoperative sphere reduction at 24 months was 1.31 ± 0.43 D (p value < 0.05) while the postoperative cylinder reduction was 1.65 ± 0.55 D (p value < 0.001).

Also, there was a highly significant postoperative spherical equivalent reduction that reached 2.23 ± 0.49 D at 24 months (p value < 0.001).

The differences in spherical equivalent, myopic component, astigmatic component and $k_{\text{max}}$ were statistically significant at 1, 6 (p = 0.0001) and 12 (p = 0.0003) months for the spherical equivalent, at 1, 6 (p = 0.0001) and 12 (p = 0.0002) months for the myopic component, at zero, 1, 6, 12, 18 (p = 0.0001) and 24 (p = 0.0002) months for the astigmatic component and at zero (p = 0.0003), 1, 6 (p < 0.0001) and 24 (p = 0.0003) months for $k_{\text{max}}$ (Fig. 2).

**Visual outcomes analysis**

This study showed improvement in both postoperative UDVA and CDVA in both A and B groups (Tables 3 and 4). In group A, preoperative UDVA and CDVA improved from 1.12 ± 0.38 and 0.58 ± 0.42 LogMAR (mean ± SD) to 0.66 ± 0.20 (p value < 0.05) and 0.20 ± 0.12 (p value < 0.001) at 24 months.

In group B, preoperative UDVA and CDVA improved from 1.26 ± 0.52 and 0.68 ± 0.36 LogMAR (mean ± SD) to 0.58 ± 0.28 (p value < 0.05) and 0.20 ± 0.16 (p value < 0.001) at 24 months.

**Complications**

Thirty-seven eyes (63.8%) in group A and 51 eyes (76.1%) in group B complained about early postoperative photophobia, pain, foreign body sensation, irritation and watery eyes (Table 5). All patients were reassured that most of these complaints will disappear within 48 hr postoperatively. Topical anaesthetic Benoxinate hydrochloride 0.4% eye drops (Benox, Pharmaceutical Industries Company, E.I.P.I.C.O., Egypt) was prescribed for all patients to be installed 4 times in the 1st postoperative day then stopped. All patients were instructed to start immediately the postoperative topical therapy on an hourly basis in the first postoperative 8 hr than then 5 times daily. Most eyes showed relief of these complains within the first 2–3 days postoperatively.

Delayed epithelial healing was recorded in 9 eyes (15.5%) in group A and 8 eyes (11.9%) in group B. All these eyes were instructed to stop installation of the steroid eye drops. Instead, non-steroidal anti-inflammatory Nepafenac 0.1% eye drops (Nepafenac, Alcon Laboratories, Inc.) were prescribed four times daily. In addition, carbamazepine solution 0.5% lubricant eye drops (Refresh Plus, Allergan, Inc, Jersey city, USA) was added twice daily. All eyes showed complete epithelial healing within 7–10 postoperative days.
In group A, anterior corneal haze was recorded in seven eyes (12.1%). Corneal haze was recorded as scale 1 in three eyes (5.1%), scale 2 in 2 eyes (3.5%) and scale 3 in two eyes (3.5%). This corneal haze after standard CXL had a dust-like appearance in the corneal stroma most probably resulting from lacunar oedema of the kerato¬cytes (Wollensak & Herbst 2010). This haze was considered as a good and normal sign of effective CXL. All these patients received Pred Forte eye drops, Hyabak and Sodium chloride 5% eye drops (Optic Saline, Advanced Pharmaceutical Industries Co., APIC, Cairo, Egypt) five times daily and tapered gradually. The corneal haze was transitory and disappeared within the first six postoperative months.

In group B, corneal haze was recorded in four eyes (5.9%). Corneal haze was recorded as scale 1 in two eyes (2.9%), scale 2 in one eye (1.5%) and scale 3 in one eye (1.5%). The corneal haze was subepithelial in nature with a reticulated appearance mostly resulted from PRK. All these patients were instructed to instil the Pred Forte and Hyabak eye drops on an hourly basis to be reduced to 5 times daily once the signs of improvement were observed. All patients showed recovery from the corneal haze within 2–4 weeks postoperatively.

In group A, a persistent epithelial defect (PED) was recorded only in one eye (1.7%). The patient was instructed to stop using the steroid eye drops. Supportive therapy was used for this patient. Frequent eye lubricants and artificial tears were prescribed. Carbomer 3 mg/g eye gel (Thilo-Tears Gel, Alcon Laboratories, Inc.) was prescribed twice daily. Sodium hyaluronate 0.15% eye drops and carboxymethylcellulose sodium solution 0.5% lubricant eye drops were prescribed five times daily. The supportive care continued for 8 weeks until the epithelial defect showed complete healing leaving a very faint paracentral corneal opacity that did not affect the overall postoperative visual outcome.
Subjective refraction

Visual acuity

keratoconus progression in either
treatment failure with postoperative
ing a localized corneal opacity.
previously mentioned supportive ther-
ing (Fig. 3). The patient received the
postoperative localized stromal scar-

Discussion

This study has proven that PRK com-
bined with AXL can significantly reduce the astigmatic and myopic
effects of keratoconus at an early post-
point with a stable long-
term effect. Remarkably, standard
CXL alone also induced a remarkable
corneal flattening effect with a signifi-
cant reduction in the myopic refractive
component at a later time-point one to
two years postoperatively. This seems
to be a unique effect of CXL which was
not observed with AXL.

These outcomes in group A could be
attributed to the fact that the standard
CXL affects all corneal meridians sym-
metrically so that it had a great influ-
ence in the postoperative sphere
reduction and almost insignificant
influence in the postoperative cylinder
reduction. The outcomes in group B
could be attributed to the fact that
PRK is effective in the postoperative
cylinder reduction while AXL had
almost no refractive gain to add to
the myopic component improvement in
the way that standard CXL managed
to reduce the postoperative sphere in
group A.

Kymionis et al. reported the use of a
modified accelerated CXL protocol
including 14 min irradiation of 9mW/
cm² or 7 min irradiance with 18mW/
cm². They concluded that accelerated
CXL protocols seem to be a valid
alternative to the standard CXL pro-
tocol (Kymionis et al. 2017). Schu-
macher et al. compared corneal
stiffness induced by standard (30 min
using UVA 3 mW/cm²) versus accel-

termined CXL (9 min using UVA 10 mW/
cm²) versus accelerated
CXL (9 min using UVA 10 mW/
cm²) using uniaxial biomechanical
measurements of porcine corneal
strips. They reported that there was
no statistical difference between both
cross-linking procedures regarding the
biomechanical changes and corneal
stiffness (Schumacher et al. 2011).

In contrast, using inflation experiments
Bao et al. recently evaluated the
biomechanical changes and corneal
 stiffening induced by different UVA
irradiances ranging from 3 mW/cm² for
30 min to 90 mW/cm² for 1 min in
seven different groups of white rabbits.
They showed that the higher the UVA
irradiance and the shorter the corneal
irradiation duration, the lower the
corneal stiffening effect. In other
words, corneal stiffening proved to be
The results of our study suggest that standard CXL may be more powerful in flattening the anterior corneal surface than AXL in the long run. Similarly, many authors have reported the good and lasting effect of standard CXL in comparison with AXL. In fact, it has been observed that AXL had a limited corneal flattening influence in topography while standard CXL had an excellent topographic corneal flattening outcome that led to keratoconus stability and postoperative visual improvement. The authors have concluded that AXL is a good therapeutic and a safe procedure to treat KC (Ghanem et al. 2014; Knezović et al. 2015; Sakla et al. 2016; Kymionis et al. 2017).

Kontadakis et al. compared the outcomes of two groups. The first group had CXL alone while the second group had topography-guided PRK combined with CXL (tPRK-CXL). Each group included 30 eyes that were followed up for 3 years. They used a solid state laser to achieve 50 μm ablation of the corneal stromal tissue (Kontadakis et al. 2016). Our study had almost the same idea of their study; however, we used AXL instead of CXL and included 125 eyes with only grade 1 keratoconus however. Both studies used the same 50 μm ablation depth as a maximum value but our PRK was not topography-guided. Their study concluded that CXL-Plus had more significantly improved visual outcomes in comparison with the CXL group. They also stated that both groups showed the same postoperative stability. However, in our study standard CXL proved to be equally effective in corneal flattening with sphere reduction and visual outcomes when compared with AXL-Plus.

Regarding corneal haze, Raiskup et al. (2009) reported clinical significant corneal haze in 8.6% of eyes with grade 1, 2 and 3 KC and they concluded that advanced KC was at more risk to develop corneal haze and localized stromal scarring. Greenstein et al. (2010) and Gutiérrez et al. (2012) reported corneal haze in the first month that decrease gradually to finally disappear from 3 to 12 months postoperatively. Moreover, Dhawan et al. reported that the corneal haze after CXL is different from the corneal haze after PRK. The haze following CXL may extend to 60% of the corneal thickness and is associated with honeycomb-like or dust-like appearance resulting from lacunar hydration and oedema of keratocytes which is usually a transient self-limiting phenomenon that disappears within few months postoperatively (Wollensak & Herbst 2010). On the other hand, the haze following PRK has a subepithelial reticulated pattern which is more superficial than the haze induced by CXL (Dhawan et al. 2011). Our study showed both types of corneal haze as 12.1% of eyes in group A had haze after CXL that disappeared within the first six postoperative months while 5.9% of eyes in group B had haze after
PRK despite the use of MMC, however the haze disappeared within the first postoperative month. Koller et al. (2009) reported many complications of CXL which included a 7.6% failure rate of CXL, central stromal scars complicated 2.8% while sterile infiltrates were recorded in 6.7% of cases. Our study recorded paracentral irreversible stromal scarring in one eye (1.3%) following CXL-Plus. In view of possible CXL-related complications corneal cross-linking can only be recommended in grade 1 KC if an active progression of ectasia or corneal thinning has been documented.

In conclusion, standard CXL showed close results to AXL-Plus at the 24th follow-up month. Standard CXL was acting as a stabilizing procedure that was associated with a significant improvement of the myopic refractive component after one to two years. AXL-Plus achieved a reduction in both the astigmatic and myopic refractive component shortly after the treatment due to the PRK-induced tissue ablation. However, there was no further improvement of the refractive and topographic parameter in the long term due to AXL. In the future, we plan to perform a study combining PRK and standard CXL thereby also combining the advantages of the early refractive corrections by PRK and the late improvements due to standard CXL.

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Correspondence:
Mohammed Iqbal, MD
Department of Ophthalmology
Faculty of Medicine
Sohag University
Sohag
Egypt
Tel: +00201068559840
Fax: +00209323230733
Email: dr_m_iqbal@yahoo.com

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