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Non-topography-guided photorefractive keratectomy combined with accelerated collagen cross linking for treatment of keratoconus

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非角膜地形图引导PRK联合角膜胶原交联术治疗圆锥角膜

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摘要

目的:评估非角膜地形图引导圆锥角膜患者行光折变角膜切除术(PRK)和角膜胶原交联术(CXL)的视力、屈光度和临床疗效。

方法:术后1mo, 3mo, 6mo and 12mo对34例患者未矫正视力(UDVA)和矫正距离视力(CDVA),平、陡角膜测量读数以及并发症进行评估。

结果:共34例患者平均年龄为23.3±4.0岁。UDVA和CDVA显著提高,且术后1a恢复平稳。通过超过1a的定期随访,*T*检验显示术前术后值有显著不同($P<0.05$)包括视力,球面和柱面变化。Fourier术后图像分析显示轴向位移垂直于术前轴。

结论:非角膜地形图引导PRK联合CXL对于治疗圆锥角膜是一种安全有效的手术选择,能够提高UDVA,CDVA和屈光状态。术后3mo达到稳定状态,与非角膜地形图引导PRK相比,地形图引导的唯一优势可能是通过Fourier术后分析,在某些患者中,球镜和柱镜轴位漂移。

关键词:圆锥角膜;屈光手术;屈光性角膜磨镶术;角膜胶联疗法;非角膜地形图引导屈光性角膜切除术;近视;散光

Abstract

• AIM: To evaluate the visual, refractive and clinical outcomes of non-topography-guided photorefractive keratectomy (PRK) and corneal collagen cross linking (CXL) in eyes with keratoconus.

• METHODS: Totally 34 cases were evaluated for uncorrected distance visual acuities (UDVA) and corrected distance visual acuities (CDVA), flat and steep keratometry readings, and complications were evaluated at 1mo, 3mo, 6mo and 12mo postoperatively.

• RESULTS: Thirty-four patients with mean age of 23.3±4.0 years. Statistically significant improvement was shown in UCVA and CDVA, with steadiness of refection for 1y postoperative. *T*-test showed a significant difference ($P<0.05$) in all means between the preoperative and postoperative values (visual acuity, spherical and cylinder changes), with stability over a 1y follow up. Fourier analysis of postoperative images showed an axis shift perpendicular to the preoperative axis.

• CONCLUSION: Simultaneous non-topography-guided PRK and CXL is safe and effective surgical alternative for keratoconus, yielding improvement in the UDVA, CDVA, and refractive status. Stabilization was achieved as early as 3mo after surgery, the only advantage of topography-guided over non-topography-guided PRK might be the minimal over correction of sphere and the cylindrical axis shift in some patients as detected by Fourier analysis of postoperative pentacam.

• KEYWORDS: keratoconus; refractive surgery; photorefractive keratomileusis; corneal cross linking; non-topoguided PRK; myopia; astigmatism
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INTRODUCTION

Keratoconus is a non-inflammatory, progressive and degenerative disease of the cornea. The disorder is characterized by central thinning and increased corneal curvature. The decrease in visual acuity can be from mild to severe. Options for visual rehabilitation in keratoconus are glasses, contact lenses (soft, rigid gas permeable, rigid, sclera and semiscleral), intracorneal ring segments, phakic

intraocular lenses and keratoplasty (penetrating or lamellar) in advanced stage[1-2].

Photorefractive keratotomy (PRK) was considered a taboo, until recently when many studies came to evaluate the progression of keratoconus after PRK[2-4]. Chelala *et al*[2] documented a 98.3% improvement after a regular PRK alone in patients having mild to moderate keratoconus, with a follow up period of 5y. In the former study corneal cross linking was used for 2 cases (1.7%) when the patient showed signs of keratoconus progression[2]. Other short term one year studies also showed safety and efficacy of PRK in mild to moderate keratoconus patients when combined with corneal cross linking[5-8]. Recently, the use of topography-guided PRK with cross linking was investigated and proved to be useful in the treatment of mild to moderate errors in keratoconus[9-11].

Here we are investigating the outcome of non-topography-guided PRK combined with corneal cross linking in the management of keratoconus patients. Retrograde Fourier analysis was applied to the preoperative and postoperative topographies to see if non-topographic-guided PRK can over correct and shift the regular component of astigmatism to a different axis.

SUBJECTS AND METHODS

This retrospective non-randomized interventional clinical study comprised patients having simultaneous non-topography-guided PRK and corneal cross linking for keratoconus. All patients provided written informed consent before surgery in accordance with the Declaration of Helsinki, and institutional review board approval was obtained from the hospital Ethics Committee at Mutah University Number (20172). Inclusion criteria were age older than 18 years, the presence of keratoconus as manifested by topography, a clear central cornea, a history of contact lens intolerance, and an expected residual corneal stromal bed thickness greater than 350 μm after a maximum ablation of 50 μm at the corneal center. Exclusion criteria included a history of corneal refractive surgery or delayed epithelial healing and pregnancy or nursing during the course of the study. Preoperatively, all patients had a full ophthalmologic examination including uncorrected distance visual acuity (UDVA), corrected distance visual acuity (CDVA), cycloplegic refraction, slit lamp evaluation, tonometry, gonioscopy, fundoscopy, corneal pachymetry, keratometry and topography (Allegro Oculyzer, Wavelight Laser Technology AG). Fourier analysis was done on topography to get the regular and irregular component of the astigmatism before surgery.

Surgical Technique Two experienced surgeons (Rattan SA and Alshamarti S) performed all surgeries. The non-topography-guided partial PRK procedures were performed using the Zeiss MEI 90 excimer laser with an optical Zone of 6.5 mm. The myopic treatment was lowered (0.75 D-1 D) to avoid hyperopic shift. Next, corneal cross linking was performed with the CCL-365 corneal cross linking system (Peschke Meditrade GmbH) using the standard procedure. Under topical anesthesia, the central 9.0 mm epithelium was removed using a surgical brush (Hyperopic Amoils Epithelial Scrubber, Innovative Excimer Solutions, Inc.). PRK refers to the correction of up to 70% of astigmatism and some of the spherical component without exceeding a 50 mm ablation (corneal center) for planned stromal removal. PRK procedure finished with mitomycin-C 0.02% application for 30s, after which the MMC was copiously washed out of the eye. To compensate for possible torsional movements with the patient supine on the surgical bed, eyes were marked preoperatively along the horizontal meridian at the limbus at 3 o'clock and 9 o'clock with the patient seated at the slit lamp.

The CXL procedure was performed according to the methodology described by Wollensak *et al*[12] Riboflavin 0.1% in 20.0% dextran T 500 solution in corneas with residual beds of 400 mm or more or riboflavin 0.1% in hypotonic solution in corneas with residual stromal beds between 350 mm and 400 mm was administered topically every 2min for 30min. Riboflavin absorption throughout the corneal stroma and anterior chamber was confirmed by slit lamp examination. The cornea was aligned and exposed to ultraviolet-A (UVA) 365 nm light for 30min at an irradiance of 3.0 mW/cm^2. During UVA exposure, riboflavin administration was continued every 2min. Antibiotic and corticosteroid drops were administered, and a bandage soft contact lens was placed.

Postoperative topical therapy included moxifloxacin eyedrops (Vigamox), prednisolone acetate 1.0% (Pred Forte), and lubricant eyedrops for 4k. The contact lens was removed after the epithelial defect had closed (3d to 5d postoperatively).

Postoperative Assessment Patients had complete examinations at 1mo, 3mo, 6mo and 12mo after surgery. Study parameters included the UDVA, CDVA, manifest refraction, and flat and steep keratometry readings recorded from the topography data. Corneal haze was documented at each postoperative visit and graded on a scale of 0 to 4 (0: clear cornea; 1: mild haze; 2: moderate haze; 3: severe haze; 4: reticular haze obstructing iris anatomy).

Data Management and Statistical Analysis Visual acuity values were converted to logMAR notation for averaging and comparison. Statistical analysis was performed using SPSS software (version 17.0, International Business Machines Corp). The normality of all data samples was evaluated with the Shapiro-Wilk test. The paired *t*-test or Wilcoxon signed rank test was used to compare pre-surgical and post-surgical parameters depending on whether normality was found or was not found, respectively. Friedman repeated-measures analysis of variance (ANOVA) on ranks with Tukey post hoc testing and descriptive statistics were used to analyze the change from baseline to 1mo, 3mo, 6mo and 12mo values as well as other successive time intervals (*i.e.* 1-3mo; 3-6mo; 6-12mo). Results are presented as the mean SD, a P value of 0.05 or less was considered statistically significant.

RESULTS

Data was collected from 34 patients with mean age of 23.3±4.0 years. The age ranged from 19 years old to 40 years of age. Twenty three patients were males, and eleven

Table 1 The parameters over 1y period

Parameters	Preoperative	3mo	6mo	12mo
Sphere	−1.97±2.45	+0.12±0.7	+0.16±0.1	+0.15±0.13
Cylinder	−2.05±1.27	−0.57±1.03	−0.36±0.18	−0.35±0.16
Axis of cylinder	56°±7.1°	112°±6.8°	116°±5.5°	114°±6.2°
UCVA	0.95±0.59	0.25±0.14	+0.21±0.025	+0.21±0.018
BCVA	0.28±0.13	0.1±0.08	0.1±0.0175	0.1±0.013
Keratometry average	45.27±1.7	42.78±1.69	42.6±0.29	42.1±0.29
Keratometry max	49.3±0.52	48.8±0.63	48.0±0.47	47.4±0.44

UCVA: Uncorrected visual acuity; BCVA: Best corrected visual acuity.

Table 2 Two tailed *t*-test for the spherical component

Parameters	Standard deviation	*P*
Preoperative sphere and 3mo	2.48±0.43	0.0001
Preoperative sphere and 6mo	2.33±0.4	0.0001
Preoperative sphere and 12mo	2.47±0.42	0.0001
Sphere change 3mo and 6mo	0.4±0.77	0.72
Sphere change 3mo and 1y	0.3±0.8	0.84
Sphere change 6mo and 1y	0.15±0.81	0.92

Table 3 *T*-test result for cylindrical component

Parameters	Standard deviation and standard error	*P*
Preoperative cylinder and 3mo	−1.5±1.01	0.0001
Preoperative cylinder and 6mo	−1.69±1.03	0.0001
Preoperative cylinder and 12mo	−1.7±0.93	0.0001
Cylinder change 3mo and 6mo	−2.0±0.5	0.024
Cylinder change 3mo and 1y	−2.6±0.56	0.03
Cylinder change 6mo and 1y	−0.15±0.39	0.891

Table 4 Uncorrected visual acuity over a year period

Parameters	Mean and standard deviation	*P*
Preoperative and 3mo	0.69±0.67	0.0001
Preoperative and 6mo	0.74±0.66	0.0001
Preoperative and 12mo	0.75±0.68	0.0001
Sphere change 3mo and 6mo	0.04±0.1	0.026
Sphere change 3mo and 1y	0.53±0.2	0.08
Sphere change 6mo and 1y	0.015±0.17	0.72

Table 5 Two tailed *t*-test value for best corrected visual acuity Log MAR, over a period of year

Parameters	Mean and standard deviation	*P*
Preoperative and 3mo after treatment	0.17±0.17	0.0001
Preoperative and 6mo	0.17± 0.19	0.0001
Preoperative and 12mo	0.17±0.14	0.0001
Sphere change 3mo and 6mo	0.00±0.08	0.8
Sphere change 3mo and 1y	0.002± 0.1	0.92
Sphere change 6mo and 1y	0.002± 0.12	0.93

were females. The preoperative and postoperative means of the sphere, cylinder, UCVA, BCVA, and average keratometry are shown in Table 1. The student paired *t*-test comparing the preoperative and postoperative values of corrected, uncorrected sphere, cylinder, axis change, and average keratometry is shown in Tables 2, 3, 4, 5 and 6. There was a statistically significant improvement in the uncorrected visual acuity means, with the presence of steadiness in the refection for a period of 1y postoperative. *T*-test showed a significant improvement in all the parameters postoperative with no difference in the means all through the period of 1y follow up ($P = 0.0001$) (Tables 2-6). In addition to the initial improvement in keratometry readings, the keratometry continued to flatten all thought the follow up period, the paired *t* - test showed a significant difference in the average keratometry and keratometry max (*P* value was less than 0.05)

Table 6 Two tailed *t*-test for the average keratometry readings

Parameters	Mean and standard deviation	*P*
Preoperative and 3mo	2.46±1.71	0.0001
Preoperative and 6mo	2.66±1.77	0.0001
Preoperative and 12mo	3.13±1.65	0.0001
Sphere change 3mo and 6mo	0.2±0.56	0.043
Sphere change 3mo and 1y	0.67±0.63	0.0001
Sphere change 6mo and 1y	0.46±0.35	0.0001

(Tables 5 and 6). Twenty-nine eyes (85.2%) gained 3 or more lines of UDVA and 1 eye (2.94%) lost 1 line of UDVA. Four cases had no change in the uncorrected visual acuity (11.74%). Fourier analysis and postoperative analysis of the cylindrical axis showed a change almost perpendicular to the original axis, suggesting an over correction of cylinder using the non- topography-guided PRK.

DISCUSSION

The present study reflects our experience in the treatment of keratoconus using non-topography-guided partial PRK and CXL. The visual outcomes in relation to the safety index (1.69) were very satisfactory, with all eyes having improved UCVA and most (85.2%) gaining 3 or more lines. At 12mo, the efficacy index was high (1.17), 53.6% of eyes had 20/20 or better UCVA compared with 0% at baseline, and the proportion of eyes with 20/40 or better UCVA was 83.9% compared with 12.9% preoperatively. Considering that the procedure did not intend to correct the full refractive preoperative error, the predictability of SE correction was also good, with 58.8% of eyes within 1.00 D range and manifest refractive cylinder decreasing from -2.05 D at baseline to -0.57 D postoperatively. The stability of the UCVA, BCVA, and postoperative refraction was achieved soon after surgery, with minor changes after the 3mo follow up visit that were likely related to improvement in corneal clarity.

It is known that CXL alone can induce a refractive improvement in certain cases, so it could be thought that PRK after a procedure that can change refraction so that lead to a bad outcome (given that data for PRK correction refer to the refractive status prior to CXL), but this is not expected to occur when both techniques are performed at the same time with the partial PRK performed using T-Cat software, because the ablation is limited to 50 mm. In fact, there were no severe adverse events in our study.

Corneal CXL seeks to increase the degree of interfibrillar linkages, potentially increasing the biomechanical stability of the cornea[4-5,10]. Several studies have documented the successful cessation of progression of keratoconus after CXL[4-5,10,13]. However, CXL does not improve the refractive status of the eye. In fact, CXL in itself is believed to freeze the non-ideal shape of the keratoconus cornea. It is therefore logical to improve the refractive status of the eye before freezing the corneal shape[12,14-15].

Keratoconus eyes with a mean follow up of 36mo, Kanellopoulos[16-17] found improvement in the UDVA and CDVA, a greater mean reduction in SE and keratometry, and less corneal haze in the simultaneous group than in the sequential group. Similarly, Coskunseven *et al*[9] report encouraging results in 31 keratoconus eyes with simultaneous topography-guided partial PRK and CXL. The combined treatment reduced the refractive error and K readings, yielding improvements in the UDVA and CDVA that remained stable at a mean follow up of nearly 20mo. The procedure has also been evaluated in eyes that developed corneal ectasia after laser in situ keratomileusis, with significant clinical improvement and apparent stability of the ectasia in 5 cases with follow up ranging from 11-37mo.

The aim of the present study was to systematically examine the evolution of the visual and refractive changes through the first year after simultaneous non-topography-guided partial PRK and CXL. Significant improvements in the UDVA, CDVA, and flat and steep K readings from preoperative levels were apparent as early as 1mo after the procedure. At 3mo, significant improvement over baseline values was found in all the parameters. The UCVA and BCVA achieved stability after 3mo of follow up. According to our study there is no difference in UCVA or BCVA in both topoguided to the non-topoguided PRK in keratoconus. However, the only draw-back in the non-topoguided was the change in the cylindrical axis to the opposite axis, although minimal it is still a problem that can be addressed by topoguided PRK[17-18].

The presence of haze in our study corresponds to previous studies of the occurrence and natural course of haze after CXL. Postoperative haze after CXL increases initially up to 1mo and gradually diminishes between 3mo and 12mo[19]. In the present study the incidence of haze was minimal, which concurs with findings reported by Kanellopoulos[20-21]. Both studies found less corneal haze development after simultaneous PRK and CXL than after sequential procedures.

Although all the parameters in our study improved further between 6mo and 12mo, the improvement was not statistically significant, indicating stabilization of visual and refractive outcomes.

The sample size in our study resulted in a statistical power between 0.75 and 0.80. Thus, the stability after 3mo must be carefully interpreted. On the other hand, it must be determined whether the stability continues after 12mo, which was the follow up in our study.

In the past decade, there has been a gradual shift in the timing of administration of surgical intervention for

keratoconus from late-stage corneal transplantation to ICRS implantation when patients become intolerant to contact lens to early-stage CXL at the diagnosis of keratoconus progression. Because keratoconus deteriorates most measures of quality of life, even in its initial stages, the ultimate aim of keratoconus treatment is to treat the disease as early as possible. If the outcomes remain good over the long term, simultaneous topography-guided partial PRK and CXL may emerge as a reasonable option to treat the keratoconus eyes soon after its diagnosis.

In summary, simultaneous non-topography-guided PRK and CXL was a safe and effective surgical alternative for keratoconus, yielding improvement in the UDVA, CDVA, and refractive status. Stabilization was achieved as early as 3mo after surgery, the only advantage that topoguided might have is the minimal over correction of sphere and the axis shift in some patients.

REFERENCES

1 Fadlallah A, Dirani A, Chelala E, Antonios R, Cherfan G, Jarade E. Non-topography-guided PRK combined with CXL for the correction of refractive errors in patients with early stage keratoconus. *J Refract Surg* 2014;30(10):688-693

2 Chelala E, Rami HE, Dirani A, Fadlallah A, Fakhoury O, Warrak E. Photorefractive keratectomy in patients with mild to moderate stable keratoconus: a five-year prospective follow-up study. *Clin Ophthalmol* 2013;7:1923-1928

3 Sakla H, Altroudi W, Munoz G, Sakla Y. Simultaneous topography-guided photorefractive keratectomy and accelerated corneal collagen cross-linking for keratoconus. *Cornea* 2016;35(7):941-945

4 Sakla H, Altroudi W, Muñoz G, Albárran-Diego C. Simultaneous topography-guided partial photorefractive keratectomy and corneal collagen crosslinking for keratoconus. *J Cataract Refract Surg* 2014;40(9):1430-1438

5 Alessio G, L'Abbate M, Furino C, Sborgia C, La Tegola MG. Confocal microscopy analysis of corneal changes after photorefractive keratectomy plus cross-linking for keratoconus: 4-year follow-up. *Am J Ophthalmol* 2014;158(3):476-484

6 Alessio G, L'Abbate M, Sborgia C, La Tegola MG. Photorefractive keratectomy followed by cross-linking versus cross-linking alone for management of progressive keratoconus: two-year follow-up. *Am J Ophthalmol* 2013;155(1):54-65.e1

7 Dirani A, Fadlallah A, Syed ZA, Chelala E, Khoueir Z, Cherfan G, Jarade E. Non-topography-guided photorefractive keratectomy for the correction of residual mild refractive errors after ICRS implantation and CXL in keratoconus. *J Refract Surg* 2014;30(4):266-271

8 Knezović I, Višnjić MB, Raguž H. Partial topography-guided photorefractive keratectomy followed by corneal cross linking in the management of progressive keratoconus: our initial ten-month results. *Acta Clin Croat* 2015;54(2):193-200

9 Coskunseven E, Jankov MR, Grentzelos MA, Plaka AD, Limnopoulou AN, Kymionis GD. Topography-guided transepithelial PRK after intracorneal ring segments implantation and corneal collagen CXL in a three-step procedure for keratoconus. *J Refract Surg* 2013;29:54-58

10 Assaf A, Kotb A. Simultaneous corneal crosslinking and surface ablation combined with phakic intraocular lens implantation for managing keratoconus. *Int Ophthalmol* 2015;35(3):411-419

11 Al-Tuwairqi WS, Osuagwu UL, Razzouk H, Ogbuehi KC. One-year clinical outcomes of a two-step surgical management for keratoconus-topography-guided photorefractive keratectomy/cross-linking after intrastromal corneal ring implantation. *Eye Contact Lens* 2015;41(6):359-366

12 Wollensak G, Spoerl E, Seiler T. Riboflavin/ultraviolet-a-induced collagen crosslinking for the treatment of keratoconus. *Am J Ophthalmol* 2003;135(5):620-627

13 Taneri S, Oehler S, Asimellis G, Kanellopoulos AJ. Influence of corneal cross-linking for keratoconus on several objective parameters of dry eye. *J Refract Surg* 2013;29(9):612-616

14 Kanellopoulos AJ, Asimellis G. Long-term safety and efficacy of high-fluence collagen crosslinking of the vehicle cornea in Boston keratoprosthesis type 1. *Cornea* 2014;33(9):914-918

15 Kanellopoulos AJ, Asimellis G. Hyperopic correction: clinical validation with epithelium-on and epithelium-off protocols, using variable fluence and topographically customized collagen corneal crosslinking. *Clin Ophthalmol* 2014;8:2425-2433

16 Kanellopoulos AJ. Topography-guided lasik versus small incision lenticule extraction (smile) for myopia and myopic astigmatism: a randomized, prospective, contralateral eye study. *J Refract Surg* 2017;33(5):306-312

17 Kanellopoulos AJ. Topography-modified refraction (TMR): adjustment of treated cylinder amount and axis to the topography versus standard clinical refraction in myopic topography-guided LASIK. *Clin Ophthalmol* 2016;10:2213-2221

18 Kanellopoulos AJ, Asimellis G. Keratoconus management: long-term stability of topography-guided normalization combined with high-fluence CXL stabilization (the Athens Protocol). *J Refract Surg* 2014;30(2):88-93

19 Kanellopoulos AJ. September consultation #5. *J Cataract Refract Surg* 2015;41(9):2028-2029

20 Kanellopoulos AJ, Asimellis G. Combined laser in situ keratomileusis and prophylactic high-fluence corneal collagen crosslinking for high myopia: two-year safety and efficacy. *J Cataract Refract Surg* 2015;41(7):1426-1433

21 Kanellopoulos AJ, Loukas YL, Asimellis G. Cross-linking biomechanical effect in human corneas by same energy, different UV-A fluence: an enzymatic digestion comparative evaluation. *Cornea* 2016;35(4):557-561