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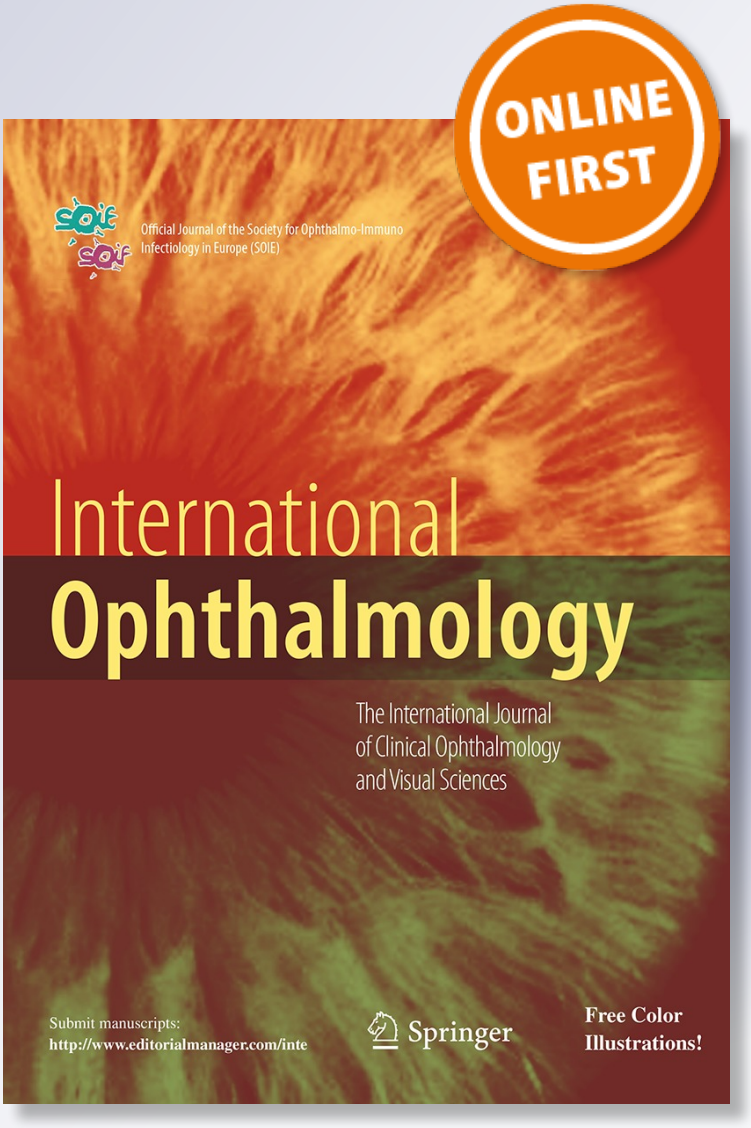

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ORIGINAL PAPER

Pediatric keratoconus and iontophoretic corneal crosslinking: refractive and topographic evidence in patients underwent general and topical anesthesia, 18 months of follow-up

Adriano Magli · Elisabetta Chiariello Vecchio · Roberta Carelli · Elena Piozzi · Felicia Di Landro · Salvatore Troisi

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Abstract To evaluate the efficiency and safety of iontophoretic transepithelial corneal crosslinking in pediatric patients with progressive keratoconus underwent general or topical anesthesia in 18 months follow-up. 13 patients (13 eyes) diagnosed with progressive keratoconus underwent corneal CXL with iontophoresis (I-CXL). Riboflavin solution was administered by iontophoresis for 5 min, and then UV-A irradiation (10 mW/cm) was performed for 9 min. Preoperative and post-operative visits at 1, 6, 12, and 18 months assessed the following parameters: uncorrected visual acuity (UCVA), best-corrected visual acuity (BCVA), slit-lamp biomicroscopy, corneal topography, optical tomography, and pachymetry with Pentacam (Oculus Optikgeräte GmbH, Wetzlar, Germany), endothelial biomicroscopy (Konan Specular Microscope; Konan Medical, Inc., Hyogo, Japan). The paired Student t test was used to compare data during the follow-up. 10 males and 3 females with a mean age of 15.4 ± 1.7 years (range 11–18 years) were included. The results showed a stabilization of the refractive UCVA and BCVA as early as the first post-operative month, with a slight improvement over time. The Kmax remained stable throughout follow-up ($p = 0.04$). Transepithelial collagen crosslinking by iontophoresis, unlike other transepithelial techniques seems to halt pediatric keratoconus progression over 18 months. This is the second study evaluating CXL with iontophoresis in pediatric patients with progressive keratoconus with 18 months of follow-up using two different ways of anesthesia.

Keywords Keratoconus · Crosslinking · Pediatric · Cornea

Introduction

Keratoconus is a degenerative disease characterized by non-inflammatory ectasia of the cornea with increased corneal curvature, reduction of the corneal thickness, progressive decrease of visual acuity and media opacities in more advanced cases. Pellucid marginal corneal degeneration (PMD) instead, is a disease of the cornea which, while enjoying some peculiar features, it is together with the keratoconus, in the general framework of corneal ectasia.

Pellucid marginal degeneration is a rare, ectatic, idiopathic, bilateral, progressive non-inflammatory

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thinning corneal disorder in a region close to the limbus which typically affects the inferior or superior peripheral cornea in a crescentic fashion [1]. Usually, in pediatric keratoconus, the changes in the shape of the cornea can happen quickly, while may occur over several years in PMD patients [2]. Even if the low CKI values hint at a large part of the population being PMDs, however, typically PMD do not progress fast and this disorder is extremely rare in the age group considered in our study.

On the other hand, both PMD and keratoconus are part of the same disease, which manifests itself in different ways according to the age of the patient and the structure of the cornea. Indeed topography data underline different location of the two diseases: PMD down, on the vertical axis, while keratoconus is usually paracentral in the inferior temporal region.

The corneal crosslinking (CXL) is currently the treatment of choice in patients with parasurgical evolving keratoconus. CXL may potentially block or slow down the progression of the disease.

In classic CXL the corneal epithelium is removed before treatment (epithelium-off CXL). Trans epithelial CXL (TE-CXL) allows avoiding removal of the corneal epithelium (epithelium-on CXL). Over the years epithelium-off CXL has shown good efficacy in slowing or blocking the evolution of the disease, in improving visual acuity and most of all in stabilizing the clinical picture over time, reducing the number of patients requiring keratoplasty [3–5].

However, in eyes treated with the traditional epithelium-off CXL, confocal microscopy has shown a marked stromal inflammatory response, highlighted with the presence of edema, activation of keratocytes and reduction of density of anterior stromal keratocytes, which remains significant even after 12 months from treatment [6, 7].

In addition, the standard technique, being more invasive, has shown a greater risk of corneal infections, intense pain, and significant decrease in vision in the first months after treatment [8, 9].

The CXL uses a substance called riboflavin or vitamin B2, creating a chemical reaction within the stroma triggered by ultraviolet light. This leads to the multiplication of the links between the collagen fibers increasing the mechanical strength of the cornea.

The achievement of an adequate stromal concentration of riboflavin for TE-CXL is possible due to a special formula (RICROLIN®, TE; SOOFT, Montegiorgio, Italy), which associates riboflavin 0.1 %, and enhancing substances that facilitate passage through the intact epithelium.

In patients treated with TE-CXL the inflammatory response shows to be minimally detectable and only during the first post-operative week, while at following visits no clear signs of stromal edema and inflammatory activation are present.

TE-CXL, not being invasive, is very well tolerated, as it results in a reduced ocular discomfort. Furthermore, it provides a faster visual recovery than the techniques involving removal of the epithelium.

However, the results of TE-CXL are partial and not entirely satisfactory because of a reduced corneal penetration of riboflavin [10].

Already in 2002 Kolozsvari demonstrated by spectrophotometry that the corneal epithelium and the Bowman's membrane allow the penetration of UV-A light (330–400 nm), but not of the UV-B light (280–330 nm) [11].

Bottos et al. in 2008 showed in 25 pig eyes the reduced capacity of penetration of riboflavin through the intact corneal epithelium undergoing UV-A irradiation, and the authors suggested to always remove corneal epithelium before crosslinking [12]. In a recent publication (February 2015) Soeters et al. showed that epithelium-off CXL results to be statistically more effective than TE-CXL, the latter not being able to block or slow the progression of keratoconus in 23 % of cases [13].

Due to these issues a non-invasive technique allowing the transfer of ionized molecules in the cornea was developed.

Iontophoresis is a method of facilitating the penetration of a drug through an intact tissue in the presence of a low-intensity electric field. It is a harmless technique for ocular tissues working at very low electric intensities, and allows reaching more homogeneous concentrations of riboflavin when compared to passive permeation, with a reduced total time of treatment.

Corneal iontophoresis allows reducing the duration of corneal crosslinking to 14 min total (5 min for imbibition with riboflavin and 9 min for irradiation with UV-A at 10 mW/cm^2).

Methods

13 patients (13 eyes) diagnosed with progressive keratoconus who underwent corneal CXL with

iontophoresis (I-CXL) at the Pediatric Ophthalmology Department, "San Giovanni di Dio e Ruggi D'Aragona" University of Salerno, Italy and Niguarda Hospital, Eye Department, Milan, Italy from November 2013 to May 2015 were enrolled.

The inclusion criteria were patients younger than 18 years, diagnosis of evolutive keratoconus, central corneal thickness greater than 370 microns in the thinnest point, an increase in the maximum cone apex curvature of at least 1.00 D in the previous 6 months, a clear cornea on slit lamp, and the absence of Vogt striae.

The exclusion criteria were presence of central or eccentric corneal opacity, central corneal thickness less than 370 microns in the thinnest point, previous history of herpetic keratitis, severe dry eye, corneal infections, autoimmune diseases, diseases of the lens or the retina, the use of rigid contact lenses for more than 4 weeks prior to treatment.

The study was conducted according to the principles of the Declaration of Helsinki. The parents of patients provided informed consent.

Preoperative and post-operative visits at 1, 6, 12, and 18 months assessed the following parameters: uncorrected visual acuity (UCVA), best-corrected visual acuity (BCVA), slit-lamp biomicroscopy, corneal topography, optical tomography and pachymetry with Pentacam (Oculus Optikgeräte GmbH, Wetzlar, Germany), endothelial biomicroscopy (Konan Specular Microscope; Konan Medical, Inc., Hyogo, Japan). The stage of keratoconus was classified according to the modified Amsler-Muckenhirn classification provided by Pentacam.

From three days before the procedure, antibiotic drops were instilled three times daily in both eyes, regardless of the eye to be treated (Monofloxofta 0.3 % eye drops, BIOOS Italy Srl, Contrada Molino 17, Montegiorgio-FM).

In 11 patients I-CXL was performed under topical anesthesia with a single dose application of lidocaine 4 % eye drops every 4 min for 4 times.

In 2 patients (1 child with Down Syndrome and 1 child), due to lack of cooperation, we performed I-CXL under general anesthesia with laryngeal mask associated with premedication with benzodiazepines.

Periocular disinfection was carried out for 5 min with diluted sterile povidone iodine 10 %. Thirty minutes before the procedure two drops of pilocarpine 2 % were instilled in the eye to be treated to reduce the amount of ultraviolet light reaching the retina. Followingly, a patch (positive electrode) was applied on the forehead of the patient after careful cleansing. After placing the blepharostat, the applicator for iontophoresis (Iontofor-CXL) is placed on the cornea to be treated, and is filled with riboflavin until complete coverage of the grid (negative electrode).

The riboflavin used for this study was specifically designed for I-CXL. It consists of riboflavin 0.1 % without dextran or sodium chloride, with the addition of two enhancers: ethylenediaminetetraacetic acid and tromethamine (RICROLIN®+; SOOFT, Montegiorgio, Italy). The device is then connected to a constant current generator (I-ON XL, SOOFT) set at 1 mA (the total dose of 5 mA/5 min is monitored by the generator).

The low-intensity electric flow allows penetration of riboflavin into the cornea in only 5 min versus 30 min required by passive imbibition.

After the 5-min iontophoresis, the ring and the residual RICROLIN® are removed and treatment is carried out with ultraviolet rays at low-intensity with an ultraviolet lamp of 10 mW/cm^2 (UV-X 2000; IROC Innocross AG, Zug, Switzerland) for 9 min. At the end of the procedure, the eye is washed with sterile saline solution.

After surgery, a scleral contact lens was applied, and was removed after 3 days after treatment. The use of contact lens in epithelium-on CXL is justified by the fact that ultraviolet light may damage the epithelium, causing discomfort in the first post-operative hours.

After 3 days the contact lens was removed and dexamethasone 21-phosphate 0.15 % eye drops were instilled.

Statistical analysis was performed using the SPSS statistical software version 20.0 (IBM Corp., Armonk, NY). Data are described as mean ± standard deviation. A Student t test for paired data was used to evaluate the significance of the differences between preoperative and post-operative data, using the same level of significance in all cases ($p < 0.05$).

Results

10 males and 3 females with a mean age of 15.4 ± 1.7 years (range 11–18 years) were included. There is a preponderance towards male population, consistent with our clinical experience in male–female

incidence in keratoconic patients, and keratoconus incidence studies [14]. The characteristics of patients at baseline are shown in Table 1. No patient was lost to follow-up. No retreatments were needed over the entire follow-up period.

Among the 13 patients, two were undergoing general anesthesia because one was suffering from Down's syndrome and another one was 11 years old and it was not possible to make a topical anesthesia.

3 patients (23.05 %) were diagnosed with grade I keratoconus, 6 patients (46.15 %) with grade II, 2 patient (15.4 %) with grade III, and 2 patient (15.4 %), with grade IV.

The results showed, after treatment, a stabilization of the refractive UCVA and BCVA as early as the first post-operative month, with a slight improvement over time ($p < 0.05$). The Kmax (0.72 D, $p = 0.04$) and keratoconus index (-0.02, $p = 0.02$) remained stable throughout follow-up. A significant improvement at month 18 was present for index of surface variance (-4, $p = 0.04$), although at month 6 there is a significant worsening (6, $p = 0.05$). No significant difference was found in central keratoconus index, index of vertical asymmetry, index of height asymmetry, index of height decentration and minimum radius of curvature.

Corneal thickness average is stable at 18 months of follow-up (1.03, $p = 0.01$), but after the first month of treatment is slightly increased (10.45 μm) in the absence of a statistically significant visual loss but.

The average count of endothelial cells was 2934.5 ± 242.48 and did not change significantly during follow-up. (Table 2) No patients developed corneal haze after treatment when examined on the slit lamp at 1-year visit. No patients developed infections. In the first few hours after treatment, some minor side effects were observed in all patients, as conjunctival hyperemia (13 out of 13 eyes), foreign body sensation (13 out of 13 eyes), and photophobia (13 out of 13 eyes) both in topical and general anesthesia.

Discussion

According to our current knowledge, this is the first study evaluating CXL with iontophoresis in pediatric patients with progressive keratoconus with 18 months of follow-up using two different ways of anesthesia.

According to the epidemiology of other studies on keratoconus the male/female ratio is in favor of males [15, 16].

Both classical and trans epithelial crosslinking have been used for many years for the treatment of keratoconus. Classic CXL is well-validated and standardized, efficacy proven, but it involves a series of side effects and discomfort that, especially in a sample of patients in pediatric age, can not be underestimated. The removal of the corneal epithelium may usually cause pain, temporary impairment of vision with corneal edema, risk of corneal haze, increased time of post-operative recovery, increased risk of infections, reactivation of herpetic keratitis, endothelial damage, permanent scarring, sterile infiltrates [17–21].

Table 1 Patient demographics, visual acuity, endothelial biomicroscopy and topograpchic data before I-CXL

	Mean ± standard deviation
Age	15.4 ± 1.7 (range 11–18-year old)
Male/female	10/3
UCVA logMAR	0.67 ± 0.22
BCVA logMAR	0.45 ± 0.28
Index of surface variance	87 ± 43.27
Index of vertical asymmetry	0.93 ± 0.39
Keratoconus index	1.22 ± 0.14
central keratoconus index	1.06 ± 0.07
Index of height asymmetry	34.85 ± 20.16
Index of height decentration	0.14 ± 0.09
Minimum radius of curvature	6.15 ± 0.76
Minimum corneal thickness (μm)	467.88 ± 36.3
Endothelial cell density cells (mm^2)	2934.5 ± 242.48
K_{max} (D)	53.26 ± 3.88

Table 2 Clinical outcomes of transepithelial iontophoresis corneal collagen cross-linking in pediatric patients

	Baseline	Month 1	Month 6	Month 12	Month 18	P
UCVA logMAR	0.67 ± 0.22	0.57 ± 0.3	0.59 ± 0.21	0.62 ± 0.34	0.63 ± 0.36	0.05
BCVA logMAR	0.45 ± 0.28	0.35 ± 0.1	0.36 ± 0.3	0.39 ± 0.38	0.42 ± 0.22	0.03
Index of surface variance	87 ± 43.27	72.33 ± 16.81	93 ± 24.99	82 ± 32.8	83 ± 38.6	0.04
Index of vertical asymmetry	0.93 ± 0.39	0.80 ± 0.27	1.01 ± 0.38	0.84 ± 0.12	0.91 ± 0.2	0.09
Keratoconus index	1.22 ± 0.14	1.16 ± 0.04	1.21 ± 0.09	1.19 ± 0.03	1.2 ± 0.04	0.02
Central keratoconus index	1.06 ± 0.07	1.03 ± 0.05	1.05 ± 0.05	1.06 ± 0.03	1.06 ± 0.05	0.07
Index of height asymmetry	34.85 ± 20.16	28.53 ± 16.78	24.32 ± 18.12	32.1 ± 20.03	33.2 ± 17.55	0.8
Index of height decentration	0.14 ± 0.09	0.1 ± 0.03	0.14 ± 0.06	0.11 ± 0.02	0.12 ± 0.07	0.2
Minimum radius of curvature	6.15 ± 0.76	6.44 ± 0.41	6.05 ± 0.40	6.01 ± 0.61	6.03 ± 0.59	0.3
Minimum corneal thickness (μm)	467.88 ± 36.3	478.33 ± 15.73	468.75 ± 37.34	469 ± 15.09	468.91 ± 15.46	0.01
Endothelial cell density cells (mm^2)	2934.5 ± 242.48	2845.2 ± 260.2	2752 ± 226.3	2902 ± 281.2	2874 ± 270.4	0.03
K_{max} (D)	53.26 ± 3.88	50.58 ± 3.53	52.97 ± 3.82	53.57 ± 5.88	53.98 ± 7.94	0.04

Sparing the corneal epithelium makes the surgery safer and more tolerable, allows respect the corneal cytoarchitecture and to spare the nerve fibers responsible for pain, reducing corneal inflammation responsible for complications. In particular, post-operative pain following classic CXL is known to be particularly intense as shown by Ghanem et al. and Murphy et al. [22, 23].

In May 2015 published in Cornea, Buzzonetti et al. treated fourteen eyes of 14 pediatric patients [mean age 13 ± 2.4 (SD) years; range, 10–18 years] demonstrating that transepithelial collagen crosslinking by iontophoresis, unlike other transepithelial techniques, seems to halt pediatric keratoconus progression over 15 months [24].

TE-CXL with iontophoresis represents the latest generation of effective stabilization of keratoconus. Another strong point is the significant reduction of the operative time enabling better compliance by the patient, reduced corneal exposure, fewer complications, fewer side effects, and particularly troublesome in the epithelium-off CXL. Iontophoresis is an excellent combination of the epithelium-off CXL and TE-CXL, making the technique faster and more effective. Furthermore, the reduced execution time allows a better patient compliance by allowing to carry out the treatment under topical anesthesia in pediatric age patients, limiting the intraoperative costs and ensuring a more rapid post-operative recovery.

A limitation of this study is the relatively small number of patients treated. However, keratoconus is not frequent in children and adolescents, although they may represent the patients that most would benefit from this treatment for their long life expectancy, for the possibility of retreatment, for the most likely progression of the disease, thereby delaying or avoiding the use of keratoplasty.

Another limitation of this study is the follow-up limited to 18 months, also missing the comparison with standard CXL.

Preliminary results of this study are very encouraging and promising and indicate I-CXL as a viable alternative to the traditional technique in the treatment of evolutive keratoconus in a pediatric age group. Further studies are needed to evaluate the long-term safety and efficacy compared to standard CXL.

Compliance with ethical standard

Conflicts of interest The authors have no conflicts of interest to disclose.

Ethical approval The study was performed with informed consent and following all the guidelines for experimental investigations required by the Institutional Review Board or Ethics Committee of which all authors are affiliated.

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