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Iontophoresis-assisted corneal cross-linking in pediatric keratoconus

Hong-Zhen Jia, Xu Pang, Na Li, Gang Li, Zheng-Jun Fan, Xiu-Jun Peng

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Department of Ophthalmology, Chinese PLA Navy General Hospital, Beijing100048, China

Correspondence to: Xiu-Jun Peng. Department of Ophthalmology, Chinese PLA Navy General Hospital, 6 Fu-Cheng Rd, Haidian District, Beijing 100048, China. pxj1@vip.sina.com

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离子导入辅助角膜交联治疗青少年圆锥角膜

贾洪真,庞 旭,李 娜,李 刚,樊郑军,彭秀军

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(作者单位:100048 中国北京市,中国人民解放军海军总医院眼科)

作者简介:贾洪真,解放军医学院在读博士,主治医师,研究方向:紫外光 A/核黄素角膜交联治疗圆锥角膜的基础和临床。

通讯作者:彭秀军,解放军医学院医学博士,教授,主任医师,博士研究生导师,政府特殊津贴专家,全军眼科专业委员会副主任委员,研究方向:白内障、眼外伤、角膜胶原交联. pxj1@vip.sina.com

摘要

目的:评估离子导入辅助的跨上皮角膜交联治疗青少年圆锥角膜的安全性和有效性。

方法:搜集 12 例(年龄 12~18 岁,平均 15.8±2.08 岁)进展期圆锥角膜患者,共 15 眼,采用 0.1% 核黄素蒸馏水溶液,离子导入(1 mA 电流)辅助跨上皮给药 5min,紫外线 A(370 nm,3 mW/cm^2)照射 30min。记录术前、术后 3mo 和 1a 的裸眼视力、最佳矫正视力、K_1、K_2、最大 K 值、平均 K 值、角膜散光度数、角膜内皮细胞密度、眼内压、最薄角膜厚度、角膜顶点厚度。角膜参数应用角膜地形图评估,角膜内皮细胞密度应用非接触角膜内皮镜检查。

结果:角膜交联 1a 后,裸眼视力、最佳矫正视力、K_1、K_2、最大 K 值、平均 K 值、角膜散光度数、角膜内皮细胞密度和眼内压均无显著变化。最薄角膜厚度从 468.08±33.40 μm 下降到 447.46±40.20 μm (t=4.379, P=0.001),差异有统计学意义。角膜顶点厚度从 476.07±35.96 μm 下降到 454.60±49.32 μm(t=4.270, P=0.001),差异有统计学意义。

结论:采用 0.1% 核黄素蒸馏水溶液的离子导入辅助的角膜交联治疗青少年圆锥角膜是安全、有效的,1a 内能够阻止病情恶化,但是长期效果有待于进一步观察。

关键词:角膜交联;离子导入;圆锥角膜;青少年;核黄素

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Abstract

• AIM: To evaluate the efficacy and safety of iontophoresis-assisted transepithelial corneal cross-linking (I-CXL) in a population of patients younger than 18y.

• METHODS: Fifteen eyes of 12 patients aged 18y or younger (mean age, 15.8±2.08y; range, 12-18y) were treated. After 0.1% riboflavin-distilled water solution was administered by iontophoresis-assisted (Current 1mA) transepithelial method for 5min in total, standard surface UVA irradiation (370 nm, 3 mW/cm^2) was performed for 30min. The uncorrected visual acuity (UCVA), best corrected visual acuity (BCVA), K_1, K_2, K_{max}, K_{mean}, corneal refractive astigmatism, endothelial cell density, intraocular pressure (IOP), the corneal apex thickness and the thinnest corneal thickness were measured preoperatively 3mo and 12mo postoperatively. Corneal parameters were assessed by corneal topography (Wavelight, Allergro Topolyzer & Topolyzer Vario, Germany). Corneal endothelium was photographed with a noncontact Specular Microscope (SP 2000, Topcon, Japan).

• RESULTS: Twelve months after the procedure, no significant changes occurred in the UCVA, BCVA, K_1, K_2, K_{max}, K_{mean}, corneal refractive astigmatism, endothelial cell density and IOP. The thinnest corneal thickness decreased from 468.08±33.40 μm to 447.46±40.20 μm (t=4.379, P=0.001). The corneal apex thickness decreased from 476.07±35.96 μm to 454.60±49.32 μm (t=4.270, P=0.001). The differences of the above were both statistically significant.

• CONCLUSION: I-CXL using 0.1% riboflavin-distilled water solution for pediatric keratoconus is effective and safe which can halt deterioration of keratoconus within 1y, but permanent effects still need to be observed.

• KEYWORDS: corneal cross-linking; iontophoresis; keratoconus; pediatric; riboflavin

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INTRODUCTION

Keratoconus is a bilateral, progressive, non-inflammatory, ectatic corneal disease which is characterized by the thinning and steepening of the central or paracentral cornea, leading to irregular astigmatism and visual damage and its onset usually is at puberty with progression of disease until patient's 35-40y old[1-2]. There were no effective and conservative methods to halt or delay the progression of the disease before corneal cross-linking (CXL) appears. In 2003, Wollensak *et al*[3] reported the standard epithelial-off CXL (S-CXL) with ultraviolet A and riboflavin for progressive keratoconus. Since then, a large number of clinical practices proved the safety and efficacy of S-CXL for progressive keratoconus and S-CXL has been recommended as the gold standard[4]. Due to pain and other shortcomings resulting from the removal of the corneal epithelium, different epithelium-on CXL methods continue to emerge such as iontophoresis-assisted CXL (I-CXL). Clinical studies have shown that I-CXL is safe and effective for progressive keratoconus[5-7]. Pediatric keratoconus is known to be more severe and to progress more rapidly and to a greater severity compared with adult keratoconus. In addition, it has a worse prognosis than adult keratoconus[8]. Therefore, clinical effects of I-CXL for pediatric keratoconus need to be studied specifically. Two studies[9-10] has been reported about I-CXL for pediatric keratoconus which both adopted the radiation protocol of 10 mW/cm^2, 9min and riboflavin solution of Ricrolin+ (a hypoosmolar riboflavin 0.1% dextran-free solution enriched with ethylene diaminetetra acetic acid and trometamol). This research will report the one-year clinical results of I-CXL for pediatric progressive keratoconus using the radiation protocol of 3 mW/cm^2, 30min and 0.1% riboflavin-distilled water solution.

SUBJECTS AND METHODS

Subjects We retrospectively reviewed the data of the patients. This study accorded with the Declaration of Helsinki. Every patient's parent provided written informed consent before the surgery. Patients included in this study were all pediatrics with progressive keratoconus who were treated with I-CXL, from Mar. 2013 to Oct. 2014. Fifteen eyes from 12 pediatric patients [mean age, 15.8±2.08y; range, 12-18y; male, 10 cases (13 eyes, 86.7%), female, 2 cases (2 eyes, 13.3%)] were recruited. Every subject was visited at least 12mo.

Diagnostic criteria were history of myopia and astigmatism; reduced visual acuity; BCVA <1.0; examinations on slit lamp includes at least one of the following positive signs: corneal stromal thinning, conical protrusion of the cornea at the apex, Fleischer ring, Vogt's striae, epithelial or subepithelial scar. Corneal topography shows that the central refractive degree at the corneal anterior surface >47.00D, the difference of refractive degree between superior and inferior 3mm distance of the corneal center >3.00D, the difference of the central refractive degree at the corneal anterior surface between both eyes >1.00D[11].

Inclusion criteria were age ≤18y, a decrease of UCVA or/and BCVA ≥1 row (Snellen chart), an increase in the manifest astigmatism or K_{max} ≥1.00D over the previous 12mo, a decrease of the thinnest corneal thickness ≥10 μm and the thinnest corneal thickness ≥400 μm, clear cornea and no Vogt's striae. Exclusion criteria were corneal opacities, history of intraocular surgery, herpetic keratitis, active keratitis, severe dry eye, and concomitant autoimmune diseases[12].

Surgical procedures All procedures were performed in an out-patient operating room under sterile conditions. Detailed operating steps refer to Li *et al*[13]. Topical anesthetic eye drops including 0.4% oxybuprocaine hydrochloride (Benoxil, Santen Pharmaceutical Co, Osaka, Japan) were instilled every five minutes for total 4 times. After subject lay supine and the forehead skin was polished and cleaned with 75% alcohol, the iontophoresis apparatus was established. The iontophoresis device consists of a power supply, two electrodes and a connection cable. The negative electrode (an eight-mm-diameter stainless steel grid) is inserted in a special rubber ring which is applied to the cornea by use of a suction ring, while the positive electrode is connected to the patient's forehead using a patch. After opening the eyelids using eye speculum, an annular suction ring of the iontophoresis device was placed on the cornea. The ring was irrigated with riboflavin 0.1%-distilled water solution and total covery of the grid was ensured. The power generator was afterward turned on and "1.0mA" constant current was selected. Iontophoresis continued for five minutes. After corneal stroma saturation was proved on slit-lamp microscopy, the eye was irradiated for 30min with UVA light beam (370 nm, 3 mW/cm^2 at a distance of one cm) originating from a radiation device (UV-A Corneal Crosslinking System, Medical Engineering Colombia). Meanwhile, 0.1% riboflavin-saline solution was instilled to the cornea every three minutes.

Postoperative medication and follow up At the end of the procedure, the cornea was immediately rinsed with normothermic saline solution, administered tobramycin and dexamethasone eye drops and placed on a bandage contact lens which was removed 3 to 5 days later depending on the epithelial condition. Drug applications were as follows: 0.3% ofloxacin eye drops for 1wk, 0.1% fluorometholone eye drops for 1mo, 0.1% bromfenac sodium hydrate ophthalmic solution for 1mo, polyethylene glycol eye drops for a month. All patients were examined in detail preoperatively. Postoperative follow-up time were arranged at the 1st, 4th, 7th, 30th day and the 3rd, 6th, 12th month after treatment, and then yearly. The examination items involved UCVA, BCVA, K_1, K_2, K_{max}, K_{mean}, corneal astigmatism, endothelial cell density, IOP, the corneal apex thickness, the thinnest corneal thickness, slit lamp examination and manifest refraction. Rigid gas-permeable contact lense wearers were advised to stop one week at least before the surgery and follow up visit. Corneal parameters were assessed by corneal topography (Wavelight, Allergro Topolyzer&Topolyzer Vario, Germany). Corneal

Table 1 Preoperative and postoperative visual acuity, corneal thicknesses and corneal curvature *et al*

Parameter	Baseline	3mo	12mo	*F*	*P*
UCVA(LogMAR)	0.62±0.43	0.58±0.39	0.53±0.42	1.412	0.231
BCVA(LogMAR)	0.35±0.28	0.30±0.26	0.29±0.23	0.506	0.537
K_1(D)	47.89±3.73	47.63±4.54	47.57±3.93	0.181	0.836
K_2(D)	51.77±4.47	51.47±4.72	51.49±4.68	1.727	0.203
K_{mean}(D)	49.74±3.92	49.37±4.41	49.43±4.19	0.527	0.531
K_{max}(D)	58.19±6.48	57.36±7.05	57.16±6.80	0.620	0.474
Corneal Astigmatism(D)	3.79±2.17	3.85±1.70	4.04±1.99	2.670	0.094
CAT(μm)	476.07±35.96	442.53±36.91	454.60±49.32	12.455	0.000[a]
TCT(μm)	468.08±33.40	435.80±28.41	447.46±40.20	15.299	0.002[a]
IOP(mm Hg)	11.82±3.07	11.75±2.83	11.59±3.30	0.457	0.643
Endothelial cell density(/mm^2)	2830±625	2651±477	2497±371	0.368	0.697

UCVA: Uncorrected visual acuity; BCVA: Best spectacle corrected acuity; K_1: Corneal dioptric power in the flattest meridian for the 3-mm central zone; K_2: Corneal dioptric power in the steepest meridian for the 3-mm central zone; K_{mean}: Mean corneal power in the 3-mm zone; K_{max}: Maximum keratometric value; IOP: Intraocular pressure; TCT: Thinnest corneal thickness; CAT: Corneal apex thickness; *P*: Friedman ANOVA test; [a]: $P<0.05$.

endothelium was photographed with a noncontact Specular Microscope (SP 2000, Topcon, Japan).

Statistical Analysis SPSS 19.0 software was used for statistical analysis. Measurement data were expressed as mean ±standard deviation ($\bar{x}\pm s$). Comparison of multiple related samples of the same parameter was per-formed with Friedman ANOVA test. The paired student *t* test was used for comparing two related samples of the same parameter in the presence of normal distribution, and Wilcoxon matched pairs test in the case of nonnormal distribution. Two tailed distribution results were accepted for *P* values. $P<0.05$ were considered statistically significant.

RESULTS

Various parameters at the preoperative and postoperative time point are presented in Table 1. K_1, K_2, K_{mean}, K_{max}, IOP and corneal endothelial cell counts slightly decreased 1y postoperatively, but the difference was not statistically significant ($P>0.05$). The UCVA (LogMAR), BCVA (LogMAR), corneal astigmatism slightly increased, however, the difference was not statistically significant as well ($P>0.05$). Corneal apex thickness and thinnest corneal thickness showed statistically significant changes ($F=12.455$, 15.299 and $P=0.000$, 0.002 respectively). Corneal apex thickness decreased from 476.07±35.96 μm preoperatively to 442.53±36.91 μm 3mo postoperatively ($t=5.746$, $P=0.000$), then increased from 442.53±36.91 μm 3mo postoperatively to 454.60±49.32 μm 12mo postoperatively ($t=1.677$, $P=0.124$), but not reached the preoperative level ($t=4.270$, $P=0.001$). Thinnest corneal thickness underwent similar changes. Thinnest corneal thickness decreased from 468.08±33.40 μm preoperatively to 435.80±28.41 μm 3mo postoperatively ($t=5.555$, $P=0.000$), then increased from 435.80±28.41 μm 3mo postoperatively to 447.46±40.20 μm 12mo postoperatively ($t=1.942$, $P=0.084$), but not reached the preoperative level ($t=4.379$, $P=0.001$).

One year postoperatively, the values of K_{max} decreased in 11 eyes and more than 1.00D in 8 eyes. The values of K_{max} increased in 4 eyes and more than 1.00D in 1 eye. All eyes showed no serious complications.

DISCUSSION

In order to mimic the natural biomechanical stiffening that takes place with ageing, CXL using ultraviolet A and riboflavin was first introduced in the late nineties of last century[14]. The basic principle of CXL is the formation of covalent bonds between corneal stromal collagen fibrils resulting in a long-term increase in the biomechanical rigidity of the cornea which improves the strength and stability of the cornea[3,15]. A series of studies have demonstrated the safety and efficacy of CXL in halting the progression of keratoconus and avoiding the need for corneal transplantation. Moreover, a certain degree of improvement in visual acuity, flattening of keratometric readings, and decrease in comatic aberrations have also been confirmed following CX[14]. Compared with the adult keratoconus, the progression of pediatric keratoconus is usually fast, treatment compliance is poor, permanent complications appear easily and the risk of requiring keratoplasty is high[9,16]. Chatzis *et al*[17] proposed performing CXL in children and pediatrics as soon as the disease has been diagnosed.

The safety and efficacy of S-CXL in the treatment of pediatric keratoconus have been reported. Furthermore, in pediatric patients, improvement in UCVA, BCVA, and a significant decrease in keratometric readings were also reported[14]. A small amount of failure cases in S-CXL for pediatric keratoconus were associated with vernal keratoconjunctivitis and/or persistent eye rubbing[17-18]. However, Chatzis *et al*[17] reported that improvement in K-values occurred within the 24 months' follow-up visit with a regression compared with preoperative readings at the 36 months' follow-up visit indicating a possible decrease in the efficacy of CXL over time. Nevertheless, the same result was not observed by Caporossi *et al*[19] or Zotta *et al*[20] who also recorded 36 months' follow-up outcomes.

In S-CXL, the deletion of the corneal epithelium may usually result in pain, temporary visual impairment, corneal edema, risk of corneal haze, prolonged time of postoperative recovery, increased risk of infections, recurrence of herpetic keratitis, endothelial injury, permanent scarring and sterile infiltrates[10]. Especially in pediatric patients, these risks cannot be underestimated. The presence of corneal epithelium in CXL will make patients more comfortable, safe and less complications which may obtain better compliance of pediatric patients. In the research by Magli *et al*[21], transepithelial CXL using riboflavin-dextran-enhancer was as the same effective as S-CXL in pediatric keratoconus within 12mo. But, the opposite result was also reported[22].

I-CXL is a recently developed techniquewhich can promote penetration of ionized molecules into or across tissues by a small electric current[7]. Sparing the corneal epithelium in I-CXL can reduce postoperative pain, visual impairment and procedure time. I-CXL provides greater, more homogeneous and deeper riboflavin saturation than that of other transepithelial techniques[7,23], but less than that of S-CXL[23]. Distilled water was adopted as the solvent of riboflavin solution in this study which is different from the previous riboflavin solution including enhancer in I-CXL. It has been observed by Li *et al*[24] that iontophoresis-assisted riboflavin delivery with 0.1% riboflavin-distilled water solution reaches the same stromal concentration as the epithelial-off technique. However, the conclusion was obtained by observation with the naked eyes, and the concentration was not measured quantitatively. In addition, the amount of riboflavin concentration required to be effective in the corneal stroma to halt keratoconus progression has not been defined yet.

This article reviewed the 1-year clinical data of I-CXL with 0.1% riboflavin-distilled water solution forpediatric keratoconus. The UCVA, BCVA, keratometric readings and endothelial cell density showed no significant changes 1y postoperatively which suggested the safety and efficacy of I-CXL in halting the progression of keratoconus. Similar studies abroad draw the same conclusions. Buzzonetti *et al*[9] treated fourteen eyes of 14 pediatric patients (mean age, 13±2.4y; range, 10-18y) which demonstrated that accelerated I-CXL (10 mW/cm^2, 9min) halted the progression of pediatric keratoconus over 15mo. In that study, the BCVA increased and the thinnest corneal thickness and other parameters showed no significant changes. Magli *et al*[10] presented 18-month follow up outcomes of I-CXL (10 mW/cm^2, 9min) for 13 patients (mean age, 15.4±1.7y; range, 11-18y) which showed a stabilization of the UCVA, BCVA, thinnest corneal thickness and other parameters. In our study, visual acuity showed no significant changes 1y postoperatively, but the corneal apex thickness and the thinnest corneal thickness reduced. Compared with the above two reports, the different changes of BCVA and thinnest corneal thickness postoperatively may correlate with different radiation protocol, riboflavin solution and demographic parameters (age, baseline visual acuity and baseline thinnest corneal thickness)[25]. Greenstain *et al*[26] also reported that the thinnest corneal thickness slightly reduced 1y after CXL. Koller *et al*[27] observed that the thinnest corneal thickness significantly decreased 1y after CXL. The reasons of the change of corneal thickness after CXL have not been elucidated. However, Bueno *et al*[28] recorded a compression of the stromal collagen of the porcine and bovine corneas after the CXL treatment using a set of second harmonic generation images. So we suppose that the change was probably because of stromal collagen fiber compression and unlikely to be as a result of deterioration of keratoconus since corneal curvatures did not increase and corneal thicknesses reduced 3mo postoperatively, then increased 12mo postoperatively than 3mo postoperatively. The specific reasons still need to be further studied.

In conclusion, our study showed that I-CXL using riboflavin 0.1%-distilled water solution could effectively halt the progression of the pediatric keratoconus within 1y. Bikbova *et al*[29] published a prospective randomized controlled trial comparing I-CXL and S-CXL several months ago. Stabilization and decrease of keratometry values were obtained in both groups, but S-CXL was more effective after 24mo of follow-up. However, I-CXL possesses its own advantages, such as shorter operation time, faster recovery and better compliance. I-CXL using 0.1% riboflavin-distilled water solution for pediatric keratoconus is effective and safe which can halt deterioration of keratoconus within 1y, but permanent effects still need to be observed.

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