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Corneal haze after accelerated crosslinking and crosslinking with excimer laser - a Scheimpflug densitometry analysis

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SUMMARY

ABBREVIATIONS LIST

CHUC – Centro Hospitalar e Universitário de Coimbra

CXL – Corneal crosslinking

KC – Keratoconus

PDFG – Platelet-derived growth factor

PRK – Photorefractive keratectomy

TGF-β – Tumor growth factor β

UV-A – Ultraviolet A

ABSTRACT

INTRODUCTION: Keratoconus (KC) remains an important cause of progressive visual impairment in young patients, so timely treatment of the disease is crucial. Crosslinking (CXL) is a procedure that strengthens the corneal stroma, avoiding its progressive deformation, and is the only intervention known to halt the progression of KC. Photorefractive keratectomy (PRK) is sometimes combined with CXL to regularize the corneal surface and improve visual acuity. Corneal haze is a known complication of both CXL and PRK, despite having different pathophysiologic pathways, and can be measured through corneal Scheimpflug densitometry.

PURPOSE: To determine the anatomical features and natural evolution of corneal haze resulting from CXL and CXL combined with PRK through Scheimpflug densitometry analysis.

METHODS: A retrospective observational study of 21 eyes from 20 patients who underwent CXL or CXL combined with PRK at Centro Hospitalar e Universitário de Coimbra (CHUC) between 2018 and 2020. The sample was divided into 2 groups according to the type of surgery. Postoperative corneal densitometry measurements of the anterior (120 μm), posterior (60 μm) and intermediate layers of the cornea and the concentrical zones with intervals ranging from 0 to 2, 2 to 6, 6 to 10 and 10 to 12 millimeters (mm) were obtained using the Scheimpflug-based scanning device. The comparison of corneal haze intensity between surgical groups and its evolution between 6 and 12 months after surgery was studied.

RESULTS: Median age at surgery was 25.0 years (IQR=11.0). Concerning both groups, statistically significant decreases were found in densitometry values of the anterior layer and total cornea in the 0-2 mm, 2-6 mm and 6-10 mm concentric regions as well as in the 6-10 mm zone of the central layer. At 12 months of follow-up, patients submitted to CXL and PRK presented higher densitometry values in the total posterior layer (p=0.011) and total cornea at 10-12 mm concentric region (p=0.025) than the CXL group. The CXL alone group showed a significant pairwise decrease in corneal densitometry in all layers and total densitometry at the 6-10 mm concentric zone (p=0.043). The CXL and PRK group had a significant decrease in densitometry values in the 0-2 mm (p=0.007), 2-6 mm (p=0.015), and total circumference (p=0.041) of the anterior layer, as well as in the 0-2 mm region of the center layer (p=0.032) and total densitometry measurement (p=0.012).

CONCLUSION: Corneal haze decreased between 6 and 12 months postoperatively when considering both procedures and individually. Additionally, corneal haze was more significant in patients who underwent CXL with PRK.

KEYWORDS

Keratoconus

Corneal crosslinking

Excimer laser

Corneal haze

Scheimpflug densitometry

RESUMO

INTRODUÇÃO: O queratocone (KC) permanece uma causa importante para a deterioração progressiva da visão em doentes jovens. Assim, o tratamento atempado é crucial. O *crosslinking* (CXL) é um procedimento que confere resistência ao estroma da córnea, evitando a sua deformação continuada, e é o único tratamento capaz de impedir a progressão do KC. A queratectomia fotorrefrativa (PRK) é por vezes combinada com CXL para regularizar a superfície da córnea e a melhorar a acuidade visual. O *haze* corneano é uma complicação conhecida de ambos os procedimentos, CXL e PRK, embora tenham processos fisiopatológicos diferentes, e pode ser medido através da densitometria por Scheimpflug.

OBJETIVO: Determinar as características anatómicas e evolução natural do *haze* corneano resultante do CXL e do CXL associado a PRK através da análise de densitometria por Scheimpflug.

MÉTODOS: Estudo retrospetivo e observacional de 21 olhos de 20 doentes submetidos a CXL e CXL combinado com PRK no Centro Hospitalar e Universitário de Coimbra (CHUC) entre 2018 e 2020. A amostra foi dividida em 2 grupos de acordo com a técnica cirúrgica. Medições pós-operatórias da densitometria da córnea das camadas anterior (120 µm), posterior (60 µm) e intermedia da córnea e de zonas concêntricas nos intervalos de 0 a 2, 2 a 6, 6 a 10 e 10 a 12 milímetros (mm) foram obtidas através de um aparelho de *scan* baseado em Scheimpflug. Foi realizada a comparação da intensidade do *haze* corneano entre grupos cirúrgicos e estudada a sua evolução dos 6 aos 12 meses após cada cirurgia.

RESULTADOS: A mediana de idade na cirurgia foi 25.0 anos (IRQ=11.0). Considerando ambos os grupos, verificou-se uma diminuição estatisticamente significativa nos valores da densitometria na camada anterior e na totalidade da córnea nas regiões concêntricas dos 0-2 mm, 2-6 mm e 6-10 mm, bem como na região dos 6-10 mm da camada central. Aos 12 meses, os doentes submetidos a CXL e PRK, apresentaram valores de densitometria superiores em toda a circunferência da camada posterior ($p=0.011$) e em toda a córnea na região dos 10-12 mm ($p=0.025$) comparativamente aos que realizaram apenas CXL. O grupo que realizou apenas CXL revelou diminuição em todas as camadas da córnea e na densitometria total na região dos 6-10 mm ($p=0.043$). O grupo submetido a CXL e PRK mostrou uma diminuição significativa nas regiões concêntricas dos 0-2 mm ($p=0.007$), 2-6 mm ($p=0.015$) e em toda a circunferência ($p=0.041$) da camada anterior, bem como na região dos 0-2 mm da camada intermédia ($p=0.032$) e na densitometria total ($p=0.012$).

CONCLUSÃO: O *haze* corneano diminuiu entre os 6 e os 12 meses pós-operatórios considerando ambos os procedimentos e individualmente. O *haze* foi mais significativo em doentes que foram submetidos a CXL com PRK.

PALAVRAS CHAVE

Queratocone

Crosslinking corneano

Laser *Excimer*

Corneal *haze*

Densitometria Scheimpflug

INTRODUCTION

Keratoconus is a non-inflammatory ectasia of the cornea in which a progressive and asymmetric decrease in its paracentral or central thickness occurs, resulting in an outward bulge at the center of the cornea with the development of a conic shape. Consequentially, the patient develops progressive myopia and irregular astigmatism with decreased visual acuity. [1-3] Its onset occurs mainly during puberty or in young adults and develops until the fourth decade of life when it stabilizes. It is a bilateral pathology that usually starts unilaterally and progresses to bilateral. [4, 5]

The etiology of this condition is multifactorial and is not well established. Genetic predisposition and environmental factors play a role in the development of keratoconus. Genome Wide Association Studies have identified numerous genes associated with keratoconus susceptibility. Moreover, having a first-degree relative with keratoconus is established as the most decisive risk factor and 10% to 25% of patients with keratoconus have reported family history. [6, 7] Considering the environmental factors, a strong association between eye rubbing and keratoconus has been widely reported. [7] Allergy, asthma, eczema, and Floppy Eyelid Syndrome are also referred to as risk factors for developing this pathology. [8] Furthermore, an association has been found between keratoconus and systemic conditions such as Down Syndrome, Marfan Syndrome and Ehler-Danlos Syndrome. [4]

According to Hashemi, it affects about 1.38 in a thousand individuals, fluctuating considerably according to the geographic distribution of the population included in the study. [8]

Treatment for keratoconus depends on the stage in which the diagnosis is made. In the early stages, the refractive errors can be corrected with glasses or soft contact lenses, but with the progression of the disease, rigid gas permeable contact lenses can be required. [9] However, nowadays, this pathology is still one of the main indications for corneal transplantation in developed countries. Timely and appropriate treatment in the initial stage of the disease is crucial to avoid a decrease in vision, keratoplasty, and future charges for the patient and society since these patients have a long-life expectancy and a social and professional active life. [8, 10]

Since the end of the 1990s, a more sophisticated procedure to treat progressive keratoconus, corneal crosslinking, emerged intending to stabilize or halt the disease progression and improve patients' visual acuity. Crosslinking is a procedure that promotes the formation of covalent bonds between collagen fibers in the corneal stroma by combining a photosensitizer (riboflavin) with ultraviolet A (UV-A) which stabilizes and stiffens the corneal stroma, thus slowing down or avoiding its progressive deformation. [1, 11] Fibrosis, collagen crosslinking, stromal melting decrease, and inhibition of ocular pruritus are reported as mechanisms resulting from CXL that contribute to stopping keratoconus progression. [12]

Several CXL protocols have been developed, including a combination of CXL with other procedures. One of these protocols advocates topography-guided excimer laser photorefractive keratectomy, in addition to CXL, to combine regularization of the corneal surface with the stabilizing effect of CXL, aiming for the improvement of visual acuity. This treatment protocol is often called the Athens Protocol. [12, 13]

Corneal haze is one of the possible adverse effects that can result from CXL, these also include pain, sterile infiltrates and, less frequently, infection, corneal melting, delayed epithelial healing, ulceration, and perforation. [12]

Corneal haze is a temporary loss of the transparency of the stroma that can result from both CXL and PRK and can cause glare and a decrease in both quality of vision and best-corrected visual acuity. [13-15] The regular spacing between the collagen fibrils and its' small uniform diameter, along with the cellular structure of stationary keratocytes, allow for corneal transparency. [16] Through the years, this postoperative complication has been the target of many studies and is considered to have different physiopathology in both procedures.

Early corneal haze is considered to have its onset within the first three months after the treatment, whereas late corneal haze appears after 6 months. [17] Several studies regarding corneal haze after CXL show an increase in corneal opacity 1 month after the procedure that is maintained until the third month of follow up and decreases from then onwards, most times returning to baseline when reaching 1 year after CXL, affecting the anterior and center layers of the cornea. [15, 18] One explanation for this hyperreflective corneal stroma after CXL is the activation of keratocytes that migrate to repopulate the wounded regions and whose composition has crystalline proteins, which are more reflective and are absent in the stationary keratocytes. [16]

Charpentier states that corneal haze following PRK has an incidence varying between 0.5% and 12%. Most often, this haze is early and transitory, corresponding to the normal healing process. However, rarely, the loss of transparency can be pathological due to subepithelial fibrosis. The normal healing process is possible because of the limbal stem cells that migrate to the de-epithelized regions of the cornea and differentiate into enhancer cells and cells from the basement membrane. As anterior keratocytes suffer apoptosis, they activate neighboring keratocytes, which acquire fibroblast or myofibroblast capacities, the first under the influence of platelet-derived growth factor (PDGF) and fibronectin and the latter due to tumor growth factor β (TGF-β) and PDFG. Typically, myofibroblasts disappear from the regions targeted by the ablation and are replaced by keratocytes that allow the normal regeneration of the basement membrane, reaching normality 1 year after PRK. The critical element in the pathological process is the proliferation and persistency of mature myofibroblasts resulting in a defective regeneration of the epithelial basement membrane. These myofibroblasts produce type I and type III collagen fibrils, the latter having a larger diameter, that are irregularly spaced in the stroma. [13, 19]

The number of myofibroblasts present in the cornea after CXL is inferior in comparison to post PRK. Thus, corneal haze after CXL would be less severe and more transitory than following PRK. [19] Clinically, PRK-related corneal haze appears to be a reticulated subepithelial opacity, whereas CXL corneal haze appears as dust in the stroma or a mid-stromal demarcation line. [16]

Corneal haze can be measured objectively through Scheimpflug densitometry. The Pentacam® (Oculus GmbH, Wetzlar, Germany) is a Scheimpflug-based scanning device that provides a high-resolution three-dimensional image of the anterior segment of the eye with the reconstruction of the anterior and posterior surfaces of the cornea that allows the creation of a pachymetric map. [13, 20] Corneal densitometry is obtained by measuring the backscattered light intensity in different layers and concentric rings of the cornea. The measurements are obtained in grey scale unit varying from 0, total transparency, to 100, total opacification. [18]

To better understand the natural course of postoperative corneal haze after CXL and CXL combined with topography-guided PRK in patients with progressive keratoconus, we compared corneal haze resulting from both procedures using Scheimpflug densitometry measurements.

MATERIALS AND METHODS

This retrospective observational study used a pre-existing anonymized database of individuals who underwent CXL or CXL combined with PRK at the Department of Ophthalmology, Centro Hospitalar e Universitário de Coimbra (CHUC) between 2018 and 2020. A sample of 21 eyes from 20 patients was obtained.

The data collected included sex, surgery date, age at the time of surgery, surgical technique performed, surgery laterality and tomographic corneal data between 4 and 8 months and between 10 and 14 months of follow-up duration. Follow-up time at 6 months and 12 months includes densitometry measurements collected between 4 and 8 months and between 10 and 14 months, respectively.

The inclusion criteria comprised documented progressive keratoconus, corneal pachymetry above 375 µm, absence of other anterior segment pathology and absence of systemic diseases that influence scar formation. Exclusion criteria included corneal pachymetry less than 375 µm, central cornea scar, previous eye surgery and dry eye syndrome.

The CXL procedure consisted of 10 min soak with 0.1% riboflavin followed by irradiation with UV-A light using 10 mW/cm² for 10 min (total dose 6 J/cm²). In the CXL and PRK group, previously to the same accelerated CXL protocol, patients underwent a phototherapeutic keratectomy debridement of 50µm in the central 7 mm epithelium followed by partial topography-guided PRK. Mitomycin C 0.02% was applied for 20 seconds in the latter group. Corneal densitometry measurements were obtained during the postoperative period using the Scheimpflug-based scanning device Pentacam® (Oculus GmBH, Wetzlar, Germany). These measures include the anterior (120 µm), posterior (60 µm) and intermediate layers of the cornea and the concentrical zones with intervals ranging from 0 to 2, 2 to 6, 6 to 10 and 10 to 12 millimeters (mm), as preset on the device.

Descriptive statistics included mean ± standard-deviation or median (interquartile range) for continuous variables as well as absolute and relative frequency for categorical variables. The distribution of the data was assessed using the Shapiro-Wilk test. Chi-square, t-test for independent samples and Mann-Whitney tests were used to compare surgical groups. Wilcoxon test was applied to test for significant changes in the distribution of corneal densitometry between 6 and 12 months after surgery. All statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS), version 25. A p-value inferior to 0.05 was considered statistically significant.

RESULTS

Table 1 - Sample's characteristics of the included eyes.

Variables	Overall (n=21)	CXL (n=5)	CXL + PRK (n=16)	P-value*
Sex, n (%)				0.606
Male	13 (61.9)	4 (80.0)	9 (56.3)	
Female	8 (38.1)	1 (20.0)	7 (43.8)	
Age at surgery (years), median (IQR)	25.0 (11.0)	22.0 (4.0)	26.5 (15.5)	0.153
Examined eye, n (%)				0.624
Right	14 (66.7)	4 (80.0)	10 (62.5)	
Left	7 (33.3)	1 (20.0)	6 (37.5)	
Follow-up time at 6 months after surgery (months), median (IQR)	6.0 (3.0)	7.0 (3.0)	5.5 (2.0)	0.153
Follow-up time at 12 months after surgery (months), mean±SD	11.4±1.6	12.2±2.6	11.1±1.1	0.413

IQR, interquartile range; SD, standard-deviation.
*P-value for Chi-square, t-test for independent samples or Mann-Whitney test.

21 eyes of 20 patients with progressive keratoconus were included in this study. The median age at surgery was 25.0 years (IQR=11.0) and the majority were males (61.9%). Considering the time intervals used for the 6 months and 12 months follow-up, the median follow-up time was 6.0 months for the first group and the mean follow-up time was 11.4 months for the latter group. The right eye was predominantly examined (66.7%). 5 eyes underwent CXL alone and 16 were submitted to CXL and PRK. There were no significant differences regarding demographic or clinical variables between surgical groups. (Table 1)

We determined the overall densitometry measurements at 6 and 12 months following surgery. Statistically significant decreases were found in densitometry values of the anterior layer and total corneal layers in the 0-2 mm, 2-6 mm, and 6-10 mm concentric regions. The central layer registered a significant decrease in densitometry values only at the 6-10 mm zone. There were no significant changes in the posterior layer. (Table 2)

Table 2 - Scheimpflug densitometry measurements at 6- and 12-months following surgery.

Variables		6-months follow-up	12-months follow-up	P-value*
Anterior	**0–2 mm**	28.3±7.1	25.1±4.5	**0.004**
	2–6 mm	21.0±2.5	19.7±2.3	**0.009**
	6–10 mm	17.7±2.7	17.1±2.8	**0.021**
	10–12 mm	24.3±6.4	22.6±5.7	0.305
	Total	21.6±2.5	20.2±2.1	**0.009**
Centre	**0–2 mm**	19.0±3.1	18.0±2.9	**0.042**
	2–6 mm	15.3±1.4	14.7±1.3	0.068
	6–10 mm	14.2±2.9	13.6±2.6	**0.046**
	10–12 mm	20.3±3.6	19.8±3.7	0.639
	Total	16.2±1.8	15.7±1.7	0.063
Posterior	**0–2 mm**	13.6±2.2	13.3±1.7	0.728
	2–6 mm	12.2±1.2	12.0±1.0	0.424
	6–10 mm	12.4±2.4	12.1±2.3	0.164
	10–12 mm	17.5±3.5	17.4±3.8	0.614
	Total	13.3±1.6	13.1±1.5	0.223
Total	**0–2 mm**	20.3±3.5	18.8±2.8	**0.014**
	2–6 mm	16.1±1.5	15.5±1.4	**0.046**
	6–10 mm	14.8±2.6	14.3±2.5	**0.046**
	10–12 mm	20.7±3.9	19.9±3.9	0.478
	Total	17.0±1.7	16.3±1.6	**0.030**

*P-values of Wilcoxon tests for pairwise comparisons.

We compared the corneal densitometry measurements according to the surgery type to study the influence of the intervention on corneal haze. The densitometry measurements at 6 months did not differ between types of surgical intervention. However, at 12 months of follow-up, patients submitted to both CXL and PRK presented higher densitometry values in the total posterior layer (p=0.011) and total corneal layers at 10-12 mm concentric region (p=0.025) compared to patients who underwent CXL solely. We found a significant pairwise decrease in corneal densitometry in all layers and total densitometry at the 6-10 mm concentric zone for patients submitted to CXL (p=0.043) but not CXL and PRK. The latter group exhibited a significant decrease in densitometry values in the 0-2 mm (p=0.007), 2-6 mm (p=0.015), and total concentric zones (p=0.041) of the anterior layer, as well as in the 0-2 mm level of center layer (p=0.032) and total densitometry measurement (p=0.012). (Table 3)

Table 3 - Scheimpflug densitometry measurements over time according to the surgery type.

Variables		6-months follow-up			12-months follow-up			P-value for pairwise comparisons*	
		CXL	CXL+PRK	P-value*	CXL	CXL+PRK	P-value*	CXL	CXL+PRK
Anterior	**0–2 mm**	25.4±6.2	29.2±7.4	0.354	24.9±6.5	25.2±3.9	0.445	0.500	**0.007**
	2–6 mm	19.5±3.1	21.4±2.2	0.208	19.0±2.9	19.9±2.1	0.445	0.345	**0.015**
	6–10 mm	16.5±1.9	18.1±2.8	0.445	15.5±1.5	17.6±3.0	0.153	**0.043**	0.070
	10–12 mm	28.9±7.0	22.8±5.7	0.075	20.5±2.3	23.3±6.3	0.548	0.080	0.959
	Total	20.7±3.0	21.8±2.3	0.398	19.2±2.3	20.5±2.1	0.240	0.080	**0.041**
Centre	**0–2 mm**	18.4±4.1	19.2±2.8	0.445	18.3±5.0	17.9±2.2	0.208	0.893	**0.032**
	2–6 mm	14.5±1.2	15.5±1.4	0.091	14.2±0.7	14.9±1.4	0.275	0.498	0.109
	6–10 mm	13.0±1.2	14.6±3.2	0.275	12.2±1.2	14.1±2.8	0.091	**0.043**	0.170
	10–12 mm	21.4±2.8	19.9±3.8	0.240	17.8±1.8	20.4±3.9	0.091	0.138	0.535
	Total	15.5±1.2	16.5±1.9	0.275	14.8±0.7	16.0±1.8	0.075	0.138	0.179
Posterior	**0–2 mm**	13.2±1.5	13.7±2.4	0.719	13.1±2.3	13.4±1.5	0.398	0.686	0.737
	2–6 mm	11.8±0.8	12.3±1.3	0.548	11.5±0.2	12.2±1.1	0.240	0.500	0.569
	6–10 mm	11.5±1.2	12.7±2.6	0.398	10.8±1.3	12.5±2.4	0.109	**0.043**	0.552
	10–12 mm	16.2±1.3	17.9±3.9	0.548	14.7±1.1	18.2±3.9	0.050	0.225	0.865
	Total	12.5±0.9	13.5±1.7	0.240	12.0±0.3	13.4±1.6	**0.011**	0.136	0.587
Total	**0–2 mm**	19.0±3.8	20.7±3.5	0.313	18.8±4.5	18.8±2.2	0.313	0.588	**0.012**
	2–6 mm	15.3±1.6	16.4±1.4	0.179	14.9±1.2	15.7±1.4	0.398	0.500	0.063
	6–10 mm	13.6±1.3	15.1±2.8	0.445	12.9±1.2	14.7±2.6	0.153	**0.043**	0.182
	10–12 mm	22.2±3.5	20.2±4.1	0.179	17.7±1.5	20.6±4.2	**0.025**	0.080	0.570
	Total	16.2±1.6	17.3±1.7	0.275	15.3±1.0	16.6±1.6	0.109	0.080	0.093

*P-values of Mann-Whitney tests for intergroup comparisons; **P-values of Wilcoxon-signed rank tests for pairwise comparisons.

DISCUSSION

In conclusion, through our study, we managed to objectively quantify the corneal haze evolution following CXL and CXL combined with PRK using Scheimpflug densitometry. Corneal haze decreased between 6 and 12 months postoperatively when considering both procedures and individually. Additionally, corneal haze was more significant in patients who underwent CXL with PRK.

The implementation of the CXL procedure was an important landmark for the management of patients with progressive keratoconus. Despite its groundbreaking significance, it is not without insufficiencies, namely its relative inability to improve the visual acuity of KC patients. The combination with other surgical techniques like PRK allows for a more personalized treatment targeting the needs of each patient. Thus, CXL with PRK allows for a concomitant refractive correction. However, many patients develop postoperative corneal haze. Studying the evolution of corneal haze following these procedures is important to improve the surgical technique and assess its impact on the patient's vision quality, visual acuity and, ultimately, quality of life.

The main purpose of our study was to evaluate the natural course of corneal haze after CXL and CXL associated with PRK and assess existing differences between them through postoperative densitometry analysis.

Considering both procedures, corneal haze evolution found in this study corroborated the decrease that happens at the studied follow-up times described in the literature. [15, 18]

Regarding the intensity of corneal haze, in this study, the results show that at 12 months, patients who underwent CXL alone had an inferior corneal haze in the posterior layer and the concentric zone encompassing 10-12 mm than the CXL and PRK group. However, there was no significant difference at the 6 months observation. These findings are in accordance with the proposed by Moraes, who found a higher incidence of corneal haze in patients submitted to the CXL and PRK combined treatment. [19] Thus, supporting the theory that, since PRK implies corneal ablation, basement membrane regeneration can be defective and increase the number of myofibroblasts present in the areas targeted by the treatment, leading to a more intense opacity as well as its perpetuation in time, and also that the myofibroblast present after CXL alone result in a less intense and more transient corneal haze. [19] Furthermore, Kyomionis reported the presence of linear haze in the posterior region of corneal stroma through slit-lamp examination after CXL combined with PRK and that despite moving towards the anterior surface between the first month and the first year after surgery, it did not disappear completely. [21] Likewise, we found higher corneal haze in the posterior layer of the cornea of patients submitted to that procedure.

Corroborating what was expected, the corneal haze was found to be more significative at the sixth month of follow up in comparison to the twelfth month in the 6-10 mm concentric region of each layer and considering all layers in patients submitted to CXL as well as in the 0-2 mm, 2-6 mm and the total circumference of the anterior layer and in the 0-2 mm concentric zone of the center layer and considering all layers in patients who underwent CXL with PRK. Thus, corneal haze significantly decreased between the observation at 6 and 12 months after surgery in both procedures but in different corneal regions.

One of the limitations of this study is that this is a retrospective, non-interventional study. The small cohort of eyes enrolled in the study, the inclusion of more patients submitted to CXL and PRK than CXL alone, and the fact that some patients presented heterogeneous follow-up times, could limit the scope and interpretation of our findings.

This study was focused on the natural history of corneal haze throughout the first year after the procedure and not so much on the severity and clinical impact of corneal haze for each surgery. We did not perform a comparative analysis with preoperative densitometry measurements, limiting our ability to shed light on the specific anatomical features of the loss of corneal transparency created by each technique.

Nonetheless, we believe our results are very relevant to understanding the differences in corneal haze resulting from the studied surgical procedures and reinforce the importance of using quantitative data to further analyze this effect in future studies.

In this study, we managed to objectively measure the natural history of corneal haze following both CXL alone and CXL combined with topo-guided PRK. For both procedures, corneal haze diminishes consistently throughout the first year after surgery. This tandem behaviour is particularly relevant since both types of surgery can, presumptively, have different pathophysiologic pathways for corneal haze.

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