Original Article

Iontophoresis-assisted versus standard corneal crosslinking for progressive keratoconus

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Background: To compare the safety and efficacy of iontophoresis-assisted epithelial-on corneal crosslinking (I-CXL) using 0.1% riboflavin-distilled water solution with standard epithelium-off corneal crosslinking (S-CXL) for progressive keratoconus.

Methods: In a retrospective analysis, progressive keratoconus patients treated with I-CXL (17 eyes of 17 patients) or S-CXL (13 eyes of 13 patients) were included. All patients were followed up at least 12 months. All patients underwent detailed ophthalmologic examinations involving pre- and postoperative visual acuity, topographic parameters and pachymetry. Intra- and postoperative complications were recorded.

Results: No statistically significant differences were observed between the two groups at baseline with respect to visual acuity, age and thinnest corneal thickness (TCT). The postoperative decreases of K1 and Kmean in the S-CXL group represented statistically significantly better results than in the I-CXL group (t=2.093 and 2.123, P=0.046 and 0.043, respectively). Alterations of other parameters showed no significant differences between the two groups. There were no failure cases in the two groups.

Conclusions: I-CXL using 0.1% riboflavin-distilled water solution provided effective treatment for progressive keratoconus at 12-month follow-up. However, the decreases of K1 and Kmean caused by I-CXL were less than those by S-CXL. Although treatment time, postoperative patient pain and risk of infection in I-CXL are all less than those in S-CXL, I-CXL is unable to completely replace S-CXL for progressive keratoconus temporarily.

Keywords: Keratoconus; corneal crosslinking; iontophoresis; riboflavin

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Introduction

Keratoconus is a bilateral, asymmetrical, non-inflammatory, progressive disease, which induces a conical cornea and visual impairment because of biomechanical changes (1). Keratoplasty is an effective method for this ectatic corneal disorder, however, donor cornea is devoid seriously especially in Asia including China. Conservative treatment approaches could not prevent deterioration of the condition before the advent of corneal crosslinking (CXL). The Dresden team presented the first clinical report of CXL in 2003, which proved the effectiveness of the treatment in halting progressive keratoconus (2). Since then, more and more researches further demonstrated that CXL is an effective and minimally invasive procedure for treating keratoconus. Debridement of the central epithelium is necessary for the protocol of standard epithelium-off corneal crosslinking (S-CXL) to facilitate penetration of riboflavin into the stroma. But epithelial debridement results in many potential risks, such as corneal infection,

sterile corneal infiltrates, sub-epithelial haze, corneal scarring, herpetic activation and endothelial damage (3-5). At the same time, the removal of epithelium can also induce temporary disopsia and evident postoperative pain. In order to avoid these defects, transepithelial CXL was developed which mainly contains two modes. One mode adds enhancers to riboflavin solution with the purpose of promoting riboflavin saturation in the corneal stroma, but its therapeutic efficacy is controversial. Some researches showed that it was less effective than S-CXL (1,6-10). Other studies indicated that its outcome was similar to S-CXL (11-13). The other mode increases intrastromal riboflavin concentration by iontophoresis which has been proved to be effective and safe for progressive keratoconus (14-16). Nevertheless, the relative efficacy of iontophoresis-assisted epithelial-on corneal crosslinking (I-CXL) compared with S-CXL remains to be determined. The aim of our study was to evaluate and compare efficacy and safety of S-CXL and I-CXL procedures for patients with progressive keratoconus.

Methods

Patients and samples

Subjects included in this study were consecutive progressive keratoconus patients who were treated with I-CXL or S-CXL, from April 2012 to June 2014. Thirty eyes from 30 patients were recruited in this study. Of those, seventeen patients (age from 14 to 26 years) were treated with I-CXL, and the other 13 patients (age from 16 to 31 years) with S-CXL. We retrospectively analyzed the data of these patients. The study conformed with the Declaration of Helsinki and was approved by the Navy General Hospital's Ethics Committee. Every patient provided written informed consent. Inclusion criteria were progressive keratoconus which was defined as an increase in the manifest astigmatism or Kmax ≥1.00 D over the previous 12 months (17), and keratoconus was mild or moderate (stages I and II on the Amsler-Krumeich scale) which was characterized by the thinnest corneal thickness (TCT) ≥400 μm, Kmean ≤53 D, clear cornea and no Vogt striae (18). Exclusion criteria were corneal opacities, history of herpetic keratitis, active keratitis, severe dry eye, any coexisting ocular disease, history of intraocular surgery and concomitant autoimmune diseases.

All eyes were examined in detail. The examinations involved pre- and postoperative uncorrected visual acuity (UCVA), best corrected visual acuity (BCVA), slit lamp biomicroscope, posterior segment, Kmax, K1, K2, Kmean, astigmatism, endothelial cell density, the TCT, intraocular pressure (IOP), pachyapex. Corneal parameters were assessed by corneal topography (Wavelight, Allegro Topolyzer & Topolyzer Vario, Germany). Corneal endothelium was photographed with a noncontact Specular Microscope (SP 2000, Topcon, Japan). Subjects enrolled in this study were visited at least 12 months. All intraoperative and postoperative adverse effects were noted. Rigid gas-permeable contact lense wearers were advised to stop one week at least before the surgery and follow up visit.

Surgical procedures

All surgeries were performed under sterile conditions in an out-patient operation room. S-CXL procedures were finished according to the Dresden protocol with partial modification (2). Topical anesthetic eye drops comprising 0.4% oxybuprocaine hydrochloride (Benoxil, Santen Pharmaceutical Co., Osaka, Japan) were instilled every five minutes for 15 minutes. The central eight-mm-diameter corneal epithelium was gently marked with a surgical trephine, then mechanically removed using a blunt hockey knife. A 0.1% riboflavin solution including 10 mg of riboflavin 5-phosphate (Sigma-Aldrich Trading Co., Shanghai) dissolved in 10 mL of 20% dextran-T-500 solution (Sigma-Aldrich) was instilled every three minutes for 30 minutes. After corneal stroma saturation was confirmed on slit-lamp microscopy, the eye was irradiated for 30 minutes 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). During the irradiation, 0.1% riboflavin-20% dextran solution was applied to the cornea every three minutes. At the end of the operation, the cornea was rinsed with normothermic saline solution, administered antibiotic and corticosteroid drops and placed on a bandage contact lens.

In the I-CXL group, the same anesthetic method as S-CXL group was applied. After patient lay supine and the forehead skin was cleaned and polished with 75% alcohol, the iontophoresis device was established. The iontophoresis system includes a connection cable, a power supply and two electrodes. 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 the eyelids were opened by eye speculum, an annular suction ring of the iontophoresis device was placed on the cornea. The ring was irrigated

Table 1 Preoperative comparison between the I-CXL group and the S-CXL group, with regard to age, baseline visual acuity and baseline thinnest corneal pachymetry

Mean ± SD	I-CXL (n=17 eyes)	S-CXL (n=13 eyes)	t(u) value	P value
Age (years)	18.94±2.88	19.77±4.55	−0.609	0.547
UCVA (LogMAR)	0.87±0.19	0.83±0.15	0.630	0.537
BCVA (LogMAR)	0.36±0.11	0.38±0.14	−0.457	0.653
TCT (μm)	466.53±32.80	479.83±21.34	−1.245	0.223

UCVA, uncorrected visual acuity; BCVA, best spectacle corrected acuity; pachyapex, thickness of corneal apex; TCT, the thinnest corneal thickness; I-CXL, iontophoresis-assisted epithelium-on corneal crosslinking; S-CXL, standard epithelium-off corneal crosslinking.

with 0.1% riboflavin-distilled water solution and total cover of the grid was ensured. The power generator was afterward turned on and "1.0 mA" constant current was selected. Iontophoresis continued for five minutes. After corneal stroma imbibition was proved, the same UVA irradiation as S-CXL group was performed. During the irradiation, 0.1% riboflavin-saline solution was applied to the cornea every three minutes. The remaining process conformed with S-CXL group. The corneal epithelium was not removed in the I-CXL group.

Data obtained at preoperative and postoperative visits were reviewed from the patients' medical records and prepared for statistical analysis.

Statistical analysis

SPSS 17.0 software was adopted for statistical analysis. The paired Student *t*-test was used for comparing preoperative and postoperative data in the same group in the presence of normal distribution, and Wilcoxon matched pairs test in the case of non-normal distribution. The unpaired *t*-test was used for analyzing inter-group data in the presence of normal distribution, and Mann-Whitney U test in the case of non-normal distribution. Two tailed distribution results were accepted for P values. P values <0.05 were considered statistically significant.

Results

Characteristics of subjects before surgery are shown in *Table 1*. Seventeen patients were recruited in the I-CXL group, and thirteen patients in the S-CXL group. There was no statistically significant difference in the parameters of age, visual acuity and TCT between the two groups at baseline (*Table 1*).

Various parameters in the I-CXL group at the preoperative and postoperative time point are presented in *Table 2*. No statistically significant changes were observed in the values of K1, K2, Kmean, astigmatism, IOP, and endothelial cell density (P=0.211, 0.054, 0.071, 0.692, 0.886 and 0.201, respectively). UCVA (LogMAR) and BCVA (LogMAR) statistically significantly increased from 0.87±0.19 to 0.78±0.18 (P=0.000) and from 0.36±0.11 to 0.23±0.10 (P=0.000) respectively when the postoperative values were compared with the preoperative. Kmax, pachyapex and TCT statistically significantly decreased from 56.61±5.47 to 55.31±5.04 (P=0.000), from 479.65±35.93 to 461.71±46.38 (P=0.001) and from 466.53±32.80 to 435.82±66.20 (P=0.031) respectively.

In the S-CXL group, all the parameters are presented in *Table 3*. No statistically significant changes were observed in the values of astigmatism, IOP, and endothelial cell density (P=0.798, 0.439 and 0.528, respectively). UCVA (LogMAR) and BCVA (LogMAR) statistically significantly increased from 0.83±0.15 to 0.72±0.14 (P=0.000) and from 0.38±0.14 to 0.27±0.12 (P=0.000) respectively when the postoperative values were compared with the preoperative. Kmax statistically significantly decreased from 56.03±7.97 to 53.82±7.28 (P=0.001), K1 from 45.82±3.41 to 44.61±3.74 (P=0.001), K2 from 49.68±4.83 to 48.56±5.20 (P=0.011), Kmean from 47.93±3.94 to 46.69±4.37 (P=0.002), pachyapex from 494.50±22.71 to 463.42±37.85 (P=0.002), TCT from 479.83±21.34 to 432.75±34.56 (P=0.000).

The differences between the values of 12 months postoperatively and baseline implied postoperative changes of various parameters. The contrast of postoperative changes between the two groups is showed in *Table 4*. No statistically significant differences were observed in most postoperative changes between the two groups, in terms of UCVA, BCVA, Kmax, K2, astigmatism, pachyapex,

Table 2 Preoperative and postoperative visual acuity and topographical data in the I-CXL group

Mean ± SD	Baseline	12 months	t(u) value	P value
UCVA (LogMAR)	0.87±0.19	0.78±0.18	12.941	0.000
BCVA (LogMAR)	0.36±0.11	0.23±0.10	7.469	0.000
Kmax (D)	56.61±5.47	55.31±5.04	4.617	0.000
K1 (D)	46.54±2.71	46.18±2.63	1.302	0.211
K2 (D)	50.25±3.63	49.75±3.48	2.081	0.054
Kmean (D)	48.31±2.85	47.86±2.84	1.936	0.071
Corneal astigmatism (D)	3.69±2.53	3.59±2.19	0.403	0.692
Pachyapex (μm)	479.65±35.93	461.71±46.38	3.918	0.001
TCT (μm)	466.53±32.80	435.82±66.20	2.364	0.031
IOP (mmHg)	12.77±2.56	12.92±1.98	−0.147	0.886
Endothelial cell density (/mm^2)	2,741.82±361.97	2,625.53±465.81	1.335	0.201

UCVA, uncorrected visual acuity; BCVA, best spectacle corrected acuity; pachyapex, thickness of corneal apex; TCT, the thinnest corneal thickness; IOP, intraocular pressure; I-CXL, iontophoresis-assisted epithelium-on corneal crosslinking.

Table 3 Preoperative and postoperative visual acuity and topographical data in the S-CXL group

Mean ± SD	Baseline	12 months	t(u) value	P value
UCVA (LogMAR)	0.83±0.15	0.72±0.14	8.634	0.000
BCVA (LogMAR)	0.38±0.14	0.27±0.12	8.487	0.000
Kmax (D)	56.03±7.97	53.82±7.28	4.144	0.001
K1 (D)	45.82±3.41	44.61±3.74	4.331	0.001
K2 (D)	49.68±4.83	48.56±5.20	3.002	0.011
Kmean (D)	47.93±3.94	46.69±4.37	3.974	0.002
Corneal astigmatism (D)	3.88±2.64	3.96±2.71	−0.261	0.798
Pachyapex (μm)	494.50±22.71	463.42±37.85	4.097	0.002
TCT (μm)	479.83±21.34	432.75±34.56	6.676	0.000
IOP (mmHg)	10.91±3.36	11.87±2.33	−0.803	0.439
Endothelial cell density (/mm^2)	2,706.23±512.29	2,632.62±460.33	0.649	0.528

UCVA, uncorrected visual acuity; BCVA, best spectacle corrected acuity; pachyapex, thickness of corneal apex; TCT, the thinnest corneal thickness; IOP, intraocular pressure; S-CXL, standard epithelium-off corneal crosslinking.

TCT, IOP and endothelial cell density. Nevertheless, the postoperative decreases of K1 and Kmean in the S-CXL group represented statistically significantly better results (P=0.046 and 0.043, respectively).

In the I-CXL group, Kmax decreased in 15 eyes, and increased in two eyes (<1.00 D). In the S-CXL group, Kmax decreased in 12 eyes, and increased in one eye (<1.00 D). In the I-CXL group, all the eyes showed no any complications, but in the S-CXL group, there was stromal haze in one eye which appeared early in the postoperative period and disappeared within five months. No systemic adverse reactions were noticed in all the subjects.

Table 4 Comparison of postoperative difference of visual acuity and corneal parameters between the two groups. Positive values signify an increase and negative values an adverse result postoperatively

Mean ± SD	I-CXL (d)	S-CXL (d)	t(u) value	P value
UCVA (LogMAR)	−0.09±0.02	−0.10±0.04	0.503	0.621
BCVA (LogMAR)	−0.11±0.04	−0.12±0.05	−0.423	0.677
Kmax (D)	−1.30±1.16	−2.21±1.92	1.506	0.149
K1 (D)	−0.36±1.15	−1.21±1.01	2.093	0.046
K2 (D)	−0.50±0.99	−1.12±1.34	1.448	0.159
Kmean (D)	−0.44±0.94	−1.24±1.08	2.123	0.043
Corneal astigmatism (D)	−0.10±1.07	0.08±1.06	−0.462	0.648
Pachyapex (μm)	−17.94±18.88	−31.08±26.28	1.570	0.128
TCT (μm)	−30.71±53.55	−47.08±24.43	0.986	0.333
IOP (mmHg)	0.15±3.54	0.96±4.13	−0.515	0.612
Endothelial cell density (/mm^2)	−116.29±359.25	−73.62±408.72	−0.304	0.763

UCVA, uncorrected visual acuity; BCVA, best spectacle corrected acuity; pachyapex, thickness of corneal apex; TCT, the thinnest corneal thickness; IOP, intraocular pressure; I-CXL, iontophoresis-assisted epithelium-on corneal crosslinking; S-CXL, standard epithelium-off corneal crosslinking; d, the difference of various parameters between postoperative and preoperative outcomes.

Discussion

In this retrospective study, we reviewed the outcomes of I-CXL in 17 eyes and S-CXL in 13 eyes. The influential factors of preoperative subject characteristics on clinical results of CXL treatment contains age, baseline visual acuity, and baseline TCT (19,20). In order to compare the efficacies of the two methods, all the three confounding factors associated with the subjects were analyzed which demonstrated that all the patients in both groups have homogeneous characteristics preoperatively. Generally speaking, I-CXL and S-CXL procedures are all effective and safe in halting progression of keratoconus, however, partial indices improved to varying degrees. The postoperative decreases of K1 and Kmean in the S-CXL group represented statistically significantly better results than in the I-CXL group (P=0.046 and 0.043, respectively). Postoperative changes of other indicators had no statistically significant differences.

Many studies have already confirmed the effectiveness of S-CXL in halting progression of keratoconus, and recommended it as the standard of care (21). However, relatively few researchers reported their results of I-CXL. Iontophoresis is a non-invasive technique which can promote penetration of ionized molecules into or across tissues (22), and has been accepted as a good means to improve the low intraocular penetration of drugs for treating various eye diseases for decades (23,24). Riboflavin is characterized by high solubility in water, small molecular weight, and negatively charged at physiological pH which is suitable for iontophoresis. Some researchers have investigated the ability of riboflavin penetration into corneal stroma assisted by iontophoresis. The corneal intrastromal riboflavin concentration obtained by iontophoresis was greater than conventional transepithelial protocol, but less than the standard (25-28). Riboflavin solutions that were used in the above iontophoresis studies contained different ions and enhancers, while Li *et al*. (29) evaluated the penetration into corneal stroma of 0.1% riboflavin-distilled water solution by iontophoresis and reported similar stromal yellow change compared with the standard protocol. Whether Li's protocol can obtained the same intrastromal riboflavin concentration with the standard need further quantitative study.

Some clinical studies also existed in the literature. Bikbova and Bikbov revealed that the depth of apoptotic keratocytes in I-CXL was 210–230 μm while it was 270–300 μm in S-CXL (16). I-CXL induced a demarcation line in corneal stroma that was less easily distinguishable and superficial than in S-CXL, but more than in traditional transepithelial CXL (30,31). Demarcation line may imply the intensity and effect

of crosslinking. Lombardo *et al.* (32) reported that I-CXL increased the stiffness of human corneas of donor eye globes almost comparable to that of S-CXL. Preliminary clinical observations (14-16) suggested that I-CXL not only stabilized the progression of keratoconus, but also improved some indices such as UCVA, BCVA, Km and astigmatism.

In our study, we used 0.1% riboflavin-distilled water solution in I-CXL group which is different from the above clinical trials. In our I-CXL research group, Km and astigmatism didn't statistically significantly improve probably because of different extent of keratoconus or/and small sample size. We observed the decreases of pachyapex and TCT in our both groups. Sharma *et al.* (33) also observed a significant reduction in corneal thickness 12 months postoperatively whose subjects had advanced keratoconus. Greenstein *et al.* (34) reported that pachyapex remained unchanged and TCT decreased 12 months postoperatively comparing with the baseline. The cause and implication of corneal thickness changes after CXL remain to be elucidated.

The main factors affecting CXL consist of intrastromal riboflavin concentration and irradiation intensity of UVA. Slight differences between the two groups in our research may be attributed to these two factors. Although iontophoresis-assisted saturation of 0.1% riboflavin-distilled water solution was considered to induce the same intrastromal riboflavin concentration as the standard epithelial-off method, it was only the result of visual observation (29). So the minor difference was likely to exist. Besides, the removal of the iontophoresis device during the UVA irradiation may decrease riboflavin supply. Corneal epithelium influences not only intrastromal riboflavin concentration but also transmissivity of UVA. About 20% of UVA is absorbed by corneal epithelium (35). In addition, corneal epithelial thickness mathematically lessens the stromal depth of UVA irradiation.

In conclusion, I-CXL using 0.1% riboflavin-distilled water solution provided effective treatment for progressive keratoconus at 12-month follow-up. However, the decreases of K1 and Kmean caused by I-CXL were less than those by S-CXL. Although treatment time, postoperative patient pain and risk of infection in I-CXL are all less than those in S-CXL, I-CXL is unable to completely replace S-CXL for progressive keratoconus temporarily. However, the limitations of our investigation involve the small number of subjects and the short follow-up period. Therefore, further researches with a larger number of patients and a longer follow-up period are necessary.

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Footnote

Conflicts of Interest: The authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/aes.2017.01.01). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Navy General Hospital's Ethics Committee and written informed consent was obtained from all patients.

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