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Research Article

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Comparative study between Epithelium-Off and Epithelium - On Corneal Collagen Cross-Linking in treatment of Keratoconus.

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Abstract

Aim: To evaluate the two different techniques of corneal cross-linking [standard epithelium-off (CXL epi-off) versus transepithelial (CXL epi-on) cross-linking] in patient with progressive keratoconus.

Methods: Forty eyes of 30 patients with progressive keratoconus were prospectively enrolled in thisrandomized comparative study, which held from September 2016 to September 2018 in Al Hayat Private Hospital. Twenty were treated by CXL epi-off and twenty by CLX epi-on, randomly assigned, and followed up fortwo years. All patients underwent a complete ophthalmologic testing that included uncorrected and best corrected visual acuity, central and peripheral corneal thickness, corneal astigmatism, simulated maximum, minimum, and average keratometry, Schirmer and break-up time (BUT) tests. Intra- and postoperative complications were recorded. The solution used for CXL epi-off comprised riboflavin 0.1% and dextran 20% (Ricrolin), whereas the solution for CXL epi-on (Ricrolin TE) comprised riboflavin 0.1%, dextran 15%, trometamol (Tris), and ethylenediaminetetraacetic acid. Ultraviolet-A treatment was performed with a UV-X system at 3 mW/cm^2.

Results: In both groups, a significant improvement in visual function (Group 1: baseline 0.36 ± 0.16 logMAR, two-year follow-up 0.22 ± 0.17 logMAR; Group 2: baseline 0.32 ± 0.18 logMAR, 2-year follow-up 0.27 ± 0.19 logMAR) was recorded. Keratometry remained unchanged in both groups. The mean corneal thickness showed a significant reduction (mean difference of corneal thickness: −55 micron and −71micron, resp.).

Conclusion: We found that both procedures are able to slow keratoconus progression. Both treatment modalities are equivalent in terms of results. CXL epi-on technique is preferable than CXL epi-off since it preserves the corneal thickness and improves visual acuity, also reducing the postoperative ocular discomfort.

Keywords: epithelium, CXL epi-off, CXL epi-on, keratoconus, Keratometry.

Introduction

Corneal collagen cross-linking (CXL) has acquired nowadays popularity for the treatment of progressive keratoconus. This technique, stabilizing the progression of keratoconus, thus, decreases the chance of corneal transplantation [1], through an increase of the corneal biomechanical strength [2]. The method was developed in 1997 at the Dresden University [3]. It involves the photoactivation of riboflavin with ultraviolet-A (UVA) radiation, that unfolds a series of photochemical reactions inducing inter- and intra-fibrillary cross links in the corneal stromal lamellae [4]. In this way, the tensile strength of the cornea prevents further thinning and deformation of the corneal profile [5] and deterioration of vision and offers some degree of functional improvement [6]. The original protocol was an epithelium-off (epi-off) procedure: the central corneal epithelium (about 8 mm) is removed, and riboflavin solution (0.1% riboflavin-5-phosphate and 20% dextran T-500) is applied to the exposed corneal stroma. CXL epi-off has been modified over time in favor of a method that does not involve the epithelium debridement [7,8], that is, the technique called epithelium-on CXL [9]. This approach was introduced to reduce the postoperative side effects of conventional epi-off CXL, as postoperative pain, corneal infections, subepithelial haze, sterile infiltrates, reactivation of herpetic keratitis, and endothelial damage [10]. Transepithelial technique combines some advantages of the conventional technique, maintaining a higher safety profile, but it increases the risk of failure with a possible need of further treatment [11]. In fact, the diffusion process of riboflavin in the stroma is limited by corneal epithelial tight junctions [12-14]. Riboflavin penetration through the epithelium can be increased by different strategies, such as changing the physicochemical properties of the riboflavin molecule by adding chemical enhancers in the riboflavin formula [15] besides the mechanical disruption of corneal epithelium [16].

Iontophoresis is a novel noninvasive system aimed at enhancing the delivery of charged molecules into tissues using small electric current [17]. Riboflavin, in the formulation used for iontophoresis, is negatively charged [18]. This last technique seems to be the best option to lock the progression of keratoconus [19,20]. Moreover, the UV penetration in this procedure is limited by the riboflavin impregnated intact corneal epithelium, making it safer compared to the epi-off.

The aim of this study is to compare these two techniques and to evaluate the efficacy and safety of them.

Materials and Methods

Forty eyes from 30 patients with progressive keratoconus, followed at Al-Hayat private hospital in Diyala, Iraq, from September 2016 to September 2018.

The patients were randomly assigned to one of the two treatment groups (20 eyes were treated with CXL epi-off, and the other 20 eyes were treated with CXL epi-on). Progression of keratoconus was documented through a clinical, topographic and pachymetry examination.

Inclusion criteria were patients with evolving keratoconus, aged between 15- 40 years, and with no evidence of corneal scarring.

Exclusion criteria were patients with central and paracentral corneal opacities, corneal thickness less than 400m, Vogt's striae, previous intraocular surgery, history of herpetic keratitis, severe dry eye, and concomitant autoimmune diseases.

All patients underwent a complete ophthalmologic examination that include uncorrected and best corrected visual acuity (BCVA), central and peripheral corneal thickness, corneal astigmatism, simulated maximum, minimum, and average keratometry, Schirmer test and break-up time (BUT) test. All intra and postoperative adverse events were recorded.

BCVA was determined using Snellen's chart and was converted to logarithm of the minimum angle of resolution (logMAR). Central and peripheral corneal thickness, K flat, K steep, and mean K were evaluated with Pentacam® (OCULUS, Germany) topography. Cornea was examined for thinning, the presence of inflammatory cells associated with the lenticule, and activation of corneal keratocytes, which may indicate the development of fibrosis [21,22].

Epi-off CXL technique was performed after instilling 4% lidocaine for topical anesthesia then8.0 mm of corneal epithelium was mechanically removed. Riboflavin (0.1% in 20% dextran solution) was administered topically every 2 minutes for 30 minutes.

The administration was continued every 2 minutes during UVA exposure. The cornea was exposed to UVA 370 nm light (UV-X System; Peschke Meditrade GmbH, Hünenberg, Switzerland) for 30 minutes at an irradiance of 3.0 mW/cm^2. At the end of the procedure, Tobramycin-Dexamethasone eye drops were administered, and therapeutic contact lens was then applied. Topical tobramycin and dexamethasone phosphate 0.1% (four times daily for 2 weeks) were prescribed. The therapeutic bandage contact lens was removed 5 days later. Lubricating eye drops were prescribed for the following three months.

In the epi-on CXL group, corneal epithelial was not removed. Corneal imbibition was obtained with 0.1% riboflavin–15% dextran solution supplemented with Tris-hydroxymethylaminomethane and sodium ethylenediaminetetraacetic acid (Ricrolin TE) applied every 2 minutes for 10 minutes.The cornea was exposed to UVA 370 nm light (UV-X System; Peschke Meditrade GmbH, Hünenberg, Switzerland) for 30 minutes at an irradiance of 9.0 mW/cm^2. Postoperatively, topical Tobramycin-Dexamethasone (four times daily for 2 week) was prescribed. All patients were operated by the same surgeon. The patients were checked at day 1, 3, 7, and 15 and then after 1, 6, 12 months.

The patients signed a written informed consentgive their permission to do the procedure, after a detailed description of the procedure's benefits and risks explained to them.

Results

The significance difference between parameters was assessed by Student's t-test for parametric values and chi-square test for nonparametric variables. The differences between the values of the two groups at the baseline and after therapy were evaluated with two sample t-test. Significance was set at $p < 0.05$.

The mean age of patients in Group 1 was 24 ± 7 years (ranging from 15 to 31 years; 13 male/7 female). In Group 2, the mean age was 31 ± 10 years (ranging from 19 to 44 years; 16 male/4 female).

In Group I, BCVA at the baseline was 0.36 ± 0.16 logMAR and improved to 0.22 ± 0.17 logMAR, whereas in Group 2, the values improved from 0.32 ± 0.18 logMAR to 0.27 ± 0.19 logMAR, those changes in the postoperative period of 2 years. At the end of the follow-up, the difference between the two groups was significant.

Mean K at the baseline was 46.19 ± 2.82 D in group 1 and 47.00 ± 2.79 D in group 2, these two values in the postoperative period of 2 years remained unchanged: 46.16 ± 3.15 D (Group 1) and 47.82 ± 4.06 D (Group 2). In addition, the differences between the two values were not significant.

K steep and K flat at the baseline in Group 1 were, respectively, 47.75 ± 3.20 D and 44.62 ± 2.63 D and in Group 2 were 48.86 ± 3.27 D and 45.84 ± 2.53 D. Two years after treatment, K steep and K flat of Group 1 reached 47.76 ± 3.47 D and 44.71 ± 3.03 D, whereas in Group 2, they were 49.75 ± 3.47 D and 46.44 ± 3.67 D. On the contrary, at the end of the follow-up, the difference between the two groups was significant for both parameters.

Mean corneal thickness after 2 years significantly change in both groups (from 556.45 ± 23.56 µm to 501.41 ± 21.91 µm and from 565.41 ± 31.91 µm to 495.45 ± 43.16 µm, respectively), but the difference between groups was not significant.

The main complications were observed in 3 patients: two in Group 1 (Vogt's striae in a patient and corneal haze in another patient) in Group 2 (Vogt's striae and in the same eye follicular conjunctivitis). Schirmer and BUT tests did not reveal lacrimation defects in both groups.

Discussion

Despite the use of topical anesthetics, the greater mean postoperative pain in the epi-off CXL group compared to the epi-on CXL group probably depends on the exposure of the corneal nerves and the release of inflammatory mediators, especially prostaglandins and neuropeptides after epithelium removal and related healing processes [25].

Table 1: Group1: (epi-off): comparison of analyzed parameters (mean+SD) before and after the end of follow-up(2 years).

	Preoperative	Postoperative	*p* Value
Mean corneal thickness (µm)	556.45 ± 23.56	501.41 ± 21.91	0.01
K flat (D)	44.62 ± 2.63	44.71 ± 3.03	0.33
K steep (D)	47.75 ± 3.20	47.76 ± 3.47	0.10
Mean K (D)	46.19 ± 2.82	46.16 ± 3.15	0.57
BCVA (log MAR)	0.36 ± 0.14	0.22 ± 0.12	0.01

Table 2: Group 2: (epi-on): comparison of analyzed parameters (mean± SD) before and after the end of follow-up (2 years).

	Preoperative	Postoperative	*p* Value
Mean corneal thickness (µm)	565.41 ± 31.91	495.45 ± 43.16	0.01
K flat (D)	45.84 ± 2.53	46.44 ± 3.67	0.25
K steep (D)	48.86 ± 3.27	49.75 ± 3.47	0.60
Mean K (D)	47.00 ± 2.79	47.82 ± 4.06	0.10
BCVA (log MAR)	0.32 ± 0.16	0.27 ± 0.13	0.01

Statistical analyses show that the mean corneal thickness, one year later, change significantly in both groups (from 556.45 ± 23.56 µm to 501.41 ± 21.91 µm and from 565.41 ± 31.91 µm to 495.45 ± 43.16 µm, respectively), as already reported [20, 26, 27]. Although epithelial remodeling and stroma edema disappear few days after treatment, it has been reported to be responsible of corneal thickness changes also over a longer time [28]. On the contrary, our findings demonstrate that corneal thickness decreases one year postoperatively. This suggests the involvement of different factors, that is, compression of collagen fibrils, changes in both corneal hydration and glycosaminoglycans synthesis, and keratinocyte apoptosis, that alone or in combination may play a detrimental role in the corneal thickening [28].

A significant increase in BCVA compared to the baseline was recorded in both groups (*p=0.01)*. However, the epi-on group exhibits a better improvement compared to the epi-off group at the end of the follow-up (Table 3).

Table 3:Epi-off versus epi-on follow-up (mean ± SD) after 2 years.

	Epi -off	Epi-on	*p* Value
Mean corneal thickness (µm)	501.41 ± 21.91	495.45 ± 43.16	0.10
K flat (D)	44.71 ± 3.03	46.44 ± 3.67	0.01
K steep (D)	47.76 ± 3.47	49.75 ± 3.47	0.01
Mean K (D)	46.16 ± 3.15	47.82 ± 4.06	0.08
BCVA (logMAR)	0.22 ± 0.12	0.27 ± 0.13	0.01

Our results are consistent with those achieved by three previous randomized clinical trials [18, 27, 29], which demonstrated a more important recovery of BCVA in the epi-on group versus the epi-off. However, it has been shown that, for progressive keratoconus patients, the standard cross-linking procedure yields better results and increases the chances of stopping the disease's progression in the long term [30]. This discrepancy could be explained assuming that the effects of cross-linking mainly reflects the biomechanical impact on stiffening the thinning cornea rather than the reforming cornea shape [31]. Therefore, the significant difference in BCVA after two years between the two study groups is more easily understood.

The activated keratocyte and fibrotic reaction are more frequent in Group 1 patients. This might be due to a rearrangement of the corneal epithelium secondary to the treatment or more likely to the much deeper cross-linking activity in the epi-off group [14, 32].

Few side effects occurred in our study: in Group 1, two patients had complications (Vogt's striae and corneal haze) and in Group 2, only one eye developed Vogt's striae. On the contrary, several complications have been reported in other previous series, especially after epi-off CXL, such as clinically significant corneal haze, endothelial damage, sterile infiltrate and infections [33, 34]. Lastly, the most significant complications after epi-off CXL are pain and photophobia, which required placement of bandage contact lens, sunglasses, and analgesia. Our study showed that these two important postoperative complications were minimal in the epi-on CXL patients.

The limit of this study is the small number of patients in each group; but the good are the prospective design and the long term follow-up (two years).

Despite the different stromal penetration demonstrated in other studies, the clinical outcomes after CXL epi-off and epi-on procedures show that keratoconus was relatively stable after 24 months, and no differences were observed comparing the two procedures. Moreover, our findings demonstrate that the CXL epi-on technique is preferable to CXL epi-off since it reduces postoperative ocular discomfort and maintaining the same profile of safety and efficacy.

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