

Analysis of the effectiveness of transepithelial crosslinking in patients with keratoconus

Análise da eficácia do crosslinking transepitelial em pacientes portadores de ceratocone

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ABSTRACT

Objective: To evaluate the clinical results of Transepithelial Crosslinking (CXL) by analyzing its efficacy in patients with progressive keratoconus. **Methods:** Retrospective cross-sectional study with 49 eyes and 37 patients aged 10 to 50 years submitted to the CXL technique in 2017 at the Instituto Panamericano da Visão, in Goiânia, Goiás, Brazil. The Avedro KXL system was programmed in pulsed mode with interval (1/1 second), using 45 mW/cm² with 7.2 J and 0.25% riboflavin solution of Avedro with irradiated corneas for 8 minutes. Data were collected: sex, age, uncorrected distance visual acuity (UDVA), corrected distance visual acuity (CDVA), astigmatism, pachymetry at the thinnest point and keratometric astigmatism in the preoperative and postoperative periods at 1, 6 and 12 months. The Kolmogorov-Smirnov, Pearson's Chi-square, Friedman, Dunnett, and the Spearman correlation were used. **Results:** Twenty-three patients (62.2%) were female and 14 (37.8%) male. The mean age was 27.89 ± 10.89 years. The UDVA and CDVA significantly improved in the preoperative period in relation to 1 month ($p = 0.01$) and ($p < 0.001$), 6 months ($p < 0.001$ both) and 12 months ($p < 0.001$ both). Astigmatism significantly reduced preoperatively in relation to 6 months ($p = 0.02$) and 12 months ($p = 0.02$). The pachymetry at the thinnest point remained constant in the period ($p = 0.95$). The difference between k2 and k1 (keratometric astigmatism) showed a significant reduction in the preoperative period in relation to 1 month ($p = 0.01$). **Conclusion:** The CXL technique was safe and effective in the treatment and stagnation of the disease in patients with progressive keratoconus.

Keywords: Crosslinking; Epithelium; Keratoconus; Disease progression

RESUMO

Objetivo: Avaliar os resultados clínicos do Crosslinking Transepitelial (CXL) analisando sua eficácia em pacientes portadores de ceratocone progressivo. **Métodos:** Estudo transversal retrospectivo com 49 olhos e 37 pacientes com idades entre 10 e 50 anos, submetidos à técnica de CXL em 2017 no Instituto Panamericano da Visão, em Goiânia, Goiás, Brasil. Foi utilizado o sistema KXL Avedro programado no modo pulsado com intervalo (1/1 segundo), usando 45 mW/cm² com 7,2 J e solução de riboflavina a 0,25% da Avedro com córneas irradiadas por 8 minutos. Foram coletados os dados: sexo, idade, acuidade visual sem correção (AVSC), acuidade visual com correção (AVCC), astigmatismo, paquimetria no ponto mais fino e astigmatismo ceratométrico no pré-operatório e pós-operatório com 1, 6 e 12 meses. Foram utilizados os testes Kolmogorov-Smirnov, Qui-quadrado de Pearson, Friedman, Dunnett à posteriori e a correlação de Spearman. **Resultados:** Vinte e três pacientes (62,2%) eram do sexo feminino e 14 (37,8%) do sexo masculino. A média de idade foi de 27,89 (±10,89) anos. A AVSC e AVCC melhoraram significativamente no pré-operatório em relação a 1 mês ($p=0,01$) e ($p<0,001$), 6 meses ($p<0,001$ ambas) e 12 meses ($p<0,001$ ambas). O astigmatismo reduziu significativamente no pré-operatório em relação a 6 meses ($p=0,02$) e 12 meses ($p=0,02$). A paquimetria no ponto mais fino manteve-se constante no período ($p=0,95$). A diferença entre k2 e k1 (astigmatismo ceratométrico) mostrou redução significativa no pré-operatório em relação a 1 mês ($p=0,01$). **Conclusão:** A técnica de CXL foi segura e eficaz no tratamento e estagnação da doença em pacientes com ceratocone progressivo.

Descritores: Crosslinking; Epitélio; Ceratocone; Progressão da doença

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INTRODUCTION

Keratoconus is characterized by a degenerative, noninflammatory bilateral progressive corneal ectasia.^(1,2) Results in thinning and protrusion of the cornea into conical shape, progressive myopia, and irregular astigmatism.⁽¹⁻³⁾ Its pathophysiology is still unknown and appears to be multifactorial, and in 13% of cases have a family history of the disease.^(1,4,5)

It is a bilateral asymmetric disease whose clinical manifestations may include drop in visual acuity and/or distorted vision and present symptoms of photophobia and hyperemia when associated with progressive myopia and astigmatism; sometimes the contralateral eye has only a high astigmatism.^(6,7)

The progression of keratoconus is characterized by: an increase of at least 1 diopter (D) in keratometric parameters in 12 months; at least 0.75 D increase in keratometric parameters in 6 months; increase of 0.75 D myopia in 12 months in refraction under cycloplegia; loss of at least two lines of sight in the best corrected vision in 12 months.⁽⁶⁾

One of the most commonly used treatments for keratoconus is Crosslinking (CXL). It consists of a minimally invasive therapeutic procedure aimed at blocking the evolution of keratoconus and reducing the need for corneal transplantation by increasing biomechanical force, leading to stiffening of corneal tissue.⁽⁸⁾ This phenomenon occurs by the additional creation of chemical bonds in the corneal stroma by means of highly localized photopolymerization that minimizes exposure of adjacent structures of the eye.^(8,9)

The classic Dresden technique, known as epithelium-off, consists in removal of the corneal epithelium by topical anesthesia, followed by the application of riboflavin solution to saturate the corneal stroma.⁽⁸⁾ Riboflavin acts as a photosensitizer that increases the absorption of ultraviolet light A by the cornea.⁽⁸⁾ Next, ultraviolet radiation A is applied using a total energy equivalent to exposure of 5.4 J/cm².⁽⁸⁾ Postoperatively, the patient may present pain, tearing, and visual blurring. This technique is more associated with a prolonged, uncomfortable recovery period, and with greater potential for infection, scarring, and chronic ocular surface disease. Among other risks.⁽⁸⁾

Transepithelial Crosslinking (without removal of the corneal epithelium: epithelium-on) has the characteristic of keeping the epithelium intact, avoiding patient discomfort, delays in visual recovery and potential risks associated with epithelium removal, such as infectious keratitis or corneal healing disorders.⁽¹⁰⁾

However, its efficacy remains controversial, since the epithelial barrier may limit crosslinking compared to CLX epithelium-off.^(11,12)

Thus, the present study had as objective the clinical results of Transepithelial Crosslinking in order to analyze its effectiveness in carrying patients of keratoconus.

METHODS

Retrospective cross-sectional study of 49 eyes of 37 patients who underwent the Transepithelial Crosslinking at the Instituto Panamericano da Visão in Goiânia, Goiás, Brazil, in 2017.

The system used for the Transepithelial (CXL) Crosslinking Technique (TE) was the KXL Avedro programmed in the interval pulse mode (1/1 second), using 45 mW/cm² for a treatment dose

of 7,2 J, with Avedro 0,25% riboflavin solution with corneas irradiated for 8 minutes.⁽⁹⁾

Included in this study were patients with Crosslinking: patients with keratoconus, aged 10 to 50 years, with worsening of corrected visual acuity of at least one line in the Snellen Table and increased maximum keratometry value of 1.0 diopter (D) in the last six months of observation.⁽⁶⁾

Exclusion criteria were corneal opacities or scars, herpes simplex infection and other infectious keratitis, severe or autoimmune eye surface disease, concomitant infection, previous disease and pregnancy.^(13,14)

The patients who underwent the Transepithelial Crosslinking Technique had the following data collected: gender, age, uncorrected visual acuity (UCVA), corrected visual acuity (CVA), astigmatism, optical fine pachymetry, optical keratometric astigmatism (difference between k2 and k1) preoperatively and postoperatively at 1 month, 6 months and 12 months.

Data were analyzed using the SPSS version 23 of statistical package (Statistical Package for Social Science). Demographic profile was characterized by absolute frequency (n) and relative frequency (%). Data normality was verified using the Kolmogorov-Smirnov test. Comparative analysis of UCVA, CVA, Astigmatism, Thinnest Point Pachymetry and Keratometric Astigmatism were performed using the Pearson Chi-square test and the Friedman test followed by the Dunnett test à posteriori, opting to using the original data, since this way in other studies is used as well, the example carried through it by Heikal et al.⁽¹⁵⁾, avoiding the use of conversions prior to statistical analysis. In order to verify the relationship between the exploratory variables, the variance between the preoperative and 1 month, 6 and 12 months postoperatively was extracted and the Spearman correlation was applied. In all analyzes, a significance level of 5% was adopted ($p < 0.05$).

The study met the ethical criteria of Resolution 466/12 of the National Health Council and was approved by the Research Ethics Committee of the Pontifícia Universidade Católica de Goiás under Opinion No. 3,236,968 / 2019.

RESULTS

Seventy-seven patients (43 male and 34 female) who underwent the Transepithelial Crosslinking at the Instituto Panamericano do Brasil, in Goiânia, Goiás, Brazil, were examined in the year of 2017. However, the results in this study were considered only for those patients who attended medical appointments at the recommended times.

Thus, the study comprised 49 eyes of 37 patients, 23 (62.2%) female and 14 (37.8%) male. All patients analyzed completed the 12 months postoperative follow-up.

The average age was 27.89 (± 10.89) years, with the lowest identified age of 10 years and the highest of 49 years. Regarding age group, there was a higher prevalence between 20 and 29 years, with a total of 12 (32.4%) patients and 43.2% of patients over 30 years, as shown in Figure 1.

In the uncorrected visual acuity (UCVA), a preoperative mean of 0.58 \pm 0.25 was obtained and in the corrected visual acuity (CVA) a preoperative average of 0.62 \pm 0.24. There was a significant increase in both from the first postoperative month and this improvement remained at all postoperative intervals ($p < 0,001$), as shown in Table 1. This reflects improved vision quality after surgery.

Preoperative astigmatism averaged 2.80 ± 2.44 diopters (D), with significant reduction mainly in the first postoperative month and remaining at all postoperative intervals ($p=0,03$) (Table 1), reflected an improvement in vision after performing the Transepithelial Crosslinking.

The pachymetry at the thinnest point had a preoperative average of $476.7 \pm 53.8 \mu\text{m}$ and there was no significant difference ($p=0,95$) (Table 1), keeping its values constant after CXL epithelium-on, revealing stabilization of this thickness after this procedure.

Regarding keratometric astigmatism, represented in Table 1 by the difference in the values of k_2 and k_1 by the symbol Δ , a preoperative average of 2.89 ± 1.90 D was observed. 1, 6 and 12 months postoperatively ($p= 0.01$), mainly from preoperative to 1 month postoperatively, resulting in clinical improvement after the completion of the Transepithelial Crosslinking.

Regarding the comparison between the analyzed intervals, uncorrected visual acuity (UCVA) and corrected visual acuity (CVA) increased significantly in the preoperative period compared to 1 month ($p=0,01$) and ($p<0,001$), 6 months ($p<0,001$ both) and 12 months ($p<0,001$ both) postoperative follow-up, respectively.

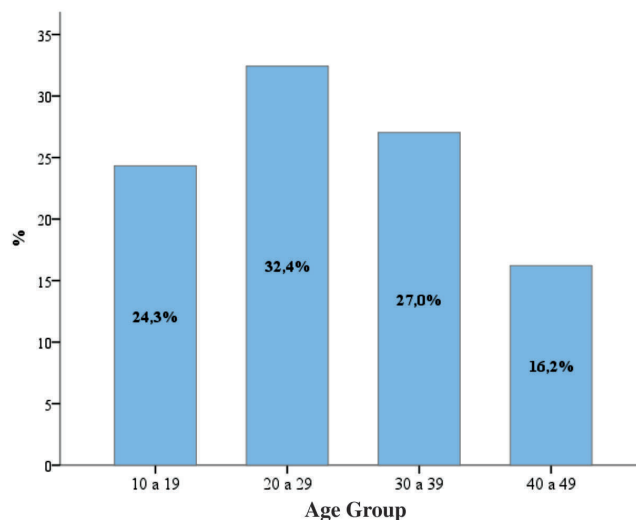


Figure 1: Relative frequency of the age range of patients undergoing Transepithelial Crosslinking.

Table 1
Pre and postoperative mean variables of patients undergoing Transepithelial Crosslinking

	Intervention (Average \pm SD)				p-Value*
	Pré-operatório	1 month	6 months	12 months	
UCVA	0.58 ± 0.25	0.69 ± 0.28	0.74 ± 0.27	0.70 ± 0.26	<0.001
CVA	0.62 ± 0.24	0.80 ± 0.22	0.79 ± 0.22	0.79 ± 0.23	<0.001
Astigmatism (diopters)	2.80 ± 2.44	2.44 ± 1.76	2.43 ± 1.87	2.30 ± 1.72	0.03
Pachymetry (μm)	476.7 ± 53.8	2.89 ± 1.90	476.7 ± 53.8	2.38 ± 1.98	0.95
Δ (D)	479.7 ± 44.6	2.49 ± 1.92	478.9 ± 42.2	2.53 ± 1.79	0.01

* Friedman test followed by Dunnett test a posteriori

SD: standard deviation; p: p value.

UCVA: uncorrected visual acuity; CVA: corrected visual acuity; Pachymetry: at the thinnest point; Δ : keratometric astigmatism: difference in K_2 and K_1 values; D: diopters.

Astigmatism significantly decreased preoperatively from 6 months ($p= 0.02$) and 12 months postoperatively ($p= 0.02$). The pachymetry at the thinnest point had no significant difference in any of the intervals, keeping its values constant before and after surgery. Keratometric astigmatism showed a significant reduction preoperatively compared to 1 month postoperatively($p= 0.01$). The average variation of each of these parameters is shown in Figure 2.

When analyzing the interference of the result of one variable over another, that is, to ascertain, for example, if the improvement of keratometric astigmatism implies an improvement of visual acuity, it was observed that only the result of uncorrected visual acuity will affect the result of corrected visual acuity, thus showing a significant correlation only in UCVA with CVA ($r = 0.61, p < 0.001$), highlighted in Table 2, showing that the variation of one will influence the variation of the other. Thus, the results of the other variables will not affect the improvement or worsening of the others.

DISCUSSION

It was observed in our study with 49 eyes of 37 patients that most patients were female (62.2%). The average age found was $27.89 (\pm 10.89)$, with the lowest identified age of 10 and the highest age of 49, with the highest prevalence age between 20 and

29 (32,4%). In our study, 43.2% of the patients were found to be between 30 and 49 years old, approaching the averages found in the studies by Hersh et al. (16) and Rush et al. (17), but which showed no significant difference. The literature shows that the prevalent age group of patients with keratoconus is puberty during the second decade of life, usually between 13 and 18, but the condition may evolve mainly during the second and third decades of life, exceptionally until the fifth decade. (1,4,5) Initial manifestation in the third decade is less frequent and quite rare after age 30. (1) There is no change in the incidence of keratoconus according to gender and race. (5)

In their work, Santhiago et al. points out that there is sufficient evidence to assert that Crosslinking is effective in stabilizing corneal ectatic disease. (18) This fact was proved in this study by showing the improvement of parameters analyzed postoperatively. Sandvik et al. observed a halving of the need for keratoplasty in keratoconus patients after the introduction of treatment with Crosslinking, revealing its effectiveness in stagnating of this disease. (19)

Akbar et al. observed in their study carried though with 26 eyes of 26 patients with Transepithelial Crosslinking that the most were male (53,85%) and average age of $24,54 (\pm 5,16)$, with significant improvement of UCVA, CVA and astigmatism, significant reduction in the thinnest point pachymetry and

maximum K at 3, 6 and 12 months after the surgery in comparison to the daily pay-operatório, without no postoperative complication

intra or told&tC;&tD;(20&tE;) &tF;They concluded that the CXL Epi&tG;on&tH; is a safe and efficient procedure that hinders the

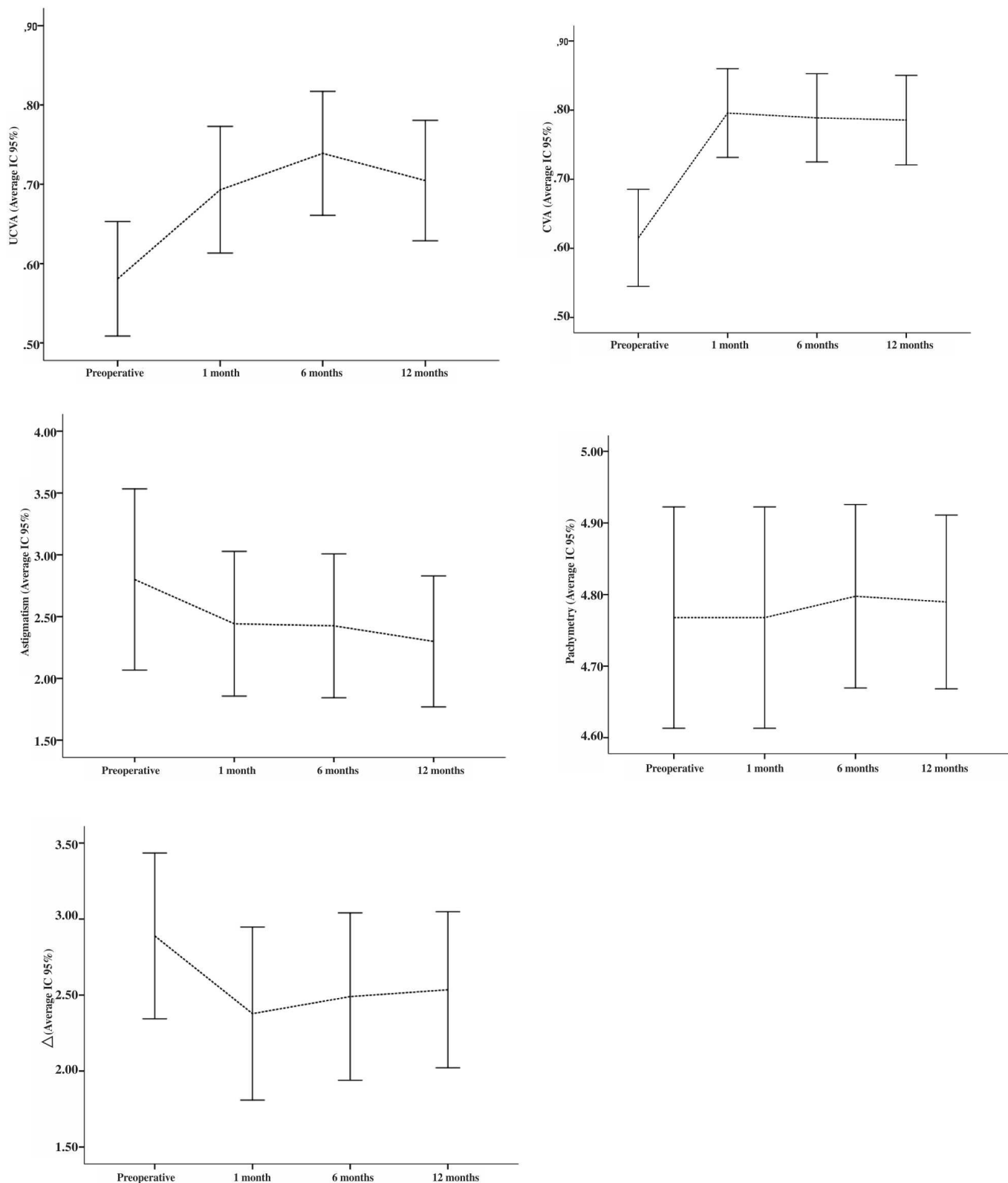


Figure 2: Evolution of variables in Pre and postoperative patients who underwent Transepithelial Crosslinking

Table 2
Correlation of variables in pre and postoperative patients who underwent Transepithelial Crosslinking

	UCVA	CVA	Astigmatism	Pachymetry
CVA	r = 0.61; p < 0.001			
Astigmatism	r = -0.07; p = 0.63	r = 0.04; p = 0.80		
Pachymetry	r = 0.05; p = 0.71	r = 0.05; p = 0.73;	r = 0.00; p = 0.99	
Δ	r = 0.22; p = 0.12	r = 0.16; p = 0.2	r = -0.07; p = 0.65	r = 0.10; p = 0.51

* Spearman correlation

UCVA: uncorrected visual acuity; CVA: corrected visual acuity; Pachymetry: at the thinnest point; Δ: keratometric astigmatism (difference between K2 and K1 values)

progression of the illness in fine keratoconus corneas, and corroborating with the present one searches to also observe the improvement of these parameters, except the reduction of the pachymetry and higher prevalence in males, with the same time of follow-up of 12 months postoperatively, also proving the effectiveness in the treatment of the progression of keratoconus observed here.

This fact was also confirmed by Hersh et al. carried through with 82 eyes of 56 patients aged 18 to 60 treated with CXL epi-on, in which it was observed that the majority (78,57%) belonged to the masculine sex, with average age of 31.4, with significant improvement only in K max and UCVA over 1 year, with transient corneal erosion and epitheliopathy reported in 21% of eyes.⁽¹⁶⁾ It was noted that minor postoperative contingencies did not impair the efficacy of CXL epi-on in the treatment of keratoconus and a higher prevalence in males.

Caruso et al. observed in their study with 25 eyes of 19 patients that the majority (60%) were male and mean age 26.3 (± 8.3) years, with significant improvement in visual acuity and keratometry in 6, 12 and 24 months of follow-up in mild keratoconus cases and also concluded that CXL epi-on safely interrupted the progression of keratoconus and achieved clinical stabilization of the disease progression in all cases, which lasted 24 months without endoscopy notable side effects.⁽²¹⁾ Thus, the longer postoperative follow-up showed the same results observed in the present 12-month follow-up study, with higher prevalence in males, and the differential of this technique did not provide relevant side effects.

Another study consistent with the present research was that of Heikal et al. carried through with 30 eyes of 18 patients aged 17 to 38 with CXL epi-on, in which they observed a mean age of 25.2 (± 6.19) and significant improvement in CVA, astigmatism and keratometry in patients with keratoconus within 12 months of follow-up, stopping the progression of keratoconus. A significant reduction in pachymetry at the thinnest site was observed after CXL epi-on and recovering toward preoperative thickness.⁽¹⁵⁾

Akbar et al., when comparing CXL epithelium-1659 on and CXL epithelium-off, with 32 eyes of 64 patients, distributed equally between the two techniques, found a mean age of 24.47 (± 4. 90) years in the CXL epi-on and 24.81 (±6,39) years in CXL epi-off, which was not statistically significant, and found in both significant improvement of the UCVA, CVA and corneal topography at 12 and 18 months postoperatively, with greater reduction in keratometry

and thinner pachymetry with CXL epi-off.⁽²²⁾ There was clinical stabilization in 94% of eyes with CXL epi-off and in 75% of eyes in CXL epi-on and progression in 25% in eyes with CXL epi-on and in 6% with CXL epi-off, and 20% of eyes with pachymetry less than 400 μm.⁽²²⁾ They concluded that CXL epi-on may be offered as a salvage treatment in patients with a pachymetry of less than 400 μm, unsuitable for an invasive procedure.⁽²²⁾

In the randomized study by Rush et al. with 144 eyes with CXL epithelium-on and CXL epithelium-off aged 11 to 58, they observed in both majority (greater than 66%) comprised of men and an average age of 29.8 (±2,5) in CXL epi-on and 31.5 (±3) in CXL epi-off, with no significant differences between groups.⁽¹⁷⁾ They observed a greater improvement in keratometry with CXL epi-off and improvement in both of CVA, with no significant difference between groups after 24 months of follow-up.⁽¹⁷⁾

The meta-analysis by Zhang et al. with 7 prospective randomized trials involving 344 eyes of 305 patients revealed significant postoperative keratometry and central pachymetry differences between patients treated with CXL epi-off and CXL epi-on but no significant differences in acuity were found. between groups, and concluded that CXL epi-on has a more protective influence on corneal thickness than CXL epi-off, and results in less postoperative corneal flattening.⁽²³⁾ This study corroborates the findings of the present study by showing improvement of these parameters, especially pachymetry, with CXL epi-on.

Kobashi et al., In their meta-analysis of 7 randomized controlled trials involving 505 eyes, found significantly greater improvement in CXL epi-off and significantly greater improvement in central pachymetry and CVA with CXL epi-on during observation periods of 1 year⁽²⁴⁾ as well as the present study which also observed improvement of these parameters with CXL epi-on.

CONCLUSION

It was observed that UCVA, CVA and astigmatism showed significant improvement in the first month, remaining stable until the sixth month. The lowest corneal thickness observed remained constant before and after surgery. There was no significant change in keratometric parameters between the preoperative period and the 6-month evaluation.

The results of our study revealed that the epithelium-on of crosslinking was safe and statistically effective in treating and stagnating of the disease in patients with progressing keratoconus.

Further studies are needed to determine the advantages and disadvantages of the epithelium-on and epithelium-off of Crosslinking larger samples and longer follow-up to make meaningful conclusions.

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