ORIGINAL ARTICLE

Stability of Crosslinking Treatment Combined with Excimer Laser for Keratoconus

Estabilidade do Tratamento de Queratocone com Crosslinking Associado a Queratectomia Fotorefrativa com Laser Excimer

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ABSTRACT

INTRODUCTION: The purpose of this study is to evaluate the stability of crosslinking (CXL) treatment associated with photorefractive keratectomy (PRK) with excimer laser in patients with keratoconus, through comparison of keratometric and topographic parameters and functional results at 6 months postoperatively and at the last evaluation.

METHODS: Seventy-four eyes of 71 patients with established kerotoconus who had contact lens intolerance and/or disease progression were included. The eyes were submitted to CXL plus partial PRK and a residual stromal thickness of 325 µm in the end of the laser procedure was required. We compared uncorrected visual acuity (UCVA), best-corrected visual acuity (BCVA), refractive sphere and cylinder, keratometric parameters (K1, K2, Kmax, average K) and minimum pachymetry at 6 months and at last evaluation.

RESULTS: The mean age was 32.12±9.73 years. We report the results at 6 months and last evaluation (occurred between 12 and 37 months postoperatively), mean 17.09±6.39 months. All parameters (K1, K2, average K, maximum K, K1 axis, spherical equivalent and minimum pachymetry) remained stable, except for BCVA which improved 0.05 logMAR (p<0.05). No patient lost more than two lines of Snellen chart and the greatest improvement was five lines.

CONCLUSION: Our results suggest that accelerated CXL with topography-guided PRK in keratoconic eyes resulted in progressive BCVA improvement between 6 months and 12 to 37 months postoperatively. Keratometric and topographic values remained stable postoperatively, confirming the efficacy of the procedure in arresting progression of keratoconus.

KEYWORDS: Combined Modality Therapy; Cross-Linking Reagents; Keratoconus; Lasers, Excimer; Photorefractive Keratectomy.

RESUMO

INTRODUÇÃO: O objetivo deste estudo é avaliar a estabilidade a longo prazo do tratamento de *crosslinking* (CXL) associado a queratectomia fotorefrativa (PRK) parcial com ablação com laser excimer, em doentes com queratocone, através da interpretação de parâmetros refrativos e topográficos aos 6 meses e na última avaliação disponível.

MÉTODOS: Foram incluídos 74 olhos de 71 doentes com queratocone, evidência de progressão e/ou intolerância a lentes de contacto, nos estadios II-III de Amsler-Krumeich, submetidos ao tratamento de CXL associado a PRK parcial, com espessura estromal residual mínima de 325 µm. Os parâmetros avaliados foram a melhor acuidade visual corrigida (MAVC), a queratometria (K1, K2, K médio e K máximo), parâmetros refrativos como o valor da esfera, cilindro e o equivalente esférico (ES) e a paquimetria no ponto mais fino.

RESULTADOS: A idade média foi 32,12±9,73 anos. Reportamos os resultados aos 6 meses e os da última avaliação, entre os 12 e os 37 meses (média de 17,09±6,39 meses). Todos os parâmetros apresentaram estabilidade a longo prazo, com exceção da MAVC que melhorou em média 0,05 logMAR (0,27±0,20 logMAR aos 6 meses 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.

CONCLUSÃO: Os nossos resultados sugerem que a associação CXL acelerado e PRK topoguiado leva a uma melhoria progressiva da MAVC dos 6 meses até aos 12 a 37 meses após o procedimento. Os parâmetros topográficos mantiveram-se inalterados durante este período, o que confirma a estabilização do queratocone.

PALAVRAS-CHAVE: Lasers de Excimer; Queratectomia Fotorefrativa; Queratocone; Reagentes para Ligações Cruzadas; Terapia Combinada.

INTRODUCTION

Keratoconus is an ectatic disease characterized by progressive corneal thinning with corneal conical protrusion, leading to irregular astigmatism. Clinical manifestations consist in decreased visual acuity and irregular astigmatism, and are usually present from the second decade of life, and progression arrests by the fourth to fifth decades.[1] The disease is thought to have a multifactorial origin; it involves biochemical and environmental factors and a genetic predisposition. A decrease in the number and disorganization of lamellae and keratocytes has been described, as well as degradation of fibroblasts in the stroma.[2,3]

Treatment options may vary according to the severity of the disease, ranging from contact lenses to intra-stromal corneal ring segments, deep anterior or penetrating keratoplasty, corneal crosslinking (CXL), and the combination of CXL with topography-guided ablation with excimer laser.[4] Crosslinking is a conservative treatment based on the principle that collagenous tissues such as the corneal stroma can be stabilized by a photochemical reaction using riboflavin, a photosensitizer, and UVA-radiation.[5–7] Excimer laser refractive surgery serves as a complementary procedure for visual improvement in keratoconus patients: topography-guided photorefractive keratectomy (PRK) comprises an ablation of the cornea with an excimer laser; customized to the patient's corneal topography in order to reshape the cornea in the desired areas.[8,9] Its efficacy in arresting progression and improving best corrected visual acuity (BCVA) has been widely proved.[9-11] However, it should be kept in mind that the refractive ablation in keratoconus could be a risk factor for further corneal ectasia. 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, to assess the safety of the procedure.

METHODS

This is a retrospective study. Inclusion criteria were patients with keratoconus in stages II to III, according to the Amsler-Krümeich classification,[12] which was based on Sheimplflug analysis by Pentacam (Optikgeräte, Wetzlar, Germany); a minimal stromal thickness of 325 µm after the procedure; and contact lenses intolerance. 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 were collected manually by reviewing the patients' post-operative Pentacam exams at 6 months and at the last evaluation available and by consulting their clinical records. The surgical procedure comprised:

1. Phototherapeutic keratectomy (PTK) of 50 µm 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, Avedro). This protocol has already been described elsewhere.[10]

The parameters evaluated were uncorrected visual acuity (UCVA) and BCVA, both measured in log of minimum angle of resolution (logMAR), refractive sphere and cylinder, measured in dioptres (D), minimum pachymetry as well as keratometry values K1 (flattest meridian), K2 (steepest meridian) and maximum K (Kmax) 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.

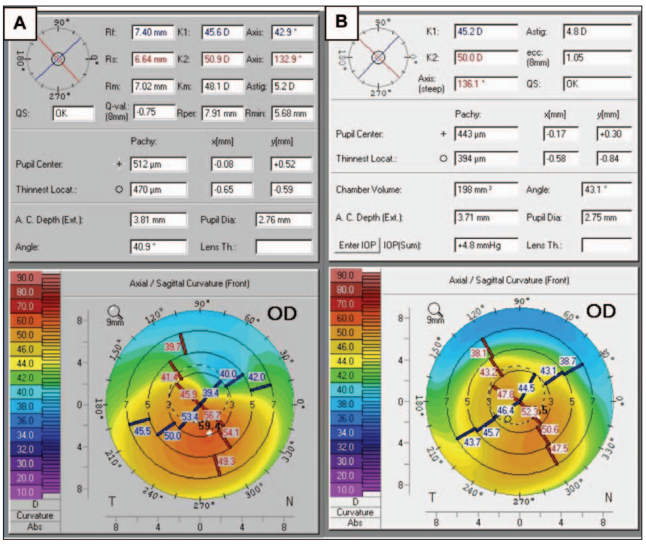

Figure 2. Pentacam exams: topographic comparison before (A) and after (B) simultaneous topography-guided photorefractive keratectomy and corneal crosslinking. In this study, we compared these parameters at 6 months after surgery with the last evaluation.

RESULTS

This study included 74 eyes of 71 patients (58.3% male), with ages between 18 and 56 years old (mean 32.12 ± 9.73 years) (Fig. 1).

The collected data comprised topography and keratometry values from Pentacam or Orbscan exams (Fig. 2), acquired before the procedure, at 6 months postoperatively and at the last follow-up evaluation, which ranged between 12 months and 37 months post-op (mean 17.09 ± 6.39 months).

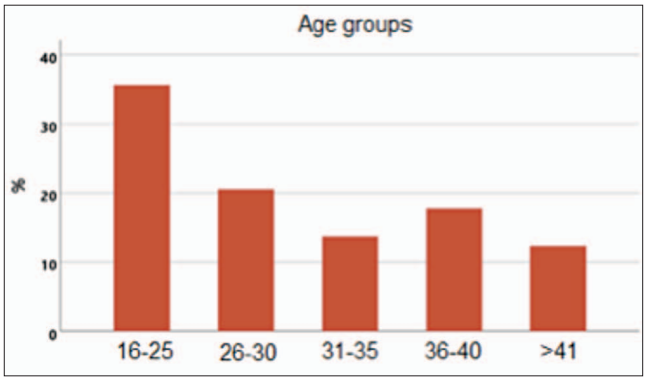

Figure 1. Age distribution of the study population.

Results at 6 months postoperatively revealed a mean BCVA of 0.27 ± 0.20 logMAR, mean UCVA of 0.52 ± 0.29 logMAR, and the sphere and cylinder were comprised between -10.00 and +2.00 D (mean -2.89 ± 2.57 D) and -7.00 and +1.00 D (mean -1.94 ± 1.35 D), respectively. Mean SE was -4.13 ± 2.80 D and ranged between -11.50 and +0.25 D. Mean K1 and K2 were 46.20 ± 3.00 D and 49.81 ± 3.87 D, respectively. Mean average K was 48.09 ± 3.19 D, mean Kmax was 52.62 ± 4.48 D and mean minimum pachymetry was 385.88 ± 52.14 µm (Table 1).

Results at last evaluation revealed a mean BCVA of 0.22 ± 0.20 logMAR, mean UCVA of 0.55 ± 0.42 logMAR and mean refractive sphere and cylinder of 2.85 ± 2.43 D and -1.66 ± 1.26 D, respectively. At the last evaluation, mean SE was -3.70 ± 2.82 D. Mean K1 and K2 were 46.64 ± 3.99 D and 50.05 ± 4.74 D, respectively. The mean average K and Kmax at the last

Table 1. Comparison between mean values of visual and refractive parameters at 6 months and at last evaluation.

Study parameters	6 months	Last evaluation	*p*-value	Stability
UCVA (logMAR)	0.52 ± 0.29	0.55 ± 0.42	0.74	Stable
BCVA (logMAR)	0.27 ± 0.20	0.22 ± 0.20	0.01	Improved
Spherical equivalent (D)	-4.13 ± 2.80	-3.70 ± 2.82	0.65	Stable
K1 (D)	46.20 ± 3.00	46.64 ± 3.99	0.24	Stable
K2 (D)	49.81 ± 3.87	50.05 ± 4.74	0.46	Stable
Kmax (D)	52.62 ± 4.48	53.39 ± 5.83	0.06	Stable
Average K (D)	48.09 ± 3.19	48.38 ± 4.26	0.40	Stable
Minimum pachymetry (µm)	385.88 ± 52.14	390.76 ± 45.4	0.15	Stable

BCVA: best-corrected visual acuity; D: diopter; UCVA: uncorrected visual acuity.

evaluation were 48.38 ± 4.26 D and 53.39 ± 5.83 D (Table 1).

When comparing mean values between assessments, we discovered a 0.05 logMAR improvement in BCVA between 6 months and the last evaluation following surgery (Fig. 3). Analysing these results with greater detail, we learned that 40% of the eyes gained 1 to 4 Snellen lines, 40% remained unchanged and 20% lost between 1 and 2 Snellen lines between the month 6 and the last evaluation (Fig. 4). These patients whose BCVA worsened were the ones with the thinnest corneas, the photorefractive ablation was therefore limited, and the full refractive sphere correction was not performed.

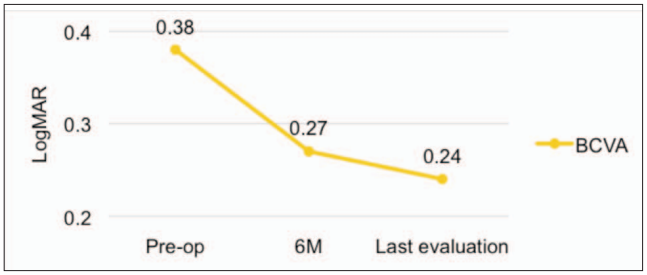

Figure 3. Change in best-corrected visual acuity in logMAR values throughout the study period.

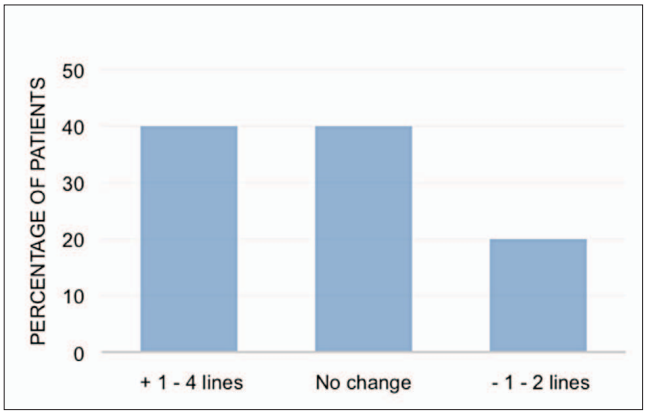

Figure 4. Percentage of eyes with improvement, stability and worsen best-corrected visual acuity regarding changes in Snellen lines between 6 months and at last evaluation postoperatively.

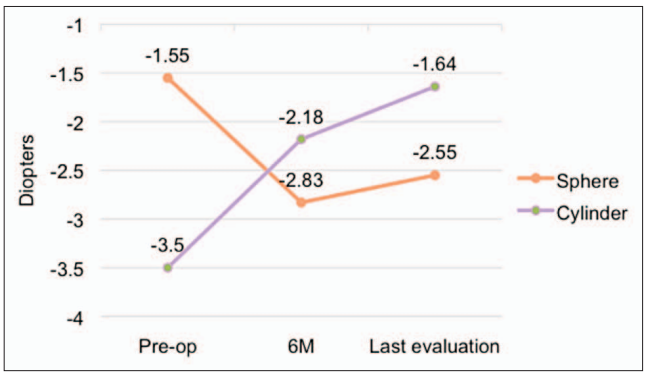

Figure 5. Change in refractive sphere and cylinder values throughout the study period.

The Paired Samples T-test and the Wilcoxon Signed Rank-test showed no statistically significant differences ($p > 0.05$) between mean values of UCVA, K1, K2, average K, Kmax and minimum pachymetry at 6 months and at last evaluation postoperatively. Also, there were no statistically significant differences between mean SE at 6 months and at last evaluation ($p > 0.05$). Although SE remained stable, the absolute value of spherical refractive correction increased, and the absolute value of refractive cylinder decreased (Fig. 5).

The only complication was mild to moderate haze in 12 eyes, with full resolution within 6 to 12 months postoperatively.

DISCUSSION

The literature strongly describes the benefits of CXL, with or without same-session excimer laser ablation, as an effective treatment to arrest the progression of keratoconus.[13-15] Keratometric and visual acuity improvement are well described, besides cornea strengthening. However, there are only a few studies focusing on stability and comparing parameters at different moments during follow-up.[14,16,17]

In this study, we investigated if partial topography-guided PRK plus CXL could achieve stable outcomes over time, given that the laser refractive treatment involves tissue ablation, which can compromise stability of the disease and reduce corneal thickness even further. The first follow-up moment was at 6 months after surgery because we needed to ensure the effects of the treatment were already established and measurable. The last evaluation was conducted beyond 12 months, since most ectasias after refractive surgery occur during this time-span.[18-20]

Our results showed that minimum pachymetry, K1, K2, average K, Kmax, SE and UCVA were stable during a follow-up period between 6 months and up to 37 months, answering the question whether an ablative procedure can be safe in keratoconic eyes when associated with CXL. Best-corrected visual acuity improved from 0.27 ± 0.20 to 0.22 ± 0.20 logMAR. A study with a 2-year follow-up assessing the stability of corneal CXL treatment with simultaneous transepithelial topography-guided PRK revealed long-term stability in K1, K2 and corneal pachymetry, similar to our findings.[17] Besides, another study with a 2-year follow-up period noticed improvement of BCVA over time,[16] and Kondontakis *et al* also showed that keratometric parameters undergo minor changes 6 months postoperatively, and UCVA and BCVA progressively improve up to 24 months.[14] The study with the longest follow-up time is a 10-year study by Kanellopoulus, which further confirms stability on the long term.[21] One author reported improved UCVA but also a continuous decrease in Kmax after CXL only, supposedly due to a progressive flattening after CXL, which was not evident in our analysis.[22]

Regarding the risk of progression of keratoconus, there was stabilization of the disease confirmed through unaltered topographic parameters between 6 and 12 to 23 months, and

we must take into consideration the age distribution, with most patients being young-aged and therefore more likely to have disease progression. The safety of the procedure in younger patients has been addressed previously.[11,23] Besides, this reassures the 325 µm residual stromal thickness as an acceptable limit to prevent complications.

We meant to understand the reason for the continued improvement of BCVA despite stability of keratometric and topographic parameters. There are three theories that could explain this finding: one is that not only epithelial but also stromal healing are part of remodeling mechanisms that happen after CXL, and the latter might not be apparent in topography measurements.[22,24] Secondly, haze resolution could be implicated in BCVA improvement; however, haze is known to have different clinical characteristics and time course in keratoconus than in normal eyes submitted to PRK, and the correlation of haze with BCVA decrease might not be linear.[25-28] Finally, with smoothening and regularization of the corneal surface there is certainly an improvement in higher order aberrations which were not measured in our analysis but could be responsible for better visual function, as stated in other studies.[16,27]

In 20% of patients BCVA worsened between 6 months and last evaluation. These patients had the thinnest corneas, thus the photorefractive ablation was limited, and the full planned sphere correction was not performed; besides, we interpret the variation of BCVA in the same manner as previously explained, as a consequence of stromal healing and other remodeling mechanisms following treatment and not an indicator of progression, because keratometric and topographic parameters remained stable.

The SE value remained unchanged between 6 months and last follow-up, in line with previous reports.[20] However, the refractive cylinder value decreased, probably due to corneal surface regularization, and the sphere absolute value increased, which can be explained by either the fact that keratoconic eyes have longer axial lengths[29] and also because the ablation profile is similar to a hyperopic laser correction, therefore inducing some regular steepening of the cornea and myopization.

The limitations of this study are its retrospective nature, a small study sample and the short follow-up period. Measurement of other parameters, such as index of surface variance, index of vertical asymmetry, index of height decentration and coma could have improved the interpretation of our results.

CONCLUSION

In our study, all parameters remained stable between 6 to 37 months postoperatively, except forbest-corrected visual acuity, which continued to improve in most eyes. Simultaneous photorefractive keratectomy with crosslinking was effective in arresting progression over time, while improving visual acuity.

PRESENTATIONS / APRESENTAÇÕES

Part of this study was presented at the 63rd Portuguese Congress of Ophthalmology in 2020. Parte deste estudo, foi apresentado no 63º Congresso Português de Oftalmologia em 2020.

RESPONSABILIDADES ÉTICAS

Conflitos de Interesse: Os autores declaram a inexistência de conflitos de interesse na realização do presente trabalho.

Fontes de Financiamento: Não existiram fontes externas de financiamento para a realização deste artigo.

Confidencialidade dos Dados: Os autores declaram ter seguido os protocolos da sua instituição acerca da publicação dos dados de doentes.

Proteção de Pessoas e Animais: Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pelos responsáveis da Comissão de Investigação Clínica e Ética e de acordo com a Declaração de Helsínquia revista em 2013 e da Associação Médica Mundial.

Proveniência e Revisão por Pares: Não comissionado; revisão externa por pares.

ETHICAL DISCLOSURES

Conflicts of Interest: The authors have no conflicts of interest to declare.

Financing Support: This work has not received any contribution, grant or scholarship

Confidentiality of Data: The authors declare that they have followed the protocols of their work center on the publication of data from patients.

Protection of Human and Animal Subjects: The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki as revised in 2013).

Provenance and Peer Review: Not commissioned; externally peer reviewed.

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