Cross-linking corneale transepiteliale mediante iontoforesi nel trattamento del cheratocono in pazienti pediatrici: *follow up* a 15 mesi

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Obiettivo

Presentare il risultato a 15 mesi dopo cross-linking corneale transepiteliale effettuato con assorbimento della riboflavina attraverso iontoforesi in pazienti pediatrici affetti da cheratocono.

Metodi

Sono stati trattati quattordici occhi di 14 pazienti pediatrici (età media 13+/-2.4 anni). È stata somministrata una soluzione di riboflavina mediante iontoforesi per 5 minuti e quindi è stata effettuata una irradiazione con UV-A (10mW/cm^2) per 9 minuti. Sono state valutate l'acuità visiva corretta, l'equivalente sferico, l'astigmatismo refrattivo, i K simulati, la coma corneale, l'aberrazione sferica, le aberrazioni di alto ordine per una pupilla di 5.0 mm ed il *thinnest point*, sia in fase preoperatoria che a 3, 6, 12 e 15 mesi dal trattamento.
È stata valutata anche la densità delle cellule endoteliali. È stato utilizzato il t test di Student per confrontare i dati appaiati durante il *follow-up*.

Risultati

Quindici mesi dopo la procedura, l'acuità visiva corretta è migliorata da 0.7 $\pm$ 1.7 a 0.8 $\pm$ 1.8 (P = 0.005).
L'equivalente sferico e l'astigmatismo refrattivo così come i dati aberrometrici e topografici non sono variati significativamente. Anche il *thinnest point* e la densità delle cellule endoteliali sono rimasti invariati. L'esame OCT ha mostrato una banda profonda, non omogenea ed iper-riflettente, nei 180 micron anteriori della cornea.
Non è stato rilevato alcun effetto collaterale.

Conclusioni

Quindici mesi dopo il trattamento, il cross-linking corneale transepiteliale con iontoforesi, a differenza di altre tecniche transepiteliali, sembra arrestare la progressione del cheratocono in pazienti pediatrici.
Non abbiamo rilevato miglioramenti significativi nelle aberrazioni di ordine elevato e negli indici topografici.

Iontophoretic Transepithelial Corneal Cross-linking to Halt Keratoconus in Pediatric Cases: 15-Month Follow-up

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Purpose: To report the results 15 months after transepithelial corneal cross-linking by iontophoresis of riboflavin performed in pediatric patients affected by keratoconus.

Methods: Fourteen eyes of 14 pediatric patients [mean age 13 ± 2.4 (SD) years; range, 10–18 years] were treated. Riboflavin solution was administered by iontophoresis for 5 minutes, and then UVA irradiation (10 mW/cm^2) was performed for 9 minutes. The corrected distance visual acuity measured as decimal number, spherical equivalent, refractive astigmatism, simulated K, corneal coma, spherical aberration, and high-order aberrations for 5.0-mm pupil and the thinnest point were measured preoperatively and 3, 6, 12, and 15 months postoperatively. The endothelial cell density was evaluated. The paired Student *t* test was used to compare data during the follow-up.

Results: Fifteen months after the procedure, the corrected distance visual acuity improved from 0.7 ± 1.7 to 0.8 ± 1.8 ($P = 0.005$). Spherical equivalent and refractive astigmatism as well as topographic and aberrometric data did not show significant changes. Also, the mean thinnest point and the endothelial cell density remained unchanged. The optical coherence tomography showed a nonhomogeneous but deep hyperreflective band with a fading effect extending through the anterior 180 μm of the cornea. No side effects were recorded.

Conclusions: Transepithelial collagen cross-linking by iontophoresis, unlike other transepithelial techniques, seems to halt pediatric keratoconus progression over 15 months. However, we did not record significant improvement in higher-order aberrations and topographic indices.

Key Words: corneal cross-linking, iontophoresis, keratoconus, children

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Keratoconus is a noninflammatory progressive ectatic disorder of the cornea. The onset typically is at puberty with progression of disease until the third or fourth decades of life.[1] It represents the commonest corneal dystrophy, affecting approximately 1 in 1750 individuals. It occurs in all racial groups and equally affects males and females, and its progression is more rapid with early onset.[2]

In 2003, Wollensak et al[3] introduced the cross-linking treatment of progressive keratoconus using riboflavin and ultraviolet-A light (UVA). This procedure is currently becoming the standard, low-invasive, safe treatment for progressive keratoconus.[4,5] The technique of corneal collagen cross-linking[6] consists of stromal collagen fiber photopolymerization, induced by the combined action of a photosensitizing substance (riboflavin) and UVA. It seems that cross-links formed during riboflavin/UVA therapy occur predominantly at the collagen fibril surface and in the protein network surrounding the collagen.[7,8]

Because riboflavin is a hydrophilic compound and cannot easily cross the intact epithelial barrier, the central corneal epithelium must be debrided to a diameter of 8.0 to 9.0 mm to provide effective adsorption of the corneal stroma. However, in pediatric patients, the severe pain induced by epithelial debridement, as well as the consequent temporary visual loss, make the postoperative management difficult. Moreover, the risks of postoperative complications (stromal haze[9] and infections[10]) and the variable period of visual recovery (2–6 months)[11–13] represent other important limitations for children.

A transepithelial cross-linking procedure alternative to the standard one has been proposed to avoid all side effects induced by epithelial debridement, but in children, it did not stop keratoconus progression.[14–16] Recently, a new transepithelial technique in which an iontophoresis system provides riboflavin delivery in the corneal stroma has been proposed.[17,18] Iontophoresis is a noninvasive delivery system designed to enhance the penetration of molecules and riboflavin into tissue using small electric current.

In this study, we report 15-month follow-up in pediatric patients who underwent iontophoresis-assisted transepithelial corneal cross-linking performed by means of riboflavin delivery to evaluate its effectiveness in children.

MATERIALS AND METHODS

Fourteen eyes of 14 pediatric patients [mean age 13 ± 2.4 (SD) years; range, 10–18 years] affected by keratoconus

(stage 1 or 2 according to Amsler–Krumeich classification) were enrolled in the study. The noncomparative case series comprised 14 eyes of 14 pediatric patients affected by keratoconus who underwent transepithelial corneal cross-linking by iontophoresis. All the treatments were performed from May 2013 through August 2013 at the Bambino Gesù Children's Hospital, Rome, Italy. All the operations were performed in the operating room under topic anesthesia (oxybuprocaine 0.4% preservative-free eye drops). All experimental investigations reported here were performed with informed consent and following all the guidelines for experimental investigation with human subjects required by the institutes with which all the authors are affiliated, following the Tenets of the Declaration of Helsinki. A history of recent worsening of vision was obtained in each case, but no disease progression documentation was required by the protocol.

Preoperatively and 3, 6, 12, and 15 months postoperatively, corrected distance visual acuity (CDVA), manifest spherical equivalent, and refractive astigmatism were measured; simulated Ks were calculated by a Sirius Scheimpflug camera (CSO, Firenze, Italy) by averaging the axial curvature from the fourth to the eighth Placido rings of the flattest and steepest meridians (the amplitude of the zone taken into consideration, therefore has a variable diameter depending on the curvature of the cornea, and the principal meridians are not necessarily 90 degrees away); corneal coma, spherical aberration, and high-order aberrations (HOAs) for 5.0-mm pupil and the thinnest point were measured by a Scheimpflug camera. The endothelial cell density was assessed using a noncontact specular microscope (CSO). As reported by Vinciguerra et al,[19] we used intraoperative optical coherence tomography (OCT) (iVue SD-OCT; Optovue, Inc, Fremont, CA) in an attempt to measure the hyperreflective band representing riboflavin depth penetration in the anterior corneal stroma.

A paired Student *t* test was used to compare preoperative and 3-, 6-, 12-, and 15-month postoperative data. A $P < 0.05$ was considered significant. The progression of keratoconus was defined as a 1.0-diopter increase in the maximum K value.[12,13]

The iontophoresis system (I-ON CXL; Sooft Italia SpA, Italy) is composed of a power supply, 2 electrodes, and a connection cable. The negative electrode (a stainless steel grid of 8.0 mm diameter) is inserted in a special rubber ring that is applied to the cornea by means of a suction ring, whereas the positive electrode is placed on the patient's forehead by means of a patch.

After the blepharostat was applied, the iontophoresis device for corneal application was placed on the cornea using an annular suction ring. It was filled with Ricrolin+ (a hypoosmolar riboflavin 0.1% dextran-free solution enriched with ethylenediaminetetraacetic acid and trometamol, specifically formulated to allow quick passage into the corneal stroma through an intact epithelium with corneal iontophoresis; Sooft Italia SpA) from the open proximal side (Fig. 1), until the grid was totally covered. The device was then connected to a constant current generator initially set at 0.5 mA and increased to 1.0 mA to find out the individual tolerance. Iontophoresis was then performed for 5 minutes. The corneal device was then removed before performing UVA irradiation. During the irradiation phase (10 mW/cm^2 for 9 minutes), good fluorescence was clearly detectable. The total treatment time was 14 minutes. The cornea was finally rinsed with saline solution, and a soft therapeutic contact lens was applied.

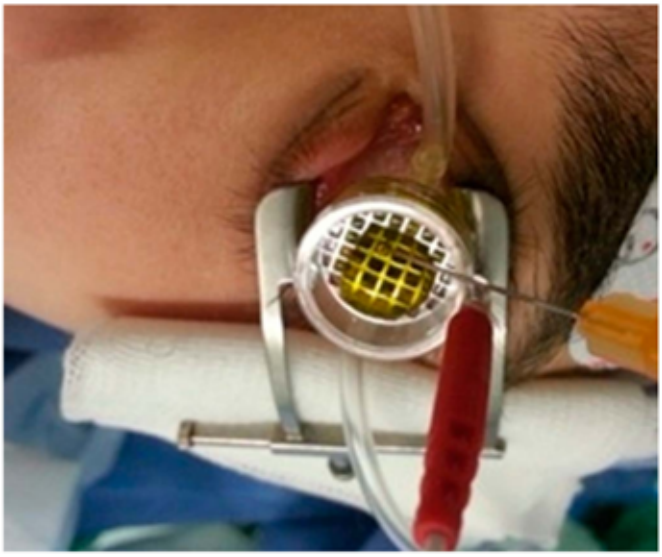

FIGURE 1. The iontophoresis device for corneal application, placed on the cornea using an annular suction ring, is filled with a hypoosmolar riboflavin 0.1% dextran-free solution enriched with ethylenediaminetetraacetic acid and trometamol from the open proximal side.

RESULTS

Table 1 shows refractive outcomes. The CDVA (measured as decimal numbers) improved throughout the 15-month follow-up: 0.7 ± 1.7 preoperatively, 0.8 ± 1.4 ($P = 0.04$) at 3 months, 0.8 ± 1.6 ($P = 0.1$) at 6 months, and 0.8 ± 1.8 ($P = 0.005$) at 12 and 15 months. Fifteen months after treatment, spherical equivalent ($P = 0.3$) and refractive astigmatism ($P = 0.1$) (Table 1), as well as topographic indices (K_{max} $P = 0.08$; K_{min} $P = 0.8$, K_{avg} $P = 0.2$) and aberrometric parameters (coma aberration $P = 0.1$; spherical aberration $P = 0.9$; high-order aberrations $P = 0.3$) (Table 2) did not show significant changes.

The maximum K value did not increase more than 1 diopter in any eye. The mean thinnest point (489 μm preoperatively and 485 μm 15 months postoperatively) and endothelial cell count (preoperative mean density 2962 ± 214 cells/mm^2; 15 months postoperative mean density 2959 ± 220 cells/mm^2) did not show significant changes ($P = 0.1$ and 0.9, respectively). The OCT analysis showed a deep hyperreflective, but not homogeneous, band with a fading effect extending on average through the anterior 180 μm of the cornea (Fig. 2).

We observed good toleration to the treatment in all pediatric patients. They reacted very well to the starting discomfort, and no postoperative complication was observed. No epithelial damage was observed (epithelial integrity was evaluated at the slit-lamp examination with fluorescein staining 1, 3, and 7 days postoperatively).

TABLE 1. CDVA, Manifest Spherical Equivalent, and Refractive Astigmatism Measured Preoperatively, 3, 6, 12, and 15 Months After Cross-linking

	Preoperative	3 Months Postoperative	6 Months Postoperative	12 Months Postoperative	15 Months Postoperative
CDVA	0.7 ± 1.7	0.8 ± 1.4 ($P = 0.04$)	0.8 ± 1.6 ($P = 0.1$)	0.8 ± 1.8 ($P = 0.005$)	0.8 ± 1.8 ($P = 0.005$)
Spherical equivalent, D	−2.2 ± 2.7	−1.7 ± 2.4 ($P = 0.6$)	−1.4 ± 1.2 ($P = 0.2$)	−1.6 ± 2.1 ($P = 0.4$)	−1.5 ± 1.8 ($P = 0.3$)
Refractive astigmatism, D	−1.8 ± 2.1	−1.2 ± 1.7 ($P = 0.07$)	−1.4 ± 1.5 ($P = 0.3$)	−1.3 ± 1.4 ($P = 0.2$)	−1.1 ± 1.3 ($P = 0.1$)

D, diopters.

DISCUSSION

Corneal collagen cross-linking with the use of riboflavin and UVA irradiation is the latest technique proposed for the stabilization of ectatic disorders such as keratoconus. The basic principle of this technique is the induction of cross-links in the corneal stroma, producing a stiffening effect and increasing corneal strength and stability.[3,6] In younger patients, the progression of keratoconus is usually fast and the risk of requiring keratoplasty[20] is high. Chatzis and Hafezi[21] suggested performing corneal cross-linking in children and adolescents as soon as the diagnosis has been made. They also observed that awaiting documentation of progression is not mandatory.

Mainly in the case of pediatric patients, very intriguing is the opportunity to perform transepithelial corneal cross-linking avoiding the epithelial debridement. Recently, transepithelial corneal cross-linking by iontophoresis of riboflavin has been introduced, in which a mild electrical current is used to enhance the penetration of electrically charged molecules into tissue.[17,22] This transepithelial approach may reduce early postoperative pain, vision impairment, and risk of infection. In addition, it could significantly reduce the procedure's duration in comparison with other methods, achieving a more homogeneous and deeper riboflavin penetration than the transepithelial epi-on technique.[17,18]

Bottos Mantovani et al[23] showed that the corneal epithelium limits the riboflavin penetration, but not the UVA transmittance. Thus, they observed that inadequate riboflavin penetration impairs the transepithelial cross-linking. Mastropasqua et al[18] found that transepithelial iontophoresis provides greater and deeper riboflavin saturation with respect to the conventional epi-on technique, however, maintaining the advantages of avoiding epithelial removal and shorter procedure time, but without reaching concentrations obtained with the standard epi-off.

In this article, we evaluate visual acuity and refractive and corneal aberrometric changes through 15-month follow-up in pediatric patients with keratoconus who underwent transepithelial corneal cross-linking by iontophoresis of riboflavin. The transepithelial cross-linking technique had not yet been shown to be effective in halting pediatric keratoconus progression.[14–16] However, in contrast to previous reports on transepithelial technique in pediatric eyes,[14] we did not report keratoconus progression over 15 months; furthermore, we did not observe an improvement in refractive, topographic, and aberrometric parameters, except for CDVA.

Higher-order aberrations are usually higher at 1 to 3 months after the epi-off technique, and their amount typically decreases 1 year after treatment. However, we observed postoperative mean topographic and aberrometric worsening up to 12 months, whereas 15 months after treatment, all evaluated parameters showed a nonsignificant decrease.

To the best of our knowledge, this is the first clinical study on transepithelial corneal cross-linking by iontophoresis of riboflavin in pediatric patients. Iontophoresis-assisted cross-linking clinical application is still a new treatment,[17] and its mechanism and efficacy are partially unknown. It has been observed that iontophoresis-assisted riboflavin delivery does not reach the same stromal level as the epi-off technique,[18] but the amount of riboflavin concentration needed to be effective in the corneal stroma to stop keratoconus progression has not yet been defined. Using intraoperative OCT, we measured the riboflavin penetration depth through the anterior 180 μm of the cornea as reported by Vinciguerra et al.[19] These results confirm the findings of Mastropasqua et al[18] about differences in riboflavin concentration in the anterior, intermediate, and posterior stroma in human donor corneas obtained with the 3 imbibition techniques currently available: standard epi-off protocol, epi-on, and iontophoresis-assisted techniques. They reported the

TABLE 2. Topographic and Aberrometric Data Measured Preoperatively, 3, 6, 12, and 15 Months After Cross-linking

	Preoperative	3 Months Postoperative	6 Months Postoperative	12 Months Postoperative	15 Months Postoperative
K_{max}, D	47.6 ± 2.0	47.9 ± 2.2 ($P = 0.04$)	48.1 ± 2.2 ($P = 0.02$)	48.2 ± 2.2 ($P = 0.07$)	48.0 ± 2.3 ($P = 0.08$)
K_{min}, D	44.5 ± 2.1	44.8 ± 2.5 ($P = 0.04$)	44.9 ± 2.4 ($P = 0.04$)	44.6 ± 2.7 ($P = 0.6$)	44.5 ± 2.7 ($P = 0.8$)
K_{avg}, D	46.1 ± 2.2	46.4 ± 2.3 ($P = 0.01$)	46.5 ± 2.3 ($P = 0.02$)	46.5 ± 2.3 ($P = 0.1$)	46.3 ± 2.3 ($P = 0.2$)
Coma aberration, μm	1.9 ± 1.1	2.0 ± 1.1 ($P = 0.1$)	2.2 ± 1.1 ($P = 0.03$)	2.2 ± 1.2 ($P = 0.04$)	2.1 ± 1.1 ($P = 0.1$)
Spherical aberration, μm	0.31 ± 0.2	0.33 ± 0.2 ($P = 0.2$)	0.33 ± 0.2 ($P = 0.6$)	0.35 ± 0.2 ($P = 0.4$)	0.32 ± 0.2 ($P = 0.9$)
High-order aberrations, μm	2.2 ± 1.1	2.4 ± 1.1 ($P = 0.1$)	2.5 ± 1.1 ($P = 0.02$)	2.5 ± 1.2 ($P = 0.02$)	2.3 ± 1.1 ($P = 0.3$)

D, diopters.

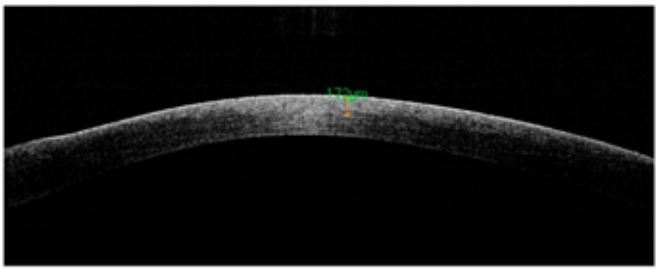

FIGURE 2. Intraoperative OCT after transepithelial corneal cross-linking by iontophoresis of riboflavin in a pediatric patient. Corneal OCT scan shows a nonhomogeneous but deep hyperreflective band with a fading effect extending through the anterior 180 μm of the corneal stroma.

lowest riboflavin concentration in the epi-on group, doubling in the iontophoresis group and again doubling in the epi-off group, which indicates that transepithelial iontophoresis imbibition did not reach the levels of the standard epi-off protocol, whereas it allowed greater and deeper riboflavin saturation in the corneal stroma with respect to the conventional epi-on technique.

However, the first clinical studies on adult patients seem to confirm our findings. Bikbova and Bikbov[17] evaluated the visual, refractive, and pachymetric outcomes after transepithelial corneal cross-linking by means of iontophoresis of riboflavin in eyes with corneal ectasia. They reported decreased K values at the apex of keratoconus 6 months after the procedure. Patients also demonstrated stable visual acuity without statistically significant changes compared with preoperative values. The results of confocal microscopy demonstrated the safety of the corneal endothelium, but an apoptotic keratocyte effect was observed only under to 210 to 230 μm of the corneal depth. Vinciguerra et al[24] reported 1-year clinical outcomes finding significant improvement in the CDVA after 3, 6, and 12 months of follow-up, whereas comatic, spherical, and higher-order aberrations remained stable during follow-up after an initial worsening. They did not record ectasia progression signs.

In conclusion, our findings suggest that iontophoresis-assisted transepithelial corneal cross-linking performed by means of riboflavin delivery could halt keratoconus progression in pediatric patients up to 15 months. However, in contrast to effects usually achieved with the epi-off technique, iontophoresis-assisted transepithelial corneal cross-linking does not improve higher-order aberrations and topographic indices.

However, corneal cross-linking performed without epithelial removal and by shortening the surgical time could represent a great advantage in children, providing local anesthesia and simplifying postoperative management. A greater sample of patients and a longer follow-up are needed to confirm these early results to indicate whether an iontophoresis-assisted riboflavin delivery system could really become an alternative to the epi-off technique, currently still considered the "gold-standard" corneal cross-linking procedure.

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