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"Outcomes of Iontophoresis Cross-Linking in Asymmetric Keratoconus: A Retrospective Analysis of High Visual Acuity Eyes Under 25 Years Old"

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Purpose: To assess the long-term outcomes of transepithelial iontophoresis cross-linking (I-CXL) for early keratoconus with high visual acuity under the age of 25.

Methods: This retrospective study was conducted at the Department of Ophthalmology, Humanitas San Pio X, Milan, Italy, on data collected between 2015 and 2020. Patients diagnosed with early keratoconus and under the age of 25 who underwent to I-CXL were retrospectively reviewed and included in the study if they fulfilled the following criteria: high visual acuity (LogMAR ≤ 0.2) before I-CXL and the fact that the fellow, most advanced eye, had been treated with epithelium off CXL (S-CXL). Corrected distance visual acuity (CDVA), spherical equivalent refraction, thinnest corneal thickness, corneal topography and tomography were assessed at baseline and at least 24 months of follow-up, using Pentacam. Statistical analysis was performed with STATA SE version 17.

Results: Twenty patients with a mean age of 18.5 ± 3.75 months were included. The median follow-up time was 24 months. The statistical analysis showed no significant change over time in CDVA, maximum keratometry and A, B, C values of the Belin Progression Display. Mean baseline CDVA was 0.03 ± 0.07 logMAR, whereas at 24-month was 0.01 ± 0.04. Mean spherical equivalent was −1.29 ± 1.38D at baseline and −1.05 ± 1.51D after 24 months. Preoperative maximum keratometry was 48.35 ± 4.95 D and 48.56 ± 4.96 D after the 2 years of follow-up. Mean baseline A value was 7.13 ± 1.66 mm and 24-month postoperative was 7.43 ± 0.48 mm. Average B value was 5.87 ± 0.55 mm prior to surgery, while it was 5.83 ± 0.60 mm after the last follow-up. Mean baseline and 24-month thinnest point were 498.9 ± 34.29 µm and 500.10 ± 33.45 µm respectively. None of the patients showed a progression of keratoconus.

Conclusion: I-CXL may be considered as a beneficial treatment option for young patients with less advanced keratoconus, although further consensus on patient selection criteria is needed.

Keywords: keratoconus, ectasia progression, cross-linking treatment, iontophoresis

Introduction

Keratoconus (KC) is a progressive corneal disorder characterized by thinning and bulging of the cornea, leading to irregular astigmatism, high order aberrations and visual impairment. Usually, KC is diagnosed in the adolescence and progresses in the first 3–4 decades of life.[1,2] One intriguing aspect of keratoconus is the presence of asymmetry, where the disease affects one eye more severely than the other. Studies have demonstrated that the severity and rate of progression can differ markedly between the eyes in individuals with keratoconus, leading to significant interocular asymmetry, which moreover increases with keratoconus severity in the worse eye.[3] The diagnosis of keratoconus can be enhanced by incorporating pachymetric, elevation-based, and high-order corneal wavefront intereye asymmetry parameters.[4,5]

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The progression of the two eyes can be very different, and it is important to evaluate them carefully. It is known that patients initially diagnosed with unilateral keratoconus, if observed for a mean period of 4 years, commonly develop keratoconus in the fellow eye.[6] The prevalence and incidence of unilateral KC has decreased with increasingly advanced detection methods,[7] spacing from 0.5% to 14.3%.[1,8,9] The Global Consensus determined that true unilateral keratoconus does not exist.[10,11]

Over the years, several treatment modalities have been developed to halt the progression of keratoconus and improve visual outcomes. Among these, corneal collagen cross-linking (CXL) has gained significant attention and is considered the gold standard treatment for keratoconus.

Standard cross-linking (S-CXL) has demonstrated efficacy in halting the progression of keratoconus, improving corneal biomechanics, and stabilizing visual acuity in numerous studies.[12,13]

However, the epithelium-off technique has some drawbacks, including postoperative pain, delayed epithelial healing, and the risk of infection.[14] To address these concerns, alternative approaches such as iontophoresis cross-linking have been developed. Iontophoresis cross-linking (I-CXL), also known as transepithelial cross-linking, aims to enhance riboflavin penetration into the cornea without removing the epithelium. This technique offers the potential advantages of faster epithelial healing, reduced postoperative discomfort and lower risk of infection.[15–17]

The purpose of our study is to assess the outcomes of transepithelial iontophoresis cross-linking for high CDVA keratoconus under the age of 25 in which the fellow, most progressive eye, had been treated with epithelium off CXL (S-CXL).

Materials and Methods

In this study, we included the fellow less advanced keratoconus eye of patients with bilateral, asymmetric keratoconus under the age of 25 who underwent to CXL at Humanitas San Pio X, Milan, Italy, between 2015 and 2020. As stated in Articles 6 and 9 of the European General Data Protection Regulation (Regulation (EU) 2016/679), the processing of personal data for scientific research purposes may be carried out without explicit informed consent, provided that appropriate safeguards are applied, such as data anonymization or pseudonymization. In this retrospective study, previously collected data were used, and the study was conducted under these provisions. The data used were previously collected for other purposes, and their processing for scientific research falls under lawful bases without the need for explicit consent.[18] However, the study was conducted according to the ethical standards of the Declaration of Helsinki.

The inclusion criteria were as follows: for each patient, the eye with the higher disease severity according to ABCD progression display underwent S-CXL; the fellow, less advanced keratoconic eye, no matter of ABCD stage, had to have a CDVA inferior to 0.2 logMAR.

Corrected distance visual acuity (CDVA), spherical equivalent (Sph Eq), thinnest corneal thickness, corneal topographic and tomographic indices were assessed at baseline and at least 24 months of follow-up, using Pentacam (Oculus Optikgeräte GmbH, Wetzlar, Germany).

The iontophoresis procedure we used has already been described.[19] Briefly, it involves the utilization of a riboflavin solution 0.1%. The electrode is connected to a constant current generator (I-ON XL; Sooft), set at 1 mA, for a total dose of 5 mA/5 minutes. Following this, the cornea is exposed to ultraviolet (UV) light from a 10 mW UV lamp (UV-X 2000; IROC Innocross AG, Zurich, Switzerland) at a working distance of 45 mm for a duration of 9 minutes.

As in other recent studies of our research group,[17,20] the definition for re-progression after CXL we have considered was at least 2/3 of the following criteria:[21]

- Progression of A parameter more than 95% CI compared to the follow-up 12 months after surgery;
- Progression of B parameter more than 95% CI to the follow-up 12 months after surgery;
- Reduction of minimal pachymetry of at least 7 µm compared to the follow-up 12 months after surgery (more than 95% CI).

The statistical analysis was performed with STATA SE version 17. All the data are reported as means ± standard deviation. The two-sided paired *T*-test was applied to evaluate the significance level of respective differences between baseline and 24-month follow-up values. The level of statistical significance was set at a P value of less than 0.05.

Table 1 Statistical Analysis Considering the Baseline and the 24-Month Follow-Up

Parameters	Baseline (mean±sd)	24-month FU (mean±sd)	p-value
CDVA (logMAR)	0.03±0.07	0.01±0.04	0.10
Sph Eq (D)	−1.29±1.38	−1.05±1.51	0.14
Kmax (D)	48.35±4.95	48.56±4.96	0.30
A (mm)	7.13±1.66	7.43±0.48	0.33
B (mm)	5.87±0.55	5.83±0.60	0.37
C (μm)	498.9±34.29	500.10±33.45	0.51

Results

Twenty eyes of 20 patients with a mean age of 18.5 ± 3.75 months fulfil the inclusion criteria. The median follow-up time was 24 months. The gender distribution was 16 males and 4 females. The included eyes were 8 right eyes and 12 left eyes. Table 1 displayed the statistical analysis, showing no significant change over time in CDVA, maximum keratometry and A, B, C values of the Belin Progression Display between baseline and 24-month follow-up.

CDVA, expressed in logMAR, displayed no significant change over time, with a mean baseline CDVA value of 0.03 ± 0.07 logMAR and a 24-month follow-up mean value of 0.01 ± 0.04 ($p = 0.10$). In the same way, Sph Eq at baseline was −1.29 ± 1.38 and −1.05 ± 1.51 24 months after, with $p = 0.14$.

About topographic and tomographic parameters assessed with the Pentacam, the statistical analysis showed no significant changes in Kmax values between baseline and 24-month follow-up measurements ($p = 0.30$), with a pre-CXL values of 48.35 ± 4.95 and 24-month post-CXL of 48.56 ± 4.96. Analogously, the A value of the ABCD progression display system remained stable ($p = 0.33$), in fact the preoperative values were 7.13 ± 1.66 mm and the post-CXL were 7.43 ± 0.48 mm, in the same way as the B value, for which the change was from 5.87 ± 0.55 mm to 5.83 ± 0.60 mm ($p = 0.37$). When evaluating pachymetry - C value, we did not find any statistically significant difference ($p = 0.51$), between the baseline (498.9 ± 34.29 μm) and the 24-month follow-up (500.10 ± 33.45).

None of the patients showed a re-progression of keratoconus according to our criteria.

Discussion

Iontophoresis cross linking (I-CXL) is nowadays considered an upcoming treatment for progressive KC, since it has the advantage of reducing patients' postoperative pain, risk of infection, treatment time and speeding the recovery of CDVA.[22,23] Little is known about the efficacy of I-CXL in halting the progression of the ectasia.[24–28] Several studies are trying to investigate the efficacy and safety of iontophoresis cross-linking, evaluating if it could become an alternative treatment option for keratoconus.[22] A recent long-term follow-up (FU) of I-CXL showed no significant change over time in CDVA, Maximum Keratometry, Thinnest point, and A, B, C values of the Belin Progression Display, instead comatic and high order aberrations decreased significantly over time after 7 years of FU, but, however, a 26% progression rate was reported.[17] Another study of the same research group found a 13-year progression rate of 7.4% for S-CXL.[20] This evidence might suggest a change in clinical practice and limit the indication for I-CXL to less advanced stages of the disease or slowly progressive keratoconic patients who are at lower risk and who has high CDVA.[29]

Moreover, a standardization for detecting re-progression after CXL had not been found yet. In fact, among these studies, Al Fayez et al[28] randomized 70 patients to undergo S-CXL or I-CXL and they followed-up them for 3 years. Progression was evaluated considering Kmax: the I-CXL group showed a re-progression of 55%. In a recent study by Belin et al[21] the upcoming version of the ABCD Progression Display was presented. This incorporation will involve displaying 80% and 95% confidence intervals for post-CXL changes using blue gates, which will be visible only when the treatment is indicated. This method of evaluation was used by Vinciguerra et al[17] who found out a progression rate of

26% in eyes treated with I-CXL in a 7-years long-term study, with limited improvement in morphological and functional parameters. Moreover, Soeters et al[30] found a progression rate of 23% at 1 year of FU.

Therefore, according to the literature, I-CXL should be reserved only for less aggressive/slowly progressive keratoconic patients.[31] In our study, we aimed to evaluate keratoconus progression in twenty eyes of twenty patients under the age of 25 treated with I-CXL in the less advanced keratoconic eye whose fellow most advanced eye underwent S-CXL. We found no significant change over time in CDVA, maximum keratometry and A, B, C values of the Belin Progression Display ($p > 0.05$ for all the parameters considered) at least 24 months of FU. The main strengths of our study are the new ABCD-based definition of re-progression and its novelty in considering the efficacy of I-CXL in the second-treated eye. Conversely, the main limitations are the low number of patients considered, the retrospective design, the lack of comparison with the fellow eye treated with S-CXL or with a control group of non-treated eyes and the relatively short period of follow-up.

Conclusion

While our findings suggest that iontophoresis cross-linking (I-CXL) may be a viable alternative for managing less advanced keratoconic eyes with high visual acuity and lower-risk patients, caution is warranted in its application. Additional research is needed to confirm these preliminary findings and establish robust guidelines for the safe and effective use of I-CXL in clinical practice.

Disclosures

None of the authors have financial interests to report.

References

1. Krachmer JH, Feder RS, Belin MW. Keratoconus and related noninflammatory corneal thinning disorders. *Surv Ophthalmol*. 1984;28(4):293–322. doi:10.1016/0039-6257(84)90094-8
2. Rabinowitz YS. Keratoconus. *Surv Ophthalmol*. 1998;42(4):297–319. doi:10.1016/s0039-6257(97)00119-7
3. Eppig T, Spira-Eppig C, Goebels S, et al. Asymmetry between left and right eyes in keratoconus patients increases with the severity of the worse eye. *Curr Eye Res*. 2018;43(7):848–855. doi:10.1080/02713683.2018.1451545
4. Mehlan J, Steinberg J, Druchkiv V, Katz T, Linke SJ. Topographic, tomographic, and corneal wavefront asymmetry in keratoconus: towards an eye asymmetry index EASIX. *Graefes Arch Clin Exp Ophthalmol Albrecht Von Graefes Arch Klin Exp Ophthalmol*. 2022;260(9):2949–2958. doi:10.1007/s00417-022-05642-5
5. Zadnik K, Steger-May K, Fink BA, et al. Between-eye asymmetry in keratoconus. *Cornea*. 2002;21(7):671–679. doi:10.1097/00003226-200210000-00008
6. Holland DR, Maeda N, Hannush SB, et al. Unilateral keratoconus. Incidence and quantitative topographic analysis. *Ophthalmology*. 1997;104(9):1409–1413. doi:10.1016/s0161-6420(97)30123-7
7. Li X, Rabinowitz YS, Rasheed K, Yang H. Longitudinal study of the normal eyes in unilateral keratoconus patients. *Ophthalmology*. 2004;111(3):440–446. doi:10.1016/j.ophtha.2003.06.020
8. Rabinowitz YS, Nesburn AB, McDonnell PJ. Videokeratography of the fellow eye in unilateral keratoconus. *Ophthalmology*. 1993;100(2):181–186. doi:10.1016/s0161-6420(93)31673-8
9. Lee LR, Hirst LW, Readshaw G. Clinical detection of unilateral keratoconus. *Aust N Z J Ophthalmol*. 1995;23(2):129–133. doi:10.1111/j.1442-9071.1995.tb00141.x
10. Imbornoni LM, Padmanabhan P, Belin MW, Deepa M. Long-term tomographic evaluation of unilateral keratoconus. *Cornea*. 2017;36(11):1316–1324. doi:10.1097/ICO.0000000000001295
11. Gomes JAP, Tan D, Rapuano CJ, et al. Global consensus on keratoconus and ectatic diseases. *Cornea*. 2015;34(4):359–369. doi:10.1097/ICO.0000000000000408
12. Wollensak G, Iomdina E. Biomechanical and histological changes after corneal crosslinking with and without epithelial debridement. *J Cataract Refract Surg*. 2009;35(3):540–546. doi:10.1016/j.jcrs.2008.11.036
13. Wollensak G, Spoerl E, Seiler T. Stress-strain measurements of human and porcine corneas after riboflavin-ultraviolet-A-induced cross-linking. *J Cataract Refract Surg*. 2003;29(9):1780–1785. doi:10.1016/s0886-3350(03)00407-3
14. Dhawan S, Rao K, Natrajan S. Complications of corneal collagen cross-linking. *J Ophthalmol*. 2011;2011:869015. doi:10.1155/2011/869015
15. Caporossi A, Mazzotta C, Paradiso AL, Baiocchi S, Marigliani D, Caporossi T. Transepithelial corneal collagen crosslinking for progressive keratoconus: 24-month clinical results. *J Cataract Refract Surg*. 2013;39(8):1157–1163. doi:10.1016/j.jcrs.2013.03.026
16. Vinciguerra P, Mencucci R, Romano V, et al. Imaging mass spectrometry by matrix-assisted laser desorption/ionization and stress-strain measurements in iontophoresis transepithelial corneal collagen cross-linking. *BioMed Res Int*. 2014;2014:404587. doi:10.1155/2014/404587
17. Vinciguerra R, Legrottaglie EF, Tredici C, Mazzotta C, Rosetta P, Vinciguerra P. Transepithelial iontophoresis-assisted cross linking for progressive keratoconus: up to 7 years of follow up. *J Clin Med*. 2022;11(3):678. doi:10.3390/jcm11030678

18. Regolamento (UE) 2016/ 679 Del Parlamento Europeo E Del Consiglio - del 27 aprile 2016 - relativo alla protezione delle persone fisiche con riguardo al trattamento dei dati personali [Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation)], nonché alla libera circolazione di tali dati e che abroga la direttiva 95/ 46/ CE (regolamento generale sulla protezione dei dati). 2016. Italian.
19. Vinciguerra P, Romano V, Rosetta P, et al. Transepithelial iontophoresis versus standard corneal collagen cross-linking: 1-year results of a prospective clinical study. *J Refract Surg Thorofare NJ 1995*. 2016;32(10):672–678. doi:10.3928/1081597X-20160629-02
20. Vinciguerra R, Pagano L, Borgia A, et al. Corneal cross-linking for progressive keratoconus: up to 13 years of follow-up. *J Refract Surg Thorofare NJ 1995*. 2020;36(12):838–843. doi:10.3928/1081597X-20201021-01
21. Belin MW, Alizadeh R, Torres-Netto EA, Hafezi F, Ambrósio R, Pajic B. Determining progression in ectatic corneal disease. *Asia-Pac J Ophthalmol Phila Pa*. 2020;9(6):541–548. doi:10.1097/APO.0000000000000333
22. Vinciguerra P, Randleman JB, Romano V, et al. Transepithelial iontophoresis corneal collagen cross-linking for progressive keratoconus: initial clinical outcomes. *J Refract Surg Thorofare NJ 1995*. 2014;30(11):746–753. doi:10.3928/1081597X-20141021-06
23. Bouman ES, van der V, Pump H, et al. Pain mechanisms and management in corneal cross-linking: a review. *BMJ Open Ophthalmol*. 2021;6(1):e000878. doi:10.1136/bmjophth-2021-000878
24. Vinciguerra P, Rosetta P, Legrottaglie EF, et al. Iontophoresis CXL with and without epithelial debridement versus standard CXL: 2-year clinical results of a prospective clinical study. *J Refract Surg Thorofare NJ 1995*. 2019;35(3):184–190. doi:10.3928/1081597X-20190128-01
25. Vinciguerra P, Montericcio A, Catania F, et al. New perspectives in keratoconus treatment: an update on iontophoresis-assisted corneal collagen crosslinking. *Int Ophthalmol*. 2021;41(5):1909–1916. doi:10.1007/s10792-021-01713-4
26. Stojanovic A, Zhou W, Utheim TP. Corneal collagen cross-linking with and without epithelial removal: a contralateral study with 0.5% hypotonic riboflavin solution. *BioMed Res Int*. 2014;2014:619398. doi:10.1155/2014/619398
27. Rossi S, Orrico A, Santamaria C, et al. Standard versus trans-epithelial collagen cross-linking in keratoconus patients suitable for standard collagen cross-linking. *Clin Ophthalmol Auckl NZ*. 2015;9:503–509. doi:10.2147/OPTH.S73991
28. Al Fayez MF, Alfayez S, Alfayez Y. Transepithelial versus epithelium-off corneal collagen cross-linking for progressive keratoconus: a prospective randomized controlled trial. *Cornea*. 2015;34(Suppl 10):S53–56. doi:10.1097/ICO.0000000000000547
29. Bikbova G, Bikbov M. Standard corneal collagen crosslinking versus transepithelial iontophoresis-assisted corneal crosslinking, 24 months follow-up: randomized control trial. *Acta Ophthalmol*. 2016;94(7):e600–e606. doi:10.1111/aos.13032
30. Soeters N, Wisse RPL, Godefrooij DA, Imhof SM, Tahzib NG. Transepithelial versus epithelium-off corneal cross-linking for the treatment of progressive keratoconus: a randomized controlled trial. *Am J Ophthalmol*. 2015;159(5):821–828.e3. doi:10.1016/j.ajo.2015.02.005
31. Cantemir A, Alexa AI, Galan BG, et al. Iontophoretic collagen cross-linking versus epithelium-off collagen cross-linking for early stage of progressive keratoconus - 3 years follow-up study. *Acta Ophthalmol*. 2017;95(7):e649–e655. doi:10.1111/aos.13538