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ORIGINAL PAPER

Results of ethanol-assisted epithelium-on corneal cross-linking with and without intrastromal corneal ring implantation

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Abstract

Purpose To evaluate the topographic, refractive, and pachymetric changes after ethanol-assisted transepithelial corneal cross-linking (CXL) to stabilize progression of keratoconus (KC).

Patients and methods This study retrospectively evaluated the long-term topographic, refractive, and pachymetric changes in patients diagnosed with KC who underwent corneal cross-linking and/or intrastromal corneal ring segment (ICRS) implantation. The subjects were divided into three groups, corresponding to eyes treated with CXL alone (group 1), CXL and ICRS at the same time (group 2), and CXL after ICRS implantation (group 3). Corrected visual acuity and refraction, steep keratometry (SteepK) values, steepest keratometry reading on sagittal curvature map, and corneal thickness were recorded preoperatively and at each visit. Changes between measurements were assessed during follow-up.

Results Corrected distant visual acuity (CDVA) values improved in all groups compared with baseline, but the differences were not statistically significant except for the first year ($p > 0.05$). In groups 1 and 3, SteepK values did not change statistically significantly during the entire follow-up ($p > 0.05$). In group 2, SteepK values statistically significantly decreased at all follow-up examinations compared with baseline, determined as the first month after ICRS implantation ($p < 0.05$). Complication rates were acceptable without any need for surgical intervention.

Conclusions Single-session ethanol-assisted transepithelial CXL with or without ICRS implantation was a safe and effective procedure to halt progression of KC.

Keywords Corneal cross-linking · Intrastromal corneal ring segments · Keratoconus · Scheimpflug imaging · Transepithelial

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Introduction

Keratoconus (KC) is a noninflammatory progressive ectatic corneal disease [1] whose course as well as progression may show significant variability [2, 3]. There are several treatment modalities that aim to improve visual acuity or stop the progression of the disease. Intrastromal corneal ring segment (ICRS) implantation has been used to improve visual acuity in

keratoconus, with relatively low complication rates and good results [4–7]. Collagen cross-linking (CXL) with riboflavin and ultraviolet (UV)-A has been shown to increase the covalent bonds between collagen in the stromal layer and the resistance to enzymatic digestion. This may increase the biomechanical stability of the cornea, which may slow down or halt the progressive nature of the disease [8]. Collagen cross-linking in adjunct with ICRS implantation has been shown to provide better visual and topographic outcomes compared with ICRS alone [9, 10].

Epithelial removal seems to be important during classical CXL (epi-off method), because intact epithelium impedes riboflavin uptake and limits UV-A transmission by the cornea, which may result in decreased efficacy. On the other hand, CXL with intact epithelium (epi-on or transepithelial method) has some advantages, such as patient comfort and safety with intact epithelial barrier function, reducing the risk of infection and haze, as well as wound-response reactions in the stroma [11–13]. Application of diluted ethanol (20%) for short duration may delaminate the hemidesmosomal attachment in the corneal epithelium and allow better riboflavin penetration through the corneal epithelium [10, 14]. This approach may increase the efficacy of transepithelial CXL without disrupting the epithelial layer, thereby decreasing problems related to epithelium removal. Because of the progressive nature of the disease and the possible long-term effects of CXL, studies with long-term follow-up are important for evaluation of the efficacy and safety of any CXL treatment approach.

In this study, we evaluated the topographic, refractive, and pachymetric changes after ethanol-assisted transepithelial CXL alone or in conjunction with/after ICRS implantation to stabilize progression of KC.

Patients and methods

This study adhered to the tenets of the Declaration of Helsinki. Four hundred eleven eyes of 247 patients who underwent ethanol-assisted CXL with or without ICRS implantation between March 2009 and December 2013 at Kudret Eye Hospital were evaluated retrospectively, and patients with at least 1 year of follow-up were included in this study. All patients included in the study provided informed consent.

Indication for treatment was progression of keratoconus, with increase in steepest keratometry readings (> 1 D) in 1 or more years or deterioration of visual acuity except for reasons unrelated to KC. Patients with history of previous corneal surgery, ocular trauma, corneal scarring, or any concurrent ocular disease that could potentially affect the outcomes were excluded.

There were three groups in this retrospective study, corresponding to eyes treated with CXL alone (group 1), CXL immediately after ICRS at the same session (group 2), and CXL after ICRS (Intacs, Addition Technology, Des Plaines, IL, USA) (group 3).

All tunnels were created using 60-Hz femtosecond laser (Intralase, Intralase Corp., Irvine, CA, USA) with 600-fs pulse duration for ICRS implantation. The inner to outer diameter of the ICRS tunnel was set from 6.0 to 7.3 mm. The spot size was 1.0 μm, and the energy was 1.5 μJ. Then, intracorneal segments were implanted into these channels.

Patients diagnosed with progressive KC underwent CXL procedure if corneal thickness was at least 400 μm centrally and at least 500 μm at the locations where the ICRS segments were to be implanted.

Surgical technique Proxymetacaine hydrochloride 0.5% (Alcaine; Alcon Lab. Inc., Fort Worth, TX, USA) eye drop was used first to achieve anesthesia, and pilocarpine HCl 2% (Pilosed; Bilim Medicine, Istanbul, Turkey) eye drop to achieve miosis, which reduces the risk for exposure of the lens. Corneal epithelium was loosened from the underlying Bowman layer in a 9.0 mm area by applying 20% ethanol using a trephine for 20–25 s, similar to the technique described by Wollensak et al. [8] without epithelial removal. After loosening the epithelium, riboflavin drops (0.1% riboflavin 5-phosphate and 20% dextran) were applied for 30 min at 3-min intervals. Riboflavin penetration to corneal stroma and anterior chamber was confirmed by slit-lamp examination, then exposure of the cornea to UV-A irradiation at wavelength of 370 nm with 3 mW/cm^2 (PESCHKE Meditrade GmbH, Hünenberg, Switzerland) from 1 cm distance for 30 min was started, while instilling riboflavin every 5 min. At the end of the treatment, tobramycin eye drop (Tobrex; Alcon Lab. Inc., Fort Worth, TX, USA) was administered. Therapeutic contact lens was not needed, because of the intact epithelium.

CXL was performed at the same session immediately after ICRS implantation in group 2, and at least 2 months after CXL in group 3. All patients were instructed to apply tobramycin eye drop (Tobrex, Alcon Lab. Inc., Fort Worth, TX, USA) four times a day for 1 week and fluorometholone 0.2% (FML; Allergan, Inc., Irvine, CA, USA) starting with four times a day for 2 weeks and then tapering to zero.

Corrected distant visual acuity (CDVA), steep keratometry (SteepK) values, steepest keratometry reading on sagittal curvature map (SsK), spherical equivalent (SE), cylinderic astigmatism (CYL), and corneal thickness from the thinnest point (CT) were recorded preoperatively and at each follow-up examination. All eyes underwent rotating Scheimpflug corneal tomography imaging (Pentacam HR, software version 1.18r08, OCULUS Optikgeräte GmbH, Wetzlar, Germany) before and after surgery at each visit. All measurements were taken by an experienced technician. All patients were examined on the first postoperative day and week. Subsequent follow-up examinations were carried out at 1, 6, and 12 months, then annually. Changes between measurements were evaluated by subtracting from the preoperative value. In group 2, to eliminate the distinctive improvement in SteepK readings and CDVA after ICRS, the baseline was accepted to be the first month.

All statistical analyses were performed using SPSS 19 for Windows (IBM SPSS Statistics, Chicago, IL, USA). Data distribution was determined by Shapiro–Wilk test. Continuous variables are expressed as mean ± standard deviation (SD), and categorical variables as frequency and percent. Pearson chi-squared test was used to determine differences between groups for categorical variables. Analysis of variance (ANOVA) or Kruskal–Wallis test was used to determine differences between three groups. Tukey test was used as post hoc test, if the ANOVA test was statistically significant. Dunn's test was used for post hoc test after Kruskal–Wallis test. Differences in continuous variables between baseline and 4-year data were compared by paired t test or Wilcoxon signed-rank test, depending on the data distribution. p-Value less than 0.05 was considered statistically significant for all tests.

Results

Two hundred sixty-five eyes of 179 patients were included in this retrospective study. Serial measurements of the three groups were evaluated. One hundred forty-seven eyes of 102 patients were treated with CXL alone (group 1), 79 eyes of 52 patients were treated with CXL and ICRS at the same time (group 2), and 39 eyes of 25 patients were treated with CXL after ICRS (group 3). Mean age, gender distribution, and follow-up time are presented in Table 1. In group 3, mean time between ICRS implantation and CXL was 25.5 ± 20.4 months.

CDVA changes during follow-up in all three groups are shown in Fig. 1. CDVA values improved in all groups compared with baseline and showed a relatively stable course during follow-up. In group 2, as expected, there was a pronounced improvement at the first follow-up due to ICRS implantation. To eliminate this significant difference, the first month follow-up was determined as the baseline. With respect to changes from baseline, there was not a difference between the three groups ($p > 0.05$). At the 12-month visits, CDVA remained stable or improved in 80, 71, and 81% of eyes in group 1, 2, and 3, respectively. At the 24-month visits, CDVA remained stable or improved in 72, 75, and 78% of eyes in group 1, 2, and 3, respectively (Fig. 2).

SteepK and SsK values in all groups are shown in Fig. 3. In all groups, SteepK values remained stable with slight changes. In group 1 and 3, SteepK values were stable during the entire follow-up. In group 2, SteepK values statistically significantly decreased at all follow-up examinations compared with baseline, determined as the first month after ICRS implantation ($p < 0.05$). At the 6-month visit, SteepK values decreased to levels similar to other groups and remained stable during the rest of follow-up. There was no significant difference between the three groups in terms of changes from baseline ($p > 0.05$). SsK showed similar changes with relatively stable course. The changes of CT were minimal, with slight increase in all groups. In all groups, mean SE and CYL values remained stable during the entire follow-up, with minor changes. Mean changes in SteepK, SsK, CDVA, SE, CYL, and CT during follow-up compared with baseline are presented in Table 2.

Thirteen patients completed 4 years of follow-up, insufficient to obtain reliable statistical analysis. Even

Table 1 Preoperative demographic characteristics

Parameter	Group 1	Group 2	Group 3	*p*-Value
Age (years, mean ± SD)	27.5 ± 7.7	26.8 ± 6.1	26.1 ± 4.7	$p = 0.710$
Gender (n = male/n = Female)	54/48	30/22	15/10	$p = 0.675$
Follow-up time (months, mean ± SD)	18.8 ± 9.5	23.7 ± 11.2*	20.3 ± 11.4	$p = 0.003$

*Statistically significant

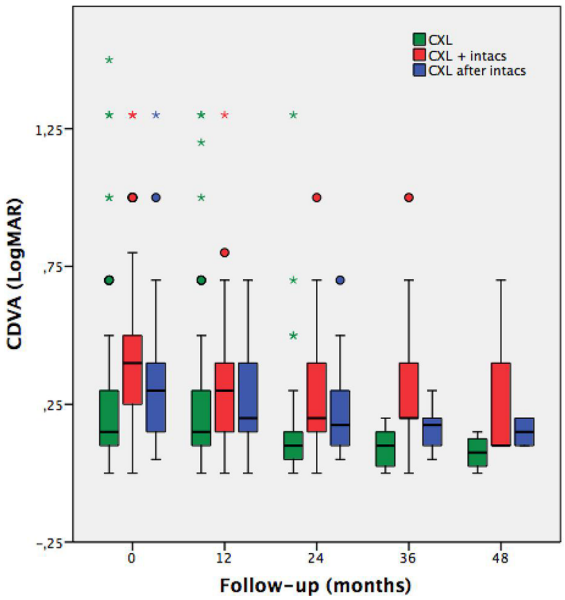

Fig. 1 Box-plot analysis of CDVA values of three groups during follow-up. CDVA, corrected distant visual acuity

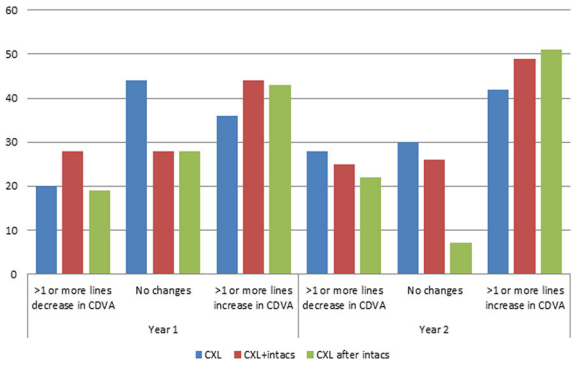

Fig. 2 Changes of CDVA at 1st and 2nd year follow-up. CDVA, corrected distant visual acuity

so, the values seemed to parallel previous follow-up values. Mean CDVA and SteepK values of the 13 patients who reached final follow-up are shown in Fig. 4.

Small (< 2 mm diameter) corneal epithelial defects were noted in 12 patients, healing in a week without any complication. Only eight patients showed mild haze during follow-up, all of which had resolved at the first month examination. No cases of keratitis were observed. Throughout the study, none of the patients required second CXL treatment. No intra- or postoperative complications associated with ICRS implantation occurred.

Discussion

In this retrospective cohort of 265 eyes of 179 patients with 4-year follow-up, we found that single-session ethanol-assisted transepithelial CXL with or without ICRS implantation was a relatively safe procedure with stable visual acuity and keratometric values. The keratometric values were found to be relatively stable with slight improvement in the first year, following a slight worsening. In our study, likely due to the ethanol application, corneal epithelial defects were noted in only 12 patients (7%), being small (< 2 mm diameter) and healing in a week without any complication. Only eight patients (4%) showed mild haze during follow-up, all of which had resolved at the first month examination. No cases of keratitis were observed. These results are comparable to previous studies assessing the effectiveness of transepithelial CXL [10, 12, 13, 15–18]. To the best of the authors' knowledge, this study includes one of the largest cohorts with relatively long follow-up time to assess the effects of ethanol-assisted transepithelial CXL treatment.

Riboflavin acts as a photosensitizer to produce free oxygen radicals and has to penetrate corneal epithelium and invade corneal stroma to achieve its inhibitory effect on disease progression by forming chemical bonds in the deeper stroma. Intact corneal epithelium impedes riboflavin uptake and limits UV-A transmission by the cornea, which may result in decreased efficacy. On the other hand, CXL with intact epithelium offers some advantages such as patient comfort and safety, and reduced risk of infection,

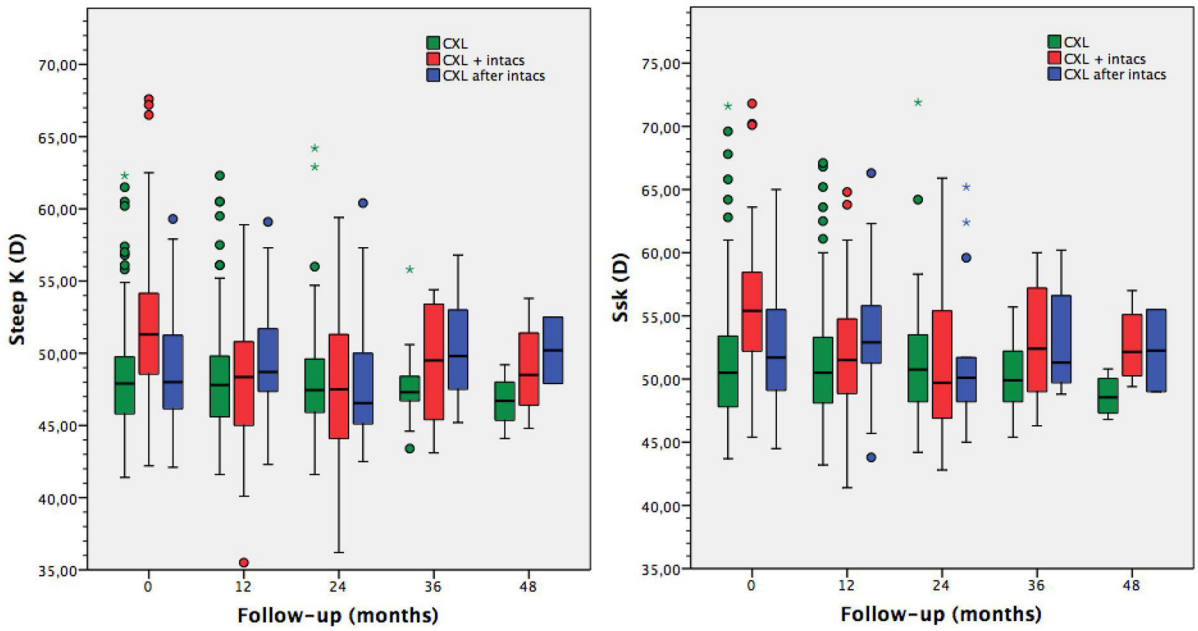

Fig. 3 Box-plot analysis of SteepK and SsK values of three groups during follow-up. SteepK, steep keratometry; SsK, steepest keratometry reading on sagittal curvature map

haze, and wound-response reactions in the corneal stroma. Many authors describe that corneal epithelium should be removed for this purpose [8, 11, 19, 20]. Several studies have shown the effectiveness of the classical epi-off CXL procedure on KC progression, with an increase in visual acuity and decrease in K max, refraction, and topographic values of KC patients [21–25].

To eliminate the potential complications of classical CXL and improve patient comfort, transepithelial CXL applications are becoming popular. Various methods have been suggested to enhance riboflavin uptake to corneal stroma during transepithelial CXL, including benzalkonium chloride (BAC), anesthetic eye drops, and iontophoresis [26]. Koppen et al. used proparacaine drops 0.5% preserved with BAC 0.005% and observed a significant increase in CDVA, but with an increase in SteepK value of 0.40 D [12]. Another study with 51 patients who underwent transepithelial CXL using various eye drops preserved with benzoate also found improvement in CDVA, and increase in mean apex curvature (0.51 D) [15]. Using diluted 20% ethanol solution while maintaining the integrity of the corneal epithelium may also allow penetration of riboflavin. Its application for 20–30 s on ocular surface leads to loosening of corneal epithelium from the Bowman membrane layer by breaking of the tight junctions without causing cellular or cohesion damage [14, 27]. In their histological study, Ozmen et al. assessed rabbit corneas after transepithelial CXL using different concentrations of ethanol. They concluded that they achieved stromal keratocyte loss having the same histological appearance as in the standard epithelial debridement procedure only with high concentration (48%) of ethanol for 30 s. On the other hand, using lower concentrations of ethanol (18 and 24%) did not lead to keratocyte loss, which might have a CXL effect to some extent [28]. In our study we applied 20% ethanol for 20–25 s. Higher concentration for longer treatment duration would help to produce more significant improvements in CDVA or keratometric values, but the toxic effects of ethanol to corneal epithelium and stroma discourage surgeons from performing such application.

The different patient groups and techniques with different levels of disease severity and follow-up duration make comparison of the efficacy of CXL procedures difficult. Nevertheless, other studies based on evaluation of the efficacy of transepithelial CXL found increased CDVA and relatively less stable keratometric values when compared with classical CXL [12, 13, 15, 16, 29]. However, patient discomfort,

Table 2 Mean changes in keratometry, corrected distant visual acuity, spherical equivalent, astigmatism, and pachymetry during follow-up compared with baseline

Follow-up		SteepK	SsK	CDVA	CT	SE	CYL
6th month ($n = 162$)	Group 1 ($n = 82$)	−0.06 ± 0.73	−0.01 ± 0.90	−0.02 ± 0.09	−0.90 ± 13.24	0.00 (−2.75 to +3.00)	0.00 (−3.50 to +4.25)
	Group 2 ($n = 57$)	−0.55 ± 0.78*	−1.11 ± 1.48*	−0.01 ± 0.12	12.03 ± 27.18*	0.06 (−1.13 to +2.50)*	0.00 (−1.00 to +1.50)
	Group 3 ($n = 23$)	0.16 ± 0.98	−0.18 ± 1.33	−0.08 ± 0.17	−3.69 ± 8.47	−0.10 (−2.75 to +1.75)	0.00 (−1.00 to +3.50)
12th month ($n = 219$)	Group 1 ($n = 126$)	−0.09 ± 0.61	0.01 ± 1.03	−0.03 ± 0.10*	−0.71 ± 15.48	0.00 (−7.50 to +3.63)	0.00 (−2.75 to +5.00)
	Group 2 ($n = 64$)	−0.77 ± 0.72*	−1.47 ± 1.53*	−0.02 ± 0.10	11.61 ± 24.68*	0.25 (−2.00 to +5.00)*	0.00 (−1.50 to +2.00)
	Group 3 ($n = 32$)	0.29 ± 0.76	0.30 ± 1.48	−0.10 ± 0.23*	4.90 ± 12.89*	0.00 (−1.75 to +2.75)	0.00 (−2.25 to +4.75)
24th month ($n = 112$)	Group 1 ($n = 55$)	0.13 ± 0.67	0.30 ± 1.06*	−0.03 ± 0.11	−0.24 ± 17.77	0.00 (−3.00 to +2.00)	−0.25 (−3.50 to +3.25)
	Group 2 ($n = 43$)	−0.55 ± 0.91*	−1.18 ± 1.81*	−0.03 ± 0.14	12.30 ± 32.58	0.31 (−1.75 to +5.00)*	0.00 (−1.25 to +2.00)
	Group 3 ($n = 14$)	0.47 ± 0.48*	−0.49 ± 1.23	−0.06 ± 0.14	2.25 ± 15.37	0.38 (−1.25 to +1.75)	0.00 (−2.00 to +6.00)
36th month ($n = 44$)	Group 1 ($n = 15$)	0.27 ± 0.79	0.89 ± 0.81*	−0.02 ± 0.08	1.29 ± 17.24	−0.50 (−1.25 to +0.88)	−0.75 (−1.25 to +0.50)*
	Group 2 ($n = 23$)	−0.42 ± 0.72*	−0.58 ± 1.81	−0.03 ± 0.19	10.87 ± 24.93	0.38 (−1.50 to +3.25)	0.00 (−1.25 to +2.00)
	Group 3 ($n = 6$)	0.01 ± 0.59	0.01 ± 1.84	−0.16 ± 0.13*	6.86 ± 12.63	0.94 (−0.75 to +2.75)	0.50 (−0.25 to +2.00)
48th month ($n = 13$)	Group 1 ($n = 5$)	0.04 ± 0.88	0.50 ± 0.87	−0.05 ± 0.13	7.40 ± 6.88	−0.25 (−0.88 to −0.13)	−0.50 (−1.50 to +0.50)
	Group 2 ($n = 5$)	−0.68 ± 0.71	−0.23 ± 1.56	−0.04 ± 0.04	15.50 ± 25.14	0.13 (−0.63 to +1.13)	−0.13 (−0.50 to +0.75)
	Group 3 ($n = 3$)	−0.23 ± 0.15	−0.83 ± 1.01	−0.12 ± 0.08	3.00 ± 1.73	1.25 (−0.75 to +1.50)	0.75 (−1.00 to +1.50)

Stp K, steep keratometry; SagStpK, steepest value on sagittal curvature map; BCVA, best corrected visual acuity; CTth, corneal thickness of the thinnest point; SE, spherical equivalent; CYL, astigmatism

*Statistically significant compared with baseline (first month for group 2) p value for difference between follow-up and baseline dataset compared using paired t test or Wilcoxon signed-rank test depending on data distribution

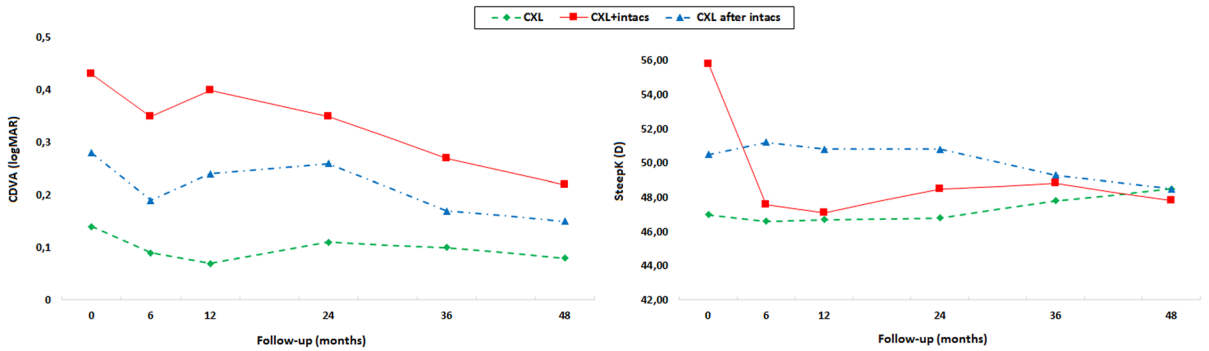

Fig. 4 Mean CDVA and SteepK values of 13 patients who reached final follow-up. CDVA, corrected distant visual acuity; SteepK, steep keratometry

pain, postoperative haze, and epithelial defect-related complications such as corneal infections were minimal in eyes that underwent transepithelial CXL. In contrast, a limited number of studies showed improvement in keratometric values [17, 18]. In our study, we found a slight improvement in CDVA, but this difference was not statistically significant. However, we found slightly better results in keratometry, with relatively stable values. The difference in the change of keratometric values after transepithelial CXL between our and previous studies may be explained by use of ethanol application. Ethanol application may increase penetration of riboflavin into the deeper stroma, which inhibits disease progression and improves corneal curvature. The reason why CDVA does not increase in parallel with keratometric improvement may be explained by the toxic effects of ethanol and subclinical epithelial/stromal ultrastructural changes that may affect the refractive properties of the cornea [12, 13, 15, 16, 29]. Our complication rates were also similar to previous reports of transepithelial CXL [12, 13, 15–18, 20]. Recently, Bikbova compared the results of standard and transepithelial CXL assisted with iontophoresis in a 24-month randomized controlled study with 149 eyes of 119 patients, finding slightly better improvement in the CDVA in transepithelial CXL group, with a significant decrease in mean K, which they attributed to increased riboflavin uptake related to iontophoresis use [26].

Chan et al. reported that CXL after ICRS implantation with intact epithelium had equal effectiveness and safety to classical epi-off CXL [9]. Being reluctant to completely remove corneal epithelium at the same time as ICRS implantation, Kilic et al. injected riboflavin into the corneal channel created for ICRS implantation. They found this approach to be safe and effective [30]. In our study, in group 2 with simultaneous ICRS implantation, we found a more distinctive improvement in SteepK with relatively low complication rates. We also did not find any complication related to ethanol use during transepithelial CXL in eyes that underwent ICRS implantation at the same time or previously.

There are some limitations of this study. First of these is its retrospective design with inevitable loss of patients during follow-up. Also, it should be noted that keratoconus is a disease with extremely variable expression. Therefore, the corneal biomechanical response would be different in each case in our study. Another limitation is the lack of assessment of postoperative pain or discomfort experienced by patients, which is the most common reason behind interest in transepithelial CXL.

In conclusion, we found that ethanol-assisted CXL without epithelial removal was effective to stop progression of KC, with or without ICRS in the same session. Further studies comparing ethanol-assisted transepithelial CXL with other transepithelial CXL methods are needed to better evaluate the efficacy of ethanol use for transepithelial CXL.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

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