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A Higher-energy Accelerated Corneal Collagen Cross-linking Method for Keratoconus: A Retrospective, Observational Cohort Study

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Abstract: Introduction: Primary keratoconus is a non-inflammatory corneal ectasia disease with an unknown cause. Nowadays, the most widely used treatment method is corneal collagen crosslinking based on the Dresden protocol. Due to the long surgery time, we have been searching for a new method which cost less time in surgery. Methods: A retrospective, observational cohort study was used. A total of 31 participants (59 eyes) with primary keratoconus were collected. Twelve of them (24 eyes) used the standard Dresden protocol, and the remaining 19 (35 eyes) used a higher-energy accelerated corneal collagen cross-linking method. Application of riboflavin solution to the de-epithelialized cornea for 10 min, then the cornea is UVA irradiated (wavelength, 365 nm and power, 30 mW/cm^2) for another 3.55 min, and the total irradiation energy is 6.4J/cm^2. Participants were followed up for 12 months after surgery and underwent complete examinations at 3, 6, and 12 months in predetermined windows of time. The examinations items include routine ophthalmological examination, uncorrected vision acuity (UCVA), best corrected visual acuity (BCVA), refraction, corneal curvature, the elevation of the thinnest point on front surface and back surface (F Ele Th, B Ele Th), the thickness of the thinnest point of the cornea (CT), and the density of the corneal endothelial cells (ECD). The independent sample t-test method was used to compare the changes of the parameters of the standard Dresden protocol and the higher-energy accelerated corneal collagen cross-linking. Results: In the A-CXL treatment group, the maximum keratometry value decreased by 1.48D from baseline, UCVA improved by an average of 0.07 logarithm of the minimum angle of resolution (logMAR) units, BCVA improved by an average of 0.15 logarithm of the minimum angle of resolution (logMAR) units. All of those are similar to standard Dresden protocol group. There were no significant changes in endothelial cell count and thickness of cornea 1 year after treatment. Conclusions: In this study, we found that accelerated corneal collagen cross-linking under 6.4J energy has a similar surgical effect as corneal collagen cross-linking under the Dresden protocol, and did not cause more adverse events.

Keywords: Keratoconus, Higher-energy, Accelerated Cornea Cross-linking

1. Introduction

Primary keratoconus is a non-inflammatory corneal ectasia disease with an unknown cause. Its onset in the center or sides of the cornea and usually asymmetric [1-3]. Traditional treatment methods include spectacles, Rigid Gas Permeable Contact Lens (RGP), intrastromal corneal ring segment (ICR), corneal transplantation, etc. [2, 4] Recent years, some scholars also reported the use of micro-lenses removed from SMILE surgery to assist in the treatment of keratoconus [5], but this solution is still being explored. However, these traditional treatments can only improve the participant's vision but not stop or reverse the progression of keratoconus. Some participants will eventually develop the condition to require a corneal transplant.

Till 2003, Wollensak G et al. reported that

Riboflavin/Ultraviolet-A-induced Collagen.

Crosslinking (CXL) can control the progression of primary keratoconus and delay the time required for corneal transplantation [6]. Corneal collagen cross-linking beginning to be applied in clinic. CXL can increase the covalent bonds between the corneal matrix collagen fibers, increase the biomechanical stability of the cornea, thereby delaying or even preventing the progression of the disease, then prolonging the time from the development of the disease to the need for a corneal transplant [1, 6, 7]. The power of UVA used in traditional CXL protocol is only 3mW/cm^2, total energy is 5.4J/cm^2, and total surgery time need at least 30 min. We also need to frequently use eye drops during the operation to keep the eye surface moist [6]. The participant's comfort is poor. Nowadays, the accelerated corneal collagen cross-linking protocol (A-CXL) appeared, which means, increasing the power of UVA to shorten the time while maintaining the total energy [8]. Improve the efficiency of surgery while making participants more comfortable and easier to cooperate with surgery. At the same time, some studies have found that higher irradiation energy can lead to better surgical results. Some researchers have increased the power of UV to 45mW/cm^2, the energy of UV to 7 J/cm^2, the concentration of riboflavin to 0.25% [9]. And the participants' indicators improved after surgery. This study will investigate whether accelerated corneal collagen cross-linking with a total energy of 6.4 J/cm^2 is a safe and effective method in the treatment of primary keratoconus or not.

2. Methods

Inclusion–Exclusion Criteria

Inclusion: Unlimited gender, Unlimited race, Age> 14, BCVA <20/20, have primary keratoconus and the disease is in the progressive stage (within 24 months, the maximum keratometry has increased by more than 1D or an increase of 1.00 D or more in manifest cylinder or an increase of 0.50 D or more in manifest refraction spherical equivalent), cornea is transparent, corneal topographic maps matching disease manifestations; maximum keratometry 47.0 diopters (D) or more on corneal topography (Pentacam HR, Oculus GmbH, Wetzlar, Germany), corneal thickness more than 400μm; no other eye diseases which may affect vision, participants are willing and able with the operation and follow-up process.

Exclusion: One-eyed participants, history of corneal surgery (including the intrastromal corneal ring segment), corneal thickness <400μm, advanced corneal keratoconus who cannot benefit from the surgery, RGP deactivation time is less than 4 weeks, acute eye infection or other active eye diseases, allergic to drugs, suffering from uncontrolled systemic diseases (such as diabetes, thyroid disease, etc.), women in pregnancy or breastfeeding, taking antipsychotics drugs in the past six months, unable to cooperate with surgery and follow-up procedures.

Treatments

The high-energy group was given 0.5% levofloxacin eye drops 4 times per day for 3 days before surgery. A topical anesthetic agent was administered and the central 9.0 mm of epithelium was removed by mechanical debridement with a blunt spatula. Eyes were spotted with riboflavin solution (0.1% riboflavin dissolved in 20% dextran solution) every 2 minutes for 10 minutes. Then the cornea was aligned and exposed to ultraviolet A (365nm) light for 3.55 minutes at an irradiance of 30 mW/cm^2 (KXL, Avedro, American). The total energy was 6.4J/cm^2. During ultraviolet A exposure, administration of the riboflavin-dextran solution was continued every 2 minutes. After surgery, a contact lens bandage was used to protect the wound. 0.5% levofloxacin eye drops were given 4 times a day surgery, tobramycin and dexamethasone eye drops were used 4 times a day, 0.3% sodium hyaluronate eye drops were used 4 times a day. The participant's epithelial recovery was observed daily after surgery. The contact lens bandage was removed after the wound had completely closed.

The control group used riboflavin solution (0.1% riboflavin dissolved in 20% dextran solution) every 2 minutes for 30 minutes. Then the cornea was aligned and exposed to ultraviolet A (365nm) light for 30 minutes at an irradiance of 3.0 mW/cm^2 (KXL, Avedro, American). The total energy was 5.4J/cm^2. The remaining conditions are the same as the high-energy group.

Participants were followed up for 12 months after surgery and underwent complete examinations at 3, 6, and 12 months in predetermined windows of time. Endothelial cell counts were measured only 12 months after surgery.

Outcome parameters

Vision acuity: The Early Treatment of Diabetic Retinopathy Study (ETDRS) vision chart was used to measure the vision acuity under a under controlled lighting conditions, including uncorrected vision acuity (UCVA), best corrected visual acuity (BCVA). And the manifest refraction spherical equivalent (SE) was tested in the same time. The measurement was started 4 m from the visual acuity chart. If participants could not read any letters at 4 m, they were tested at 2 m. The visual acuity was recorded by decimal recording method, and the logarithm of the minimum angle of resolution (logMAR) units was used for statistical analysis.

Topography: We used a rotating Scheimpflug camera (Pentacam HR; Oculus GmbH, Wetzlar, Germany) for topography measuring. The topographic data were measured before surgery and 3, 6, and 12 months after surgery. In order to objectively describe and quantify the corneal topographic changes, we chose the corneal flat keratometry (K1), steep keratometry (K2), maximum keratometry (Kmax), and the elevation of the thinnest point on front surface and back surface (F Ele Th, B Ele Th). These indicators can measure the characteristics of the keratoconus, that is, the steepness of the topographic distortion of the keratoconus. Objective, quantitative endpoints can also be provided. In this study, each measurement was performed by the same hardware and software. The thickness of the thinnest point of the cornea also was measured by Pentacam.

Safety Analysis: Endothelial cell count was obtained using specular microscopy (Topcon) before surgery and 12 months after surgery. The measurement was repeated 3 times, and the

average cell count for each eye was used in the analysis.

Statistical Analysis

A retrospective, observational cohort study was used. The primary end point was the difference between the A-CXL group and the control group for the mean change in K1, K2, Kmax from baseline to month 12. All parameters are represented by $\bar{x} \pm s$. The differences in mean changes between the A-CXL treatment group and the control group were evaluated using a 2-sample t test. A P value of 0.05 or less was considered statistically significant.

Compliance with ethics guidelines

All study protocols were approved by the local ethics committees and were conducted in compliance with the International Conference for Harmonization, Harmonized Tripartite Guideline E6 for Good Clinical Practice. All participants in this study were provided written informed consent before undergoing any study procedures.

3. Results

A total of 31 primary corneal participants (59 eyes) were collected in this study.. In the experimental group, 19 participants (35 eyes) had an average age of 22.22±3.27 years. The control group consisted of 12 participants (24 eyes) with an average age of 16.00 ± 4.24 years. Participant demographics are presented in Table 1. All participants underwent corneal collagen crosslinking according to the original plan.

Table 1. *Preoperative Population Characteristics.*

	A-CXL group	Control group	Total
Patients, no.	19	12	31
Age (yrs)	22.22±3.27	16.00±4.24	21.09±4.09
Gender (male/female)	11/8	7/5	18/13
Maximum keratometry (D)	64.56±10.90	56.70±6.54*	63.48±10.67
Thickness of cornea (μm)	462.08±30.03	452.50±19.19**	460.76±28.70

*: There is no significant difference between two group. P Value is 0.18.

**: There is no significant difference between two group. P Value is 0.55.

Topography Changes

In the A-CXL treatment group, there was a decrease in K1 (0.24±1.62D), K2 (0.74±1.87D) and Kmax (1.48±3.80D) between baseline and 12 months after surgery. In the control group, there was an increase in K1 (0.83±0.43D), K2 (0.35±0.39D) and Kmax (0.13±1.42D). The changes of the elevation of the thinnest point on front surface in the A-CXL treatment group was a decrease of 4.52±13.67D and there was an decrease of 1.00±2.94D in control group. The changes of the elevation of the thinnest point on back surface in the A-CXL treatment group was an increase of 4.36±15.71D and there was a decrease of 5.00±4.69D in control group. The above differences are not statistically significant (Table 2).

Table 2. *Topography Alternation.*

		Before surgery	3 M after surgery	6 M after surgery	12 M after surgery	Change	P Value
K1 (D)	A-CXL group	48.96±5.00	48.82±5.87	48.77±4.39	48.72±5.31	-0.24±1.62	0.21
	Control group	47.38±3.68	48.01±3.87	48.15±4.42	48.20±4.06	0.83±0.43	
K2 (D)	A-CXL group	54.66±7.43	54.22±8.34	54.05±7.22	53.92±6.80	-0.74±1.87	0.26
	Control group	50.78±4.38	50.98±5.42	51.22±4.44	51.13±4.24	0.35±0.39	
Kmax (D)	A-CXL group	64.56±10.90	63.98±27.88	63.49±30.46	63.08±56.83	-1.48±3.80	0.42
	Control group	56.70±6.54	56.68±10.78	56.73±8.32	56.83±6.73	0.13±1.42	
F Ele Th (μm)	A-CXL group	26.44±12.85	23.78±13.98	22.39±14.89	21.92±16.21	-4.52±13.67	0.62
	Control group	26.00±10.55	25.57±8.82	25.33±8.12	25.00±7.70	-1.00±2.94	
B Ele Th (μm)	A-CXL group	59.56±21.10	61.78±22.79	62.20±20.96	63.92±20.51	4.36±15.71	0.25
	Control group	60.50±17.60	58.44±15.80	56.78±14.80	55.50±13.48	-5.00±4.69	

Changes of the Thickness of Cornea (Table 3)

Compared to the baseline, there was a decrease in the thickness of cornea in A-CXL group (10.96±26.46μm) and there was an increase in the thickness of cornea in control group (1.50±3.70μm). The P value is 0.36.

Table 3. *Change of thickness of cornea.*

	Before surgery	3 M after surgery	6 M after surgery	12 M after surgery	Change	P Value
A-CXL group (μm)	462.08±30.03	458±30.73	455±33.57	451.12±32.63	-10.96±26.46	0.36
Control group (μm)	452.50±19.19	453.49±22.33	454.48±17.78	454.00±16.31	1.50±3.70	

Visual Acuity (Table 4)

Uncorrected vision acuity (UCVA). Compared to baseline, UCVA improved by 0.07±0.17 logarithm of the minimum angle of resolution (logMAR) units in A-CXL group. In the control group, the UCVA lost 0.17±0.30 LogMAR units. The P value is 0.09.

Best corrected visual acuity (BCVA). BCVA improved by an average of 0.15±0.14 logarithm of the minimum angle of resolution (logMAR) units in A-CXL group. In the control group, the BCVA improved 0.18±0.24 logMAR units. The P value is 0.70.

Table 4. *Change of visual acuity.*

		Before surgery	3 M after surgery	6 M after surgery	12 M after surgery	Change	P Value
UCVA	A-CXL group	1.08±0.47	1.03±0.39	1.03±0.44	1.01±0.50	-0.07±0.17	0.09
	Control group	0.91±0.08	1.01±0.21	1.04±0.32	1.09±0.38	0.17±0.30	
BCVA	A-CXL group	0.69±0.34	0.59±0.29	0.55±0.33	0.52±0.31	-0.15±0.14	0.70
	Control group	0.51±0.29	0.37±0.22	0.35±0.27	0.33±0.19	-0.18±0.24	

Changes of Refractive Error (Table 5)

In the A-CXL treatment group, there was a 0.47±4.52D increase in SE from before surgery to 12 months after surgery. In the control group, there was a decrease of 1.33±1.05D from before surgery to 12 months after surgery. The difference in SE change at 1 year between the CXL treatment and control groups was not statistically significant.

Table 5. *Change of Manifest Refraction Spherical Equivalent.*

	Before surgery	3 M after surgery	6 M after surgery	12 M after surgery	Change	P Value
A-CXL group (D)	-6.81±3.11	-6.96±4.21	-7.11±4.56	-7.28±4.90	-0.47±4.52	0.52
Control group (D)	-4.46±1.49	-3.77±0.98	-3.32±1.22	-3.13±0.45	1.33±1.05	

Endothelial Cell Analysis (Table 6)

The endothelial cell counts of the A-CXL group and the control group increased slightly compared with that before surgery. The A-CXL group increased by about 3.81%, and the control group increased by about 0.72%. There was no statistical difference in endothelial cell count changes between the two groups.

Table 6. *Change of Endothelium Cell Density.*

	Before surgery	12 M after surgery	Change	P Value
A-CXL group (cells/mm^2)	2888.83±391.46	2974.58±432.15	110.86±200.24	0.10
Control group (cells/mm^2)	3354.00±378.51	3387.00±321.36	24.75±49.50	

Adverse Events

All 31 participants (59 eyes) had different degrees of discomfort such as dry eyes, eye pain, increased lacrimation, decreased visual acuity, and foreign body sensation after surgery, but the extent was within the participants' own acceptable range. All symptoms were reduced until disappeared within 24 to 48 hours after surgery. No serious adverse events such as HAZE and keratitis occurred in all the participants.

4. Discussion

Since Sporl et al. first reported that Riboflavin/Ultraviolet-A–induced collagen crosslinking can increase corneal stiffness and may be effective in controlling the progression of keratoconus in 1997 [10], research on this has begun. In 2003, Wollensak G et al. Reported the first clinical trial based on riboflavin / UV-a-induced corneal collagen cross-linking (CXL) [6], which confirmed that CXL can control the progression of primary keratoconus. Since then, CXL has gradually become a widely recognized new method for keratoconus treatment. During the treatment, riboflavin is excited from the singlet state to the triplet state under the action of UVA and releases active oxygen. These active oxygens enhance the covalent bonding between the corneal collagen layers, thereby increasing the corneal biomechanical strength. And control the progress of the keratoconus [11]. As an inducer, riboflavin also absorbs most of the ultraviolet rays, protecting the corneal endothelium and deeper structures.

The traditional CXL protocol, also known as Dresden protocol, has a long riboflavin immersion time (30min), low UV irradiation energy (3mW/cm^2), and long UV irradiation time (30min). The total surgery time usually exceeds 1 hour [6]. The patient's comfort is poor during the entire treatment process. As the operation time increases, the patient's cooperation gradually decreases. Not only that, the patient's post-surgery response is also heavier. In 2008, Rocha et al. first introduced the concept of "flashing-linking" [8], which also called “accelerated cross-linking” now. They used polyvinyl pyrrolidone instead of riboflavin, with a wavelength of 370 nm and delivering an irradiance of 4.2 mW/cm^2 at a distance of 1.2 cm, irradiate only 30S. The effect is comparable to the CXL of the traditional protocol. This also brought corneal collagen cross-linking into the era of accelerated cross-linking. However, the optimal conditions for accelerated cross-linking in clinical practice are still unclear. Three key conditions, riboflavin concentration, total irradiation energy, and irradiation intensity, need to be optimized. Some of the current accelerated cross-linking schemes include those that maintain the irradiation energy of 5.4 J/cm^2, and some that increase the irradiation energy to varying degrees. The highest protocol has increased the irradiation energy to 7J/cm^2, also achieved good results [9]. Some studies have also explored different types of irradiations, such as pulsed irradiation. A one-year clinical study showed that compared to traditional continuous light, the accelerated cross-linking of pulsed ultraviolet light can penetrate deeper into the corneal stroma, providing excellent treatment results [12-14]. However, there is also a study which states that under

the premise of keeping the irradiation energy constant, we cannot reduce the irradiation time by increasing the irradiation intensity without limit. Under the conditions of extremely high irradiation intensity and very short irradiation time, cross-linking will not achieve the effect we hope [15]. In this study, after using 10 minutes of riboflavin eye drop, we used an irradiation intensity of 30 mW/cm^2, an irradiation time of 3.55 minutes, and a total irradiation energy of 6.4 J/cm^2. The total operation time is controlled to about 20min. The new protocol can improved the speed and efficiency of the surgery, also improved the comfort of the patient during the surgery, which is more conducive to the cooperation of the patient, and the post-surgery response is lighter. The corneal status of the patient remained stable at 1 year after surgery, and there was no significant difference from the traditional corneal collagen cross-linking protocol.

Topography is currently the primary indicator of keratoconus [2, 16]. The Belin ABCD classification proposed in recent years is also based on this [17]. In this study, we chose the corneal flat keratometry (K1), steep keratometry (K2), maximum keratometry (Kmax), and the elevation of the thinnest point on front surface and back surface (F Ele Th, B Ele Th) to evaluate changes in corneal topography. In previous clinical studies, after surgery, the maximum keratometry decreased under a range from 1 to 2D [1, 6, 14, 18]. In this study, the maximum keratometry decreased 1.48±3.80D in the high-energy treatment group, which is similar to the traditional Dresden protocol group. It prompts that the A-CXL protocol under the energy of 6.4J/cm^2 can stabilize the keratoconus disease, delay or stop the disease progress. The elevation of the thinnest point of the cornea is a less-used item in traditional research. Usually, the thinnest point of the cornea is the most serious area. The deviation of elevation from the surface can prompt the severity of the disease to some extent. In this study, the elevation of the thinnest point on front surface in the A-CXL treatment group was a decrease of 4.52±13.67D. Prompt us that after the corneal collagen cross-linking surgery, the anterior surface of the cornea becomes more regular, and the surgery has achieved curative effect.

Vision acuity is an important subjective indicator. Patients with keratoconus are often suffered by high myopia and irregular astigmatism. Many patients have low vision when they come to the hospital, which has had a great impact on their daily lives [19-21]. Even a small improvement in vision acuity will bring a great improvement to the patient's quality of life. Nowadays, our surgical goal is to control the progression of the disease rather than improve vision, but the improvement of corneal topography and the decrease of curvature can indirectly improve the patient's vision acuity. It also provides better eye conditions for the next RGP fitting. In this study, there was no significant change in UCVA of the two groups of participants, and the BCVA is slightly improved compared to before surgery, which prove that our protocol can make the patient's corneal topography better and indirectly improve vision acuity. It also proves that the protocol used in this study is safe for the treatment of primary keratoconus.

After surgery, patients have different degrees of dry eye, eye pain, foreign body sensation and other discomfort, but their intensity is within the patient's acceptable range. Within 24 to 48 hours after surgery, all symptoms were alleviated until disappeared. No serious adverse events such as HAZE and keratitis occurred. Slit lamp examination also found no obvious abnormal changes in the anterior chamber, iris, and lens. There was no significant change in corneal endothelial cell count between the two groups after operation. These results indicate that the protocol adopted by this study is a safe treatment protocol.

5. Conclusions

After a comprehensive analysis of corneal topography, visual acuity and other parameters, we can come to a conclusion that, compared with the traditional Dresden protocol, the higher-energy accelerated cross-linking protocol we used achieves a surgical effect similar to the Dresden protocol. At the same time, it did not bring any more complications, and can shorten the surgery time and bring a better experience. We hope this protocol can become a new option for keratoconus treatment.

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Authorship

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Compliance with Ethics Guidelines

All study protocols were approved by the local ethics committees and were conducted in compliance with the International Conference for Harmonization, Harmonized Tripartite Guideline E6 for Good Clinical Practice. Every participants in this study were provided written informed consent before undergoing any study procedures.

Data Availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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