• Original Article •

Efficacy and safety of accelerated corneal collagen cross-linking in patients with keratoconus

Yonrawee Piyacomn, Ngamjit Kasetsuwan, Vilavun Puangsricharern, Usanee Reinprayoon, Vannarut Satitpitakul, Patchima Chantaren

Excellence Center of Cornea and Limbal Stem Cell Transplantation; Department of Ophthalmology, King Chulalongkorn Memorial Hospital, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand

Correspondence to: Ngamjit Kasetsuwan. Excellence Center of Cornea and Limbal Stem Cell Transplantation, Department of Ophthalmology, King Chulalongkorn Memorial Hospital, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand. Ngamjitk@gmail.com

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Abstract

● **AIM:** To study the efficacy and safety of accelerated collagen cross-linking in keratoconus.

● **METHODS:** Medical records of keratoconic corneas underwent accelerated collagen cross-linking at King Chulalongkorn Memorial Hospital, Thailand between April 2015 and August 2018 were reviewed. Preoperative and postoperative data at 1y of visual acuity, auto-refraction, corneal topography, higher-order aberrations (HOA), topometric indices and corneal densitometry were evaluated. Age of 24-30 (mean age 23.43±7.26)y, maximum keratometric value (Kmax) of 55 D, and baseline best corrected visual acuity (BCVA) of 20/40 (or 0.3 in LogMAR unit) were used as cut-off values to highlight the cross-linking effects. The effect of age, preoperative Kmax and BCVA were analyzed. The association between the change of corneal densitometry and other factors including preoperative Kmax, Kmean, manifest refraction spherical equivalent (MRSE), visual acuity, thinnest pachymetry, the change in Kmax, and the change of those parameters were also analyzed. *P*<0.05 was considered statistically significant.

● **RESULTS:** One hundred and fifty-five patients (185 eyes) were included. Male to female ratio was 3:31. According to Amsler-Krumeich classification, stage 1 and 2 were dominant (37.84% and 35.14% respectively). At 1y, mean LogMAR uncorrected visual acuity (UCVA) improved by 0.1 (*P*<0.05). The number of eyes of which postoperative BCVA improved more than 0.2 LogMAR was higher in the worse baseline BCVA group (preoperative BCVA ≥0.3) compared to the better baseline BCVA group (preoperative BCVA <0.3) (78.26% *vs* 21.74%, *P*<0.05). Mean Kmax decreased from baseline by 2.36 diopters (D) (*P*<0.05). Seventy-three percent of the eyes of which Kmax reduced more than 2.0 D had preoperative Kmax ≥55 D. Q-value showed less prolate by 0.06 (*P*<0.05). Corneal HOA at 6 mm from corneal apex decreased by 0.40 (*P*<0.05). Corneal densitometry at 0-6 mm zone increased at 1mo and persisted 1y postoperatively (*P*<0.05). The relationship of the increase in densitometric value and the decrease of thinnest pachymetry at 1y were in linear fashion. Index of surface variance, index of vertical asymmetry, keratoconus index, index of height decentration decreased at 1y (*P*<0.05). Success rate at 1y was 90.24%. Postoperative corneal haze was found 11.35%, 30.27%, 15.67%, 10.27% and 2.16% at 1wk, 1, 3, 6mo and 1y respectively. No eyes developed corneal edema. There was one case of sterile keratitis.

● **CONCLUSION:** Accelerated collagen cross-linking in keratoconus was effective to flatten, reshape the cornea, improved visual acuity, HOA and topometric indices. Great Kmax reduction was found in advanced keratoconus. The magnitude of Kmax reduction is also greatest among previous reports.

● **KEYWORDS:** keratoconus; cross-linking; higher-order aberration; corneal densitometry; topometric index; keratometry

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INTRODUCTION

Keratoconus is a progressive corneal ectatic disease. The characteristics of this disease are corneal thinning,

corneal protrusion and irregular steepening resulting in progressive myopia and myopic astigmatism. Corneal collagen crosslinking is known to halt the disease progression by strengthening the corneal stiffness.

Considering the concept of corneal collagen cross-linking, riboflavin is used in combination with ultraviolet-A (UVA) irradiation. The wavelength of the irradiation is 365 nanometres[1-2]. Riboflavin acts as a photosensitizer for the production of singlet oxygen and the free oxygen radicals then trigger the interaction of riboflavin and UVA. As a result, there are formations of intra- and inter-fibrillar carbonyl-based covalent bonds. Consequently, the keratoconic corneal stroma becomes stiffer[2].

Conventional Dresden protocol collagen cross-linking was first reported by Wollensak *et al*[1] using 30min of 3 mW/cm^2 UVA irradiation. This deals with debridement of the central 8-9 mm zone of corneal epithelium after application of topical anesthetic eye drop, then instilling a solution of 0.1% riboflavin in 20% dextran every 2min for 30min. Then, UVA light is irradiated to the cornea for 30min at 3 mW/cm^2 irradiance (5.4 J/cm^2 total energy). This protocol shows promising results and long-term corneal stabilization. Accelerated protocol was developed to reduce the procedure time. Regarding the Bunsen-Roscoe law of reciprocity, equal photochemical effects on the cornea can be reached by using higher intensities but a shorter period of time in order to achieve the same amount of cumulative doses[3-4]. The proposed advantages include decreased exposure time, better patient comfort, and lower risk of infection. We studied the one-year efficacy and safety of accelerated collagen cross-linking in Thai patients diagnosed with keratoconus.

SUBJECTS AND METHODS

Ethical Approval This study was approved by the Institutional Review Board, Faculty of Medicine, Chulalongkorn University, Thailand and adhered to the tenets of Declaration of Helsinki. The study was conducted at King Chulalongkorn Memorial Hospital, Bangkok, Thailand.

Study Design The study was retrospective chart review. Medical records of keratoconus patients underwent accelerated collagen cross-linking between April 2015 and August 2018 were reviewed by single investigator.

Study Population Inclusion criteria were all keratoconus eyes performed accelerated cornea collagen crosslinking in our center during the time period previously mentioned. The indication for collagen cross-linking in our study were age under 24y or 2 progressive keratoconus which was defined by one of the following criteria. 1) maximum keratometric value (Kmax) increased more than 1.0 diopter (D) in 6mo; 2) mean keratometric value (Kmean) increased more than 1.5 D in 6mo; 3) Manifest cylinder increased more than 1.0 D in 6mo; 4) Thinnest pachymetry decreased more than 5% in 6mo. Exclusion criteria are medical charts of which patients failed to follow-up for at least 6mo. In addition, we have contraindications for corneal collagen crosslinking as follows. 1) Thinnest pachymetry less than 350 microns; 2) Previous herpetic ocular infection; 3) Severe corneal scarring; 4) Concurrent ocular infection; 5) Neurotrophic keratopathy; 6) Autoimmune disorders; 7) History of poor epithelial wound healing; 8) Pregnancy.

Surgical Technique Corneal epithelium was re ved at 8-9 millimeters in diameter using Hockey knife. One drop of 0.1% isotonic riboflavin in 1.1% hydroxypropyl methylcellulose solution (Medicross M, Behrensbrook, Neudorf, Germany) was instilled every 2min for ten times. The pachymetry was measured to ensure that the pachymetry value was more than 400 microns. If the values were less than 400 microns, 0.1% riboflavin in sterile water (Medicross H, Behrensbrook, Neudorf, Germany) was instilled every 2min until the pachymetry value was above 400 microns. The anterior chamber flare was then checked. UVA was irradiated for 5min with a fluence of 18 mW/cm^2 (CCL-365 Vario crosslinking system, Peschke Meditrade GmbH, Huenenberg, Switzerland). All eyes were covered with soft contact lens for 1wk. The patients were given a combination of topical 0.5% moxifloxacin and 0.1% dexamethasone eye drops four times daily for 1mo postoperatively. The cross-linking was performed by five experienced corneal specialists.

Outcome Measurements Baseline characteristics of the patients, visual acuity [both uncorrected visual acuity (UCVA) and best corrected (BCVA)] and refraction were recorded. Corneal tomography (Pentacam; Oculus, Inc., Wetzlar, Germany) was used to evaluate Kmax, Kmean, corneal astigmatism, Q-value, thinnest pachymetry, higher-order aberrations (HOA) at 6 mm zone from vertex, topometric indices and corneal densitometry. Corneal densitomtry, a method to measure the backscattered light from the cornea, divided into three zones (0-2, 2-6 and 6-10 mm diameter from corneal apex) and three depth layers (anterior 120 microns, posterior 60 microns and between). The topometric indices included index of surface variance (ISV), index of vertical asymmetry (IVA), keratoconus index (KI), central keratoconus index (CKI), index of height asymmetry (IHA), index of height decentration (IHD), the minimum radius of curvature (Rmin). Demarcation line was evaluated by slit lamp biomicroscopy and by anterior segment imaging using CASIA SS-1000 OCT (Tomey, Nagoya, Japan). All data were analyzed at 1, 3, 6mo and 1y. All the reported eyes at each time interval are the same. Sub-group analysis according to Amsler-Krumeich classification was analyzed. Moreover, we also studied the effectiveness of the collagen crosslinking regarding the characteristics of the eyes. Age of 24 and 30 years, Kmax of

55 D, and baseline BCVA of 20/40 (or 0.3 in LogMAR unit) were used as cut-off values to highlight the crosslinking effects. The association between the change of corneal densitometry and other factors including preoperative Kmax, Kmean, manifest refraction spherical equivalent (MRSE), visual acuity, thinnest pachymetry, the change in Kmax, and the change of those parameters were also analyzed. All complications were recorded.

Statistical Analysis Baseline characteristics of patients were described using mean±standard deviation (SD) for the continuous data and frequency and percentage for the categorical data. For visual acuity, manifest refraction spherical equivalent, Kmax, Kmean, corneal astigmatism, Q-value, thinnest pachymetry, HOA, topographic indices and corneal densitometry, multilevel data analysis (mixed linear model) was used to compare the difference of these values between each visit. The effect of age, preoperative Kmax and BCVA were analyzed by using Chi-squared test or Fisher's exact test. Association factors were determined by Logistic regression analysis for categorical data and linear regression analysis for continuous data. Statistical analyses were performed with STATA®, Release 13.1 (StataCorp, 2013. College Station, TX, USA). Statistically significant change was considered when *P* value was less than 0.05.

RESULTS

One hundred and fifty-five patients (185 eyes) were included. The demographic data were shown in Table 1 and the baseline values were shown in Table 2.

Visual Acuity and Manifest Refraction Spherical Equivalent (MRSE) UCVA and BCVA demonstrated significant improvement at 3mo postoperatively ($P<0.05$). At 1y, UCVA (LogMAR) improved from baseline value of 0.78±0.57 to 0.66±0.52 ($P<0.05$) but BCVA was not statistically different from baseline ($P>0.05$; Table 3). However, the improvement of BCVA was found in stage 1 at 1y ($P<0.05$; Figure 1). MRSE transiently increased at 1mo ($P<0.05$) and showed no significant change at 1y ($P>0.05$; Table 3).

Best Corrected Visual Acuity Effect We used cut-off baseline BCVA value of 0.3 in LogMAR unit to count the number of the eyes of which BCVA improved more than 0.2 LogMAR at 1y. At 1y, the number of eyes of which BCVA improved more than 0.2 LogMAR was higher in the group of which preoperative BCVA worse than 0.3 compared to the group of which preoperative BCVA better than 0.3 (78.26% *vs* 21.74%, $P<0.001$).

Maximum keratometry value (Kmax) and mean keratometry value (Kmean) Kmax statistically significantly decreased at 3, 6mo and 1y ($P<0.001$). At 1y, mean Kmax difference was 2.36 D compared to preoperative level (Table 3). Kmean transiently increased at 1mo ($P=0.049$; Table 3).

Table 1 Demographics data *n* (%)

Total population	155 patients (185 eyes)
Age	23.43±7.26 (range 11-51)
Gender	
M	119 (76.77)
F	36 (23.23)
Unilateral *vs* Bilateral	110 (70.97) *vs* 45 (29.03)
Amsler-Krumeich classification	
Stage 1	70 (37.84)
Stage 2	65 (35.14)
Stage 3	17 (9.19)
Stage 4	33 (17.84)
Riboflavin solution used	
Isotonic solution	180 (97.30)
Hypotonic solution	5 (2.70)
Previous history of intracorneal ring insertion at least 9mo before collagen cross-linking	49 (26.49)

At 6mo, Kmean began to decrease statistically compared to baseline level ($P=0.004$). At 1y, Kmean was statistically significantly lower than baseline level by 0.84 D ($P<0.001$). In all stage subgroups, we found that Kmax and Kmean statistically decreased at 1y ($P<0.05$). Furthermore, the more the severity, the more decrease in Kmax value was observed (Figure 1; Table 4).

Age and Kmax Effect In those who had Kmax reduction ≥2.0 D at 1y postoperatively, the subgroup analysis was performed using the cut-off value of age at 24, 30 years and preoperative Kmax of 55.0 D. The results were shown in Table 5.

Success of the Procedure Success rate after the procedure was defined as a decrease in the maximum K reading or increase not more than 1 D at the first postoperative year. Of eighty-two eyes of patients who had follow-ups at 1y, there were seventy-four eyes (90.24%) that were defined as success.

Corneal Asphericity (Q-value) Q-value in each visit was shown in Table 3 and was statistically decreased at 1 year ($P<0.05$).

Thinnest Pachymetry The thinnest pachymetry began to statistically decrease at 1mo ($P<0.001$) as shown in Table 3. At 1y, the thinnest pachymetry was statistically lower than that baseline value by 6.78 microns ($P<0.001$).

According to stage subgroup analysis, at 1y, only eyes in stage 1 had statistically decreased thinnest pachymetry compared to baseline level ($P<0.001$) while eyes in other stages showed no statistical change at 1y (Table 6).

Higher-order aberration (HOA) The HOA did not statistically change at 1, 3 and 6mo ($P>0.05$). However, HOA statistically decreased at 1y ($P=0.022$) as shown in Table 3.

Topographic Indices The means and standard deviations of each topographic indices values were shown in Table 3. ISV (a unitless standard deviation of individual corneal sagittal radii from the mean curvature which is a general measure

Table 2 Outcome parameters at baseline (min-max) mean±SD

Parameters	All stages	Stage 1	Stage 2	Stage 3	Stage 4
UCVA (logMAR)	0.78±0.57 (-0.1 to 2.6)	0.56±0.51 (0 to 2)	0.72±0.49 (-0.1 to 2)	0.93±0.55 (0.4 to 2)	1.28±0.58 (0.3 to 2.6)
BCVA (logMAR)	0.34±0.39 (-0.1 to 2.6)	0.16±0.21 (-0.1 to 0.88)	0.30±0.23 (-0.1 to 1)	0.41±0.18 (0.15 to 0.81)	0.82±0.59 (0.2 to 2.6)
MRSE (D)	-6.70±4.70 (-20.875 to 1.31)	-4.42±4.17 (-19.81 to 1.31)	-7.21±3.21 (-17.75 to -0.56)	-11.07±3.82 (-18.18 to -5.06)	-14.72±3.77 (-20.88 to -10.38)
Kmax (D)	58.45±8.60 (44.6 to 87.6)	51.18±3.56 (44.6 to 58.4)	58.60±5.03 (44.7 to 72.6)	63.88±3.58 (57.7 to 71.1)	71.29±6.72 (61.5 to 87.6)
Kmean (D)	49.82±5.79 (38.9 to 74.3)	45.11±1.71 (38.9 to 48)	49.17±2.4 (42.8 to 53)	53.24±1.91 (48.5 to 54.9)	59.41±4.72 (55.1 to 74.3)
Corneal astigmatism (D)	4.67±2.75 (0 to 17.9)	3.36±1.69 (0.3 to 9.9)	5.46±2.31 (1 to 10.5)	6.67±3.88 (1.8 to 16)	4.88±3.48 (0 to 17.9)
Q-value	-0.96±0.64 (-2.59 to 1.07)	-0.48±0.30 (-1.27 to 0.6)	-0.86±0.48 (-1.79 to 1.07)	-1.91±0.35 (-2.59 to 1.01)	-1.91±0.35 (-2.59 to -1.01)
Thinnest pachymetry (microns)	462.23±48.39 (356 to 477)	491.85±43.04 (406 to 619)	463.52±38.86 (367 to 544)	416.50±28.89 (365 to 476)	419.56±34.02 (356 to 477)
HOA (rms)	2.73±1.57 (0.374 to 10.738)	1.66±0.94 (0.37 to 4.19)	2.78±1.19 (0.38 to 5.92)	3.28±1.00 (1.30 to 5.28)	4.51±1.70 (2.67 to 10.74)
Topographic indices					
ISV	91.21±43.59 (19 to 284)	57.35±25.04 (19 to 137)	90.76±28.40 (28 to 185)	113.13±19.95 (74 to 137)	148.47±39.37 (91 to 284)
IVA	0.79±0.44 (0.11 to 2.84)	0.59±0.36 (0.11 to 1.67)	0.85±0.41 (0.16 to 2.15)	0.87±0.32 (0.35 to 1.41)	1.07±0.48 (0.53 to 2.84)
KI	1.22±0.18 (0.33 to 2.26)	1.13±0.10 (0.98 to 1.53)	1.20±0.16 (0.33 to 1.66)	1.28±0.08 (1.13 to 1.43)	1.40±0.22 (1.12 to 2.26)
CKI	1.08±0.13 (0.07 to 1.5)	1.02±0.13 (0.07 to 1.13)	1.07±0.14 (0.11 to 1.5)	1.14±0.05 (1.07 to 1.24)	1.19±0.06 (1.05 to 1.29)
IHA	37.07±25.05 (0.1 to 117.3)	28.79±20.31 (0.1 to 86.1)	41.86±24.67 (1.6 to 117.3)	49.07±33.88 (0.2 to 101.3)	38.33±25.78 (0.4 to 96.6)
IHD	0.13±0.8 (0.001 to 0.54)	0.09±0.06 (0.001 to 0.30)	0.13±0.06 (0.02 to 0.29)	0.14±0.06 (0.03 to 0.25)	0.20±0.09 (0.09 to 0.54)
Rmin	5.86±0.84 (3.85 to 7.57)	6.65±0.47 (5.78 to 7.57)	5.78±0.50 (4.65 to 7.55)	5.24±0.33 (4.54 to 5.82)	4.75±0.46 (3.85 to 5.63)
Corneal densitometry (grey scale unit; GSU)					
Anterior, mm					
0-2	27.74±7.88 (18.6 to 93.2)	25.74±2.04 (20.7 to 31.4)	27.85±5.68 (18.6 to 52.7)	26.50±2.20 (20.5 to 28.4)	32.03±15.55 (21.7 to 93.2)
2-6	23.71±3.80 (16.6 to 51.6)	22.8±1.96 (18.8 to 29)	24.24±4.75 (16.6 to 51.6)	23.17±1.58 (18.8 to 25.5)	14.7±4.74 (19 to 45.4)
6-10	20.29±3.92 (14.3 to 45.2)	21.20±3.55 (14.3 to 29.5)	20.49±4.83 (15 to 45.2)	18.19±1.60 (15.1 to 22)	10.06±2.61 (16.2 to 31.1)
Center, mm					
0-2	16.84±5.90 (12 to 69.7)	15.68±1.25 (13.3 to 19.6)	16.42±2.09 (12 to 26)	15.81±1.03 (13.7 to 17.3)	20.43±12.80 (14.2 to 69.7)
2-6	14.68±2.21 (11 to 25)	14.64±2.35 (11.9 to 25)	14.94±2.40 (11 to 23.8)	13.73±1.15 (11.9 to 16.1)	14.72±1.80 (12 to 20)
6-10	13.47±2.17 (7.6 to 23.1)	13.73±2.05 (7.6 to 17.3)	13.72±2.56 (10.1 to 23.1)	12.09±0.87 (10.6 to 13.2)	13.10±1.75 (10.3 to 19.3)
Posterior, mm					
0-2	12.48±2.92 (6.6 to 33.4)	12.91±2 (8 to 22.1)	12.26±1.63 (7.6 to 16.5)	11.07±1.89 (6.6 to 14.40)	12.73±5.56 (7.7 to 33.4)
2-6	13.08±1.97 (7.2 to 22.4)	13.09±2.14 (7.6 to 22.4)	13.22±2.06 (7.2 to 19.2)	12.35±1.49 (9 to 14.7)	13.12±1.57 (9.3 to 16.6)
6-10	12.61±2.04 (8.4 to 18)	13.34±2.09 (8.9 to 18)	12.70±2.15 (8.4 to 17.9)	10.97±1.17 (8.4 to 13.5)	11.75±1.13 (9.8 to 14.2)

BCVA: Best corrected visual acuity; CKI: Central keratoconus index; GSU: Grey scale unit; HOA: Higher-order aberration; IHA: Index of height asymmetry; IHD: Index of height decentration; ISV: Index of surface variance; IVA: Index of vertical asymmetry; KI: Keratoconus index; LogMAR: Logarithm of the minimum angle of resolution; MRSE: Manifest refraction spherical equivalent; Rmin: Minimal radius of curvature; rms: root mean square; UCVA: Uncorrected visual acuity.

of corneal surface irregularity) and IVA (a measure of the difference between superior curvature and inferior curvature in the cornea) began to statistically decrease at 6mo and 1y (P<0.05) as shown in Table 3. KI and IHD calculated with Fourier analysis of corneal height to quantify the degree of vertical decentration, statistically decreased at 1y (P=0.001). IHA, a measure similar to the IVA but based on corneal elevation, statistically decreased at 6mo (P=0.023). CKI did not statistically change (P>0.05). Rmin statistically increased at 3, 6mo and 1y (P<0.05).

Corneal Densitometry The means and standard deviations of corneal densitometry in each position of cornea were shown in Table 3. Anterior central cornea demonstrated the greatest densitometry. Densitometric declined towards posterior and peripheral area. Increase of the densitometry was found significant at 1mo postoperatively in almost all depth and area. Gradual reduction of densitometric values was evidenced but remained statistically higher than baseline level at 0-2 and 2-6 mm zone at 1y (P<0.05). Subgroup analysis regarding the stage of the disease showed similar results (Table 7).

The increase of densitometry at anterior and center layer of 0-6 mm zone was associated with the change of the thinnest pachymetry at 1y compared with baseline level (Linear regression analysis, P<0.05). The relationship of the increase in densitometric value and the decrease of thinnest pachymetry at 1y were in linear fashion as follows: “y=kx+c”, wheare “y” is the change of densitometric values at 1y (GSU); “x” is the change of the thinnest pachymetry at 1 year (microns); if at

Table 3 Clinical measures in each visit mean±SD

Parameters	Preoperative	1mo	3mo	6mo	1y
UCVA (LogMAR)	0.78±0.57	0.80±0.50	0.70±0.52[a]	0.71±0.52	0.66±0.52[a]
BCVA (LogMAR)	0.35±0.39	0.39±0.39	0.30±0.33[a]	0.29±0.36[a]	0.30±0.43
MRSE (Diopter)	-6.70±4.70	-7.47±5.08[a]	-6.84±7.34	-6.21±4.83	-6.14±4.41
Kmax (Diopter)	58.45±8.60	57.98±8.87	57.27±8.23[a]	57.08±8.96[a]	56.09±7.70[a]
Kmean (Diopter)	49.82±0.43	50.11±0.43[a]	49.59±0.43	49.35±0.43[a]	48.98±0.44[a]
Corneal astigmatism (Diopter)	4.67±2.75	4.49±2.61	4.39±2.67	4.38±2.57	4.45±3.50
Q-value	-0.96±0.65	-0.96±0.65	-0.94±0.61	-0.91±0.61	-0.90±0.53[a]
Thinnest pachymetry (microns)	462.23±48.39	447.91±50.59[a]	445.85±49.15[a]	450.66±50.45[a]	455.45±50.90[a]
HOA	2.73±1.57	2.75±1.78	2.72±1.84	2.51±2.09	2.33±1.28[a]
Topographic indices					
ISV	91.21±43.59	90.83±43.76	87.63±42.20	83.02±43.44[a]	82.32±36.20[a]
IVA	0.80±0.44	0.79±0.44	0.79±0.39	0.73±0.42	0.73±0.38[a]
KI	1.22±0.18	1.22±0.20	1.22±0.16	1.20±0.14	1.16±0.20[a]
CKI	1.08±0.13	1.09±0.07	1.09±0.10	1.07±0.11	1.08±0.06
IHA	37.07±25.05	37.23±23.05	32.14±24.25	31.04±23.87[a]	34.45±25.02
IHD	0.13±0.08	0.12±0.09	0.12±0.10	0.11±0.10[a]	0.11±0.06[a]
Rmin	5.86±0.84	5.87±0.84	5.97±0.79[a]	6.03±0.95[a]	5.96±0.86[a]
Corneal densitometry (GSU)					
Anterior					
0-2 mm	27.63±7.88	36.18±7.66[a]	37.31±7.70[a]	35.23±9.16[a]	32.86±8.70[a]
2-6 mm	23.71±3.80	30.85±4.58[a]	30.10±4.25[a]	27.69±3.22[a]	26.18±3.73[a]
6-10 mm	20.29±3.92	23.73±3.74[a]	21.90±3.50[a]	21.22±3.61[a]	20.71±3.13
Center					
0-2 mm	16.84±5.90	21.82±6.44[a]	20.94±5.77[a]	19.39±5.19[a]	18.27±5.47[a]
2-6 mm	14.68±2.21	18.85±3.42[a]	17.61±2.94[a]	16.30±2.79[a]	15.50±2.56[a]
6-10 mm	13.47±2.17	14.75±2.43[a]	14.20±2.62[a]	13.93±2.42	13.62±2.21
Posterior					
0-2 mm	12.48±2.92	15.00±3.68[a]	13.94±2.38[a]	13.64±2.61[a]	13.02±3.00[a]
2-6 mm	13.08±1.97	14.52±2.45[a]	14.12±2.27[a]	13.88±2.19[a]	13.55±1.77[a]
6-10 mm	12.61±2.04	13.18±2.15[a]	13.08±1.98[a]	13.03±2.47	12.95±2.22

BCVA: Best corrected visual acuity; CKI: Central Keratoconus; HOA: Higher-order aberration; IHA: Index of height asymmetry; IHD: Index of height decentration; ISV: Index of surface variance; IVA: Index of vertical asymmetry; KI: Keratoconus index; MRSE: Manifest refraction spherical equivalent; Rmin: Minimal radius of curvature; UCVA: Uncorrected visual acuity; GSU: Grey scale unit; [a]*P* value<0.05.

Table 4 Kmax in each stage and one year difference mean±SD

Kmax (Diopter)	Preoperative	1mo	3mo	6mo	1y	1y difference
Stage 1	51.18±3.56	51.64±4.08	51.21±3.76	49.80±3.31[a]	49.69±3.51[a]	1.49 (0.45)[a]
Stage 2	58.60±5.30	57.79±6.16	56.91±4.67[a]	56.42±4.99[a]	56.09±4.70[a]	2.51 (0.53)[a]
Stage 3	63.88±3.58	63.48±5.51	61.44±5.76[a]	62.83±5.13	59.53±5.88[a]	4.35 (0.64)[a]
Stage 4	71.29±6.72	71.32±8.06	70.42±6.70	70.69±6.89	66.05±8.65[a]	5.24 (0.55)[a]

[a]*P* value<0.05.

anterior layer of the 0-2 mm zone; k= -0.016 and c=5.810; if at anterior layer of the 2-6 mm zone; k= -0.039 and c=2.046; if at central layer of the 0-2 mm zone; k= -0.058 and c=1.226; if at central layer of the 2-6 mm zone; k= -0.033 and c=0.687. However, preoperative Kmax, Kmean, MRSE, UCVA, BCVA, thinnest pachymetry and the change of these parameters were not associated with the densitometry change (Linear regression analysis, *P*>0.05).

Complications Postoperative corneal haze was found 11.35%, 30.27%, 15.67%, 10.27% and 2.16% at 1wk, 1, 3, 6mo and 1y respectively. No eyes developed corneal edema. Ninety-eight percent of eyes were free of complications at 1y. There was one case of sterile keratitis after the collagen cross-linking. The infiltrate was multiple round white dots at the peripheral cornea both with and without epithelial defects occurred within one week and responded well to intensive topical steroid within a

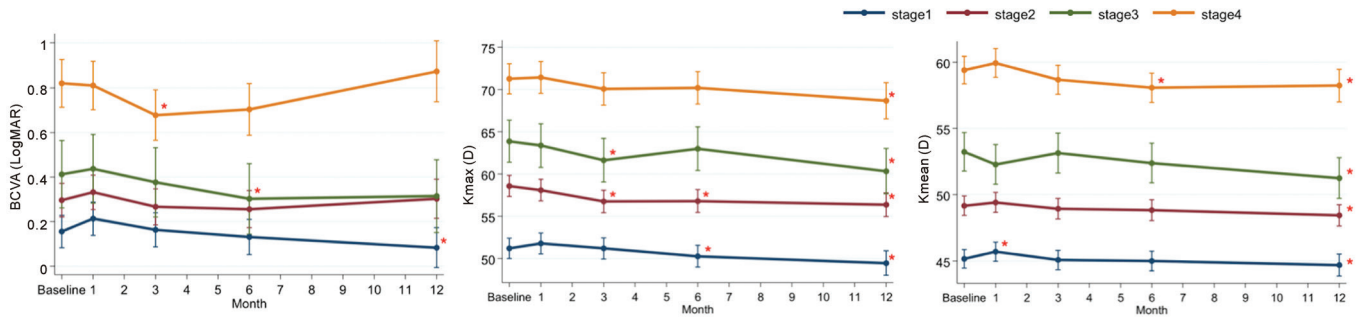

Figure 1 Best corrected visual acuity, Kmax, Kmean in each stage of the disease (compared to preoperative value *P*<0.05).

Table 5 Number and percentage of eyes of which Kmax decrease less or more than 2 diopters at 1 year regarding cut-off age value of 24 and 30 and Kmax value of 55 diopters *n* (%)

Parameters	Kmax decrease <2 D compared to baseline level (*n*=49)	Kmax decrease ≥2 D compared to baseline level (*n*=37)	*P* (Pearson's Chi-squared test)
Age <24	26 (55.32)	21 (56.76)	>0.05
Age≥24	21 (44.68)	16 (43.24)	
Age<30	34 (72.34)	29 (78.38)	>0.05
Age≥30	13 (27.66)	8 (21.62)	
Kmax<55 D	24 (48.98)	10 (27.03)	<0.05
Kmax≥55 D	25 (51.02)	27 (72.97)	

D: Diopter (s); Kmax: Maximum keratometry value.

Table 6 Thinnest pachymetry in each stage mean±SD

Thinnest pachymetry (microns)	Preoperative	1mo	3mo	6mo	1y
Stage 1	491.85±43.04	476.67±45.26[a]	474.04±45.26[a]	477.46±46.39[a]	479.52±54.27[a]
Stage 2	463.52±38.86	447.24±41.10[a]	444.89±39.05[a]	457.63±40.93[a]	463.56±41.83
Stage 3	416.50±28.89	407.54±39.62	398.15±25.43[a]	406.08±29.38	422.00±37.03
Stage 4	419.56±34.02	401.79±38.12[a]	407.57±37.91[a]	406.29±37.55[a]	409.00±35.20

[a]*P* value<0.05.

week. There was one case of presumed bacterial keratitis. The patient presented with red eye one week after the procedure. Empirical topical 0.5% moxifloxacin was initiated every hour for five days and then tapered to four times daily after clinical improvement. Culture of contact lens revealed negative for organisms.

DISCUSSION

Considering previous studies using accelerated protocol with 18 mW/cm^2 irradiation of UVA for 5min, our study showed greatest reduction of Kmax[5-8]. At 1-year result, our study showed that Kmax statistically decreased by 2.36 D wheaeas Hashemi *et al*[6] found that Kmax decreased by 0.06 D at 18 months and Chow *et al*[5] found that Kmax decreased by 0.47 D at 12mo. At 1-year result, our study showed Kmean statistically decreased by 0.84 D. In contrast, Shetty *et al*[7] showed decrease in K1 and K2 by 0.29 and 0.52 D at 12mo. Hashemi *et al*[6] and Chow *et al*[5] showed decrease in Kmean by 0.21 D at 18mo and by 0.19 at 12mo respectively. Our significant flattening of the cornea was comparable to reported results using conventional Dresden protocol[9-11]. This probably resulted from several reasons. One is that in our study the mean Kmax of patients included in the study was higher. The mean preoperative Kmax in study by Chow *et al*[5] and Hashemi et al were 51.96 D and 47.89 D respectively whearas that in our study was 58.45 D. This is in concordance with the Kmax effect that we found the number of eyes of which Kmax decreased more than 2.0 D was higher in baseline Kmax ≥55 D group. Another reason is our number of population was quite high enough to detect this result. According to the results that Kmax reduction more than 2.0 D at 1y was found higher in patients whose preoperative Kmax ≥55.0 D, this finding was consistent with results from conventional Dresden protocol studied by Greenstein *et al*[12]. This would provide information for ophthalmologists to predict the outcome from preoperative Kmax and Kmean readings.

Regarding visual acuity, we found that UCVA statistically decreased significantly at 1y. This is similar to previous studies[5-6]. This probably resulted from flattening effect of corneal cross-linking. However, at 1y, BCVA showed no statistical difference compared with baseline. This is also consistent with previous studies[5-6]. This was probably because the MRSE remained statistically unchanged in both our results

Table 7 Corneal densitometry in each stage mean±SD

Corneal densitometry (GSU)	Preoperative	1mo	3mo	6mo	1y
Anterior 0-2 mm	27.63±7.88	36.18±7.66[a]	37.31±7.70[a]	35.23±9.16[a]	32.86±8.70[a]
Stage 1	25.74±2.04	33.77±4.57[a]	35.48±6.05[a]	34.43±6.16[a]	32.52±5.80[a]
Stage 2	27.85±5.68	35.94±6.94[a]	38.92±8.68[a]	34.40±5.64[a]	32.33±4.52[a]
Stage 3	26.50±2.20	40.58±9.05[a]	36.39±5.34[a]	33.31±4.05[a]	30.59±6.07[a]
Stage 4	32.03±15.55	40±11.27[a]	38.95±9.58[a]	39.93 ±18.07[a]	36.85±18.65[a]
Anterior 2-6 mm	23.71±3.80	30.85±4.58[a]	30.10±4.25[a]	27.69±3.22[a]	26.18±3.73[a]
Stage 1	22.80±1.96	29.42±3.59[a]	29.17±4.56[a]	27.88±3.26[a]	26.28±3.31[a]
Stage 2	24.24±4.75	31.27±4.00[a]	31.30±4.38[a]	28.03±3.13[a]	26.30±2.51[a]
Stage 3	23.17±1.58	33.48±6.41[a]	29.05±3.59[a]	27.01±2.59[a]	25.25±2.68
Stage 4	23.17±1.58	33.48±6.41[a]	29.05±3.59[a]	27.01±2.59[a]	25.25±2.68[a]
Anterior 6-10 mm	20.29±3.92	23.73±3.74[a]	21.90±3.50[a]	21.22±3.61[a]	20.71±3.13
Stage 1	21.20±3.55	23.93±3.48[a]	22.31±3.09[a]	22.05±3.60[a]	21.28±3.38
Stage 2	20.49±4.83	24.06±4.20[a]	22.43±4.14[a]	21.62±3.65	21.41±3.05
Stage 3	18.19±1.60	23.33±3.93[a]	19.18 ±1.56[a]	18.96±1.97	18.77±2.96
Stage 4	19.06±2.61	22.80±3.18[a]	21.46±3.17[a]	19.85±3.58	19.31±1.87[a]
Center 0-2 mm	16.84±5.90	21.82±6.44[a]	20.94±5.77[a]	19.39±5.19[a]	18.27±5.47[a]
Stage 1	15.68±1.25	20.06±2.66[a]	20.75±6.95[a]	18.85±2.43[a]	17.40±2.19[a]
Stage 2	16.42±2.09	21.42±3.34[a]	20.78±3.94[a]	18.52±2.34[a]	17.62±2.20[a]
Stage 3	15.81±1.03	24.08±7.02[a]	20.74±2.96[a]	19.52±2.20[a]	18.21±2.38
Stage 4	20.43±12.80	25.56±12.84[a]	21.93±7.40[a]	22.23±11.30[a]	21.83±12.84[a]
Center 2-6 mm	14.68±2.21	18.85±3.42[a]	17.61±2.94[a]	16.30±2.79[a]	15.50±2.56[a]
Stage 1	14.64±2.35	18.33±3.07[a]	17.43±3.20[a]	16.53±3.27[a]	15.24±2.87[a]
Stage 2	14.94±2.40	19.36±3.51[a]	18.02±2.82[a]	16.37±2.32[a]	15.62±2.29
Stage 3	13.73±1.15	19.45±4.75[a]	17.02±2.94[a]	16.11±2.45[a]	15.44±2.34
Stage 4	14.72±1.80	18.65±3.20[a]	17.54±2.57[a]	15.75±2.80[a]	15.80±2.93
Center 6-10 mm	13.47±2.17	14.75±2.43[a]	14.20±2.62[a]	13.93±2.42	13.62±2.21
Stage 1	13.73±2.05	14.93±2.20[a]	14.49±2.26[a]	14.17±2.26	13.74±2.22
Stage 2	13.72±2.56	15.11±2.83[a]	14.77±2.66[a]	14.30±2.63	14.20±2.38
Stage 3	12.09±0.87	13.72±1.63[a]	12.35±0.72	12.43±1.31	12.34±1.56
Stage 4	13.10±1.75	14.12±2.22[a]	13.44±3.49	13.51±2.60	12.96±1.70
Posterior 0-2 mm	12.48±2.92	15.00±3.68[a]	13.94±2.38[a]	13.64±2.61[a]	13.02±3.00[a]
Stage 1	12.91±2.00	14.95±3.19[a]	14.57±2.15[a]	14.35±1.56[a]	13.15±2.47
Stage 2	12.26±1.63	14.80±2.59[a]	13.70±2.32[a]	13.20±1.64[a]	12.80 ±1.54
Stage 3	11.07±1.89	15.75±4.33[a]	13.25±2.16[a]	12.53±2.02	12.38±1.70
Stage 4	12.73±5.56	15.14±5.92[a]	13.31±2.95[a]	13.56±5.10	13.85±6.30
Posterior 2-6 mm	13.08±1.97	14.52±2.45[a]	14.12±2.27[a]	13.88±2.19[a]	13.55±1.77[a]
Stage 1	13.09±2.14	14.43±2.51[a]	14.14±2.27[a]	14.01±2.44[a]	13.24±1.82
Stage 2	13.22±2.06	14.55±2.34[a]	13.92±2.41	13.87±2.08[a]	13.59±1.77
Stage 3	12.35±1.49	15.15±3.17[a]	14.32±2.14[a]	13.98±1.77[a]	13.85±1.86
Stage 4	13.12±1.57	14.35±2.19[a]	14.38±2.14[a]	13.51±2.19	13.82±1.72
Posterior 6-10 mm	12.61±2.04	13.18±2.15[a]	13.08±1.98[a]	13.03±2.47	12.95±2.22
Stage 1	13.34±2.09	13.82±2.12[a]	13.65±2.00	13.52±2.70	13.44±2.19
Stage 2	12.70±2.15	13.33±2.32[a]	13.45±2.07[a]	13.45±2.46[a]	13.52±2.35
Stage 3	10.97±1.17	11.85±1.09[a]	11.22±0.62	11.32±1.15	11.11±1.19
Stage 4	11.75±1.13	12.04±1.47	12.08±1.11	11.87±1.61	12.00±1.53

[a]*P* value<0.05.

and the results of previous studies[5-6]. We also found that eyes with worse preoperative BCVA were more likely to have an improvement. This is consistent with previous study by Greenstein *et al*[12]. Consequently, it might be reasonable to state that eyes with worse vision would allow more chance of improvement.

Considering the Q-value, we found that collagen cross-linking could improve the corneal asphericity. This showed that cornea shape was less prolate. This was probably because the flattening effect of the procedure.

Regarding the thinnest pachymetry, we found that collagen cross-linking made the thinnest cornea thinner by 6.78 microns at 1y. Although this difference was statistically significant, the amount of the change was little and less than 5% which is one of the criteria for progressive disease[3]. This result is consistent with previous studies[1,3,5-7,11]. This thinning effect may be the consequence of increase keratocyte apoptosis. The decrease in corneal thickness has been reported up to 36mo postoperatively[13]. Change in corneal thickness could also be due to epithelial remodeling.

Considering higher-order aberration (HOA), the effect of collagen cross-linking remained controversial. Uysal *et al*[14] and Greenstein *et al*[15] found that collagen crosslinking effect could improve HOA at 1y. Ghanem *et al*[16] also found similar results at 2a. However, Wisse *et al*[17] found that HOA remained unchanged at 1y. All mentioned studies used standard Dresden protocol for collagen cross-linking[14-17]. To date, our study was the first to evaluate the HOA after accelerated protocol of collagen cross-linking. We found that HOA statistically decreased at 1y. This improvement of HOA might be associated with UCVA. Nevertheless, further studies to show the association or cause-and-effect result are yet to be performed. Further studies involving the glare test or questionnaire dealing with HOA are needed.

Considering topographic indices, in keratoconus there are increases in all topographic indices (ISV, IVA, IHD, IHA, KI, CKI) except Rmin. Rmin decreases in keratoconus. We found that 1y after collagen cross-linking, ISV, IVA, KI, IHD decreased whereas CKI and IHA remained unchanged at 1y after cross-linking. Decrease in ISV reflects a decrease in variation of corneal curvature compared with the mean curvature. Decrease in IVA means there was decrease in difference of superior and inferior curvature of cornea. Since KI is derived from the ratio of the mean superior radius of curvature to the inferior radius of curvature and KI usually increases in keratoconus, decrease in KI implies that postoperative topography of the cornea become more normal. IHD is based on Fourier analysis of the elevation data and shows the amount of vertical decentration. This index tends to be steeper in keratoconus. Decrease in IHD reflects less degree of vertical decentration. Moreover, in our study Rmin increased as we expected. All five parameter improvements after collagen cross-linking may be attributable to the flattening and reshaping effect of the procedure. We can infer that after collagen cross-linking the cornea becomes more symmetric, regular and flattening. Previous studies also showed some improvements in common. Koller *et al*[18] found improvements in CKI, KI, IHA and Rmin 1y after cross-linking while Greenstein *et al*[19] found improvements in ISV, IVA, KI and Rmin 1y after Dresden protocol crosslinking. Omar *et al*[20] found significant reduction in ISV, IVA, and KI but not in IHA and IHD 1y after accelerated protocol. However, the protocol that Omar *et al*[20] used was different from ours. 0.1% Riboflavin drops were instilled over the de-epithelized cornea four times every 2min while in our protocol with ten times every 2min. Exposure to 365 nm UVA was performed with a total surface dose of 7.2 joules which was pulsed (1s on, 1s off) for 5min and 20s, achieving a total delivery of 120 mWatt which were higher than our energy[20].

Considering the corneal densitometry, Greenstein *et al*[21] found a significant increase in densitometry at 1mo and a significant reduction between 6mo and 12mo. On the contrary, Kim et al found that the densitometry peaked at 1mo and returned to baseline level after 6mo[22]. However, in our study, most of the areas of the cornea reached their maximum density at 1mo after the procedure and decreased over time. At 1y, the densitometry values at 0-6 mm zone were still statistically higher than those at baseline regardless of the depth of the cornea whereas the densitometry values at 6-10 mm zone were not statistically different from baseline level. We also found that decrease of the thinnest pachymetry was associated with the increase in densitometry. This provided ophthalmologist instant useful information to indirectly expect the increase of the densitometry by notice the alteration of the thinnest pachymetry. This evidence was novel. Corneal densitometry provides a quantitative method of haze measurement. Increase in densitometry might affect vision. Previous studies estimated that after cross-linking, the keratocyte apoptosis might lead to lacunar edema[22-24]. Studies using *in vivo* confocal microscopy found that there were increase in density of the extracellular fibrillar matrix and reduce in density of anterior keratocytes[25-26]. This might lead to transient haze after cross-linking. In our study, only 4 eyes had clinical corneal haze at 1y while the other eyes were free of haze at 1y. This means that the clinical haze was undetected while the corneal densitometry still remained.

Opting between epithelium-off and transepithelial cross-linking, we took both efficacy and safety of the procedures into account. Soeters *et al*[27] in 2015 found that although transpithelial cross-linking was a safe procedure without epithelial healing problems, 23% of cases showed a continued keratoconus progression after 1y. Therefore, at that time, they did not recommend replacing epithelium-off cross-linking by transepithelial cross-linking for treatment of progressive keratoconus[27]. Also, a recent systematic review and Meta-analysis by Nath *et al*[28] in 2020 found that the efficacy

of transepithelial cross-linking remained inferior to the epithelium-off approach, although it was significantly safer. They found that the gap in decrease in maximum keratometric value between the two protocols was widening over time. The incidence of disease progression at 12mo after treatment was noted to be significantly higher with transepithelial cross-linking when compared with conventional cross-linking. Regarding usual adverse events, haze in cross-linking was encountered commonly but did not impact visual function substantially. Moreover, haze after cross-linking was often self-limiting. Focusing their attentions on more severe adverse events, such as corneal melt, persistent epithelial defects, and visually significant, non-resolving haze, they found that although these complications were determined to be more likely a result of epithelium-off cross-linking (RR, 0.22), the overall rate of complications remained low at 4% within the epithelium-off group and 2% in the transepithelial group[28]. All things considered, we continued using epithelium-off technique rather than transepithelial technique in our study.

Since the number of the experienced specialists performing collagen cross-linking in our study was five, there was still a chance that could bias the outcomes. However, we included all cases performed in our center during that period of time in order to reduce the bias as much as possible. Another limitation was that in our study was a retrospective before-after study. Long-term outcomes of randomized controlled trials remain to be studied.

In conclusion, the accelerated corneal collagen cross-linking in progressive keratoconus and in patients under 24 years of age was effective to flatten, reshape the cornea, and also improve the unaided visual acuity and higher-order aberration. Also, the cross-linking improved most of the topographic indices. However, the corneal densitometry at one year after the surgery is still higher but tends to decrease over time[29].

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