International Journal of Enhanced Research in Medicines & Dental Care (IJERMDC),
ISSN: 2349-1590, Vol. 6 Issue 8, August -2019, Impact Factor: 3.015

The Use of Retention Ring with Trephined Bandage Contact Lens Assisted with Continuous Application of Riboflavin and Pulsed Light Accelerated Corneal Collagen Cross-Linking in Keratoconus Progression

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ABSTRACT

Abstract

Background: To investigate the efficacy of retention ring assisted continuous application of 0.1% riboflavin in pulsed accelerated corneal collagen cross-linking on the progression of keratocouns.

Methods: the medical records of 24 eyes of 20 patients with progressive keratoconus who received collagen cross- linking at our private clinics were retrospectively reviewed. Isotonic 0.1% riboflavin was continuously applied for 10 min using an 8.0mm retention ring before the irradiation and accelerated cross linking was applied with 40mw pulsed altraviolet light at wave length of 365 nm for eight minutes without further intermittent application of riboflavin, visual acuity, refractive error, topographic index, corneal thickness and endothelial cell density were evaluated before the operation and at 1,3,6,12 months.

Results: The best corrected visual acuity in log MAR improved from preoperative 0.46 to 0.12 in 12 months. Maximiumkeratometry decreased from 51.9 D to 50.5D at 6 months and 50.1 at 12 months. Astigmatism decreased from preoperative 5.0 D to 4.3 D at 12 months. The thinnest corneal thickness decreased at 3 and 6 months but recovered in 12 months . Endotheleal cell density decreased at post-operative 1 month but gradually recovered in 12 months.

Conclusion: Retention ring assisted continuous application of riboflavin for 10 minutes in pulsed light accelerated cross linking is a comparably safe and effective treatment for halting the progression of keratoconus in 12 months compared with the outcome of standard Dresden protocol shown in previous reports.

Keywords: Cornea, Keratoconus, retention ring, Riboflavin.

INTRODUCTION

Keratocouns is an ectatic corneal disorder characterized by progressive thinning and protrusion, accompanied by irregular astigmatism and myopic progression, hence deteriorating visual function. The conventional treatment is keratoplasty in advanced keratoconus [1]. Corneal cross linking has recently been investigated to intervene in progression of moderate keratoconus. In corneal cross linking riboflavin (Vit. B2) acts as photosensizer. When it is combined with ultraviolet A (UVA) of 365 nm wavelength, oxygen radicals are produced by photochemical reaction. Oxygen radicals introduce interfibrillar and intrafibrillar bond among collagen fibrils[2,3] . Such chemical bonds can increase the corneal rigidity and its resistance to enzymatic degradation of keratoconic cornea [4].

In the standard Dresden protocol , cornea is deepithalialized using alcohol 20% solution and soaked in isotonic 0.1% riboflavin with 20% dextran solution for 30 min. The cornea is then irradiated with UVA of 3m w/Cm2 for 30 min. Riboflavin is intermittently applied before and during the irradiation[5]. This protocol can effectively stabilize the cornea of progressive keratoconus [6]. However it is considered time consuming. An accelerated cross –linking protocol was then introduced to shorten the procedure. It applies UVA of greater intensity for shorter irradiation time[7]. Surgical procedure of accelerated protocol is basically the same as the standard Dresden protocol except two aspects; the intensity (from 9 to 30 mW/cm2) and irradiation time of UV-A (from 3 to 15 min) [8-16]. Many studies have reported that clinical results of the accelerated protocol are comparable to those of the standard Dresden protocol. Recent meta-analyses have shown that the standard Dresden protocol has better treatment efficacy in the depth of demarcation line and change of keratometric values than the accelerated protocol [15,16].

There is no standardized method for riboflavin application in the accelerated protocol. The protocol recommends intermittent application of isotonic riboflavin every 2 minutes for a total of 10 minutes. Shorter application time (every 2 minutes for 10 min) seems to have lower efficacy, even in pulsed light accelerated protocol, than the standard protocol [12] . in addition, our group has demonstrated damage to the limbal stem-cell area by exposure to riboflavin during cross-linking [21]. Thus, it is necessary to protect the corneal limbal area from exposure to riboflavin and UV.

To enhance the efficacy of cross-linking in progressive keratoconus and add limbal protection, our group adopted two modifications. First, we introduced a retention ring for the application of riboflavin in order to apply riboflavin continuously (10 min) for better penetration into the cornea and reducing exposure of limbal area to riboflavin. Second we applied a trephined silicone hydrogel bandage contact lens on limbal area during irradiation of UV-A to protect it from toxic effect of UV-A [21]. UV-A was irradiated in a pulsatile mode (1Sec on and off) for a total of 8 min with total energy of 7.5J/cm2.

METHODS

This study was review of our private clinics it included 24 eyes of 20 patients with progressive keratoconus who received CXL. The medical records of the 20 patients (16 male and 4 female patients) were retrospectively reviewed. The mean age was 28.0 ± 7.8 (range 18-42) and all patients were treated with the same protocol.

Inclusion and exclusion criteria:

The patients who were diagnosed with progressive keratoconus and underwent accelerated CXL were included in the study. Progression was confirmed by an increase of maximum keratometry of more than 1 diopters (D)/ year in serial topography. Those with preoperative Kmax greater than 58 D or central corneal thickness (CCT) less than 400 μm or thinnest corneal thickness (TCT) less than 390μm were excluded. Patients combined with other ocular surface diseases were also excluded.

Clinical evaluation:

Preoperative and postoperative examinations included best-corrected visual acuities (BCVA) as a logarithm of the minimum angle of resolution (log MAR), refractive errors by Auto Kerato-Refractometer, Keratometric values including maximum (Kmax), minimum (Kmin), average (Kavg), and 3mm and 5mm irregular index by topography. Corneal thickness was measured by anterior segment optical coherence tomography. Noncontact specular microscopy was used to measure endothelial cell density. Preoperative measurements were compared with the postoperative measurements at (1 , 3 , 6 , 12) months[28].

Surgical procedure:

Eyes were anesthetized with topical 2% xylocaine. The central 9.0 mm corneal epithelium was peeled off using a crescent knife. Intraoperative pachymetry was performed to make sure that the corneal thickness was greater than 325 m. A retention ring 8.0 mm in diameter was applied on the epi-off corneal surface, and 0.1% isotonic riboflavin with dextran free hydroxypropyl methylcellulose was continuously applied for 12 minutes within the retention ring, then a trephined silicone bandage contract lens was applied to cover the limbus from UV irradiation . Pulsing (1 S. on/off) 40 mW/cm2 intensity of 365-nm wavelength UV-A was irradiated for 8 minutes. During the irradiation, riboflavin was not applied. After irradiation, the corneal surface was irrigated with a balanced salt solution, and the silicone hydrogel bandage contact lens was applied. The bandage contact lens was maintained for 7 days with topical 0.5% moxifloxacin and 1% prednisolone four times a day[28].

RESULTS

This study analyzed a total of 24 eyes of 20 patients over a mean postoperative follow-up of 12.4 ± 1.0 months. The mean age at the time of the procedure was 27 ± 7.6 years. Mean depth of the demarcation line was 288 ± 36.8 μm. The best corrected visual acuity gradually improved from preoperative 0.46 ± 0.45 log MAR to 0.12 ± 0.1 log MAR at 12 months (Fig. 1a) and uncorrected visual acuity also improved, from 0.71 ± 0.35 log MAR to 0.42 ± 0.50 log MAR at 12 months. Refractive errors decreased from -7.2 ± 2.6 D to -6.35 ± 3.22 D in spherical. -4.91± 1.46 D to -4.0 ± 2.05 D in cylinder and remained stable thereafter respectively (Fig. 1c, d).

The keratometric values were delineated as Kmax significantly decreased from 51.9 ± 4.13 D to 50.5 ± 3.50 D at 6 months and 50.11 ± 3.82 D at 12 months. Kmin decreased from 46.50 ± 2.3 D to 45.99 ± 2.27 D at 12 months. Kavg decreased from 49.2 ± 2.4 D to 48.55 ± 2.80 at 6 months, and 48.00 ± 2.69 D at 12 months. Topographic astigmatism was significantly reduced from preoperative 5.6 ± 2.80 D to 4.5 ± 2.48 D at 6 months, and 4.12 at 12 months. Irregular index at 3mm and 5 mm decreased from preoperative 6.4 ± 2.0 D to 5.01 ± 1.49 D and 6.2± 1.88 D to 5.05 ± 1.38 D and the reductions were statistically significant at 12 months. (Fig. 2e and f).

Central corneal thickness decreased from 495 ± 35.0 μm to 480 ± 40.0 μm in 12 months. The thinnest corneal thickness was temporarily decreased at 6 months , but recovered to 460 ± 39.2 mm in 12 months (Fig. 3b). Endothelial cell density significantly decreased, from preoperative 2685 ± 250 cell/mm2 to 2460 ± 440 cell/mm2 at 1 months, but gradually recovered back in 12 months (2621 ± 466 cell/mm2) without any significant change compared with preoperative level or 3 months (Fig. 3c).

Table 1: Baseline characteristics of the patients who underwent pulsed accelerated cross-linking in the study

Demographic factors	
Eyes	24 eyes of 20 patients
Sex	16 male 4 female
Age (year)	27 ± 7.6
Systemic disease / Atopy	0.0% 12%
POD (month)	12.6 ± 1.0
BCVA (logMAR)	0.46 ± 0.45
UCVA (logMAR)	0.71 ± 0.35
Refractive error :	
Spherical (diopter)	-7.2 ± 2.6
Cylinder (diopter)	-4.6 ± 1.46
Topography :	
Kmax (diopter)	51.9 ± 4.11
Kmin (diopter)	46.4 ± 2.3
Kavg (diopter)	49.2 ± 2.4
Astigmatism	5.6 ± 2.9
IR, 3 mm	6.4 ± 2.1
IR, 5 mm	6.2 ± 1.84
AS-OCT :	
CCT(μm)	495
TCT(μm)	462
ECD (cell/mm^2)	2685 ± 223
Depth of demarcation line after 1 mo of cross-linking (μm)	288 ± 36.6

Values are presented as mean ± SD, FU, follow up ; POD, postoperative date; BCVA, best-corrected visual acuity ; UCVA, uncorrected visual acuity; logMAR; irregular astigmatism; CCT, central corneal thickness; TCT, thinnest corneal thickness; AS-OCT, anterior segment optical coherence tomography; ECD, endothelial cell density.

Table 2: Comparison of the application method of UV/ riboflavin and parameter values in standard Dresden and accelerated cross-linking of previous studies. The first three studies used pulsed UV irradiation, while the others used continuous UV.

	Irradiation*	Total Dose* (J/cm²)	Riboflavin application*: Before/during irradiation	FU (mo.)	Standard Dresden protocol						Accelerated protocol					
					N	Δ BCVA (log MAR)	ΔKmax (diopter)	ΔCCT (μm)	Δ ECD (cell/cm²)	DDL (μm)	N	Δ BCVA (log MAR)	ΔKmax (diopter)	ΔCCT (μm)	Δ ECD (cell/cm²)	DDL (μm)
Our study	40mW/cm² for 8min (1 S. on/off)	7.6	With HMPC for 12min, continuous/Not applied	12	Not	Available					24	−0.34	−1.7	−15.0	−64	288
Mazzotta [20]	15mW/cm² for12 min (1 S. on/off)	5.4	With HMPC every 1 min for 10min/NR	24	Not	Available					132	−0.14	−0.42	5.03	NP	280
Jiang[19]	30mW/cm² for 8min (1 S. on/off)	7.2	With HMPC every 2 min for 10min/every 3min	12	31	-0.12	−1.80	NR	−109	285	36	−0.09	−1.31	NR	−247	202
Bouheraoua[24]	30mW/cm² for 3 min	5.4	20% dextran every 1 min for 10 min/NR	6	15	-0.05	−1.80	-1	+4	303	15	−0.01	0.50	-3	20	184
Brittingham[25]	9mW/cm² for 10 min	5.4	20% dextran every 5 min for 20 min/every 2 min	12	81	NR	−0.76	NR	NR	323	50	NR	0.72	NR	NR	245
Hagem[26]	9mW/cm² for 10 min	5.4	With HMPC for 20 min /every 2min	12	20	-0.11	−1.40	NR	-112	442	20	-0.09	−0.50	NR	-54	317
Ng[27]	9mW/cm² for 10 min	5.4	20% dextran every 2 min for 25 min/every 5 min	13.9	14	-0.13	−1.80	-2.1	NR	283	12	0.02	−0.30	2.1	NR	209
Shetty[8]	18mW/cm² for 5 min	5.4	20% dextran every 2 min for 30 min/every 2 min	15.3	36	0.04 (decimal)	−1.32	NR	-166	280	33	0.10 (decimal)	−0.52	NR	-162	203

* Irradiation and riboflavin application method of accelerated protocol, Values are presented as mean value, FU, follow up; N, number ; mo, months; BCVA, best-corrected visual acuity; logMAR, logarithm of minimum angle of resolution; Kmax, maximum keratometry; CCT, central corneal thickness; ECD, endothelial cell density; DDL, depth of demarcation line; NR, not reported; ΔBCVA (log MAR), BCVA at last FU- preoperative BCVA; ΔKmax, kmax at last FU- preoperative Kmax; Δcct, cct at lst FU- preoperative CCT; DECC, ECC at last FU – preoperative ECC.

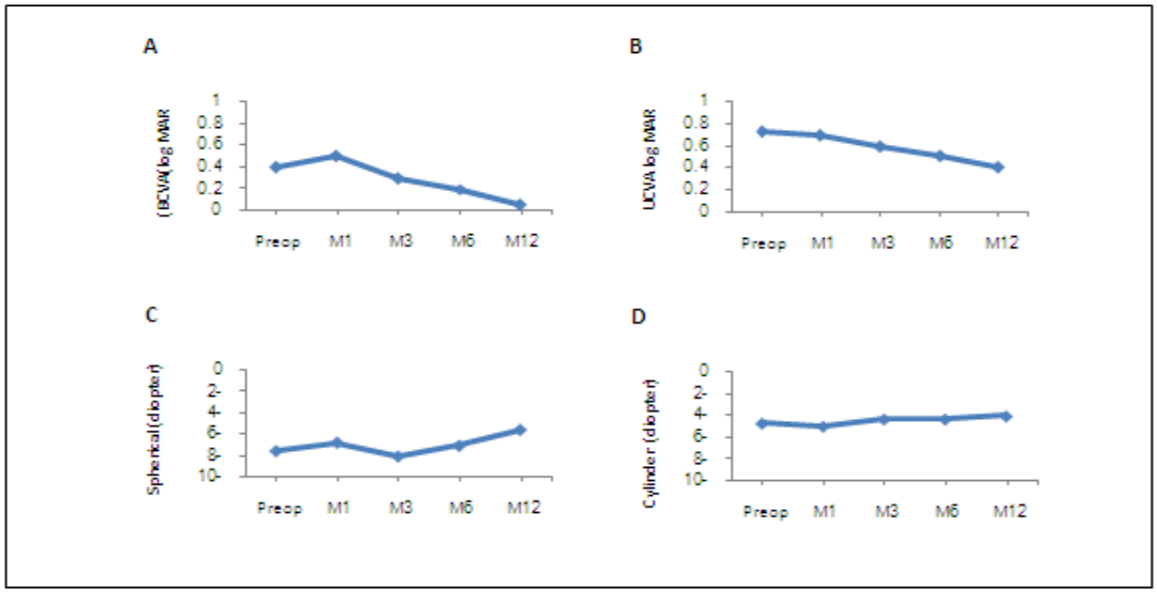

Fig 1: Changes of best corrected visual acuity (BCVA, log MAR) (a), uncorrected visual acuity (UCVA, log MAR) (b) and spherical (c), cylindrical (d) refractive errors (diopter) over time following modified pulsed-light accelerated cross-linking.

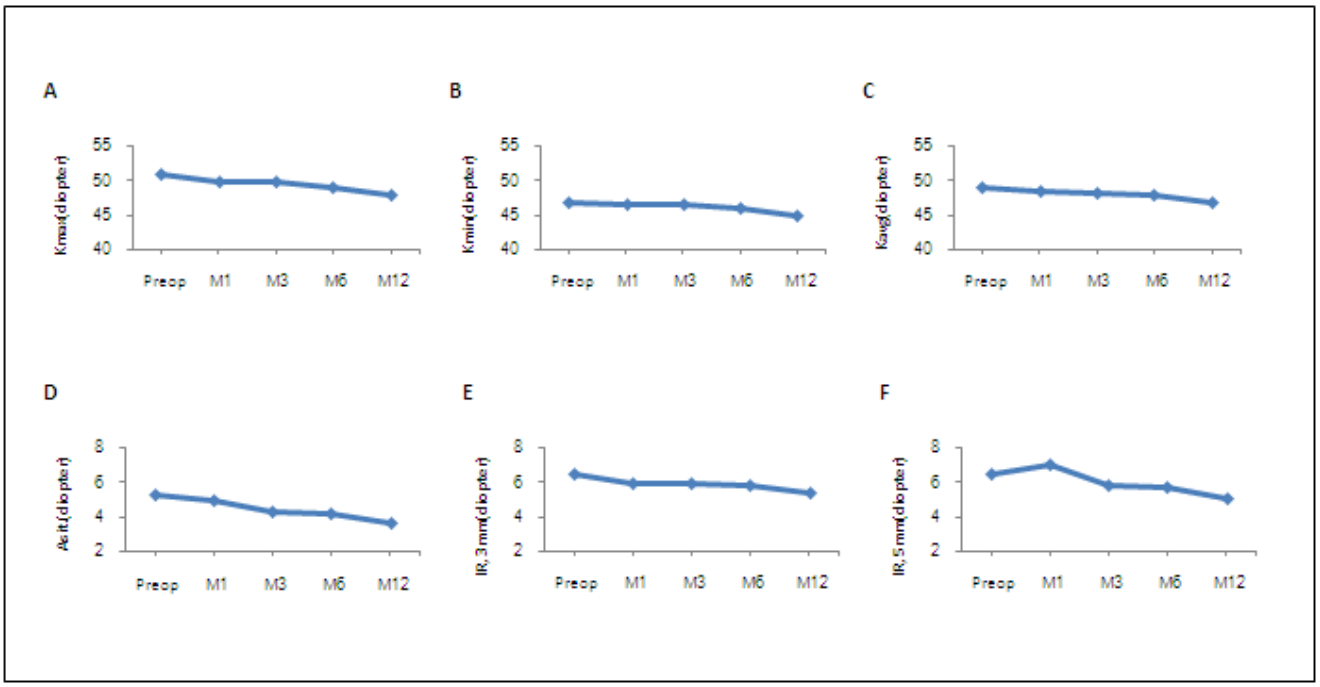

Fig (2) : Corneal topographic changes (diopter) following modified pulsed–light accelerated cross-linking over time, K_{max}(a), K_{min}(b), K_{avg}(c), astigmatism (d), and irregular astigmatism (IR) at 3 mm (e) and at 5 mm (f).

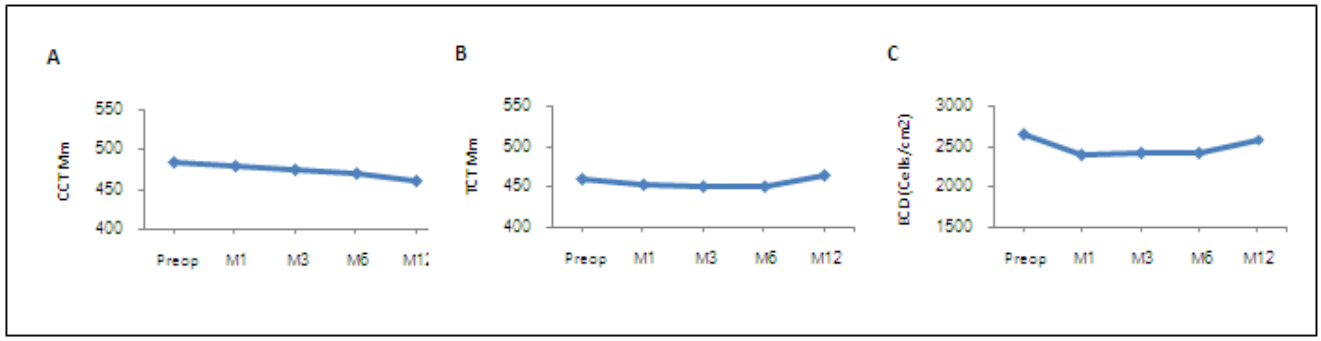

Fig 3: Changes of central corneal thickness (µm) (a), thinnest corneal thickness (µm) (b) and endothelial cell density (c) (cells/cm^2) following modified pulsed-light accelerated cross-linking at different postoperative periods.

DISCUSSION

In this study, we report that retention ring-assisted continuous application of riboflavin for 10 minutes in pulsed – light accelerated cross-linking is a effective as standard Dresden protocol or more effective than other pulsed – light accelerated cross-linking protocols for halting the progression of keratoconus in 12 months [28].

To improve efficacy, a pulsed-light accelerated protocol was first introduced, showing better functional outcomes in 1 year by optimizing intraoperative oxygen availability than the standard Dresden protocol[18]. Recent studies generally indicate that the standard Dresden protocol has better efficacy that for the accelerated protocol with a deeper demarcation line [15,16]. Continuous application of riboflavin using a retention ring might induce deeper penetration of riboflavin and increase the availability of riboflavin in corneal tissue, thus enhancing the efficacy of treatment.

To shorten the procedure we modify the application method of riboflavin by using a retention ring before irradiation. The overall clinical effect of our modified protocol on visual acuity, topographic parameters and demarcation line depth was comparable to that of the standard Dresden protocol or better that other studies with accelerated cross-linking (Table 2). The mean visual improvement was -0.20 logMAR in our study , which was better than the outcome in the accelerated protocol (-0.01 ~ -0.14 logMAR) and the standard Dresden protocol (-0.05 ~ -0.13 logMAR). The mean reduction of

maximum keratometry was -1.7 D in our study. It was greater that of other accelerated protocols (-0.3 D ~ -1.2 D), therefore, our modified ten-mintute continuous application of riboflavin in a pulsed – light accelerated protocol has better efficacy than other accelerated protocols . it is as efficient as the standard Dresden protocol.

Because of the possibility of limbal stem cell damage during riboflavin application and UV irradiation [21], modification of the previous protocol as essential. In our experiments [21], a significantly greater decrease of stem cells was observed when riboflavin was dropped on the whole corneal surface in accelerated cross-linking when compared to the protocol using the retention ring. In our study, endothelial cell density was significantly reduced in postoperative 1 month compared to that preoperatively. Continuous application of riboflavin may penetrate deeper microscopically than the depth that the grossly visible demarcation line indicates. This may subsequently lead to effect of UV on endothelial cell immediately post-operation, endothelial cell density gradually recovered and maintained up to postoperative 12 months. The study was limited because it did not include a direct control group with Dresden protocol. Instead, we compared the efficacy and safety of our modified protocol with those of the Dresden protocol described in previous reports (Table 2)[28] .

CONCLUSION

Retention ring-assisted continuous application of riboflavin for 10 minutes in pulsed-light accelerate cross-linking is a comparably effective for halting the progression of keratoconus in 12 months when compared to outcomes of the standard Dresden protocol described in previous reports.

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