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STABILITY OF CROSSLINKING TREATMENT COMBINED WITH EXCIMER LASER

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Resumo

Objetivo: O objetivo deste estudo é avaliar a estabilidade a longo prazo do tratamento de crosslinking, quando associado a ablação com laser excimer, em doentes com queratocone, através da avaliação de parâmetros refrativos e topográficos.

Métodos: Estudo retrospetivo que compara um único grupo de doentes em duas avaliações distintas (6 meses após cirurgia *versus* última avaliação disponível), submetidos ao tratamento de crosslinking, em associação com queratectomia fotorefrativa parcial.
O estudo incluiu 74 olhos de 71 doentes e os dados (paquimetria mínima, K1 - meridiano mais plano, K2 - meridiano mais curvo, K médio, K máximo, esfera, cilindro e equivalente esférico) foram obtidos através dos exames complementares de diagnóstico pós-operatórios (Pentacam e Orbscan) e consulta dos processos clínicos. Os valores de acuidade visual corrigida e não corrigida foram avaliados nos mesmos termos.

Resultados: O estudo incluiu 74 olhos de 71 doentes (idade média de 32.12±9.73 anos). Quando comparados os parâmetros aos 6 meses após a cirurgia com a última avaliação (média de 17.09±6.39 meses), descobrimos que todos apresentavam estabilidade a longo prazo, com exceção da acuidade visual corrigida ($p<0.05$), que melhorou em média 0.05 logMAR.
A média da acuidade visual corrigida foi 0.27±0.20 logMAR, aos 6 meses pós-op, e 0.22±0.20 logMAR, na última avaliação. Nenhum doente perdeu mais de 2 linhas na escala de Snellen e a melhoria mais acentuada verificou-se num doente que recuperou 5 linhas.
O K1 médio foi 46.20±3.00 dioptrias (D), aos 6 meses pós-op, e 46.64±3.99D na última avaliação, permanecendo estável ao longo do tempo ($p>0.05$). Os resultados dos outros parâmetros foram semelhantes. K2 (49.81±3.87D e 50.05±4.74D), K médio (48.09±3.19D e 48.38±4.26D), acuidade visual não corrigida (0.52±0.29logMAR e 0.55±0.42 logMAR), equivalente esférico (-4.13±2.80D e -3.70±2.82D) e paquimetria mínima (385.88±52.14 µm e 390.76±45.40 µm).
A esfera e o cilindro aos 6 meses pós-op variaram entre -10.00 e +2.00D, com uma média de -2.89±2.57D e -7.00 e +1.00D, com uma média de -1.94±1.35D, respetivamente. Na última avaliação, a esfera e o cilindro variaram entre -10.00 e +1.00D (média de 2.85±2.43D) e -4.50 e +2.25D (média de -1.66±1.26D), respetivamente.

Conclusão: Os nossos resultados sugerem que a combinação do laser topoguiado com crosslinking leva a uma progressiva melhoria da acuidade visual. Os parâmetros topográficos parecem manter a estabilidade aos 12 meses.

Palavras-chave Queratocone; Crosslinking; Excimer laser; Estabilidade; PRK; Córnea

Abstract

Purpose The purpose of this study is to evaluate the stability of crosslinking treatment associated with excimer laser in patients with keratoconus, through comparison of keratometric and topographic parameters and functional results at 6 months postoperatively with those collected at the last visit.

Methods This study is a retrospective clinical study comparing the results of a group of patients in two different evaluations (6 months *versus* last evaluation) submitted to crosslinking treatment combined with partial topography-guided postoperative keratectomy (PRK).
Seventy-four eyes of 71 patients were assessed and data was collected by reviewing post-operative exams and consulting clinical records.

Results Seventy-four eyes of 71 patients (mean age 32.12±9.73 years) were assessed. When comparing postoperative data at 6 months with the last evaluation (mean follow-up time 17.09±6.39 months), we discovered that all parameters (K1, K2, average K, maximum K, K1 axis, UCVA, spherical equivalent and minimum pachymetry) remained stable, except for BCVA (p-value<0.05). Mean BCVA was 0.27±0.20 log of minimum angle of resolution (logMAR), at 6 months post-op, and 0.22±0.20 logMAR at the last evaluation. It did not show stability over time (p<0.05), instead it improved 0.05 logMAR. No patient lost more than 2 lines of Snellen chart and the greatest improvement was 5 lines.
Mean K1 was 46.20±3.00 dioptres (D), at 6 months post-op, and 46.64±3.99D at the last evaluation, remaining stable over time (p>0.05). The other parameters results were similar, except for BCVA; K2 (49.81±3.87D to 50.05±4.74D), average K (48.09±3.19D to 48.38±4.26D), spherical equivalent (-4.13±2.80D to -3.7±2.82D), UCVA (0.52±0.29logMAR to 0.55±0.42 logMAR) and minimum pachymetry (385.88±52.14 µm to 390.76±45.40 µm).
Sphere and cylinder, at 6 months post-op, ranged from -10.00 and +2.00D (mean -2.89±2.57D) and -7.00 and +1.00D (mean -1.94±1.35D), respectively. At the last evaluation, sphere and cylinder ranged from -10.00 and +1.00D (mean 2.85±2.43D) and -4.50 and +2.25D (mean -1.66±1.26D), respectively.

Conclusion In our study, keratometric and topographic values remained stable at 6 and 12 months postoperatively. Best corrected visual acuity showed a tendency to improve over time.

Keywords Keratoconus, corneal crosslinking, excimer laser, stability, Cornea, PRK

Introduction

Keratoconus is an ectatic disease characterized by progressive corneal thinning with corneal conical protusion, usually more pronounced in the infratemporal[1] and central zones, although other locations have been described[2,3], leading to irregular astigmatism. It affects both genders[4], with a slight male predominance[5] and it typically manifests during the second decade of life[5], commonly around puberty, although earlier[6] and later onsets were also described.

The etiology of the disease is not yet completely understood, however, it is thought to have a multifactorial origin. It involves biochemical and environmental factors in patients with a genetic predisposition.

A decrease in the number of lamellae and in keratocyte density have been described, as well as degradation of fibroblasts in the stroma.[4] Also, changes in lamellae organization and an irregular distribution of the collagen fibrillar mass have been reported, especially around the apex of the cone.[7] An increased activity of proteinase enzymes combined with a decrease in proteinase inhibitors, with subsequent reduction in biomechanical stability is believed to be related to stromal thinning.[8]

Various signs and symptoms may be present, according to the severity of the disease. Decreased visual acuity is usually the first sign and can be followed by corneal thinning, ectasia, Fleisher's rings, Vogt's striaes, corneal scarring, stromal oedema and acute hydrops, as described in the literature.[2,4,9,10,11]

Suspicion of the onset of keratoconus arises when a patient has irregular astigmatism and the diagnosis can be confirmed through corneal topography. Family medical history may also be a clue to the diagnosis.

Keratoconus can appear as an isolated condition, but several systemic disorders have been described in association, such as atopy (eczema, asthma, hay fever), vernal keratoconjunctivitis (VKC), Down syndrome and connective tissues disorders (osteogenesis imperfecta, Marfan syndrome, Ehlers-Danlos syndrome and others). Repeated trauma caused by contact lenses, eye rubbing and allergic eye disease are also strongly associated with keratoconus.[12,13,14] Blepharitis and meibomian glands disfunction were found to be more prevalent in keratoconus patients.[15]

Treatment options may vary according to the severity of the disease, ranging from contact lenses to deep anterior lamellar keratoplasty (DALK), corneal crosslinking (CXL), intra-stromal corneal ring segments (ICRS), penetrating keratoplasty (PK) and, more recently, the combination of CXL with topography-guided ablation with excimer laser, which will be addressed in this study.

Topography-guided photorefractive keratectomy (PRK) comprises an ablation of the cornea with an excimer laser. Corneal CXL consists in a transepithelial administration of riboflavin followed by a high-fluence UVA in a specific toric pattern[17].

The aim of this investigation is to evaluate if the results of this treatment modality can be sustained over time, with stability of the various parameters and, therefore, assess the safety of the procedure.

Methods

This study received approval from the CHUC Ethical Committee.

This is a retrospective, non-randomized clinical study. The inclusion criteria were keratoconus stages II to III, according to de Amsler-Krümeich classification[18], which was based on Sheimplflug analysis by Pentacam (Optikgeräte, Wetzlar, Germany) and corneal topography with Orbscan II (Bausch and Lomb Orbscan Corneal Analysis System, Germany), visual acuity (VA), refraction and slit-lamp examination, contact lenses intolerance and a minimum corneal thickness (CT) of 325µm, after the laser procedure. The exclusion criteria were concomitant eye disease, previous ocular surgery and no follow-up available at the time of the investigation. Patients included in this study were treated between 2016 and 2019. Data was collected manually by reviewing the patients' post-operative Orbscan or Pentacam exams at 6 months and the last evaluation available and by consulting their clinical records. The surgical procedure combined phototherapeutic keratectomy (PTK) and, partial topography-guided photorefractive keratectomy (PRK) followed by same-day high-fluence CXL. The protocol comprised:

1. PTK of 50µm debridement of the epithelium;
2. Partial topography-guided excimer ablation;
3. Mitomycin C 0.02% 20 seconds application;
4. Accelerated corneal collagen CXL.

The CXL consists of applying 0.1% riboflavin, 10 min soak, followed by irradiation with UV-A light (KXL I UVA system, 10 mW/cm², 10 min, total dose 6 J/cm²). This protocol has already been described elsewhere.[19]

The parameters evaluated were uncorrected visual acuity (UCVA) and best corrected visual acuity (BCVA), both measured in log of minimum angle of resolution (logMAR), sphere and cylinder, measured in diopters (D), minimum pachymetry, measured in micrometers (µm), as well as keratometry values (K1 – flattest meridian; K2 – steepest meridian), measured in D. The spherical equivalent (SE) and average K were calculated.

The statistical analysis was conducted using SPSS v26.0 software. Normality was assessed using the Kolmogorov-Smirnov test.

When samples followed a normal distribution, a parametric test was preferred (Paired Samples T-test). If not, a non-parametric test was used (Wilcoxon Signed-Rank Test). P values lower than 0.05 were accepted as statistically significant.

Results

This study included 74 eyes of 71 patients (41.7% female and 58.3% male), with ages between 18 and 56 years old (mean 32.12±9.73 years).

The collected data comprised topography and keratometry values from Pentacam or Orbscan exams (Figure 1), acquired at 6 months post-operatively and at the last follow-up evaluation, which ranged between 12 and 37 months post-op (mean 17.09±6.39 months).

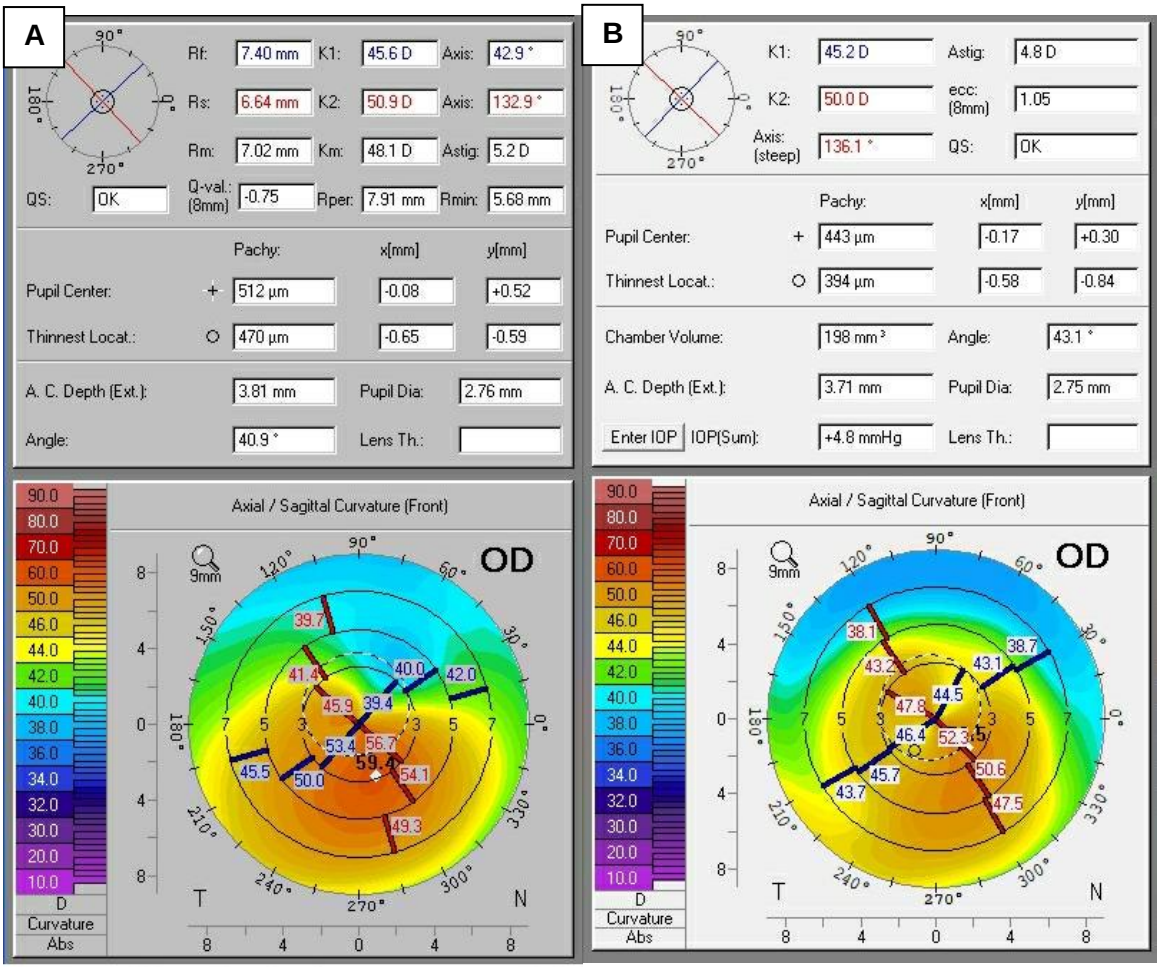

Figure 1. Pentacam exams: topographic comparison before (A) and after (B) simultaneous topography guided photorefractive keratectomy and corneal crosslinking. In this study, we compared these parameters at 6 months after surgery with the last evaluation.

Results at 6 months after surgery revealed a mean K1 (flattest meridian), K2 (steepest meridian) and average K of 46.20±3.00D, 49.81±3.87D and 48.09±3.19D, respectively. The mean BCVA at 6 months post-op was 0.27±0.20 log of minimum angle of resolution (logMAR), the mean UCVA was 0.52±0.29 logMAR and the sphere and cylinder were comprised between -10.00 and +2.00 (mean -2.89±2.57D) and -7.00 and +1.00D (mean -1.94±1.35D), respectively.

Mean SE was -4.13±2.80D and varied between -11.50 and +0.25D and mean minimum pachymetry was 385.88±52.14µm. (Table I)

Table I Stability of topographic and keratometric parameters, as well as visual acuity at 6 months after surgery and at the last evaluation, displayed as mean and standard deviation with the respective p-value acquired by comparison of the two moments.

	N	6 months	N	Last Evaluation	Test	P-value	Stability
Minimum pachymetry (µm)	59	385.88±52.14	59	390.76±45.40	T-Test	0.15	Stable
Average K (D)	51	48.09±3.19	51	48.38±4.26	T-Test	0.40	Stable
Maximum K (D)	48	52.62 ± 4.48	48	53.39±5.83	T-Test	0.06	Stable
Spherical Equivalent (D)	59	-4.13±2.80	58	-3.70±2.82	Wilcoxon	0.65	Stable
K2 (D)	50	49.81±3.87	50	50.05±4.74	T-Test	0.46	Stable
K1 (D)	63	46.20±3.00	58	46.64±3.99	Wilcoxon	0.24	Stable
UCVA (logMAR)	8	0.52±0.29	8	0.55±0.42	T-Test	0.74	Stable
BCVA (logMAR)	67	0.27±0.20	58	0.22±0.20	Wilcoxon	0.01	Improved

D (Diopters); logMAR (log of minimum resolution angle); µm (micrometre); k1 (flattest meridian); K2 (steepest meridian); UCVA (uncorrected visual acuity); BCVA (best corrected visual acuity).

Results at last evaluation following surgery revealed a mean K1, K2 and average K of 46.64±3.99D, 50.05±4.74D and 48.38±4.26D, respectively. Mean BCVA was 0.22±0.20 logMAR, the mean UCVA was 0.55±0.42 logMAR and the sphere and cylinder were comprised between -10.00 and +1.50D (mean 2.85±2.43D) and -4.50 and +2.25D (mean -1.66±1.26D), respectively. The mean SE was -3.70±2.82D and varied between -12.00 and +1.00D. The mean minimum pachymetry was 390.76±45.40µm. (Table I). At 6 months following surgery, BCVA ranged from 0 to 1.00 logMAR, with a mean value of 0.27±0.20 logMAR. At the last evaluation, it ranged from 0 to 1.00 logMAR, with a mean value of 0.22±0.20 logMAR. There was a 0.05 logMAR improvement, although 20 eyes (27%) showed no improvement. In 23 eyes (31%) there was an improvement between 0.10 and 0.50 logMAR (one eye improved 5 lines, another eye improved 4 lines, one eye improved 3 lines, six eyes improved 2 lines and

fourteen improved 1 line). In 31% of cases, BCVA improved during the follow-up period. (Figure 2)

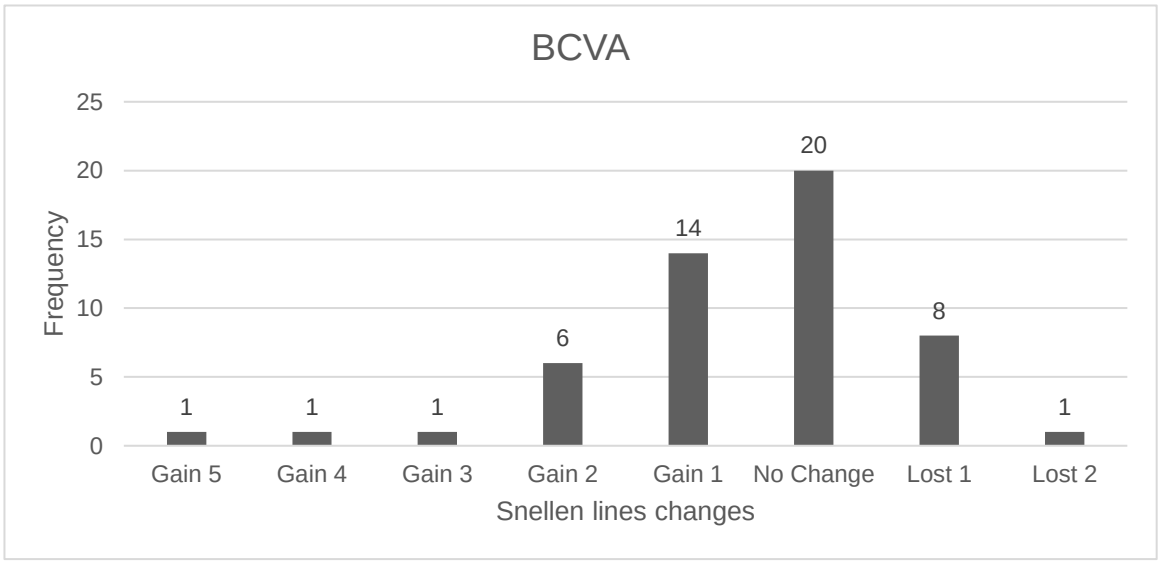

Figure 2: BCVA: Long-term changes in Snellen lines.
BCVA best corrected visual acuity

The Paired Samples T-Test showed no statistically significant differences ($p>0.05$) between means of the minimum pachymetry, average K, maximum K, K2 and UCVA, between 6 months and last evaluation postoperatively.

The Wilcoxon Signed Rank-Test revealed no statistically significant differences ($p>0.05$) between mean spherical equivalent and K1. The test showed, however, a statistically significant difference ($p<0.05$) between the means of BCVA, at 6 months and at the last visit, the only parameter that did not remain stable over time.

The different parameters ranges are presented in Table II.

Table II Minimum and Maximum values of all parameters assessed, at 6 months after surgery and at the last evaluation.

	6 months		Last Evaluation	
	Minimum	**Maximum**	**Minimum**	**Maximum**
Minimum pachymetry (µm)	264.00	589.00	285.00	574.00
Average K (D)	42.60	57.20	40.95	67.30
Maximum K (D)	44.20	63.60	43.50	78.40
Spherical Equivalent (D)	-11.50	-0.25	-12.00	1.00
Sphere (D)	-10.00	1.50	-10.00	1.00
Cylinder (D)	-7.00	1.00	-4.50	2.25
K2 (D)	43.40	59.60	41.90	69.30
K1 (D)	41.00	54.00	40.00	65.30
K1 Axis (º)	0.00	180.00	0.00	180.00
UCVA (logMAR)	0.10	0.90	0.10	1.30
BCVA (logMAR)	0.00	1.00	0.00	1.00

D (Diopter); logMAR (log of minimum resolution angle); µm (micrometre); k1 (flattest meridian); K2 (steepest meridian); UCVA (uncorrected visual acuity); BCVA (best corrected visual acuity).

Discussion

In this study, we investigated if partial topography guided excimer ablation associated with accelerated corneal CXL could achieve stable outcomes over time, in 74 eyes of 71 patients. Our results showed that minimum pachymetry, K1, K2, average K, maximum K, SE and UCVA achieved stability in this follow-up period. Best corrected visual acuity improved from 0.27±0.20 to 0.22±0.20 (p-value=0.01). Ten percent of the eyes lost 1 or 2 lines, 27% showed no improvement and 31% recovered 1 to 5 lines. Most eyes improved between evaluations and, although BCVA did not achieve stability over time, this was due to improvement.

Corneal CXL is easy to perform and thus is a widely used procedure [20]. Corneal CXL alone is an effective treatment for the stabilization of keratoconus but it does not improve visual acuity. Excimer laser refractive surgery serves as a complementary procedure for visual improvement in keratoconus patients.[21,22] It can be customized to the patient's corneal topography and, in theory, it can reshape the cornea in the desired locations.

Corneal CXL with topography guided laser excimer requires careful pre-operative planning, but it is minimally invasive with few manageable complications[23].

Partial ablation with excimer laser has been introduced for the correction of stable or fruste keratoconus[24]. It involves tissue ablation, which can compromise stability of the disease after corneal CXL, given that it reduces corneal thickness even further. Alpins and Stamatelatos[24] reported a case series (32 eyes evaluated) of patients treated with PRK and a 10-year follow-up with no evidence of progression of the disease.

Moreover, it is worth mentioning several recent articles that report the benefit of sequential ICRS and CXL in regularizing corneal geometry and halting progression[25,26,27,28]. Crosslinking combined with ICRS cannot be performed simultaneously, and thus implies two surgical moments. There is a risk of thermal injury of the cornea around the ring, which can be a disadvantage of this treatment. However, a comparison between the stability of the topographic and keratometric values after CXL with PRK and CXL with ICRS would be of interest, since it would establish which procedure is worth performing the most.

Most of the studies available addressing corneal CXL, with or without PRK, focus on the comparison between parameters before and after surgery, assessing only the efficacy of the treatment. There are only a few studies focusing on stability and comparing parameters at different moments during follow-up. We believe it is important not only to evaluate efficacy of CXL and PRK in keratoconus patients, but also its stability, which was the scope of this thesis. The first follow-up moment was at 6 months after surgery because we needed to ensure the effects of the treatment were already observed. The last evaluation was conducted beyond 12 months, since most ectasias after refractive surgery occur in this period.[29] Randleman et al.[30] described cases of ectasia after refractive surgery as early as a few weeks after the procedure or as late as several years after. However, 50% occurred within the first year of follow-up.

The literature strongly describes the benefits of CXL, with or without same-session excimer laser ablation, when it comes to the progression of keratoconus disease.[31,32] Keratometric and visual acuity improvement are well described, besides cornea strengthening. However, it is crucial to comprehend the long-term stability of the changes induced by the treatment. The aim of this investigation was to establish if patients submitted to CXL treatment combined with partial topography guided PRK could maintain visual acuity, topographic and keratometric parameters throughout the recovery period. Worsening of the condition was our greatest concern since we believed the treatment needed to achieve long-time stability, in order to be considered worth performing.

Previous studies have demonstrated that there is stability in UCVA over time, or even a small improvement, after CXL alone. Witting-Silva et al.[33] reported a 0.09 logMAR improvement in BCVA, and 0.15 logMAR in UCVA, in a prospective comparative study, with a 3-year follow-up period.

Our results are in line with the literature.[34,35,36,] Kondatakis et al.[34] described long term stability in keratometric parameters, in a study comparing simultaneous topography guided PRK followed by CXL with CXL alone.
A study with a 2-year follow-up period[37] assessing the stability of corneal CXL treatment with simultaneous transepithelial topography guided PRK revealed, when comparing results at 6

months after surgery with those at 12 months post-op, long-term stability in UCVA, spherical equivalent K1, K2 and corneal pachymetry. However, similarly to our findings, BCVA did not achieve stability, when comparing values at 6 months after surgery with those at 12 months, having improved over time (0.05 logMAR between evaluations).

The limitations of this study are its retrospective nature, lack of a control group and a small study sample. It would be advisable to extend the follow-up period to at least 3 years. Other parameters, such as index of surface variance, index of vertical asymmetry, index of height decentration and coma were also considered in numerous investigations and would improve the accuracy of the evaluation.

As surgical skills are perfected and with better preoperative characterization of keratoconus patients, new studies are warranted to allow clearer results to arise, guiding us to the best approach for each case individually, improving the chances of achieving stability over time.
In conclusion, we accomplished the main goal of this research by proving that simultaneous CXL combined with PRK can achieve long-term stability and even improve BCVA, which demonstrates the benefits of this treatment modality over time.

Conclusion

In our study, all parameters, except for BCVA, proved to be stable over time when comparing post-operative values at 6 months with the last evaluation.
Best corrected visual acuity was the only parameter that did not achieve stability over time, instead it continued to improve, in most eyes.
Results are limited by the follow-up period and the sample size. It would be advisable to conduct new studies with larger sample population and longer follow-up periods.
Simultaneous PRK with CXL is a treatment worth performing, with encouraging capacity of reaching stability or even improvement over time.

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