

A Comparative Study of Corneal Changes in Continuous and Pulsed Light Accelerated Corneal Cross-linking

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Abstract:

Purpose: This study compared corneal changes (thickness, demarcation line depth on AS-OCT) and functional outcomes between pulsed and continuous accelerated corneal cross-linking (P-ACXL vs. C-ACXL) in patients with corneal in AS-OCT.

Patients and Methods: This is a prospective interventional study; 33 eyes (18 patients) underwent epithelium-off P-ACXL or C-ACXL. Assessments included BCVA, refractive error (MRSE), keratometry (average K, KMAX), and AS-OCT-measured corneal parameters.

Results: BCVA improved significantly in both groups at 1 and 3 months ($p < 0.001$), with no intergroup differences. Inferior corneal thickness was lower in C-ACXL vs. P-ACXL ($478.94 \pm 30.58 \mu\text{m}$ vs. $500.50 \pm 38.17 \mu\text{m}$; $p=0.04$). Corneal thickness decreased significantly from baseline in both groups ($p<0.001$). The demarcation line was shallower in C-ACXL at 1 and 3 months ($p<0.001$).

Conclusions: Both P-ACXL and C-ACXL safely improved vision and reduced corneal thickness. The shallower demarcation line with C-ACXL may reflect distinct stromal remodeling patterns, warranting further study.

Keywords: Keratoconus, corneal cross-linking, demarcation line (DL) in anterior segment OCT, pulsed light corneal cross-linking, ultraviolet A corneal cross-linking.

Introduction:

Ectatic corneal diseases (ECD), or corneal ectasia, refer to a range of conditions marked by the progressive thinning and protrusion of the cornea. Several types of ECD have been identified, such as keratoglobus, pellucid marginal degeneration (PMD), and keratoconus (KC) (1). Keratoconus (KC) is the most common ectatic corneal disease (2). When assessing patients with ectatic corneal disorders, clinicians should consider various key diagnostic approaches: screening, confirming the diagnosis, classifying the type of ectasia, staging the severity, evaluating prognosis, and conducting clinical follow-ups to tailor individualized treatments. (3).

Since cross-linking was introduced in the late 1990s, it has become a primary treatment for corneal ectatic disease worldwide (4,5).

The technique of strengthening the corneal tissue is through the formation of chemical bonds between the collagen fibrils, which leads to inhibition of the ectatic progression of the cornea (6).

With the use of ultraviolet-A light and riboflavin, these bonds can be created (7). In CXL, riboflavin acts as a photosensitizer, while UVA improves the formation of inter-fibrillar covalent bonds by oxidative photosensitization (8,9).

The standard CXL protocol (also referred to as the Dresden protocol or conventional CXL) presents several challenges, including the lengthy treatment duration, risk of overtreatment, and a higher incidence of complications. Recently, it has been largely replaced by newer accelerated protocols (A-CXL) (10,11,12). In relation to

A-CXL protocols, pulsed light fractionation (pl-CXL) is considered preferable to continuous light application (cl-CXL), as it permits periods of re-oxygenation in the stroma, which is crucial for achieving an effective photochemical reaction(13).

The depth and effectiveness of treatment can be assessed by measuring the demarcation line, which typically appears 10 to 14 days after CXL(14). This line represents an area of hyper-reflectivity, caused by the differing refractive indices or reflective properties of cross-linked versus untreated corneal stroma (15). Anterior segment optical coherence tomography (AS-OCT), which is an imaging technique that provides both qualitative and quantitative data on the anterior segment of the eye, including the cornea, iris, anterior chamber angle, and crystalline lens, is used to evaluate the depth of the demarcation line and, by extension, the extent of the cross-linking effect (16).

Areas of CXL haze will often become unnoticeable by one year post-CXL(17). The method's success rate in stabilizing corneal ectasia is higher than 95%(18).

This study aims to assess corneal changes following CXL both clinically and through AS-OCT, and to determine whether there is a difference in the extent of the treatment between two accelerated corneal crosslinking protocols (P-CXL vs. C-CXL).

Patients and Methods

This prospective interventional, non-randomized study involved patients who underwent corneal cross-linking (CXL). All patients met the inclusion criteria, and the study included 33 eyes from 18 patients treated between 2021 and 2023 at Assiut University Hospital's Ophthalmology Department—Cornea Unit and Al-Noor Eye Care Center. The study was approved by the Institutional Review Board/Ethical Committee of Assiut University Hospital (IRB Approval No. 17101664).

A total coverage technique was applied here. All patients who met the selection criteria during the study period were enrolled. A total of 33 eyes were recruited in the study(31 patients with keratoconus and 2 with post-LASIK ectasia). A total of 16 (48.5%) eyes were managed with pulsed accelerated CXL, and the other 17 (51.5%) eyes were managed with continuous accelerated CXL.

Inclusion Criteria:

Patients with progressive ectatic corneal disease, documented by serial topography and with corneal thickness above 400 microns at the thinnest location, were recruited for the study. All patients provided informed consent to participate. Each patient was thoroughly informed about their condition, the nature of the procedure, and potential consequences.

Exclusion Criteria:

Patients with corneal thickness below 400 microns, corneal opacity or scarring, uveitis, a history of herpetic keratitis, pregnancy, autoimmune diseases, and/or chronic corticosteroid therapy were excluded from the study.

All eligible patients underwent a preoperative assessment that involved taking a detailed history to evaluate the onset and progression of symptoms, previous ocular history, and pregnancy or lactation status. The ophthalmological examination included assessments of best-corrected visual acuity (BCVA), keratometry readings, and a slit-lamp biomicroscopic examination of the anterior and posterior segments. BCVA was converted into logMAR for statistical analysis.

All patients also underwent AS-OCT evaluation for two different parameters. The first parameter was corneal thickness, assessed before the procedure and post-procedure (one month and three months). The second parameter was the demarcation line, which appeared in AS-OCT as a stromal boundary separating the more reflective

anterior corneal stroma from the less reflective posterior corneal stroma. The depth of the demarcation line was measured using a software caliper tool. Measurements were

taken at five points on horizontal and vertical line scans (center, and 2 mm temporally, nasally, superiorly, and inferiorly) to determine corneal thickness and demarcation line depth. The mean values were then calculated.

The same ophthalmologist (Duaa M. M.Ali) conducted all AS-OCT measurements. OCT scans were performed using the Solix full-range OCT (Optovue Inc., Fremont, CA, USA).

The cross-linking procedure

The same steps were done for all patients. All patients were positioned on their backs, with a lid speculum and Benoxinate hydrochloride 4% (Benox, Epico) was used as a topical anesthetic.

The central 7mm was removed by mechanical debridement with a blunt hockey stick knife in all patients.

Instillation of Riboflavin

*To protect Riboflavin from light

The room lights were dimmed before starting the riboflavin installation to prevent any changes or effects on the riboflavin.

The syringe containing it was wrapped with a sterile towel and stored in the fridge at +4 to +8 °C, and the towel was thrown away right after the surgery.

Vibex Rapid isotonic solution (riboflavin 0.1% vitamin B2 in hydroxypropyl methylcellulose) was used, a preloaded glass syringe of 1.5 ml, and applied to cover the whole cornea every 2 minutes.

Patients were divided into two treatment groups:

Pulsed Light Treatments: 16 eyes of 9 patients aged 18-30 years underwent epithelium-off pulsed light ACXL (pl-ACXL) using the KXL I UV-A source (Avedro Inc., Waltham, MA, USA) with 8

minutes (1 second on/1 second off) of UV-A exposure at 30 mW/cm² with an energy dose of 7.2 J/cm².

Continuous Light Treatments: Seventeen eyes of nine patients, aged 11 to 24 years, underwent epithelium-off continuous light

ACXL (cl-ACXL) using the same instrument. The treatment involved 30 mW/cm² UV-A power for 4 minutes of continuous UV-A light exposure, delivering an energy dose of 7.2 J/cm². The cornea was moistened every 2 minutes with 0.1% riboflavin and tetracaine drops throughout the procedure. After irradiation, a therapeutic soft contact lens was applied and removed the next day. Both procedures utilized Avedro's corneal cross-linking system (KXL, Avedro, Inc., Waltham, MA).

Postoperative Care

Postoperative care included the application of preservative-free moxifloxacin 0.5% (Vigamox®; Alcon) eye drops five times daily for 15 days. A preservative-free tear substitute, Propylene Glycol 0.3% (Systane Ultra®), was used every hour for the first few days and then five times daily for three months. Oral analgesics such as Ibuprofen (Brufen®; Abbott) 400 mg were taken thrice daily to alleviate pain until the epithelium reformed. Patients were advised to wear sunglasses for a month.

Postoperative follow-up was conducted to detect and treat any complications. Patients were examined at the slit-lamp on the first, third, and sixth postoperative days, then at 2 weeks, 1 month, and 3 months.

At 1 and 3 months postoperatively, measurements were taken of best-corrected visual acuity (BCVA), mean refractive spherical equivalent (MRSE), average K, and corneal evaluation using anterior segment OCT (AS-OCT)

Statistical Analysis

Data were collected and analyzed using SPSS (Statistical Package for the Social Sciences, version 20, IBM, Armonk, New

York). The Shapiro-Wilk test was applied to assess the normality of the data distribution. Normal distribution of Quantitative data was expressed as mean (SD) and compared using the Student's t-test (between both groups) and Paired t-test (between baseline and follow-up data in each separate group). Nominal data are frequency (n) and percentage (%). The χ^2 test was implemented on such data. Pearson's correlation coefficient determined the correlation between the line of demarcation and corneal thickness. The p-value of less than 0.05 was considered statistically

significant, and the confidence level was 95%. This study was approved by the local ethical committee of our university, and the institutional review board approval number is 17101664/2022.

Results

A total of 33 eyes were recruited in the study. 16 (48.5%) eyes were managed with pulsed accelerated CXL, and the other 17 (51.5%) eyes were managed with continuous accelerated CXL, with the following characteristics in **Table (**

1)

Table 1: Demographics among the enrolled participants

	N= 33
Age (years)	22.06 ± 3.69
- Range	15-30
Sex	
- Male	9 (27.3%)
- Female	24 (72.7%)
Previous ocular surgeries (LASIK)	2 (6.1%)
Indication of surgery	
- Post-LASIK ectasia	2 (6.1%)
- Keratoconus	31 (93.9%)
Type of CXL	
- Pulsed accelerated	16 (48.5%)
- Continuous accelerated	17 (51.5%)

Data is expressed as mean (SD) and frequency (percentage).

Table (2) and Figure (1) show no significant differences between the two groups regarding BCVA and refraction. In each separate group, there were no significant changes in refraction either after one month or three months compared to the baseline assessment. Meanwhile, BCVA was

significantly improved after one month and three months compared to the baseline assessment in both groups separately. (Data expressed as mean (SD). *P*-value was significant if < 0.05. BCVA: best corrected visual acuity.

Table (2): Shows the mean difference in best corrected Visual acuity and refraction based on the type of CXL

	Pulsed CXL (n= 16)	Continuous CXL (n= 17)	P1 value
BCVA			
- Preoperative	0.54 ± 0.16	0.47 ± 0.19	0.26
- After one month	0.59 ± 0.17	0.51 ± 0.16	0.17
- After three months	0.62 ± 0.14	0.54 ± 0.19	0.21
- P2 value	< 0.001	0.04	
- P3 value	< 0.001	0.007	
Spherical equivalent			
- Preoperative	- 4.65 ± 2.63	- 4.53 ± 3.30	0.90

- After one month	- 4.63 ± 2.15	- 4.83 ± 4.07	0.49
- After three months	- 4.59 ± 2.19	- 3.19 ± 3.92	0.54
- P2 value	0.49	0.29	
- P3 value	0.88	0.12	

P1 value compares between both groups; **P2 value** compares preoperative and after one-month assessment in each separate group; **P3 value** compares preoperative and after three-month assessment in each separate group.

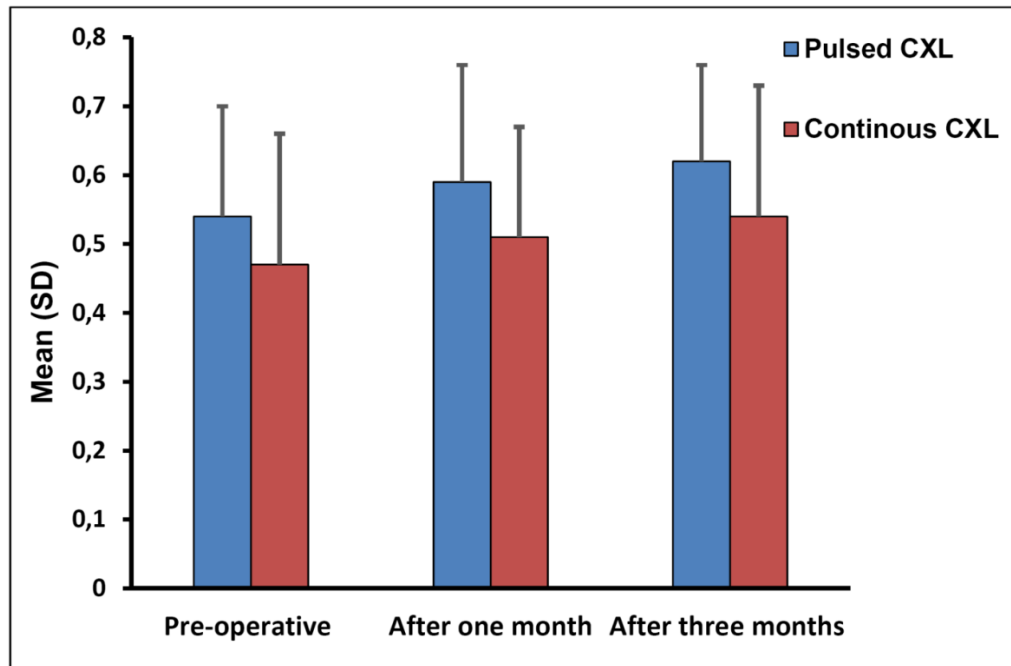


Figure (1): Assessment of best corrected visual acuity in studied groups. CXL: collagen cross-linking

Table (3) and Figure (2) show that both groups had insignificant differences regarding average *K* either at baseline, after one month, and after three months ($p > 0.05$).

In each separate group, there was an insignificant difference regarding average *K* after one month or three months ($p > 0.05$) compared to the baseline assessment.

Table (3): Change in average *K* based on type of CXL

Average <i>K</i>	Pulsed CXL (n= 16)	Continuous CXL (n= 17)	P1 value
Average <i>K</i>			
- Baseline	46.09 ± 4.08	47.40 ± 3.55	0.33
- After one month	45.57 ± 4.20	47.36 ± 3.59	0.19
- After three months	45.54 ± 4.20	47.23 ± 3.79	0.23
- P2 value	0.09	0.84	
- P3 value	0.08	0.32	

Data expressed as mean (SD). *P*-value was significant if < 0.05 . **P1 value** compares between both groups; **P2 value** compares preoperative and after one-month assessment in each separate group. **The P3 value is compared preoperatively and after a three-month assessment in each separate group.**

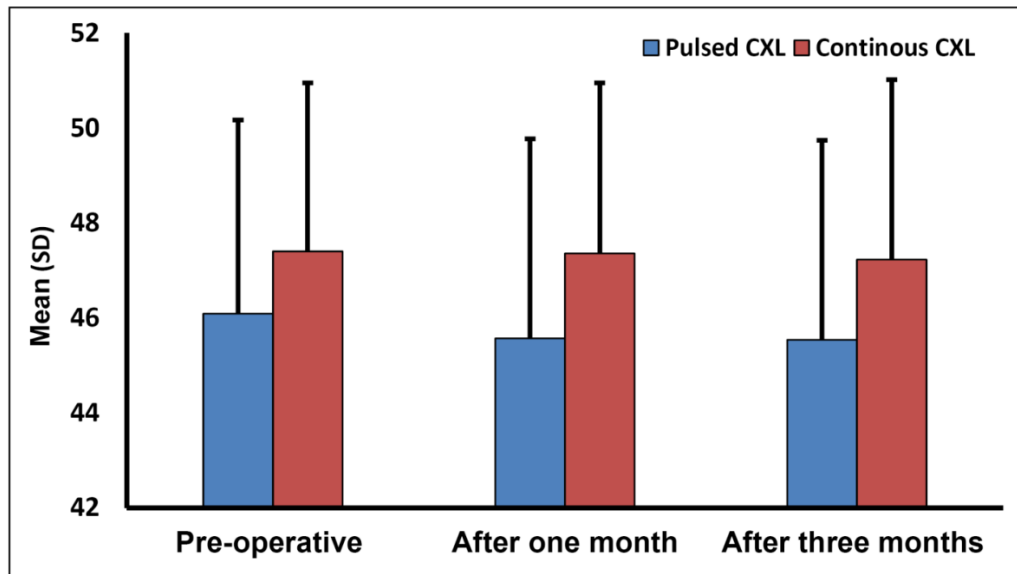


Figure (2): Assessment of average K in studied groups

Table (4) shows that both groups had insignificant differences regarding KMAX at baseline or after 6 months.

There was no significant difference regarding KMAX after 6 months in each group.

Table (4);

Table (2): KMAX	Pulsed CXL (n=6)	Continuous CXL (n=6)	P1 value
KMAX			
- Baseline	46.040 ± 2.037	49.817± 2.55	0.1251
- After six months	45.96 ± 1.51	49.817± 2.55	0.0961
- P2 value	0.739	1.00	

Data expressed as mean (SD). *P*-value was significant if < 0.05. **P1 value** compares between both groups; **P2 value** compares between preoperative and after 6-month assessment in each separate group

Table (5) shows no significant differences between both groups as regards changes in corneal thickness except for significantly lower inferior CT among patients who underwent continuous CXL

(478.94 ± 30.58 vs. 500.50 ± 38.17; *p* = 0.04) in comparison to pulsed CXL. Also, in each group, there was a significant decrease in CT either after one month or three months compared to baseline CT (*P* < 0.001).

Table (5): Change in corneal thickness based on the type of CXL.

CT (um)	Pulsed CXL (n= 16)	Continuous CXL (n= 17)	P1
Central			
- Preoperative	483.31 ± 43.25	464.41 ± 25.21	0.13
- After one month	462.81 ± 44.95	452.82 ± 22.28	0.42
- After three months	470.06 ± 44.05	457.53 ± 22.71	0.30
- P2 value	< 0.001	< 0.001	
- P3 value	0.002	< 0.001	

CT (um)	Pulsed CXL (n= 16)	Continuous CXL (n= 17)	P1
Nasal			
- Preoperative	529.44 ± 33.29	518.35 ± 20.82	0.25
- After one month	515.88 ± 34.54	504.65 ± 19.83	0.26
- After three months	521.69 ± 34.83	509.21 ± 18.25	0.20
- P2 value	< 0.001	< 0.001	
- P3 value	< 0.001	< 0.001	
Temporal			
- Preoperative	507 ± 34.96	485.06 ± 27.65	0.06
- After one month	485.31 ± 37.52	472.88 ± 32.63	0.28
- After three months	497.88 ± 37.12	477.41 ± 27.06	0.07
- P2 value	< 0.001	< 0.001	
- P3 value	< 0.001	< 0.001	
Superior			
- Preoperative	540.50 ± 40.22	517.82 ± 32.28	0.25
- After one month	519.75 ± 39.65	506.94 ± 19.87	0.24
- After three months	526.25 ± 39.09	511.47 ± 19.65	0.18
- P2 value	0.004	< 0.001	
- P3 value	0.03	< 0.001	
Inferior			
- Preoperative	508.31 ± 37.14	483.18 ± 17.73	0.15
- After one month	494.44 ± 37.94	474.44 ± 17.27	0.06
- After three months	500.50 ± 38.17	478.94 ± 30.58	0.04
- P2 value	< 0.001	< 0.001	
- P3 value	< 0.001	< 0.001	

Data expressed as mean (SD). *P*-value was significant if < 0.05. **P1 value** compares between both groups; **P2 value** compares preoperative and after one-month assessment in each separate group; **P3 value** compares preoperative and after three-month assessment in each separate group.

Table (6) shows the change in demarcation line based on the type of CXL, where it was found that pulsed CXL had a significantly deeper demarcation line in comparison to continuous CXL after one month and after three months ($p < 0.001$).

In each separate group, the demarcation line was significantly deeper after three months ($p < 0.001$) compared to the one-month assessment.

Table (6): Change in demarcation line based on type of CXL:

Demarcation line (um)	Pulsed CXL (n= 16)	Continuous CXL (n= 17)	P value
Central			
- After one month	281.56 ± 46.33	216.18 ± 13.46	< 0.001
- After three months	287.94 ± 43.58	224.47 ± 13.23	< 0.001
- P2 value	0.04	0.03	
Nasal			
- After one month	264.56 ± 39.84	210.41 ± 18.97	< 0.001
- After three months	269.75 ± 39.87	219.06 ± 18.21	< 0.001
- P2 value	< 0.001	< 0.001	

Demarcation line (um)	Pulsed CXL (n= 16)	Continuous CXL (n= 17)	P value
Temporal			
- After one month	246.44 ± 33.36	194.41 ± 18.01	< 0.001
- After three months	251.19 ± 32.56	203.24 ± 17.08	< 0.001
- P2 value	0.001	< 0.001	
Superior			
- After one month	256.13 ± 28.55	196.41 ± 19.95	< 0.001
- After three months	261 ± 28.19	204.47 ± 16.51	< 0.001
- P2 value	< 0.001	< 0.001	
Inferior			
- After one month	266 ± 41.91	197.82 ± 18.05	< 0.001
- After three months	271.50 ± 39.60	207.53 ± 19.09	< 0.001
- P2 value	< 0.001	< 0.001	

Data expressed as mean (SD). *P*-value was significant if < 0.05. **P1 value** compares between groups.

P2 value compares after one-month and three-month assessments in each group.

No postoperative haze was noticed in either the pulsed or continuous group.

Discussion

The clinical use of collagen crosslinking (CXL) of the cornea has greatly enhanced the management of ectatic cornea by halting the progression of the disease (19).

The first study comparing the standard and accelerated techniques was conducted by Tomita et al. (2014). They found no significant differences in postoperative changes in uncorrected visual acuity (UCVA), best-corrected visual acuity (BCVA), manifest refraction, or changes in keratometric readings in the postoperative period and corneal biomechanical responses between the two methods (20).

The pulsed nature in pulsed light cross linking allows for more controlled energy delivery, leading to more effective cross-linking of polymers or tissues without excessive heat, which can degrade materials or tissues. Also, pulsed light minimizes heat exposure to surrounding tissues or materials, reducing the risk of thermal damage. Pulsed light cross linking can limit the formation of reactive oxygen species (ROS), which can be detrimental in many biological applications, thereby enhancing safety and efficacy.

In the current study, insignificant differences were found in both groups as regards BCVA and refraction, either

preoperatively or postoperatively. In this study, the MRSE showed nonsignificant improvement. Our results were consistent with *those of El-Kateb et al. (2017), who found insignificant change at the 6-month visit*, with statistically significant worsening at the one-year visit (21). According to the previously mentioned study, the significant worsening of MRSE at the one-year visit can be attributed to the relative, although nonsignificant, increase in the corneal asphericity (Q-value) at the one-year visit, which may have led to some increase in the myopic element of refraction due to increased central steepening. Most of the similar studies found a nonsignificant change of MRSE during their follow-up visits; *Elbaz et al (2014)(22)* and *Ozgurhan et al (2014)(23)*.

Another finding in our study was that in each group separately, BCVA significantly improved after one month and three months compared to the baseline assessment. These results were confirmed by another previous study (24).

In agreement with our study, A significant improvement in the mean BCVA was observed in the previous study, which increased from 0.30 ± 0.16 logMAR at baseline to 0.23 ± 0.17 logMAR at 24 months ($P = 0.04$) in the p-ACXL group,

and from 0.36 ± 0.22 logMAR to 0.26 ± 0.27 logMAR ($P = 0.02$) in the c-ACXL group. Another study observed similar results. (25).

The mechanism of improved vision in KCN eyes after CXL is unclear. Significant cornea flattening is commonly believed to cause decreased refractive error and improved vision. Hence, simultaneous keratorefractive surgery and CXL in thin corneas (26). Besides, decreased corneal steepness, decreased refractive error, corneal astigmatism, and improvement in other definable topographic indices may be the underlying mechanisms in improving vision (27).

Regarding changes in average K based on the type of CXL, insignificant differences in average K either at baseline, after one month, or after three months ($p > 0.05$) were found in our study. In each separate group, there was no significant difference regarding average K after one month or three months ($p > 0.05$) compared to the baseline assessment. Also, an insignificant change was found after 6 months regarding KMAX.

The K max changes in the context of continuous accelerated cross-linking (CXL) and pulsed light cross-linking (CXL) typically refer to the maximum stiffness or mechanical properties of corneal tissue after these treatments. Continuous Accelerated Cross-Linking generally increases corneal rigidity and stability, leading to higher K max values. Pulsed Light Cross-Linking (CXL) may also increase K max, but the changes can vary based on the specific parameters (intensity, duration, and riboflavin concentration). Continuous CXL often significantly increases K max compared to pulsed CXL, primarily due to the longer exposure times and more uniform cross-linking throughout the corneal stroma. However, no significant changes regarding KMAX were found in our study in either group.

A meta-analysis found that eyes treated with the Dresden protocol showed a KMAX reduction of 0.76 D at one year and 1.22 D at two years (28). Conversely, another study reported that patients undergoing the continuous accelerated CXL (c-ACXL) protocol experienced a greater reduction in KMAX compared to those treated with pulsed accelerated CXL (p-ACXL) at the two-year mark (29). This contrasts with earlier findings, which indicated that p-ACXL led to a larger KMAX reduction at 12 months than c-ACXL (30).

One of the main findings in the current study was that no significant differences between the groups as regards changes in corneal thickness, except for significantly lower inferior CT among patients who underwent continuous CXL (478.94 ± 30.58 vs. 500.50 ± 38.17 ; $p = 0.04$) in comparison to pulsed CXL. Also, in each group, there was a significant decrease in CT either after one month or three months compared to baseline CT ($P < 0.001$).

Consistent with our research, the study by Kang et al. (2021) found that both groups exhibited significant reductions in the thinnest and central corneal thickness (all $P < 0.001$). However, the pulsed group demonstrated a significantly lower thinnest corneal thickness ($P = 0.017$) (31). Another study found no significant differences in corneal thickness between the groups; however, both groups showed a significant reduction in corneal thickness over the follow-up period. (29).

Shen et al. (2016) also observed a consistent decrease in the corneal densitometry measurements in patients treated with ACXL, with values dropping below baseline levels after six months and continuing to decline through the twelve-month follow-up (32).

Lastly, the depth of the demarcation line (DL), which represents the boundary between untreated and treated corneal stroma, has traditionally been used to assess

the effectiveness of ultraviolet treatment. Variations in DL have been observed based on factors such as the duration of irradiation, whether pulsed CXL or continuous CXL was used, corneal epithelium removal, and the concentration of riboflavin applied (33). Our study observed a significantly shallower demarcation line depth in the continuous CXL group compared to the pulsed CXL group after one month and three months ($p < 0.001$). Within each group, the demarcation line was significantly deeper at one month and three months ($p < 0.001$) compared to the baseline assessment.

Consistent with the study of *Kang et al (2021)*, corneal densitometry measurements obtained with the Pentacam device increased in both groups (all $P < 0.001$), with the pulsed CXL group showing significantly higher densitometry values ($P = 0.013$). The demarcation line depth was greater in the pulsed group ($P = 0.015$) (34). However, some studies have not observed a significant difference in DD between the two groups (29, 35).

Previous studies comparing pulsed CXL (pl-CXL) and continuous CXL (cl-CXL) generally support the benefits of pl-CXL. Mazzotta et al. (2014) found that while both pl-CXL and cl-CXL (each with a total energy dose of 7.2 J/cm^2) produced similar functional results, pl-CXL resulted in deeper corneal penetration. However, their study had a small sample size, with only 10 eyes in each group, and used a power of 30 mW/cm^2 for 4 minutes in the cl-CXL group, whereas our protocol utilized 12 mW/cm^2 for 10 minutes (30).

As observed in transepithelial CXL, a shallower DL may indicate less effective cross-linking, potentially leading to suboptimal treatment outcomes. However, studies like that of Abdel-Radi et al. suggest that despite a deeper DL in epi-off techniques, both methods can effectively halt keratoconus progression (36).

No postoperative haze was noticed in either the pulsed or continuous group, but

the continuous group was more prone due to longer time of UV exposure.

Conclusion

In summary, our results indicate that both c-ACXL and p-ACXL treatments are safe methods for halting the progression of corneal ectasia over a 3-month follow-up period. Generally, both of them seem to be effective regarding the visual, refractive, and keratometric outcomes. Meanwhile, more corneal tissue penetration and a deeper demarcation line were noticed with p-ACXL.

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