ORIGINAL ARTICLE

Transepithelial (Epi-on) Corneal Collagen Cross-linking with Supplemental Oxygen as a Treatment for Patients with Progressive Keratoconus in Oman: 1-year Results

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Abstract

Objectives: This prospective study aimed to assess the 1-year outcomes of transepithelial [epithelium-on (Epi-on)] corneal collagen cross-linking (CXL) with supplemental oxygen in patients with progressive keratoconus (KC) in Oman. The study sought to assess efficacy, and effectivity associated with this modified CXL technique.

Methods: A total of 50 eyes of 35 patients with progressive KC underwent Epi-on CXL with supplemental oxygen. Clinical evaluations were performed at various time intervals over 1 year, assessing parameters including uncorrected visual acuity (UCVA), best-corrected visual acuity (BCVA), corneal thickness, and keratometry. The demarcation line depth was also measured.

Results: The results revealed non-significant improvements in UCVA, modest enhancements in BCVA, and corneal thickness stabilization. Notably, keratometry parameters showed initial increases followed by reductions, with a significant decrease in K-mean. The demarcation line reached an average depth of 333.18 microns, signifying deep cross-linking equivalent to conventional CXL.

Conclusion: Transepithelial cross-Linking with supplemental oxygen shows promise in halting the progression of KC. The approach, which avoids epithelial removal, proves effective in stabilizing corneal shape and improving visual acuity. Particularly beneficial for younger patients, this modified CXL technique offers a less invasive alternative to conventional methods, thereby enhancing the management of progressive KC. While further research is needed for validation, current evidence positions transepithelial CXL as a valuable advancement with the potential to significantly impact the treatment landscape for KC.

Keywords: Corneal biomechanics, Corneal collagen cross-linking, Epi-on corneal collagen cross-linking, Keratoconus, Supplemental oxygen, Transepithelial, Visual acuity.

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Introduction

Keratoconus (KC) is a progressive corneal disorder characterized by the thinning and conical deformation of the cornea and leads to irregular astigmatism and a decrease in visual acuity.[1,2] The disease progression typically manifests during adolescence or early adulthood and, if left untreated, can result in severe visual impairment.[3] Keratoconus is associated with visual disturbances and often leads to deterioration in the patient's quality of life.[4] Keratoconus is a global concern that affects individuals of various age groups,[5–7] causing not only visual impairment but also a considerable psychological burden.[5–7] In the Sultanate of Oman, the incidence of KC is reported to be relatively high, and it represents a major public health issue.[8]

The conventional corneal collagen cross-linking (CXL), also known as the Dresden protocol, includes removing the central 8–9 mm zone of corneal epithelium after applying local anesthesia in a sterile environment. Then, a solution of 0.1% riboflavin in 20% dextran is applied every 2 minutes for duration of 30 minutes. Following the pre-treatment phase, the cornea is exposed to ultraviolet A (UVA) light with a wavelength of 370 nm for duration of 30 minutes at an intensity of 3 mW/cm^2 (resulting in a total energy of 5.4 J/cm^2). During this time, the riboflavin solution is applied every 2 minutes. Given a minimum central corneal thickness of 400 µm before exposure to ultraviolet (UV) radiation, it is anticipated that there will be no harm to the endothelium or other tissues within the eye.[9] This method has been considered a gold standard for treating patients with progressive KC or ectasia.[9] However, the classic "epithelium-off" (Epi-off) approach is not without its complications, which include delayed epithelial healing, infection risk, and the potential development of corneal haze.[10] Considering these, an alternative technique known as "epithelium-on" (Epi-on) CXL has gained attention due to its potential to mitigate these adverse effects.[11]

The Epi-on CXL technique, which retains the corneal epithelium during the procedure, addresses some of these concerns, but it has historically been considered less effective in halting the progression of KC.[12] Researchers have explored various methods to enhance the

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absorption of riboflavin into the stroma and increase the efficacy of Epi-on CXL which includes iontophoresis, increasing riboflavin concentration, higher fluence of UVA irradiation, addition of permeability enhancers such as benzalkonium chloride.[13]

One such approach, which forms the basis of our study, involves the application of transepithelial riboflavin combined with supplemental oxygen to promote effective CXL.[12–14] The first important mechanism for effective CXL technique is the presence of an aerobic environment, meanwhile, higher UV intensity significantly creates a hypoxic environment and thus supplementary oxygen is required for potentially deeper and more effective CXL.[15]

The significance of this study lies in the potential of Epi-on CXL with supplemental oxygen to strike a balance between the efficacy of Epi-off CXL and the reduced risk of complications associated with the Epi-on technique.[16] By examining the 1-year outcomes of this innovative approach, we aim to contribute valuable insights into the feasibility of using Epi-on CXL with supplemental oxygen as a primary treatment modality for progressive KC.[17]

The Epi-on CXL technique, if found to be efficacious with supplemental oxygen, could offer a less invasive and more comfortable treatment experience, potentially leading to improved patient compliance and better visual outcomes.[18–20] Additionally, the study's findings can inform ophthalmologists and healthcare providers in Oman and beyond, providing them with evidence-based recommendations for treating KC. This research has the potential to impact clinical practice, influence treatment guidelines, and ultimately enhance the quality of life for individuals living with progressive KC.

Therefore, this study was conducted with the objective of determining the efficacy of transepithelial (Epi-on) CXL with supplemental oxygen treatment in patients with progressive KC in Oman. By assessing the 1-year outcomes of Epi-on CXL with supplemental oxygen, we endeavor to provide a deeper understanding of the technique's efficacy.

Materials and Methods

Study Setting

This prospective study was conducted from December 2021 to February 2023 at the MOD Hospital, a tertiary care facility situated in Muscat, the capital of Oman. The data were collected from participants over the course of 1 year to assess the outcomes of Epi-On CXL with supplemental oxygen in patients with progressive KC.

Study Participants

For this study, we enrolled a total of 35 patients with progressive KC, amounting to 50 eyes in total. The inclusion criteria encompassed patients with a diagnosis of progressive KC who were 12 years of age or older and willing to provide informed consent.

Progression of KC was assessed using Belin ABCD progression display on Pentacam. It was defined as the presence of 1 of 3 parameters (anterior radius of curvature, posterior radius of curvature, and thinnest pachymetry) beyond a 95% confidence interval on KC database or 2 of 3 parameters beyond an 80% confidence level.

Exclusion criteria included the presence of ocular pathologies other than KC, a history of previous corneal surgery, pregnancy, or lactation in female participants, known contraindications to the CXL procedure, and unwillingness to adhere to the specified follow-up visits.

Study Procedure

The study procedure involved subjecting the enrolled participants to Epi-on CXL with supplemental oxygen. To ensure the utmost precision and patient comfort, the procedure was conducted under aseptic conditions with the administration of topical anesthesia. Subsequently, the cornea of each eye was soaked with a transepithelial riboflavin formulation (Avedro ParaCel Transepi Kit – Parts 1 and 2) over a 10-minute period, allowing for effective riboflavin penetration into the corneal stroma. During the soaking time, two drops of Riboflavin part 1 were instilled every 60 seconds for 4 minutes. After 4 minutes, Part 1 Riboflavin was rinsed away with Part 2 Riboflavin and continued applying the same, two drops every 30 seconds for 6 minutes. Following riboflavin soaking, UV irradiance was applied to the cornea at a UV power of 30 mW/cm^2 in pulse mode, delivering a total energy dose of 10 J/cm^2. The total duration of the UV exposure was 5 minutes and 33 seconds. The application of supplemental oxygen was integrated into the procedure, during the UV exposure with specialized goggles to ensure oxygen saturation levels exceeding 90% within the treatment chamber. Subsequently, patients were observed and assessed over the course of 1 year, with key parameters, including uncorrected visual acuity (UCVA), best-corrected visual acuity (BCVA), depth of the corneal stromal demarcation line, and corneal tomography, being meticulously measured and recorded. All 50 eyes of the 35 patients were diligently followed throughout the study, underscoring the completeness of the data collection process and ensuring the robustness of the study's findings.

Sampling Technique

A total of 50 eyes from 35 patients with progressive KC were included in this study. Participants were selected through convenience sampling, where individuals meeting the inclusion criteria were invited to participate in the study. The study aimed to include all eligible patients who presented during the specified study period.

Statistical Analysis

Data collected during the study were analyzed using the IBM statistical package for the social sciences (SPSS) software, version 27.0. Descriptive statistics were employed to present the baseline characteristics of the participants. For comparative analysis, unpaired Student's *t*-tests were used for quantitative data and the Chi-square test for qualitative data. Statistical significance was set at a *p*-value of less than 0.05.

Results

In this study, 50 eyes of 35 patients were included in this analysis. Out of 35 patients, 24 (68.6%) were males, and 11 (31.4%) were females. The mean age of the study participants was 18.52 ± 4.66 years. The median [interquartile range (IQR)] age was found to be 17 (15.75–23) years, and the minimum and maximum ages were 12 years and 29 years, respectively.

The preoperative parameters are given in Table 1. Uncorrected visual acuity exhibits a mean ± SD value of 0.311 ± 0.275 decimals. Best-corrected visual acuity had a value of 0.556 ± 0.312 decimals; thinnest pachymetry had a value of 451.28 ± 40.27 µm. Furthermore, the "K_{max} [diopter (D)]" and "K_{mean} (D)" had values of 57.27 ± 7.43 D, and 48.90 ± 3.87 D, respectively.

Table 2 provides a concise overview of the preprocedure distribution of topographic keratoconus (TKC) stages among the study participants. Notably, the highest percentage is observed in

"KC 3–4," representing 24% of the cases, followed closely by "KC 2," which accounts for 22% of the cases. Furthermore, the table highlights the presence of various stages, including "KC 1," "KC 1–2," "KC 2–3,""KC 3," and "Possible" with varying percentages, which collectively portray the diversity in TKC stages within the study sample.

Table 3 assesses key variables pre- and postprocedure at various time points. Uncorrected visual acuity improved from 0.311 to 0.318 (months 1–12), with nonsignificant changes ($p > 0.05$). Best-corrected visual acuity has improved up to 3 months and becomes stabilized thereafter. It improved slightly although not clinically significant.

The thinnest pachymetry value has reduced over the first 3 months and stabilized thereafter. Both K_{max} and K_{mean} show a minor increase over 3 months period, but both reduced over 1 year with K_{mean} displaying statistically significant decrease, from 48.90 to 48.57 D ($p < 0.05$). All these data are illustrated in Figures 1 to 5. The mean ± SD of the demarcation line was 333.18 ± 30.48 microns. The mean percentage of penetration was found to be 74%.

Discussion

Keratoconus is a progressive and potentially vision-threatening condition that has been the subject of extensive research to identify effective treatment modalities. Corneal collagen cross-linking has emerged as a pivotal approach for managing progressive KC. This study investigated the outcomes of transepithelial (Epi-on) CXL with supplemental oxygen in patients with progressive KC in Oman, offering insights into the efficacy of this technique.

Oxygen play a vital role during CXL procedure which has an impact on efficiency and corneal stiffening. The beneficial effect of CXL on cornea occurs during aerobic conditions and is referred to as the type-II mechanism, where the riboflavin triplets directly react with oxygen and form less toxic singlet oxygen that cross-links collagen. After 10–15 seconds of the reaction, oxygen levels are completely depleted and reactive oxygen free radicals are released by riboflavin photolysis (type-I mechanism) which decreases the CXL efficacy. When higher fluences (increased intensity of UV radiation) are used oxygen is rapidly depleted and its stromal rediffusion is restricted. So, to enhance the effect of CXL on corneal biomechanics previous studies suggested the use of oxygen enrichment during Epi-on CXL protocols.[18,19] In our study, we used specially designed goggles (Boost Oxygen goggles) which create a chamber around the cornea maintaining a constant airflow once connected to the oxygen supply through a humidifier bottle. With a flow rate of 2.5 L/min, it helped us to maintain a constant Oxygen saturation of more than 90% throughout the procedure which was confirmed by an atmospheric oxygen level monitor (gas analyzer). Higher oxygen saturation is thought to enhance the optimization of the photochemical processes related to cross-linking, leading to a more resilient and effective fortification of the corneal tissue.[20] This process is particularly pertinent in the scenario of transepithelial CXL, where exposure to riboflavin and UVA occurs through the intact epithelium.[21] Research findings indicate that the presence of oxygen during the CXL procedure contributes to the production of reactive oxygen species (ROS), fostering the creation of additional cross-links.[22] These heightened effects in cross-linking are believed to provide added stability to the corneal structure, effectively impeding the progression of KC.[20–22]

Our study found that most patients were male (68.6%), consistent with prior studies reporting a male preponderance in KC prevalence.[23] This gender-based difference raises questions about potential genetic or hormonal factors contributing to the pathogenesis of KC. A previous review by Gomes et al.[24] suggested that both genetic and environmental factors might influence KC development, highlighting the complexity of the disease.

The mean age of participants in our study was 18.52 years, aligning with previous research indicating the condition's onset

Table 1: Baseline parameters in the study participants

Parameter	*Mean ± SD*
UCVA (decimal)	0.311 ± 0.275
BCVA (decimal)	0.556 ± 0.312
Thinnest pachymetry value (µm)	451.28 ± 40.27
K_{max} (D)	57.27 ± 7.43
K_{mean} (D)	48.90 ± 3.87

D, diopter

Table 2: Distribution of preprocedure TKC stages

TKC stages	*Number*	*Percentage*
KC 1	5	10
KC 1–2	3	6
KC 2	11	22
KC 2–3	8	16
KC 3	8	16
KC 3–4	12	24
Possible	1	2
Data not available	2	4

Table 3: Comparison of parameters at different periods

Parameter	*Preprocedure (mean ± SD)*	*Postprocedure values (mean ± SD, p-value)*				
		Month 1	*Month 3*	*Month 6*	*Month 9*	*Month 12*
UCV (decimal)	0.311 ± 0.275	0.299 ± 0.278, $p = 0.558$	0.275 ± 0.235, (p =0.203)	0.303 ± 0.245, $p = 0.736$	0.313 ± 0.256, $p = 0.824$	0.318 ± 0.257, $p = 0.727$
BCVA (decimal)	0.556 ± 0.312	0.561 ± 0.272, $p = 0.850$	0.577 ± 0.275, $p = 0.473$	0.576 ± 0.275, $p = 0.394$	0.578 ± 0.274, $p = 0.362$	0.582 ± 0.273, $p = 0.387$
Thinnest pachymetry value (micrometer)	451.28 ± 40.27	446.54 ± 36.33, $p = 0.011$	444.60 ± 36.41, $p = 0.013$	446.45 ± 37.47, $p = 0.140$	445.96 ± 37.25, $p = 0.111$	446.30 ± 37.17, $p = 0.084$
K_{max} (D)	57.27 ± 7.43	57.86 ± 6.78, $p = 0.133$	57.30 ± 7.05, $p = 0.316$	57.17 ± 7.06, $p = 0.589$	56.82 ± 6.58, $p = 0.175$	56.76 ± 6.69, $p = 0.237$
K_{mean} (D)	48.90 ± 3.87	48.97 ± 3.89, $p = 0.833$	49.02 ± 3.99, $p = 0.815$	48.74 ± 3.98, $p = 0.156$	48.68 ± 4.01, $p = 0.067$	48.57 ± 3.94, $p = 0.015$

D, diopter

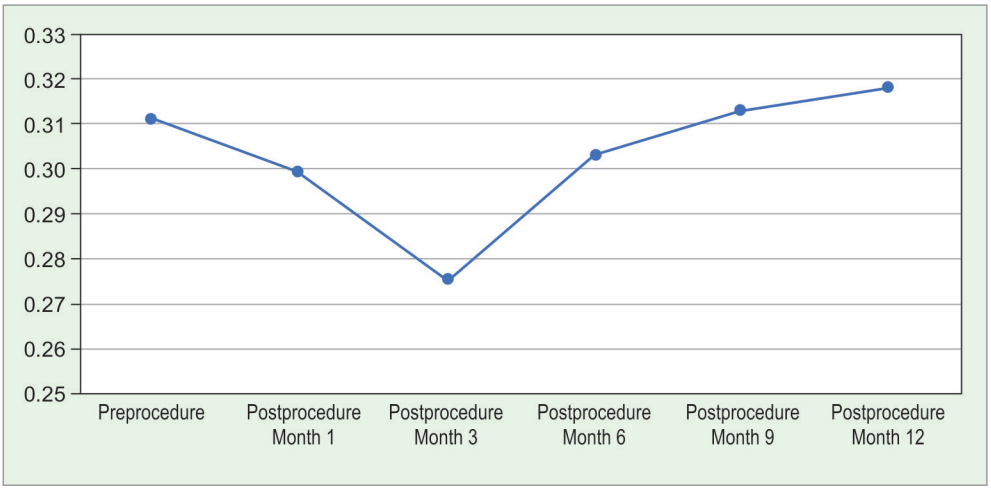

Fig. 1: Changes in mean UCVA over different timelines

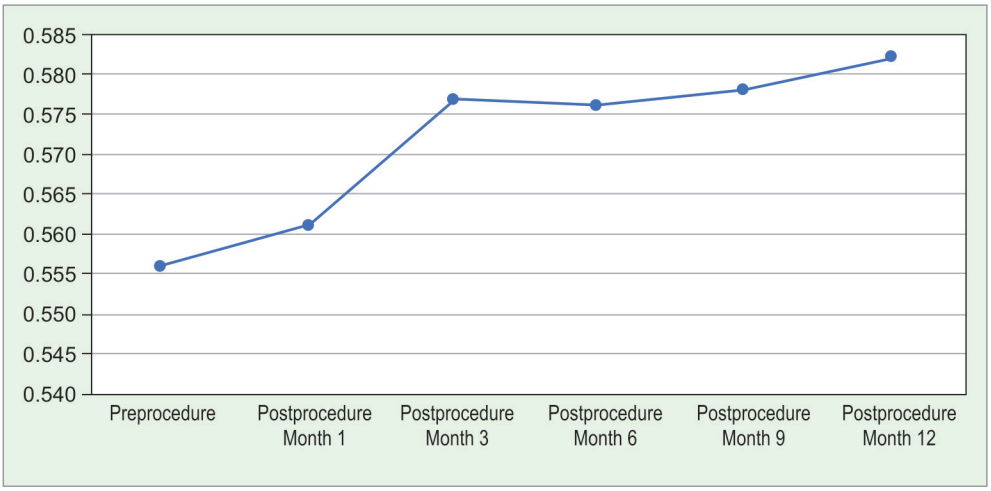

Fig. 2: Changes in mean BCVA over different timelines

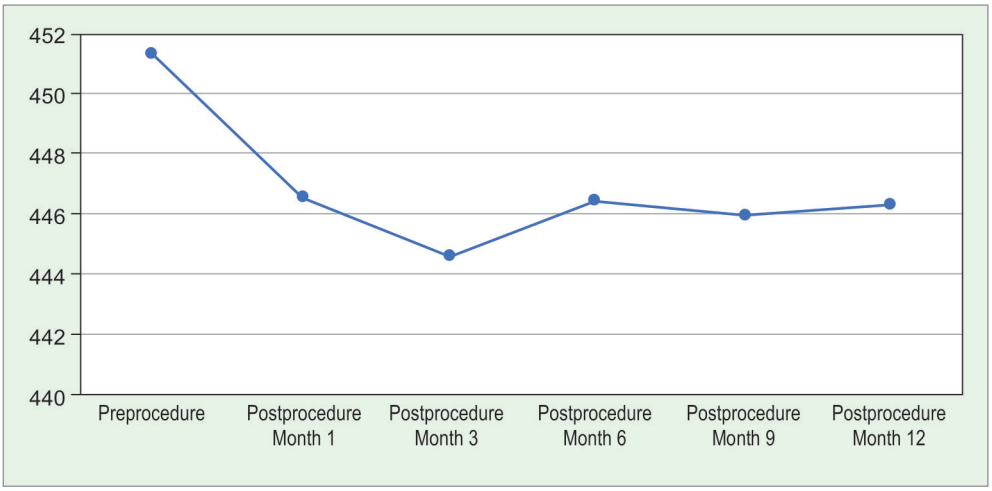

Fig. 3: Changes in mean thinnest pachymetry values over different timelines

during adolescence or early adulthood.[25–27] This age range underscores the importance of identifying effective treatment strategies, as KC can significantly impact the quality of life in young individuals.

The results of our study demonstrated improvements in UCVA, though these changes were non-significant over the 1-year follow-up period. This observation agrees with earlier studies, such as those conducted by Hashemi et al.[28] and O'Brart et al.,[29] which

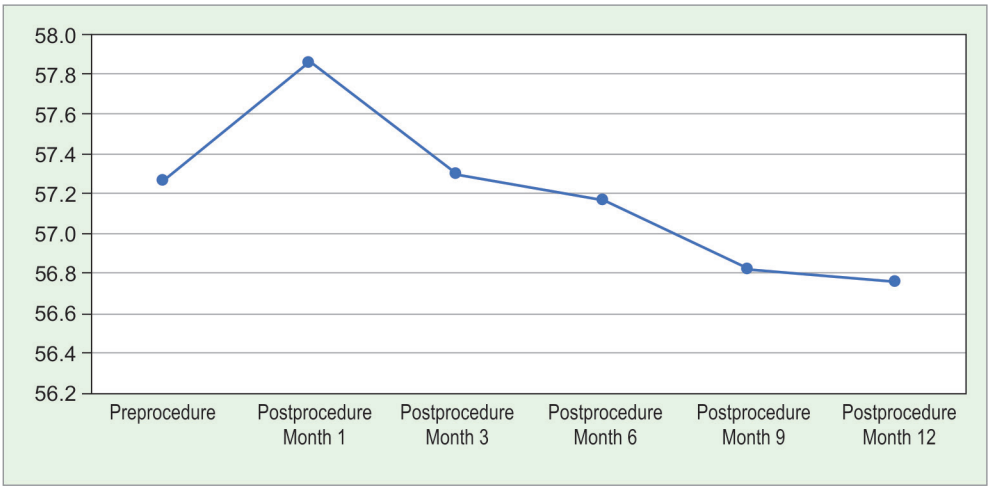

Fig. 4: Changes in mean K_{max} values over different timelines

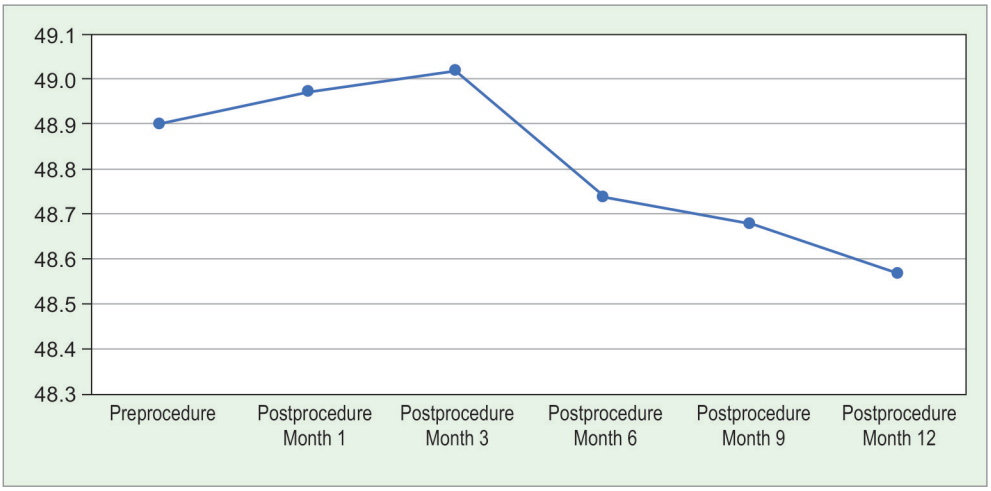

Fig. 5: Changes in mean K_{mean} values over different timelines

also reported modest or non-significant improvements in UCVA following CXL. The modest changes in UCVA can be attributed to the procedure's primary goal, which is to stabilize the cornea rather than to enhance visual acuity. Our findings, therefore, align with the existing body of literature, reinforcing that CXL primarily serves to halt KC progression and may not necessarily lead to substantial visual improvement.

Best-corrected visual acuity displayed slight improvements up to the 3-months mark, after which it stabilized. This pattern concurs with the typical response observed in CXL studies.[30–32] The initial improvement in BCVA can be attributed to the biomechanical stabilization of the cornea, reducing irregular astigmatism, and improving the patient's ability to achieve better-corrected visual acuity.

The thinnest pachymetry value decreased during the first three months and subsequently stabilized. This trend in thinnest pachymetry is consistent with studies by Wittig–Silva et al.[33] and Caporossi et al.,[34] which reported post-CXL corneal thinning before achieving a plateau. The initial reduction in corneal thickness can be attributed to the loss of corneal hydration following the procedure.[33,34] Over time, as the cornea adapts to the new biomechanical state, it reaches a state of equilibrium, as seen in our findings. The stability in the thinnest pachymetry values after this initial reduction is indicative of the procedure's ability to maintain corneal thickness within a safe and acceptable range.

Keratometry parameters, specifically K_{max} and K_{mean}, displayed a minor increase over the first 3 months but subsequently decreased over the 1-year follow-up. Similar trends have been observed in prior studies, such as the work of Godefrooij et al.[35] and Hashemi et al.[36] The initial increase in keratometry values may be attributed to corneal swelling and corneal remodeling following the procedure. The subsequent decrease over the 1-year period, especially the significant reduction in K_{mean}, indicates the procedure's effectiveness in stabilizing corneal shape. This is in line with the goal of CXL, which aims to halt the progression of KC and reduce irregular astigmatism.

The mean demarcation line depth in our study was found to be 333.18 ± 30.48 microns. Additionally, the mean percentage of penetration was calculated to be 74%. The assessment of the demarcation line is an essential component of evaluating CXL efficacy. Our findings indicate that the demarcation line was achieved at a depth sufficient to confer biomechanical stability, as supported by other studies.[37–39] The mean depth of the

demarcation line in our study aligns with the suggested range of 300–400 microns,[38] indicating that the CXL procedure effectively reached the desired corneal depth.

Comparing our results with other studies, we observe substantial consistency in the outcomes of Epi-on CXL with supplemental oxygen in the treatment of progressive KC.[40–42] Our study's findings echo the existing body of evidence regarding the non-significant improvement in UCVA, modest improvements in BCVA, corneal thinning in the initial postoperative phase, and subsequent stability, as well as changes in keratometry parameters indicative of biomechanical stabilization.

While the results of 1-year outcomes are promising, it is imperative to conduct long-term follow-up studies to assess the sustained effects of this technique on KC stabilization and visual outcomes. Furthermore, conducting randomized controlled trials comparing Epi-on CXL with and without supplemental oxygen may provide additional insights into the effectiveness of this modification.

Conclusion

In conclusion, our study adds to the growing body of evidence regarding the safety and efficacy of Epi-on CXL with supplemental oxygen as a treatment for progressive KC. The findings corroborate existing trends in terms of visual acuity, corneal thickness, and keratometry parameters. The unique aspect of our study lies in the concurrent delivery of supplemental oxygen, which requires further exploration to ascertain its long-term impact and comparative effectiveness with traditional CXL. Keratoconus management is a dynamic field, and our study contributes to the evolving landscape of treatment options.

Limitations and Future Directions

Our study has several limitations that should be acknowledged. First, the absence of a control group treated with conventional Epi-off CXL limits our ability to directly compare the two approaches. A comparative analysis between Epi-on CXL with supplemental oxygen and Epi-off CXL is a valuable avenue for future research. Second, the follow-up duration of 1 year provides insights into short-term outcomes, but long-term data are essential to determine the durability of the treatment effect. Furthermore, larger sample sizes and multi-center studies can enhance the generalizability of our findings.

Clinical Significance

The clinical significance of the study's results lies in the validation of transepithelial (Epi-on) CXL with supplemental oxygen as an effective and safe treatment for patients with progressive KC. The findings provide valuable insights into the one-year outcomes, demonstrating that this modified CXL approach can stabilize KC, reduce irregular astigmatism, and improve visual acuity. Importantly, the procedure showcases a favorable safety profile, reaffirming its potential as an alternative to traditional Epi-off CXL. These results offer clinicians a promising option for managing progressive KC, particularly in younger patients, thus enhancing the quality of care and preserving visual function in this population.

Ethical Approval

This study adhered to ethical guidelines and principles. Informed consent was obtained from all participants or legal guardians if underaged, outlining the nature of the study, potential risks, and benefits. The study protocol was reviewed and approved by the institutional review board at MOD Hospital. Confidentiality of patient data and privacy were strictly maintained, and participants were informed of their right to withdraw from the study at any time without any impact on their standard of care.

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