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RESEARCH ARTICLE

Transepithelial *versus* Epithelium off Crosslinking for Treating Keratoconus among Jordanians

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Abstract:

Background:

The progression of keratoconus is stabilized with the help of corneal collagen cross-linking (CXL) supported through photosynthesized riboflavin.

Objective:

This study aims to compare the effectiveness of the transepithelial procedure and epithelium off procedure of corneal collagen crosslinking among keratoconus patients in Jordan.

Methods:

The study recruited 80 patients suffering from progressive keratoconus, from a tertiary care setting in Jordan. These participants were randomly divided into two groups; group 1 with 40 participants subjected to transepithelial (Corneal collagen cross-linking) CXL; and 40 participants in group 2 received conventional epithelium off CXL.

Results:

Improvement was observed in the mean contact lens, which corrected distance visual acuity (CDVA) from logMAR 0.332 ± 0.09 (group 1), 0.35 ± 0.09 (group 2) to 0.241 ± 0.07 (group 1), 0.21 ± 0.07 (group 2), respectively at the end of follow-up (12 months). The mean pachymetry improved from 429.81 ± 18.96 µm (group 1), 430.08 ± 17.05 µm (group 2) to 436.5 ± 15.49 µm (group 1), 436.44 ± 12.53 µm (group 2), respectively, after twelve months. Additionally, the mean Sim K astigmatism declined from 7.0 ± 2.0 (group 1), 6.73 ± 1.98 (group 2) to 5.97 ± 1.88 (group 1), 5.53 ± 0.08 (group 2) respectively at twelve months post-treatment. Majority of the patients in group 2 experienced more pain as compared to group 1 participants.

Conclusion:

The effectiveness of a cross-linking procedure related to keratometry readings and corneal thickness showed that conventional (epithelium off) CXL method is more effective than transepithelial CXL.

Keywords: Keratoconus, Collagen, Cornea, Crosslinking, Visual acuity, Keratoplasty.

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1. INTRODUCTION

Keratoconus is an eye condition characterized by a progressive paracentral and central thinning and protrusion of cornea, which leads to visual function impairment and irregular astigmatism [1]. A recent investigation has suggested that keratoconus is associated with inflammatory etiology [2]. The initial histopathologic characteristics include corneal stromal ectasia and thinning, breaks in Bowman's layer, and deposition of iron in the epithelial basement membrane [3]. Its association has been established with Leber's congenital amaurosis, Down syndrome, and Turner's syndrome [4, 5]. Its treatment includes wearing contact lenses, glasses, intrastromal corneal rings, and penetrating keratoplasty [6].

Keratoconus mostly begins during puberty age, and its progression stops in the third or fourth decade, ranging from 5-20 per 10,000 populations. This prevalence rate identified

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Table 1. Studies on Effectiveness of collagen crosslinking procedure.

Author	Study Design	Follow-Up Period	Results
Wittig-Silva *et al.,* [14]	Randomized Controlled trial	12-month	Collagen crosslinking procedure was effective against progression of keratoconus.
Hersh *et al.,* [15]	Complex study design	12-month	1.5 D reduction in average keratometry and 2 D decline was observed in maximum keratometry among the patients treated for keratoconus.
O'Brart *et al.,* [16]	Randomized prospective study	18-months followup period	Utilization of the collagen crosslinking procedure assists in the mitigating keratoconus progression.
Spoerl *et al.,* [21]	Review Paper	-	Results highlights the use of the safety protocols which include riboflavin application for half an hour before exposure to ultraviolet radiations, removal of epithelium, ultraviolet irradiance of 370 nm wavelength, and 400 μm minimum corneal thickness. The adequate technique and safety procedure must be followed as it can lead to damage of retina, lens, and endothelium.
Baiocchi *et al.,* [29]	Randomized retrospective study	-	Epithelium removal helps in the effective and safe concentration of riboflavin.
Wachler *et al.,* [30]	Review Paper	-	Concentration of critical micelle and tetracaine lowers the retreatment rate.
Stojanovic *et al.,* [26]	Non-randomized retrospective study	12-month followup period	Transepithelial technique was effective in decreasing Kmax, cylindrical equivalent, SE, and enhanced CDVA without any considerable harmful effects.
Raiskup *et al.,* [32]	Experimental analysis		Regardless of the concentration of alcohol content in blood, similar riboflavin absorption level is observed through the cornea epithelium.
Kocak *et al.,* [33]	Retrospective study	12-months followup period	Epithelium-off technique was effective in declining keratoconus progression.
Choi *et al.,* [42]	Quantitative study		Corneal thickness improved by 107% post CXL administration in ex vivo models.

that keratoconus is considered one of the leading corneal ectasia [7]. Considering the population of Jordan, a study has found that 5% of bilateral or unilateral blindness existed due to keratoconus [8]. Another study stated that keratoconus was the most common cause behind penetrating keratoplasty among Jordanians, constituting 65.6%, related to visual result after penetrating keratoplasty [9]. On the other hand, it has been suggested that keratoconus is more prevalent among females than males across the world [7, 10, 11]. Crosslinking is a common technology used in several industries for different medical processes [12]. Introduced in 1997, cross-linking was induced in corneal collagens which constructed an optimistic perspective of all kinds of corneal ectasia, particularly keratoconus [13] (Table **1**).

Several studies have been conducted previously to find the effectiveness of the collagen crosslinking procedure. Wittig-Silva *et al.,* illustrated the progression of keratoconus after a year in the treated eyes. Though, only one-third of the participants completed the whole 12-month follow-up [14]. Complex study design was implemented by Hersh *et al.,* [15] to find the effectiveness of crosslinking. 1.5 D reduction in average keratometry and 2 D decline was observed in maximum keratometry among the patients treated for keratoconus. Remarkably, no changes were observed in refraction, keratometry, and visual acuity at 1 year, presenting a halt in the disease's progression [15]. Similarly, O'Brart *et al.,* [16] conducted a study with 18 months follow-up period after the procedure. None of the eyes presented the progression of keratoconus. However, another study proposed certain limitations for the treatment including the absence of calculation of sample size, the age of the patients, and the difference in progression rate of the two groups [17].

Some studies have reported adverse effects of collagen crosslinking namely, sterile keratitis, Acanthamoeba, fungal, and bacterial keratitis [18 - 20]. Spoerl *et al.,* [21] presented safety guidelines and recommended it to be followed during the crosslinking technique. Nevertheless, epithelium debriding imposes the potential risk of infection in the cornea, herpetic activation, endothelial damage, corneal scarring, sterile corneal infiltrates, and subepithelial haze [22 - 25]. Therefore, transepithelial procedure was introduced by combining the benefits of epithelium off technique with higher safety [26].

2. MATERIALS AND METHODS

2.1. Study Participants

The study has recruited participants (n = 80), from a Jordan tertiary care setting, who were presented with progressive keratoconus on topography with a 1-year follow-up period. After the selection of participants, the keratoconus patients were allocated to one of the two groups in a random fashion in accordance with the odd-even number allocation method, known as a randomized control trial.

2.2. Inclusion Criteria

The individuals with keratoconus aged 18 years or above with documented progression of keratoconus (greater than 0.5 D rise in six months or greater than 1 D rise in steep K/12 months), keratometry (between 46 D and 56 D along with the corneal thickness being ≥400 μm) from the thinnest point, and no corneal scarring on presentation were included in this study.

2.3. Evaluating Parameters

The participants were evaluated to obtain certain para-

meters with the help of corneal topography (on pentacam) before the process of crosslinking. These parameters included contact lens Corrected Distance Visual Acuity (CDVA); Uncorrected Distance Visual Acuity (UCDVA); and Central Corneal Thickness (CCT) by utilizing ultrasonic pachymetry. A computerized test chart was used to measure CDVA using MiQ 720 that is controlled remotely using Apple iPad. An HD LED screen or monitor is used as a mirror for displaying. The entire procedure takes around 10 – 15 minutes. Values for keratometric astigmatism, flattest keratometry (Kmin), and steepest keratometry (Kmax) were gathered from pentacam. The procedure on the participants was carried out in appropriate and strict aseptic surroundings of the operation theater.

2.4. Clinical Procedure

In group 1 (trans-epithelial method); 0.5% of Proparacaine anesthetic drops were administered three times with an interval of 5 minutes before introducing 0.1% riboflavin's isotonic solution in 20% dextran. Post cleaning and covering of the eye, riboflavin drops were administered after every 3 to 5 minutes for about half an hour, in addition to recurrent eye drops of proparacaine. The biomicroscopy end result was established through monitoring anterior chamber fluorescence on the slit lamp at the end of half hour. UVA radiation was then provided to the patients with the help of 2 ultraviolet diodes. The intensity of desired radiation was 3 mW/cm2, along with a UVA meter placed at a centimeter distance. This radiation of 370 nm wavelengths was provided to the patients for about half an hour. During this period, proparacaine and riboflavin eye drops were administered after every 3 to 5 minutes.

The loosening of epithelium in the epithelium-off group was performed by administrating proparacaine eye drops in every 5 minutes. A disposable corneal trephine was used to label or mark the corneal epithelium center. This marked corneal epithelium of 7 mm was scraped off by using a merosel sponge. Later, the analogous to the above-mentioned protocol for CXL was followed. For participants in group 2, a soft dressing contact lens was recommended, which was then removed after three to five days. This assured that the epithelium has been healed completely. It was recommended to the patients that moxifloxacin 0.3% topical drops should be instilled four times a day. Similarly, 0.1% fluorometholone QID was administered to Group 2 after healing of epithelium and since 1st day to group 1 participant (lessen slowly and stopped after a month). Moreover, artificial eye drops were used at least four times daily.

Daily follow-up was performed among the group 2 participants until complete formation of the epithelium was reported. However, group 1 participants were assessed on day 1 and day 7. Consequently, participants of both the groups were followed-up at 3, 6, and 12 months after the procedure of crosslinking. Pachymetry, topography, CDVA, and UCDVA were recorded at every follow-up visit. Moreover, subjective pain analysis was performed to document the experience of each participant.

2.5. Data Analysis

Visual acuity was measured with the help of Snellen's chart to analyze the results of procedures. The obtained measurements were converted to logarithm of the minimum angle of resolution (logMAR) to calculate the means. All the obtained variables were tailored into a normal distribution that enables the utilization of parametric analysis (mean and standard deviation) to evaluate quantitative data. Chi-square test for nonparametric variables and Student's t-test for paired values was used to evaluate the significance between parameters or variables. The difference between the observations of the two groups was established at baselines and after therapy, with the help of t-test. The significance was considered to be $P < 0.05$ for this study.

3. RESULTS

In group 1 (transepithelial), the mean age of the participants was 23.55 ± 4.01 years (age range: 18 to 27 years). In group 2 (epithelium-off), the mean age was 22.89 ± 3.99 years (age range: 18 to 29 years). Considering the age of the participants, there was no significant difference between group 1 and group 2 ($P = 0.19$). Seventy-five percent of the patients were male, and the remaining 25% were female. In group 1, there were 31 males (77.5%) and nine females (11.25%); whereas, in group 2, there were 29 males (72.5%) and 11females (27.5%). Therefore, it can be argued that gender distribution was comparable ($P = 0.8$). The CDVA presented in the units of logMAR showed that there was a statistically significant improvement ($P < 0.001$) in both the groups when acuity at baseline was compared with acuity after CXL at all points.

In group 1, the vision was 0.332 ± 0.09 logMAR at preoperative stage or baseline, which was improved to 0.324 ± 0.08 after 3 months and then further improved to 0.241 ± 0.07 after 12 months ($P < 0.001$). Likewise, in group 2 CDVA improved from 0.35 ± 0.09 logMAR at preoperative phase to 0.21 ± 0.07 at 12 months ($P < 0.001$). Markedly, with regard to visual acuity among group 1 and group 2, there was no remarkable difference between the groups at baseline ($P = 0.26$) and at any follow-up period till 12 months ($P = 0.80$) (Table **2**).

In group 1, mean Km at baseline was 51.05 ± 0.08 D, with a range of 47.01 D to 51.89 D. However, mean Km was 49.97 D ± 1.98 D, with a range of 47.04 D to 51.01 D in group 2. At baseline, the difference between groups 1 and 2 was not significant ($P = 0.46$). At the preoperative stage, the mean Sim K astigmatism was 7.0 ± 2.0 D in group 1, with a range of 4.8 D to 11.0 D. While, mean Sim K astigmatism was 6.73 ± 1.98 D in group 2 (range 4.3 D to 11.1 D). There was a significant difference between the two groups ($P = 0.02$). In group 1, the mean Spherical Equivalent (SE) refraction was found to be −6.75 ± 1.82 DS (range – 3.01 DS to – 7.95 DS) and −5.98 ± 2.01 DS (range − 3.05 DS to − 9.05 DS) in group 2 ($P = 0.2$). At the baseline, no difference existed in the calculated topographic indices of both the groups (Table **3**).

In group 1, the mean baseline keratometric astigmatism, flattest keratometry, and steepest keratometry were 6.01 ± 2.37 D, 48.11 ± 5.13 D, and 54.04 ± 3.99 D, respectively.

Conversely, in group 2, the mean baseline keratometric astigmatism, flattest keratometry, and steepest keratometry were 6.56 ± 3.02 D, 46.96 ± 4.71 D, and 54.88 ± 4.06 D respectively. Considering the calculated topographic indices, no significant difference between the two groups was found in any of the values at the baseline. A slight decrease was observed in the flattest and steepest values of K-readings at 3, 6, and 12 months, after cross-linking in group 1 ($P < 0.05$). However, in group 2, no statistically significant difference was observed after 3 and 6 months, but moderate difference was observed in contrast to baseline values after twelve months.

In group 1 participants, keratometric astigmatism decreased from 6.01 ± 2.37 D at baseline to 5.11 ± 2.19 D after 12 months. Moreover, flattest K declined from 48.11 ± 5.13 D to 47.51 ± 4.76 D and steepest K changed from 54.04 ± 3.99 D to 53.07 ± 4.48 D at the end of 12 months follow-up. Correspondingly, participant in epithelium-off group (group 2) also showed decrease in keratometric astigmatism from 6.56 ± 3.02 D at baseline to 5.29 ± 2.94 D at the end of twelve months. Lowest K declined from 46.96 ± 4.71 D to 45.84 ± 4.66 D and steepest K changed from 54.88 ± 4.06 D to 53.48 ± 4.58 D at the end of 12 months.

In group 1, the mean CCT at baseline was 429.81 ± 18.96 µm, and after 6 and 12 months, the values were 432.6 ± 15.89 µm and 436.5 ± 15.49 µm, respectively. Statistically, significant difference was found between baseline and 12 months ($P < 0.001$) after crosslinking. Likewise, in the epithelium off group, the mean CCT at baseline was 430.08 ± 17.05 µm, at six months 433.27 ± 19.54 µm and 435.44 ± 12.53 µm after twelve months. This group depicted increase in corneal thickness while comparing between baseline and last follow-up of 12 months ($P = 0.002$). Moreover, no significant change in corneal thickness was observed at 6 months when paralleled with baseline values ($P = 0.2$). At baseline, there was no significant difference between group 1 and 2 at baseline, six months, or at twelve months follow-up.

No complication was observed among the patients of group 1 or trans-epithelial group. On the other hand, in group 2 (epithelium off) participants, stromal haze was present in the posterior stroma of four eyes that was detected in the initial post-operative period and persevered till three to four months. Majority of the participants in group 2 reported to have experienced photophobia and pain on the first two days; however, this was not the case among the patients of group 1. Among both the groups, none of the participants complained of edema or considerable increase in intraocular tension. Moreover, none of the eyes were presented with sterile infiltrates or infection after cross-linking. No other adverse effects or incidents were documented among all the participants.

4. DISCUSSION

Corneal collagen cross-linking enhances the ability of cornea through the development of a covalent cross-linkage between the collagen fibers, which in turn, contributes up to 300% of the corneal rigidity. It minimizes the chances of morbidity related to the progression of the disease that eventually reduces the demand of corneal transplantation [22]. On the other hand, the performance of CXL through trans-epithelial method has emerged as a current technique and is introduced in the area of health care for the purpose of reducing the potential risks posed by complications related to the conventional method of debridement [22 - 24].

Transepithelial cross-linking also provides an opportunity to subject thinner cornea to CXL, which projects range of CCT less than 400 µm [27]. It has been observed that the subbasal nerve plexus in epithelium-on technique patients can be preserved, as compared to the patients treated with a conventional method [28]. Baiocchi *et al.,* claimed that CXL

Table 2. CDVA, and mean keratometric indices between the two groups.

Mean ± SD	CDVA (logMAR)			Mean Km (D)		
-	1	2	P (1-2)	1	2	P (1-2)
Pre-operative	0.332 ± 0.09	0.35 ± 0.09	0.2	51.05 ± 0.08	49.97 D ± 1.98	0.6
3 months	0.324 ± 0.08	0.29 ± 0.08	0.2	50.50 ± 2.96	48.8 ± 2.99	0.7
6 months	0.31 ± 0.08	0.28 ± 0.05	0.45	49.77 ± 2.95	47.41 ± 3.16	0.75
12 months	0.241 ± 0.07	0.21 ± 0.07	0.75	48.85 ± 2.99	46.32 ± 3.21	0.08
P value (preoperative-12 months)	< 0.001	< 0.001		< 0.001	< 0.001	

*Mean Km=Mean keratometry, CDVA=Corrected Distance Visual Acuity, SD=Standard Deviation

Table 3. Keratometric indices between group 1 and 2.

Mean ± SD	Sim Ka (D)			SE (in minus) (D)		
-	1	2	P (1-2)	1	2	P (1-2)
Pre-operative	7.0 ± 2.0	6.73 ± 1.98	0.3	6.75 ± 1.82	5.98 ± 2.01	0.3
3 months	6.71 ± 1.78	6.41 ± 1.90	0.3	6.45 ± 1.71	5.65 ± 1.8	0.3
6 months	6.36 ± 1.85	5.99 ± 1.87	0.5	6.27 ± 1.70	5.15 ± 1.78	0.5
12 months	5.97 ± 1.88	5.53 ± 0.08	0.7	5.85 ± 1.65	4.88 ± 1.70	0.75
P (preoperative-12 months)	< 0.001	< 0.001		< 0.001	< 0.001	-

*SE=Spherical Equivalent, Sim Ka=Simulated keratometric astigmatism

provides effective and safe concentration of riboflavin when epithelium removal has been performed and not in the case of the intact epithelium [29]. Wachler *et al.,* utilized concentration of critical micelle and tetracaine in their alteration of transepithelial procedure and claimed that this technique was efficacious with a very low retreatment rate of four years [30]. Drops of proparacaine were conserved with benzalkonium chloride 0.01% to enhance the penetration of riboflavin through chemical disruption of epithelium tight junctions [31].

Stojanovic *et al.,* [26] used more than one method to improve the permeability of riboflavin in epithelium. These methods included protracted riboflavin-induction usage, superficial epithelium's mechanical disruption, and epithelial tight junctions' disruption [26]. They showed that transepithelial technique was effective in decreasing Kmax, cylindrical equivalent, SE, and enhanced CDVA without any considerable harmful effects. Raiskup *et al.,* [32] suggested that the concentration of alcohol content in blood whether low or high obtain a similar level of riboflavin absorption through the epithelium of cornea. On the other hand, Kocak *et al.,* [33] compared the effectiveness of both the procedures and proposed that epithelium-off technique was effective in halting the progression of keratoconus; while transepithelial technique was ineffective in stopping keratoconus progression.

In this study, riboflavin 0.1% was used in 20% dextran in addition to continuous administration of anesthetic drops, which aid in the penetration of riboflavin through corneal stroma. Utilization of this technique clinically has shown beneficial effects among some groups [34 - 36]. Both the groups showed an increase in the values of central pachymetry at 6 and 12-months post-treatment in contrast to the pre-operative values. Few studies have proposed that decline in CCT at one month after the treatment is caused by CXL, which improved to normal thickness at 3 and 6 months of follow-up [37, 38]. Other studies have reported that no change occurred in the corneal thickness over a long follow-up period [39, 40]. Nevertheless, the ultimate corneal thickness increase has been claimed by some authors [39, 41].

A study conducted by Choi *et al.,* [42] illustrated an increase of 107% in corneal thickness after administration of CXL in ex vivo models. The study has provided evidence that epithelial debridement has no effect on the absolute pachymetry reading. These findings are similar to the outcomes, depicted by few of the previous studies [27, 43, 44]. The posterior stromal haze was observed in the epithelium off group, which was recognized to be secondary to myofibroblast generation, among four of the participating eyes [45, 46]. The absence or presence of haze was not found to be correlated with clinical findings [45]. The potential risk of development of haze is higher in advanced keratoconus cases [47].

CONCLUSION

The study has identified that the effectiveness of transepithelial treatment of CXL by utilizing isotonic riboflavin in dextran along with frequent anesthetic drops, is slightly lower than the conventional technique in halting keratoconus progression (BAC 0.05%). The two procedures were equivalent with regard to postoperative complications and clinical results, with the exception of stromal haze in 10% of participating eyes among the epithelium-off group. Moreover, higher ocular comfort was observed among Jordanian patients in the transepithelial group. However, the effectiveness of epithelium-off procedure related to keratometry readings and corneal thickness showed that conventional CXL method is more effective; therefore, further research is needed to establish the effectiveness of transepithelial treatment. Previously, no research has provided evidence that one method of corneal crosslinking is more effective than another with regard to prevention of corneal haze formation. However, large sample size is needed to prove this relationship statistically. This study has certain limitation including short follow-up period and a small number of participants in each group.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was ethically approved from the Ethics Committee in Faculty of Medicine-Mutah University.

HUMAN AND ANIMAL RIGHTS

No Animals were used in this research. All human research procedures followed were in accordance with the ethical standards of the committee responsible for human experimentation (institutional and national), and with the Helsinki Declaration of 1975, as revised in 2013.

CONSENT FOR PUBLICATION

Informed consent was obtained from the participants to ensure the confidentiality and anonymity of the study.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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