УДК 617-713-007.253: 617.753.2-053.2

Riboflavin-UVA corneal collagen cross-linking (CXL) and flat fitting RGP lens in progressive keratoconus

Mokbel T., Samra W. A.
Mansoura University, Mansoura, Egypt

SUMMARY

Aim. to evaluate the safety, efficacy and possible additive role of flat fitting RGP lens following riboflavin-UVA corneal collagen cross-linking (CXL) in management of progressive keratoconus.

Subject and Method. Prospective comparative study of 30 eyes without RGP lens and 34 eyes fitted with RGP lens with apical bearing (flat fitting) from 2 to 10 weeks post-CXL. None of the patients had been wearing contact lens (CL) before CXL. The effect of the CXL without and with RGP lens was measured by the change from the baseline of best spectacle corrected visual acuity (BSCVA), refractive sphere and cylinder, maximal keratometry value (K max), simulated keratometry, astigmatism and I-S value. The results of these measurements are reported pre-CXL and at 6-month intervals up to 24 months post-CXL.

Result. In the eyes without CL, none of the study parameters showed a significant change from baseline. Only in the group of eyes fitted with CL post-CXL, several parameters showed a significant improvement: refractive cylinder, I-S value, K max, simulated keratometry and astigmatism.

Conclusion. RGP lens with flat fitting can be a safe additive factor in improvement of topographical parameters following CXL.

Keywords: cornea, keratoconus, keratometry, contact lens, collagen cross-linking, dinamic.

INTRODUCTION

Corneal collagen cross-linking (CXL) is a technique in which extra cross-links are created in the corneal stroma to increase the rigidity of the corneal tissue [1]. Clinical reports indicate that CXL is effective to stop the progression of keratoconus and conclude a statistically significant improvement of visual acuity and topography in a majority of patients [2–6]. However reports on the efficacy of CXL should ideally only include patients who are not wearing CL due to topographic changes occurred by rigid gas permeable (RGP) lens fitting in patients with keratoconus. However, such patients present with the need of both stabilization through CXL and optical correction with RGP lenses.

Different strategies can be adopted when fitting RGP contact lenses to keratoconic patients, these include «apical bearing» (flatter fitting) and «apical clearance» (steeper fitting) fittings as explained by Korb et al. [7] and «three-point touch» fit which is often favored over a flatter or a steeper fit as it is believed to relieve some of

the pressure on the cone by distributing the weight of the RGP lens over more of the cornea [8]. Nevertheless, the literature suggests that many keratoconic patients are still fitted with RGP contact lenses using a flat-fitting technique, which can offer comparatively better visual acuity than steeper-fitting lenses [9]. At present, no published study has addressed the effect of flat lens fittings in keratoconic eyes treated with CXL.

The purposes of this study are to evaluate the results of UVA/riboavin CXL for stabilization of progressive keratoconus in patients who have never worn CL before and to address the possible influence of flat fitted RGP lens on the visual and topographical results.

MATERIALS AND METHODS

This prospective longitudinal study was conducted on 64 eyes of 35 patients with progressive keratoconus that underwent riboflavin/UVA CXL treatment. Females were more frequent than Males (20 vs 15). The average age of the patients was 27.6 ± 8.2 years (range, from 18 to 35 years). None of the patients had a history of CL wear. 30 eyes did not need CL correction, while 34 eyes were fitted with Rose K2 lenses 2 to 10 weeks post-CXL treatment.

This study was conducted in accordance with the principles of the Declaration of Helsinki. All patients read and signed the informed consent form; for patients under 18 years, both parents were required to sign.

Ophthalmological examination and follow-up

Clinically and instrumentally documented keratoconus progression was considered in the study. Progressive keratoconus was defined as 1 or more of the following changes over 12 months: an increase of 1.00 diopter (D) or more in the steepest K, an increase of 1.00 D or more in manifest cylinder, or an increase of 0.50 D or more in the manifest refraction spherical equivalent. All stages of keratoconus were treated except advanced cones with scarring (stage 4 of the Krumeich classification). Exclusion criteria included a history of corneal surgery, corneal pachymetry less than 400 mm, a history of chemical injury or delayed epithelial healing, and any other ocular or systemic disease.

Patients were examined at baseline and at 6, 12, 18 and 24 months post-CXL. Subjective parameters were registered: best spectacle corrected visual acuity (BSCVA), refractive sphere and cylinder. Objective parameters were established on a corneal topographer (Shinnippon, Tokyo, Japan): K max, IS value, simulated keratometry measurements (K1, K2) and simulated astigmatism.

CXL Treatment

After topical anesthetic eye drops administration, 10 % alcohol was applied on the corneal epithelium for 30 seconds. The epithelium was mechanically removed within the central 8.5 mm diameter area using a Beaver blade. Next, riboflavin (0.1 % solution, 10 mg riboflavin-5-phosphate in 10 ml dextran-500 20 % solution) (Ricrolin, Sooft

Italia, Montegiorgio, Italy) was applied every 3 minutes for 30 minutes until the stroma was completely saturated and aqueous stained yellow.

Ultraviolet-A irradiation was accomplished using a commercially available UVA system (UVX, Peschke Meditrade, Switzerland). Before treatment, the intended 3 mW/cm^2 surface irradiance (5.4 J/cm^2 surface dosage after 30 minutes) was calibrated using a UVA meter (LaserMate-Q, LASER 2000, Wessling, Germany). During treatment, riboflavin solution was applied every 5 minutes to ensure saturation and balanced salt solution (BSS) was applied every 3 minutes to moisten the cornea. Topical anesthetic drops were instilled every 10 minutes throughout the procedure.

A drop of Moxifloxacin 0.5 % (Vigamox, Alcon) and a bandage contact lens (AcuVue, Johnson and Johnson Vision Care Inc.) were applied at the end of the surgery. Postoperative treatment included Vigamox eye drops 5 times daily for 1 week and Diclofenac 0.1 % eye drops (Voltaren, Novartis Ophthalmics) 3 times daily for 1 week. Fluorometholone eye drops (FML, Allergan Inc.) were used twice daily for 1 month.

Contact lenses fitting

All eyes were fitted with a reverse-geometry lens design namely Rose K IC after measuring precisely lens parameters according to a special trial set of this design consisting of 19 lenses with base curves (BC) ranging from 6.5 to 8.4 mm. All lens overall diameters in the fitting set are 11.2 mm with changing power to approximate final lens power. All lenses in the fitting set have a standard edge lift design. However, we can order the lens with a BC ranging from 5.7 mm to 9.3 mm, with diameter ranging from 9.4 mm to 12 mm, with any power and with standard, flat or steep edge lift.

The goal of the central lens- cornea relationship was «apical bearing» which could be obtained by ordering the lens 0.2 flatter than optimal central fit «three point touch». When an optimal central lens-cornea relationship was obtained, the peripheral edge lift was evaluated. If the trial lens gave a desirable edge lift, then standard edge lift was ordered for that eye. If minimal or excessive edge lift was observed, increased or decreased edge lift was ordered respectively. After finding the optimal trial lens for each eye, an over-refraction was performed while the subject was wearing the trial lenses to determine the contact lens power. All Rose K lenses were ordered from David Thomas Company (UK) with high Dk materials eg Boston XO_2.

Statistical method

For statistical evaluation of the study parameters, the 64 keratoconus eyes were divided into two groups, depending on the necessity of CL fitting for optical correction:

– group 1: keratoconus eyes without CL correction (30 eyes);

– group 2: keratoconus eyes fitted with CL post-CXL (34 eyes).

To detect any influence of CL wear on the results, the above- mentioned parameters were evaluated for each group separately.

All statistical analyses were done using student t test and the significance was adjusted at 0.05.

RESULTS

Pre-CXL data were available for all eyes of this study group. Patents characteristics are summarized in table 1. No significant difference was demonstrated in any studied parameters between both groups

For group 1, none of the study parameters showed a significant cant change (all p values > 0.05) compared to baseline at different time points (table 2). For group 2 in whom reverse geometry CL was flatly fitted for optical correction after CXL, several parameters on topography showed a clearly significant improvement from baseline: K1, K max, simulated astigmatism and I-S value at 12, 18 and 24 months of follow up. K2 showed a significant improvement only at 18 and 24 months. Also refractive cylinder was significantly improved at 6, 12 and 18 months follow up (table 3).

In order to establish the failure rate in this study, the evolution of K max in individual eyes needs to be investigated. 2 eyes of a 17 years old boy in the first group (non-CL wearers) had obvious treatment failure. They developed 3 diopters at 24 months, accompanied by a subjective decrease in BSCVA.

COMPLICATIONS

After cross-linking, one eye showed an epithelial defect with asymptomatic iritis-like reaction. Tfhis complication resolved after a month of topical steroid therapy, so the treatment was continued. Apart from the usual CL problems like irritation, allergy and dry eye, No relevant adverse events were observed from flat fitting of the CL in the second group at 6, 12, 18 and 24 months.

Table 1
Pre CXL patients characteristics

Parameter	All eyes	Group 1 (without CL)	Group 2 (with CL)	Difference (G1 vs G2) p value
UCVA	0.17 ± 0.08	0.17 ± 0.06	0.16 ± 0.09	0.56
BSCVA	0.48 ± 0.21	0.49 ± 0.23	0.47 ± 0.19	0.45
Sphere (D)	−4.12 ± 2.4	−4.32 ± 2.5	−3.99 ± 2.4	0.22
Cylinder (D)	−3.8 ± 1.17	−3.9 ± 1.22	−3.7 ± 1.11	0.26
K1 (D)	52.1 ± 3.55	52.3 ± 3.45	51.9 ± 3.67	0.34
K2 (D)	48.2 ± 4.22	48.5 ± 4.72	47.9 ± 3.69	0.68
K Max. (D)	55.5 ± 5.1	55.7 ± 4.9	55.1 ± 5.2	0.89
Sim. Astigmatism (D)	4.3 ±1.2	4.5 ±1.3	4.2 ±1.2	0.12
I-S Value (D)	7.3 ± 3.8	7.2 ± 3.9	7.4 ± 4.1	0.09

Table 2
The pre and post operative measured parameters of the studied patients without CL (mean ± SD)

Parameter	Pre op.	Post operative				p value
		6 M	12 M	18 M	24 M	
UCVA	0.17 ± 0.06	0.16 ± 0.04	0.16 ± 0.06	0.18 ± 0.07	0.19 ± 0.08	0.09
BSCVA	0.49 ± 0.23	0.47 ± 0.20	0.49 ± 0.19	0.51 ± 0.21	0.51 ± 0.18	0.08
Sphere (D)	−4.32 ± 2.5	−4.36 ± 2.3	−4.34 ± 2.2	−4.30 ± 1.9	−4.29 ± 2.1	0.09
Cylinder (D)	−3.9 ± 1.22	−3.9 ± 1.10	−3.8 ± 1.31	−3.7 ± 1.30	−3.8 ± 1.26	0.26
K1 (D)	52.3 ± 3.45	52.6 ± 3.32	52.4 ± 3.51	52.4 ± 3.41	52.2 ± 3.39	0.98
K2 (D)	48.5 ± 4.72	48.7 ± 4.55	48.5 ± 4.45	48.4 ± 4.39	48.2 ± 4.69	0.82
K Max. (D)	55.7 ± 4.9	55.9 ± 4.8	55.6 ± 5.1	55.3 ± 4.7	55.1 ± 5.3	0.49
Sim. Astigmatism (D)	4.5 ±1.3	4.7 ± 1.7	4.4 ± 1.5	4.4 ± 1.4	4.2 ± 1.6	0.08
I-S Value (D)	7.2 ± 3.9	7.4 ± 4.1	7.3 ± 3.8	7.2 ± 4.3	7.3 ± 4.4	0.28

Note. *p is significant at < 0.05.

Table 3
The pre and post operative measured parameters of the studied patients with CL (mean ± SD)

Parameter	Pre op.	Post operative				p value
		6 M	12 M	18 M	24 M	
UCVA	0.16 ± 0.09	0.17 ± 0.07	0.18 ± 0.09	0.18 ± 0.08	0.19 ± 0.11	0.06
BSCVA	0.47 ± 0.19	0.48 ± 0.16	0.48 ± 0.17	0.49 ± 0.12	0.50 ± 0.14	0.09
Sphere (D)	−3.99 ± 2.4	−4.1 ± 2.3	−4.2 ± 1.8	−4.1 ± 2.1	−3.85 ± 1.9	0.06
Cylinder (D)	−3.7 ± 1.11	−3.4 ± 0.9	−3.1* ± 1.17	−3.1* ± 1.13	−2.8* ± 1.28	0.05
K1 (D)	51.9 ± 3.67	51.7 ± 3.8	50.9* ± 3.69	50.8* ± 3.86	50.1* ± 3.9	0.04
K2 (D)	47.9 ± 3.69	47.4 ± 3.73	47.2 ± 3.81	46.9* ± 3.70	46.7* ± 3.86	0.05
K Max. (D)	55.1 ± 5.2	54.9 ± 4.9	54.1* ± 4.7	53.9* ± 5.1	53.7* ± 5.2	0.01
Sim. Astigmatism (D)	4.2 ± 1.2	4.1 ± 1.6	3.7* ± 1.5	3.40* ± 1.3	3.1* ± 1.5	0.02
I-S Value (D)	7.4 ± 4.1	7.2 ± 4.6	6.70* ± 4.8	6.60* ± 4.4	6.3* ± 4.3	0.05

Note. *p is significant at < 0.05.

DISCUSSION

In this investigation, we systematically applied special RGP contact lenses with a reverse-geometry design (Rose K IC) in keratoconic eyes after CXL. All eyes in CL group were fitted with apical bearing type. The aim was to evaluate how both clinical and topographical parameters change with respect to this type of fitting.

The results of CXL in this study agreed with the findings of previous authors who noted that progressive keratoconus could be stabilized by UVA/riboflavin CXL [1, 6, 10–12]. However, most of them reported a statistically significant improvement of a majority or even all of the studied parameters, while, our results show a more differentiated picture. Taking into account the influence of CL wear: In the eyes without CL, none of the study parameters showed a significant change from baseline (all p values > 0.05). Only in the group of eyes fitted with CL post-CXL, several parameters showed a significant improvement including the refractive cylinder, I-S value, K max, simulated keratometry and astigmatism.

The findings of this study agree with the previously published literature that demonstrated improvement in most of topographical values only in the group of eyes fitted with CL post-CXL [13]. Other studies reported better LogMAR visual acuities and reduced aberrations with flatter-fitting RGP [14, 8, 9, 15, 16]. This report supports the original hypothesis by Zadnik and Mutti that the back surface of an apical bearing RGP lens will «flatten» and «mould» the irregular corneal distortions typically found in keratoconic eyes [16]. This corneal moulding will effectively give the anterior corneal surface a more «normal» curvature profile by exerting pressure on the apex of the cornea, perhaps regularizing its shape similar to what made by orthokeratology.

At present, the long-term effects of wearing flat-fitting contact lenses on ocular surface are unknown. The literature shows that flat-fitting lenses may cause damage at the cone apex leading to anterior stromal scarring [7, 9, 17]; such changes in the cornea could induce additional aberrations and perhaps even limit the improvement visual performance given by the contact lens. Although contact lens wearing does not necessarily cause this scarring, it is likely to exacerbate it [8]. The hypothesis that acceleration of scarring can be caused by flat-fitting lenses was addressed by the study by Korb [7] but the sample size was very small, having only seven keratoconus subjects (14 eyes). Despite of that debated risk of corneal scaring imposed by flat fitted CL, most CLEK Study patients wear flat-fitting lenses. Overall, rigid lenses were fitted an average of 2.86 D (SD +/− 3.31 D) flatter than the first definite apical clearance lens.

However, in our study we didn't face any scar from such fitting during follow up period. This is can be explained by the stiffness of the central part of the cornea induced by CXl prior to CL wearing and also may be due to high Dk material of the manufactured lens and the adjusted edge lift fitting that allows good tear exchange underneath the lens.

Also, we do not know, however, if the improved topographic parameters are permanent after CXL treatments combined with CL wear or if the reported effects are transient warpage phenomena [18]. In order to elucidate this question, patients would have to stop CL wear, which is ethically not feasible because it would involve a long period of incapacity to pursue their everyday activities.

In conclusion, we have found that CXL has led to stabilization of keratoconus in all studied eyes, but improvement of topographic values could only be established in the group of patients wearing flat fitted CL after the CXL treatment So, RGP lens with flat fitting can reshape the keratoconic cornea without significant adverse reactions adding a safe toll in improvement of clinical and topographical parameters following CXL.

However, further investigation into long-term changes in such parameters with different RGP lens designs and fittings in eyes with keratoconus will be needed. This may address the efficacy of apical bearing fitting with CXL in management of keratoconus and help to improve our current understanding of how contact lens fit affects the optical performance.

Рибофлавін-УФА колагеновий крос-лінкінг рогівки та плоскі контактні лінзи у прогресуванні кератоконуса

Мокбел Т., Самра В. А.
Університет Мансури, м. Мансура, Єгипет

Резюме. Мета роботи – оцінити безпеку, ефективність і, можливо, додатковий вплив погано підігнаних плоских жорстких контактних лінз (ЖКЛ) з подальшою процедурою рибофлавін-УФА крос-лінкінгу колагену рогівки (ККР) у лікуванні прогресуючого кератоконуса.

Проведено порівняльне дослідження 30 очей без ЖКЛ і 34 очей зі встановленими ЖКЛ з апікальним тиском (плоска посадка) від 2 до 10 тижнів після ККР. Жоден з пацієнтів не носив контактні лінзи (КЛ) до ККР. Ефект ККР без і з ЖКЛ визначався за зміною від базового рівня найкращої коригованої гостроти зору (НКОЗ), показника сфери та циліндра, максимального значення кератометрії (K_{max}), умовної кератометрії та астигматизму. Результати цих вимірювань представлені до рогівкового ККР і в термін 6–24 місяці після лікування. В очах без КЛ жоден з параметрів дослідження не показав значної зміни в порівнянні з вихідним. Тільки у групі очей зі встановленою КЛ, після ККР, за динамікою зміни деяких параметрів спостерігали значне поліпшення: рефракційного циліндра, значення I-S, K_{max}, умовної кератометрії та астигматизму.

ЖКЛ з плоскою посадкою можуть бути безпечним додатковим фактором у поліпшенні топографічних параметрів рогівки після ККР.

Ключові слова: рогівка, кератоконус, кератометрія, контактна лінза, колагеновий крос-лінкінг, динаміка.

Рибофлавин-УФА коллагеновый кросс-линкинг роговицы и плоские контактные линзы в прогрессировании кератоконуса

Мокбел Т., Самра В. А.
Университет Мансуры, г. Мансура, Египет

Резюме. Цель работы – оценить безопасность, эффективность и, возможно, дополнительное влияние плохо подогнанных плоских жестких контактных линз

(ЖКЛ) с последующей процедурой рибофлавин-УФА кросс-линкинга коллагена роговицы (ККР) в лечении прогрессирующего кератоконуса.

Проведено сравнительное исследование 30 глаз без ЖКЛ и 34 глаз с установленными ЖКЛ с апикальным давлением (плоская посадка) от 2 до 10 недель после ККР. Ни один из пациентов не носил контактные линзы (КЛ) до ККР. Эффект ККР без и с ЖКЛ определялся по изменению от базового уровня наилучшей корригированной остроты зрения (НКОЗ), показателя сферы и цилиндра, максимального значения кератометрии (K_{max}), условной кератометрии и астигматизма. Результаты этих измерений представлены до роговичного ККР и в сроки 6–24 месяца после лечения. В глазах без КЛ ни один из параметров исследования не показал значительного изменения по сравнению с исходным. Только в группе глаз с установленной КЛ, после ККР, по динамике изменения некоторых параметров наблюдали значительное улучшение: рефракционного цилиндра, значения I-S, K_{max}, условной кератометрии и астигматизма.

ЖКЛ с плоской посадкой могут быть безопасным дополнительным фактором в улучшении топографических параметров роговицы после ККР.

Ключевые слова: роговица, кератоконус, кератометрия, контактная линза, коллагеновый кросс-линкинг, динамика.

REFERENCES

1. Wollensak G., Spoerl E., Seiler T. Riboflavin/ultraviolet-a-induced collagen crosslinking for the treatment of keratoconus. *American Journal of Ophthalmology*. 2003; (135): 620–627.
2. Zhang Y., Conrad A. H., Conrad G. W. Effects of Ultraviolet-A and Riboflavin on the Interaction of Collagen and Proteoglycans during Corneal Cross-linking. *Journal of Biological Chemistry*. 2011; (286): 13011–13022.
3. Wittig-Silva C., Whiting M., Lamoureux E., Lindsay R. G., Sullivan L. J., Snibson G. R. (2008) A randomized controlled trial of corneal collagen cross-linking in progressive keratoconus: preliminary results. *Journal of Refractive Surgery*. 2008; (24): 720–725.
4. Wollensak G., Spoerl E., Seiler T. Riboflavin/ultraviolet-a-induced collagen crosslinking for the treatment of keratoconus. *American Journal of Ophthalmology*. 2003; (135): 620–627.
5. Mencucci R., Marini M., Paladini I., Sarchielli E., Sgambati E., Menchini U., Vannelli G. B. Effects of riboflavin/UVA corneal cross-linking on keratocytes and collagen fibres in human cornea. *Clinical & Experimental Ophthalmology*. 2010; (38): 49–56.
6. Agrawal V. B. Corneal collagen cross-linking with riboflavin and ultraviolet – a light for keratoconus: results in Indian eyes. *Indian Journal of Ophthalmology*. 2009; (57): 111–114.
7. Korb D. R., Finnemore V. M., Herman J. P. Apical changes and scarring in keratoconus as related to contact lens fitting techniques. *Journal of the American Optometric Association*. 1982; (53): 199–205.
8. Leung K. K. RGP fitting philosophies for keratoconus. *Clinical and Experimental Optometry.* 1999; (82): 230–235.
9. Edrington T. B., Szczotka L. B., Barr J. T., Achtenberg J. F., Burger D. S., Janoff A. M., Olafsson H. E., Chun M. W., Boyle J. W., Gordon M. O. Rigid contact lens fitting relationships in keratoconus. Collaborative Longitudinal Evaluation of Keratoconus (CLEK) Study Group. *Optometry and Vision Science.* 1999; (76): 692–699.
10. Arbelaez M. C., Sekito M. B., Vidal C., Choudhury S. R. Collagen cross-linking with riboflavin and ultraviolet-A light in keratoconus: One-year results. *Oman Journal of Ophthalmology.* 2009; (2): 33–38.

11. Ashar J. N., Vadavalli P. K. Long-term results of riboflavin ultraviolet A corneal collagen cross-linking for Keratoconus in Italy: the Siena eye cross study. *American Journal of Ophthalmology.* 2010; (150): 588–589.
12. Constantin M., Corbu C. Corneal collagen cross-linking--results in keratoconus. *Oftalmol. Buchar. Rom*. 2009; (53): 85–88.
13. Koppen C., Gobin L., Mathysen D., Wouters K., Tassignon M.-J. Influence of contact lens wear on the results of ultraviolet A/riboflavin cross-linking for progressive keratoconus. *British Journal of Ophthalmology.* 2011; (95): 1402–1405.
14. Jinabhai A., Radhakrishnan H., O'Donnell C. Visual acuity and ocular aberrations with different rigid gas permeable lens fittings in keratoconus. *Eye Contact Lens*. 2010; (36): 233–237.
15. Zadnik K., Barr J. T., Edrington T. B., Everett D. F., Jameson M., McMahon T. T., Shin J. A., Sterling J. L., Wagner H., Gordon M. O. Baseline findings in the Collaborative Longitudinal Evaluation of Keratoconus (CLEK) Study. *Optometry and Vision Science*. 1998; (39): 2537–2546.
16. Zadnik K., Mutti D. O. Contact lens fitting relation and visual acuity in keratoconus. *Optometry and Vision Science*. 1987; (64): 698–702.
17. Macsai M. S., Varley G. A., Krachmer J. H. Development of keratoconus after contact lens wear. Patient characteristics. *Archives of Ophthalmology.* 1990; (108): 534–538.
18. Maeda N., Klyce S. D., Hamano H. Alteration of corneal asphericity in rigid gas permeable contact lens induced warpage. *Contact Lens*. 1994; (20): 27–31.

Рецензент: Kushnir Pablo, Dr. Med. Sc., Prof.
Стаття надійшла в редакцію 01.03.2015 р.