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Epithelium-off corneal cross-linking versus transepithelial diluted alcohol and iontophoresis-assisted corneal cross-linking in keratoconus patients with thin corneas

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ABSTRACT

Aims: To evaluate the efficacy and safety of transepithelial diluted alcohol and iontophoresis-assisted corneal cross-linking (DAI-CXL) and compare 24-month visual and topographic outcomes with accelerated CXL using hypo-osmolar riboflavin (A-CXL) in keratoconus patients with thin corneas (below 400 µm with epithelium).

Methods: This retrospective study included keratoconus patients who underwent DAI-CXL or A-CXL. Uncorrected and corrected distance visual acuity (UDVA and CDVA) and data obtained from corneal topography were analyzed at baseline and 12 and 24 months of follow-up. Corneal demarcation line depth (DLD) at 1 month and corneal endothelial cell density (ECD) at 24 months were also evaluated.

Results: The study included 25 eyes of 25 keratoconus patients (mean age: 25.48±6.69 years, male: 52%). DAI-CXL and A-CXL groups consisted of 13 and 12 patients, respectively. In both groups, median UDVA improved significantly at 24 months ($p<0.05$) whereas CDVA was similar despite a trend towards improvement. Median K-max decreased by 2.77 [interquartile range (IQR): 2.67] D and 2.24 (IQR: 4.38) D in DAI-CXL group ($p=0.033$) and A-CXL group ($p=0.060$), respectively. Corneal HOAs showed a significant improvement in only the DAI-CXL group ($p=0.004$). Average DLD was 237±67 µm in DAI-CXL and 242±57 µm in A-CXL ($p=0.346$). No significant changes in ECD were observed in both groups. Median follow-up changes in UDVA, CDVA, K-max, HOAs, and ECD were similar in the groups.

Conclusions: We observed similar efficacy of transepithelial DAI-CXL to A-CXL in slowing down the progression of keratoconus in thin corneas without notable effects during a 24-month follow-up period.

Introduction

Standard (epithelium-off) corneal cross-linking (CXL) has become the gold standard treatment to prevent or slow the progression of corneal ectatic disorders, with satisfactory long-term outcomes (1). After epithelial debridement, the minimum stromal thickness should be at least 400 µm to protect corneal endothelium and other intraocular tissues from irreversible adverse effects of ultraviolet (UV) irradiation based on experimental and clinical research (2,3).

A significant portion of keratoconus patients (25%) are diagnosed at an advanced stage, with a corneal thickness of less than 400 µm, and these patients are at a higher risk of potential progression even after CXL therapy (4,5). To achieve safe and effective stabilization in progressive keratoconus patients with thin corneas (<400 µm), numerous modifications of the standard protocol have been proposed. These modifications include stromal swelling by using hypo-osmolar riboflavin (6), transepithelial and iontophoretic CXL (7,8), pachymetry-guided epithelial debridement (9), contact lens-assisted CXL (10), lenticule-assisted CXL (11), and recently introduced individualized CXL (sub400 protocol) (12).

Transepithelial (epithelium-on) approaches have several advantages over other epithelium-off techniques, including

protection against complications associated with epithelial debridement and preservation of thin corneal thickness before UV irradiation (13). Transepithelial CXL with modified riboflavin solutions including chemical enhancers has been developed to overcome the barrier effect of corneal epithelium against riboflavin. However, when compared with the epithelium-off CXL technique, transepithelial CXL has a reduced efficacy in arresting the progression of ectatic disorders (14,15).

Iontophoresis-assisted CXL (I-CXL), a recently introduced transepithelial treatment, has been found to enhance stromal riboflavin saturation in human cadaveric corneas much more than other transepithelial procedures (16,17). An electric current of 1 mA is used to transmit a negatively charged riboflavin solution with chemical enhancers through the epithelium into the stroma for 5 minutes in standard I-CXL (18). Several clinical trials have shown that the I-CXL is a safe and successful method in the treatment of progressive keratoconus; however, it has a lower therapeutic efficacy compared to epithelium-off CXL (19-22). With these promising outcomes, various changes to the original I-CXL have been proposed to enhance its efficacy (23-28). The total dose of UV-A exposure has been increased in one of these modifications to compensate for the natural barrier effect of epithelium against UV-A that is required for effective CXL (24,25). The iontophoresis cycle (imbibition period) was doubled in the other studies to increase stromal riboflavin saturation (26,28).

Bilgihan et al. (25) have also introduced a new modified I-CXL technique called transepithelial diluted alcohol and iontophoresis-assisted corneal cross-linking (DAI-CXL). Briefly in this technique, two enhancers, which are diluted alcohol (10% ethanol) and iontophoresis (DAI), are utilized to improve the stromal riboflavin saturation while protecting epithelial integrity, and the total UV-A dose was increased to 7.2 J/cm^2 to ensure proper cross-link formation in the stroma (29). The long-term clinical results of this new method have shown similar visual improvement and topographic changes compared to epithelium-off CXL during the 4-year follow-up (30). The present study was performed to compare the longitudinal effects of DAI-CXL and epithelium-off CXL using hypo-osmolar riboflavin on the prevention of the disease progression and visual, refractive and topographic outcomes in keratoconus patients with thin corneas.

Methods

Patient selection

This single-center, retrospective study included patients with thin corneas (<400 μm) who underwent DAI-CXL or accelerated CXL with hypo-osmolar riboflavin solution (A-CXL) for progressive keratoconus between July 2018 and June 2019. After obtaining approval from the Local Ethics Committee of Gazi University Faculty of Medicine (approval number: E.32700, date: 22.02.2021), data were collected from the electronic medical records of the patients.

Patients who had undergone CXL due to keratoconus progression in their clinical follow-up and had preoperative minimum corneal thickness (MCT) between 350 μm and 400 μm (with epithelium) were included in the current study. In addition, patients with a postoperative follow-up of at least 24 months were included in the analysis. Exclusion criteria were previous ocular surgery, the presence of a corneal scar, a history of herpetic keratitis, pregnancy, or lactation at the time of CXL treatment.

CXL procedures

In our clinical approach, based on the outcomes of a previous study (31), A-CXL is performed only in cases with preoperative MCT above 370 μm. If MCT is lower than 370 μm, the DAI-CXL method has been chosen for treatment to preserve the corneal thickness. The key differences between DAI-CXL and A-CXL are summarized in Table 1, and the routine procedures chosen in our clinic were briefly described below.

DAI-CXL protocol

The cornea is soaked in a dextran-free hypotonic riboflavin solution of 0.2% via a corneal iontophoresis device following exposure to 10% ethyl alcohol for 10 seconds. The positive (passive) electrode is placed on the same side of the treated eye's lateral malar area, while the negative (active) electrode, a plastic barrel with a stainless-steel mesh, is placed on the corneal surface. The riboflavin solution is poured into the barrel until the steel mesh is completely coated. Subsequently, the device is set to 1.0 mA for 5 minutes, and iontophoresis is repeated for additional 5 minutes.

Following the double-cycle corneal iontophoresis, the uniformity of riboflavin distribution in the stroma, as well as the presence of riboflavin solution in the anterior chamber is verified with a blue-cobalt filter. The riboflavin that remained on the corneal surface is carefully rinsed off before UV-A irradiation to avoid the attenuation of UV-A transmission through the cornea. The cornea is irradiated by a UV-A light of 365-nm wavelength at 9 mW/cm^2 power for 13 minutes (total energy density: 7.2 J/cm^2). During irradiation, a balanced salt solution is administered to the corneal epithelium every 1 minute to keep it wet and minimize the probability of an epithelial defect. At the end of the procedure, the corneal surface is treated with a topical antibiotic and a therapeutic contact lens was applied.

A-CXL protocol

Corneal epithelium debridement is performed within an 8-mm diameter and corneal stroma is saturated with iso-osmolar riboflavin solution 0.1%, one drop every minute for 30 minutes. Then, hypo-osmolar 0.1% riboflavin solution is applied every 30 seconds until the MCT reaches 400 μm before UV

irradiation. Corneal thickness is measured 3 times by ultrasonic pachymetry in the area corresponding to the thinnest location according to the preoperative pachymetry map. Finally, CXL is performed by exposing the cornea to UV-A light at an irradiance of 9 mW/cm^2 for 10 minutes (total energy density: 5.4 J/cm^2). One drop of hypo-osmolar riboflavin solution is applied over the cornea every 2 minutes during irradiation. A topical antibiotic is applied at the end of the procedure, and a therapeutic CL is placed over the cornea.

Data collection and outcome measures

In our clinical practice, examination of visual acuity including the manifest refractive correction and also corneal topographic evaluation is performed to determine the status of disease progression. Moreover, the demarcation line depth (DLD) at 1 month and annual specular microscopic evaluation are routinely performed in all patients undergoing CXL procedure, and all data obtained are stored in their medical files. Data obtained from preoperative and postoperative 12- and 24-month follow-ups of patients with at least 2 years of postoperative follow-up were analyzed.

The main outcomes in the current analysis were visual, refractive, and topographic parameters. The decimal values of uncorrected distance visual acuity (UDVA) and corrected distance visual acuity (CDVA) measured by the Snellen chart and converted to logarithm of the minimum angle of resolution (logMAR) units were retrieved for statistical analysis. Further, the manifest spherical equivalent (MSE) values were recorded. The parameters obtained from the corneal topography were as follows; maximum keratometry (K-max), mean keratometry (K-mean), cylindrical reading, MCT, and total corneal higher-order aberrations (HOAs). Corneal aberrations are routinely measured for a pupil diameter of 4 mm.

Data from the anterior segment optical coherence tomography (AS-OCT) were analyzed to evaluate the corneal demarcation line at 1 month. The distance from the corneal epithelium to the visible hyperreflective line in the stroma, measured using a flap tool option provided by the device, was defined as the DLD. The results of corneal endothelial cell density (ECD) measurement using specular microscopy were also recorded.

Statistical Analysis

Statistical analysis was performed with Statistical Package for the Social Sciences (SPSS) 20 (IBM Corp., Armonk, NY, USA). The distribution of the data was analyzed by the Shapiro-Wilk test. Differences between visits within groups were analyzed using paired t-test for normally distributed data and Wilcoxon signed-rank test for non-normally distributed data. Inter-group analyses were performed by using the t-test for normally distributed data and Mann-Whitney U test for non-normally distributed data. Categorical variables were analyzed by using Fisher's exact test. P values less than 0.05 were considered statistically significant.

Results

Electronic medical records of 187 CXL patients were reviewed and 13 patients [27.46±7.52 (19-34) years, 9 female (69.3%)] who underwent DAI-CXL and 12 patients [23.33±5.12 (17-29) years, 9 male (75.0%)] who underwent A-CXL between July 2018 and June 2019 were included in the analysis. Age distribution was similar in the two groups (p=0.152), whereas male sex ratio was more prominent in the A-CXL group (p=0.004). Preoperative and postoperative visual, refractive, and topographic data of the patients were summarized in Table 2. Baseline clinical parameters in the two groups were comparable in terms of visual acuity, K-readings, corneal thickness, and corneal aberrations (p>0.05) (Table 2).

Table 1. CXL methods

	DAI-CXL	A-CXL
Epithelium status	On	Off
Protocol modification	Ethanol 10% for 10 seconds	Accelerated UV application
Chromophore (concentration)	Riboflavin 0.2%	Riboflavin 0.1%
Chromophore carrier	No enhancer, no dextran	Dextran
Chromophore osmolarity	Hypo-osmolar	Iso-osmolar and hypo-osmolar
Iontophoresis current (mA)	10	NA
Saturation time (minutes)	10 (2 cycles of 5 minutes)	30
Intensity of UVA (mW)	9	9
Duration of UVA (minutes)	13	10
Irradiation mode	Continuous	Continuous
UVA source	CXL-Vario; Peschke Meditrade GmbH, Switzerland	CXL-Vario; Peschke Meditrade GmbH, Switzerland
Total fluence (J/cm^2)	7.2	5.4

DAI-CXL: Transepithelial diluted alcohol and iontophoresis assisted corneal cross-linking, A-CXL: Accelerated corneal cross-linking with hypo-osmolar riboflavin solution, UVA: Ultraviolet A

Table 2. Comparison of preoperative and postoperative visual, refractive and topographic outcomes of DAI-CXL (n=13) and A-CXL (n=12) groups

	Group	Baseline	12 month	P‡	24 months	P‡	Median change	P‡
UDVA (logMAR)	**DAI-CXL**	1.30 (0.20)	1.30 (0.52)	0.144	0.70 (0.10)	**0.028**	-0.50 (0.30)	0.387
	A-CXL	0.52 (0.84)	0.52 (0.90)	**0.039**	0.52 (0.60)	**0.046**	0.00 (0.66)	
	P†	0.251	0.456		0.332			
CDVA (logMAR)	**DAI-CXL**	0.39 (0.12)	0.39 (0.17)	0.273	0.30 (0.10)	0.109	-0.12 (0.10)	0.277
	A-CXL	0.30 (0.50)	0.22 (0.51)	**0.050**	0.30 (0.19)	0.068	-0.08 (0.55)	
	P†	0.829	0.601		0.730			
MSE (D)	**DAI-CXL**	-2.50 (3.50)	-2.50 (2.75)	0.102	-2.00 (2.20)	**0.028**	0.50 (0.95)	0.470
	A-CXL	-5.00 (7.00)	-6.25 (4.13)	0.678	-5.00 (7.50)	0.953	-0.50 (2.50)	
	P†	0.360	0.220		0.299			
K-max (D)	**DAI-CXL**	62.64 (7.12)	63.34 (11.38)	0.972	59.29 (7.45)	**0.033**	-2.77 (2.67)	0.936
	A-CXL	60.40 (16.19)	64.74 (18.34)	0.875	64.02 (14.74)	0.060	-2.24 (4.38)	
	P†	0.376	0.295		0.270			
K-mean (D)	**DAI-CXL**	56.81 (7.10)	57.16 (7.76)	0.196	56.58 (8.26)	0.422	-0.23 (1.58)	0.270
	A-CXL	52.03 (6.10)	53.37 (7.75)	0.480	51.76 (7.06)	0.092	0.10 (1.13)	
	P†	0.152	0.152		0.098			
Topographic cylinder (D)	**DAI-CXL**	-8.11 (2.05)	-6.81 (3.02)	0.507	-5.51 (3.50)	0.388	1.19 (2.50)	0.936
	A-CXL	-4.04 (4.60)	-4.42 (4.52)	**0.019**	-4.46 (4.55)	0.347	-0.15 (1.22)	
	P†	0.728	0.689		0.936			
MCT (mm)	**DAI-CXL**	362.00 (64.50)	352.00 (26.00)	0.674	380.00 (41.00)	0.814	-15.00 (50.00)	0.503
	A-CXL	380.00 (41.50)	390.00(56.50)	0.814	372.00 (42.50)	0.754	10.00 (45.00)	
	P†	0.060	0.295		0.810			
Corneal HOAs (mm)	**DAI-CXL**	2.02 (1.59)	1.29 (1.36)	0.098	1.41 (1.73)	**0.004**	-0.27 (0.58)	0.114
	A-CXL	1.82 (1.35)	1.50 (0.86)	0.328	1.50 (0.93)	0.195	-0.27 (0.47)	
	P†	0.406	0.376		1.000			

Data were shown as median (interquartile range). †Wilcoxon signed-rank test, ‡Mann-Whitney U test. Boldface, significant values, p<0.05. Median change was calculated for each parameter as 24 months postop-preop. DAI-CXL: transepithelial diluted alcohol and iontophoresis assisted corneal cross-linking, A-CXL: Accelerated corneal cross-linking with hypo-osmolar riboflavin solution, UDVA: Uncorrected distance visual acuity, CDVA: Corrected distance visual acuity, logMAR: Logarithm of the minimum angle of resolution, MSE: Manifest spherical equivalent, K-max: Maximum keratometry, K-mean: Mean keratometry, D: Diopter, MCT: Minimum corneal thickness, HOAs: Higher-order aberrations

Visual acuity and refractive outcomes

Median UDVA improved significantly in the A-CXL group at 12 and 24 months compared to baseline (p=0.039 and p=0.046, respectively). In the DAI-CXL group, UDVA improved only at 24 months (p=0.028). The improvement in both groups was similar at the 24-month follow-up visit (p=0.387). There was a trend of improvement in CDVA at 24 months in both groups, but not statistically significant. Comparative analysis of the change in CDVA was similar in both groups at the 24-month follow-up visit (p=0.277). Although median MSE decreased significantly only in the DAI-CXL group at 24 months (p=0.028), the changes in MSE values in both groups were similar at 24 months (p=0.470).

Topographic outcomes

Median K-max decreased by -2.77 [interquartile range (IQR): 2.67] D and -2.24 (IQR: 4.38) D in DAI-CXL group (p=0.033) and A-CXL group (p=0.060), respectively at 24 months. These improvements in K-max were similar in both groups (p=0.936). Median K-mean slightly improved in both groups, without statistical significance (p=0.363 and p=0.311, respectively). Similarly, no difference was found in improvement in K-mean between groups at the end of the follow-up (p=0.270). The median topographic cylinder improved statistically only in the A-CXL group at 12 months and inter-group analyses did not show statistical significance (p=0.936). During the follow-up, there was a non-significant decrease in MCT in the A-CXL group and the changes in corneal thickness were similar between the groups at 24 months (p=0.503). Total corneal HOAs analysis showed a significant improvement in only the DAI-CXL group at 24 months (p=0.004), but there was no difference in the median changes in HOAs between groups at the 24-month follow-up visit (p=0.114).

Efficacy of procedures

An evident corneal demarcation line was identified using AS-OCT in all eyes 1 month after the procedures, with an average

DLD of 237.07±67.91 μm (range: 145 to 301 μm) in DAI-CXL and 242.55±57.52 μm (range: 154 to 317 μm) in A-CXL (p=0.346). At the 24-month follow-up visit, the K-max values in the DAI-CXL group remained stable (≤1 D change) or decreased more than 1 D in 12 eyes (92.31%). Similarly, stabilization or improvement in K-max was observed in 11 eyes (91.67%) in the A-CXL group. Disease progression (increase in K-max >1 D) further occurred in 1 eye in each group during the follow-up period (p=1.000).

Safety of procedures

At 24 months, mean ECD changed from 2534.12±163.20 cells/cm^2 to 2418.75±186.42 cells/mm^2 in DAI-CXL group and from 2504.42±126.07 cells/cm^2 to 2425.64±109.31 cells/mm^2 in A-CXL group at 12 months postoperatively (p=0.273 and p=0.099, respectively). The mean change of ECD was not statistically significant between the groups (-113.75±119.93 cells/cm^2 in DAI-CXL vs -76.85±63.12 cells/cm^2 in A-CXL, p=0.927).

The postoperative epithelial defect was not observed in any patient and contact lenses were removed from all patients on the first postoperative day in the DAI-CXL group. After A-CXL treatment, the epithelial defect was closed within 3-4 days, after which the contact lens was removed. None of the treated patients in either group developed vision-threatening haze/scar or infection during the follow-up.

Discussion

Herein, we demonstrate that DAI-CXL is as effective as A-CXL with hypo-osmolar riboflavin in the stabilization of keratoconus in patients with very thin corneas (below 400 μm with epithelium) during the 2-year follow-up. Moreover, visual and corneal topographic changes are similar between groups without any deterioration in ECD at 2 years.

The management of keratoconic corneas thinner than 400 μm is still an important issue to be solved. One of the suggested methods is transepithelial I-CXL which is effective and safe in halting keratoconus progression in thin corneas (8). However, I-CXL still has a less therapeutic effect compared to standard CXL (20,21). To improve the efficacy of the original I-CXL, many modifications have been proposed (23-28). Transepithelial DAI-CXL is one of these techniques which improves the stromal riboflavin concentration while preserving epithelial integrity via 10% ethanol instead of enhancers in riboflavin solution. The preliminary and long-term clinical results of this new method have shown similar visual and topographic improvement compared to standard CXL (25,30).

To overcome the epithelial barrier to riboflavin, dilute alcohol (10% for 10 seconds) was administered to loosen the adhesions of hemidesmosomes to increase epithelial permeability in the DAI-CXL procedure (32). The other enhancer was iontophoresis, which increased riboflavin diffusion. Furthermore, compared to standard I-CXL, the iontophoresis cycle time was doubled (10 minutes). Because the concentration of riboflavin in corneas treated with 5-minute iontophoresis is two-fold lower in conventional I-CXL than that in corneas treated with an epithelium-off protocol (16,33). Although the exact concentration of stromal riboflavin needed for proper corneal cross-link formation is unknown, preclinical and clinical studies have shown that doubling the imbibition time (2 cycles of iontophoresis) enhanced riboflavin saturation to up to 80% of that yielded with the epithelium-off technique, as well as the effectiveness of the I-CXL in halting the disease progression (26-28,34).

The epithelial photo attenuation of UV-A energy during corneal exposure is another aspect that could limit the CXL reaction in the epithelium-on method. This limitation could be overcome by increasing the overall UV-A fluence (29). In DAI-CXL, the total fluence was increased from 5.4 J/cm^2 to 7.2 J/cm^2. Similarly, Mazzotta et al. (24) enhanced the UV-A energy dose to 7 J/cm^2 and utilized pulsed-light UV-A irradiation (18 mW/cm^2 for 6.28 minutes of exposure duration). The 3-year clinical findings of this modified approach, called enhanced fluence pulsed light iontophoresis (EF I-CXL), showed that it was able to stop keratoconus progression with a significant reduction in K-max of 1.4±0.8 D, but no changes in CDVA and corneal thickness. These findings are in line with our 2-year results. We observed that median CDVA and MCT remained stable, while median K-max improved significantly by 2.77 (IQR: 2.67) D in the DAI-CXL group and the median changes in K-max did not differ between groups after 2 years of follow-up.

Cantemir et al. (8) reported the first clinical outcomes of standard I-CXL in keratoconus patients with thin corneas (below 400 μm with epithelium). Fifteen eyes of 15 patients were evaluated and postoperative follow-up was 12 months. The authors have demonstrated improvements in UDVA and CDVA by 0.15 LogMAR which is consistent with our results on UDVA. However, CDVA was not changed after DAI-CXL in our study cohort. There was a significant decrease in K-max by 0.4 D in the previous study but in our case series there was an improvement in K-max by 1.54 D. Moreover, a visible demarcation line was only observed in 5 patients (30%) with an average depth of 184±26 μm in their case series, while there was a prominent demarcation line in all our patients with an average depth of 237±67 μm. Considering the improvement in K-max and DLD values, our results are more favorable compared to the aforementioned study by Cantemir et al. (8), which could be due to changes in the DAI-CXL protocol, such as a combination of extended imbibition time and compensated UV-A irradiation.

According to several authors, the depth of the demarcation line evaluated by AS-OCT or confocal microscopy is an indirect predictor of CXL therapy success (35,36). This measurement could be more beneficial when evaluating the efficacy of a new modified approach, particularly in cases involving I-CXL. In

most standard I-CXL studies, the penetration depth varied from 100 to 240 µm (8,19,37). Wu et al. (34) extended the imbibition period (two cycles of iontophoresis) in EI-CXL and obtained a penetration depth approximately two-fold higher (251 µm) than that achieved with the same iontophoretic device for 5 minutes. After a 5-year follow-up, this 10-minute iontophoretic imbibition improved penetration depth, resulting in comparable keratometric and visual results to standard CXL. Nonetheless, the DLD in the EI-CXL group was still more shallow than in the standard CXL group (34). Furthermore, increasing the total UV-A fluence in EF I-CXL allowed the demarcation line to appear in 80 % of eyes with an average depth of 285 µm (24). In DAI-CXL with the combination of these two modifications, the demarcation line was visible in all patients at an average depth of 237 µm. This is slightly lower than that of the A-CXL group (242 µm), but this difference was not statistically significant.

The protection of the corneal endothelium from UV irradiation is a major safety concern of the CXL technique in thin corneas. Kymionis et al. (3) found a significant decrease in ECD following the standard CXL protocol in keratoconus patients with MCT less than 400 µm after epithelial removal. Permanent endothelial damage caused by CXL could result in a corneal scar and consequent significant visual loss (38). In addition to the efficacy of modified CXL treatment in thin corneas, its safety should be demonstrated by clinical data, including ECD. The safety of this modified method has been also verified by measuring ECD and the maintenance of corneal clarity after the procedure. There was no significant change in ECD 2 years after DAI-CXL. Similarly, Cantemir et al. (8) have also stated the safety of standard I-CXL in thin corneas with no evident changes in ECD.

Cantemir et al. (8) demonstrated an improvement in visual and topographical results in thin corneas following standard I-CXL. However, due to the lack of a control group treated with the epithelium-off approach in the previous study (8), no definite conclusion could be reached regarding the efficacy of the I-CXL method.

This study has several strengths and limitations. The inclusion of a reference intervention is considered the major strength of the present study. However, the single-center and retrospective study design, small sample size, and uneven gender distribution limit the generalizability of the results. We were also not able to perform adjusted analyses due to the low sample size. Finally, although a 24-month follow-up period may be considered sufficient to draw sound conclusions, a longer follow-up duration is required to demonstrate the clinically important outcomes.

Conclusion

In conclusion, DAI-CXL has been proved to be effective in halting keratoconus progression in thin corneas without any side effects during the 2-year follow-up period. This modified I-CXL method could provide a safe and effective alternative epithelium-on CXL treatment option in advanced keratoconus patients.

Ethics

Ethics Committee Approval: The study was approved by the Gazi University Faculty of Medicine of Local Ethics Committee (approval number: E.32700, date: 22.02.2021).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: B.S.U., M.C.Ö., B.A., K.B., Concept: B.S.U., M.C.Ö., K.B., Design: B.S.U., M.C.Ö., B.A., K.B., Data Collection or Processing: M.Y., Analysis or Interpretation: B.S.U., M.C.Ö., B.A., K.B., Literature Search: B.S.U., M.Y., Writing: B.S.U., M.C.Ö., K.B.

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