ORIGINAL ARTICLE

Comparison of Accelerated Crosslinking Results Performed with Hydroxypropyl Methylcellulose-Based or Dextran-Based Riboflavin Solutions

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ABSTRACT

Purpose: To compare the visual acuity, topographic and the biomicroscopic features in patients who had accelerated corneal crosslinking (CXL) by using hydroxypropyl methylcellulose-based (HPMC) or dextran- based riboflavin solutions.

Materials and Methods: In this study, 62 eyes with progressive keratoconus were included. Accelerated CXL has been performed to all patients. Riboflavin with dextran (0.1% Riboflavin, 20% dextran) (n: 33) or HPMC (0.1% Riboflavin, 1.1% HPMC) (n: 29) were used as photosensitizer in CXL procedure. Visual acuity, topographic measurements and biomicroscopic features were compared between 2 groups in 12 months of follow-up.

Results: Totally 62 eyes (34 right and 28 left) of 62 patients (25 female, 37 male) with a mean age of 24.37±6.93 years were included. Although best corrected visual acuity (0.29 ±0.16 vs 0.28±0.16; *p*= 0.89) and uncorrected visual acuity (0.62 ±0.34 vs 0.48±0.29; *p*=0.08) were both better in dextran free riboflavin group at 12th month of follow-up, the differences between 2 groups were not statistically significant. There was not any statistically significant difference between groups regarding any of the topographic findings. The biomicroscopic findings were also very similar in first, sixth and 12th months of follow-up in both groups. Corneal haze was the most common finding in the 1st month of follow up in all cases.

Conclusions: Accelerated CXL procedures performed by using riboflavin with dextran or HPMC represent similar affects in corneal parameters during the 12 months of follow-up period. Larger studies with longer follow-up periods are warranted to define the differences and similarities of these 2 photosensitizers.

Keywords: accelerated crosslinking, hydroxypropyl methylcellulose, keratoconus, riboflavin.

INTRODUCTION

Corneal crosslinking (CXL) is a conservative treatment method in progressive keratoconus that increases the mechanical and biochemical strength of the cornea.[1-2] In this treatment, using ultraviolet A (UV-A) and a photosensitizer (riboflavin), chemical covalent bond formation and bridging between collagen fibrils are induced.[3-4] The interaction between riboflavin and UV-A in corneal tissue induces a photodynamic process that results in the reactive oxygen species (ROS) formation and ROS are the main mediators of crosslink formation between collagen fibers. [5] With the delivery of the same UV-A energy dose in a shorter time, accelerated crosslinking procedure was defined.[6] Accelerated and standard CXL were determined to have similar effects in preventing the progression of keratoconus.[7]

There are different forms of riboflavin available in market for epi-off CXL procedure. Riboflavin solution with dextran (0.1% riboflavin, 20% dextran), HPMC (0.1% riboflavin, 1.1% HPMC) and hypotonic riboflavin solution (0.1% riboflavin) are the main forms. Hypotonic riboflavin was reported to better maintain consistent corneal thickness during UV administration and it was advised for preoperatively thin corneas under 400 µ.[8] But

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its effect on the increase in the corneal thickness has been shown to be short acting throughout the CXL procedure.[9] It is also known that the use of riboflavin with dextran decreases the corneal thickness both intraoperatively and postoperatively.[10-11] On the other hand, it was shown that HPMC does not cause any corneal thinning during surgery, but it provides a very little increase in corneal thickness.[12] Theoretically, it is thought that, riboflavin without dextran does not cause fluid loss from the cornea, so does not cause any reduction in its thickness; for that reason it may be associated with low levels of complications after CXL. In this study, we aimed to compare the visual acuity, topographic and the biomicroscopic features in patients who had accelerated CXL by using riboflavin with dextran or HPMC.

MATERIALS AND METHODS

In this study, consecutive 62 eyes of 62 patients with progressive keratoconus who underwent accelerated CXL between January 2018 and July 2018, in Beyoglu Eye Training and Research Hospital, Istanbul, Turkey were included. The study was carried out with the ethical standards of the Helsinki Declaration and approved by the Okmeydani Training and Research Hospital Ethic Committee (Ref no: 123). Patients with keratoconus who had at least 2 lines of visual acuity loss and an increase in keratometry (K) more than 1 diopter (D) were included in the study. The exclusion criteria were as follows; history of corneal surgery, chemical injury or delayed epithelial healing, having a corneal pachymetry less than 400 µ, and being pregnant or lactating for women.

Accelerated crosslinking has been performed to all patients. After installation of topical anesthetic agent, a blunt spatula was used to remove the central 8.0 mm epithelium. Riboflavin with dextran (0.1% Riboflavin, 20% dextran) (n: 33) or HPMC (0.1% Riboflavin, 1.1% HPMC) (n: 29) solution was then administered topically every 3min for 30min. Before UV-A administration the cornea was washed out with 20 ml salin. Patients were divided into 2 groups randomly. The UV-A 365 nm light for 5 minutes at an irradiance of 18 mW/cm^2 was applied to the cornea (LightLink-CXL, Light Med, San Clemente, CA, USA).Postoperatively, a soft contact lens bandage was attached. The contact lens was removed after epithelial healing. Antibiotics and corticosteroid drops were continued for 2 weeks, respectively. Patients were examined before surgery, and at 1st, 3rd, 6th and 12th months following CXL treatment.

Visual acuity that was obtained with Snellen charts converted to logMAR units for statistical analysis. Topographical measurements were recorded from Sirius (Costruzione Strumenti Oftalmici, Italy) topography device. The data obtained by slit-lamp biomicroscopic evaluation were also recorded. All data were obtained at preoperative period and in 1st, 3rd, 6th, and 12th months postoperatively.

Statistical analysis

All analyses were performed with the Statistical Package for Social Sciences software (SPSS, Windows version 21.0; SPSS Inc.; Chicago, IL, USA). Results were expressed as mean±SD (standard deviation) for continuous variables and as proportions (%) for categorical variables. Student's *t*-test (paired or independent, as appropriate) was used for the analyses of continuous variables. Categorical variables were compared with descriptive statistics and chi square analysis. A *P* value of less than 0.05 was considered statistically significant.

RESULTS

Totally 62 eyes (34 right and 28 left) of 62 patients (25 female, 37 male) with a mean age of 24.37±6.93 years were included. Demographic features of patients are summarized in Table 1.

Although best corrected visual acuity (BCVA) and uncorrected visual acuity (UCVA) were both better in HPMC group at 12th month of follow-up, the differences between 2 groups were not statistically significant (Table 2). When the progressive alterations in BCVA and UCVA were evaluated in each group, separately (in-group analysis); the alterations in BCVA and UCVA in 12 months were statistically significant in both of the groups (Table 2).

Table 1: *Comparison of demographic features of participants.*

	Riboflavin with dextran (n:33)	HPMC (n:29)	*p*
Age (years)	25.15±7.12	23.48±6.73	0.35
Gender (F/M)	13/20	12/17	0.87
Right eye / Left eye	16/17	18/11	0.32

HPMC: hydroxypropyl methylcellulose

Table 2: *Comparison of the best corrected and uncorrected visual acuities between 2 groups.*

	Riboflavin with dextran (n:33)	**HPMC (n:29)**	***p***
Pre-op BCVA (logMAR)	0.42±0.23	0.40±0.24	0.72
BCVA-1st month (logMAR)	0.45±0.18	0.44±0.25	0.86
BCVA-6th month (logMAR)	0.31±0.19	0.28±0.19	0.50
BCVA- 12th month (logMAR)	0.29 ±0.16	0.28±0.16	0.89
P^x	0.001	0.001	
Pre-op UCVA (logMAR)	0.76±0.31	0.63±0.35	0.11
UCVA-1st month (logMAR)	0.78±0.26	0.68±0.31	0.18
UCVA-6th month (logMAR)	0.67±0.31	0.52±0.33	**0.06**
UCVA- 12th month (logMAR)	0.62 ±0.34	0.48±0.29	**0.08**
P^x	0.002	0.009	

HPMC: hydroxypropyl methylcellulose; **BCVA**: Best corrected visual acuity; **UCVA**: Uncorrected visual acuity, P^x is the *p* value of the paired samples *t* test analysis between results of preoperative period and 12th month, **Pre-op:** Preoperatively.

The alterations in topographic findings are summarized in Tables 3 and 4. There was not any statistically significant difference between groups regarding any of these parameters. In in-group analysis; the apical keratoscopy front (AKf) values and the pachymetry at the thinnest point of the cornea significantly reduced in both groups on the 12th month of follow-up as well as the volume of the cornea (P<0.05). The results of other in-group analysis performed between the data of preoperative period and 12th month are summarized in Tables 3 and 4.

Table 3: *Comparison of alterations in keratometric readings between 2 groups.*

	Riboflavin with dextran (n:33)	HPMC (n:29)	*p*
Pre-op K1 (D)	45.46±1.69	45.73±2.76	0.63
K1-1st month	45.85±2.17	45.87±2.89	0.97
K1-6th month	45.35±1.97	45.56±2.66	0.73
K1-12th month	45.32 ±1.92	45.69 ± 2.91	0.56
P^x	0.50	0.81	
Pre-op K2 (D)	48.69±2.31	49.45±3.45	0.31
K2-1st month	49.49±2.53	50.12±3.60	0.43
K2-6th month	48.48±2.35	49.44±3.38	0.19
K2-12 th month	48.42 ±2.36	49.47±3.69	0.19
P^x	0.09	0.89	
Pre-op Avg K (D)	47.02±1.98	47.51±3.00	0.45
Avg K -1st month	47.58±2.21	47.88±3.11	0.66
Avg K -6th month	46.86±2.03	47.39±2.87	0.40
AvgK-12 th month	46.84 ±2.02	47.49 ±3.18	0.34
P^x	0.22	0.94	
Pre-op AKf	55.48±3.89	56.20±5.27	0.54
AKf-1st month	56.18±4.40	57.12±5.17	0.45
AKf-6th month	54.76±3.81	55.51±5.04	0.51
AKf-12th month	54.74±3.93	55.49 ±5.54	0.54
P^x	**0.001**	**0.02**	
Pre-op AKb	80.55±9.80	81.02±10.35	0.85
AKb-1st month	82.05±12.41	82.76±9.53	0.80
AKb-6th month	83.67±9.84	85.84±11.37	0.43
AKb-12th month	83.43± 10.64	85.52±11.84	0.47
P^x	**0.01**	**0.001**	

HPMC: hydroxypropyl methylcellulose; **K1**: Flat Keratometry value; **K2**: Steep Keratometry value, **avgK**: Average Keratometry value, **Akf**: Apical Keratoscopy Front, **Akb**: Apical Keratoscopy Back, P^x is the *p* value of the paired samples t test analysis between results of preoperative period and 12th month, **Pre-op:** Preoperatively.

Table 4: *Comparison of alterations in symmetry indexes, cylinder, corneal volume and pachymetry at the thinnest point of the cornea between 2 groups.*

	Riboflavin with dextran (n:33)	HPMC (n:29)	*P*
Pre-op Sif	6.31±2.89	6.21±3.43	0.89
Sif -1st month	6.60±3.38	6.47±3.65	0.88
Sif -6th month	5.89±2.87	6.18±3.33	0.72
Sif-12th month	5.86 ± 2.86	6.02±3.42	0.85
P^x	**0.003**	0.29	
Pre-op SIb	1.61±0.71	1.59±0.80	0.91
SIb -1st month	1.52±0.75	1.55±0.91	0.90
SIb -6th month	1.65±0.76	1.67±0.86	0.89
Sib-12th month	1.69 ±0.74	1.66±0.88	0.91
P^x	0.10	0.16	
Pre-op Cyl	3.22±1.47	3.71±1.55	0.21
Cyl -1st month	3.64±1.59	4.24±1.83	0.17
Cyl -6th month	3.13±1.47	3.86±1.74	0.08
Cyl-12th month	3.12 ± 1.52	3.78 ± 1.66	0.11
P^x	0.24	0.47	
Pre-op CV (mm^3)	55.84±3.34	56.13±3.24	0.72
CV -1st month	53.15±4.11	53.63±3.67	0.63
CV -6th month	54.01±3.92	54.64±3.63	0.71
CV-12th month	54.63 ± 3.59	54.65± 3.51	0.89
P^x	**0.001**	**0.001**	
Pre-op Thin (µm)	456.36±32.27	457.28±31.78	0.91
Thin -1st month (µm)	412.39±44.21	421.83±47.32	0.42
Thin -6th month (µm)	421.10±43.06	420.79±38.26	0.98
Thin-12th month(µm)	427.52 ±44.31	430.31±40.62	0.79
P^x	**0.001**	**0.001**	

HPMC: hydroxypropyl methylcellulose; **SIf**: Symmetry Index front, **SIb**: Symmetry Index back, **Cyl**: Topographic cylindrical value; **CV**: Total volume of cornea, **Thin**: Pachymetry at thinnest point of the cornea, P^x is the *p* value of the paired samples t test analysis between results of preoperative period and 12th month, **Pre-op:** Preoperatively.

The biomicroscopic findings were also compared between 2 groups and they were very similar in first and sixth months of follow-up (Table 5). Ring like haze was the most common finding in 1st month of follow up that disappeared in the 6th month in all cases.

DISCUSSION

In the present study, we have compared the visual acuity and topographic and biomicroscopic findings in 12 months of follow-up period after accelerated CXL performed by using 2 different types of riboflavin, with dextran or HPMC as photosensitizer. Although HPMC group showed a slightly better BCVA and UCVA at 12th month of follow-up, there was not any statistically significant difference between the two treatment modalities. The topographic and biomicroscopic findings at 1st, 6th and 12th month of follow-up were very similar in 2 groups.

Accelerated CXL has been defined as an effective and safe treatment method for progressive keratoconus. Cinar et al.[13] determined a significant improvement in the visual acuity at the 6th month after CXL with a significant decrease in mean cylinder. Moreover keratometry values were also reported to be significantly reduced at the 6th month after CXL. Similarly, Sharma et al.[14] evaluated that UCVA improved significantly, the refractive cylinder decreased significantly as well as the central corneal thickness and the maximum keratometry at 6th month after CXL treatment. Similarly, in our study, we also determined significant improvements in UCVA, BCVA and AKf in both groups on the 6th and 12th months of follow-up period after CXL compared with the preoperative period. On the other hand, pachymetry at the thinnest point of the cornea and the volume of it were determined to be significantly decreased in both groups but did not differ significantly between 2 groups. However In their study comparing

Table 5: *Biomicroscopic data.*			
	Riboflavin with dextran (n:33)	HPMC (n:29)	*P*
1st month			0.96
Ring like haze	8 (24.2%)	7 (24.1%)	
Haze without stria	5 (15.2%)	3 (10.3%)	
Haze with stria	3 (9.1%)	2 (6.9%)	
Minimal stromal scar	3 (9.1%)	2 (6.9%)	
Stria without haze	7 (21.2%)	6 (20.7%)	
Transparent cornea	7 (21.2%)	9 (31.0%)	
6th month			0.90
Haze with stria	1 (3.0%)	1 (3.5%)	
Minimal stromal scar	3 (9.1%)	2 (6.9%)	
Stria without haze	1 (3.0%)	2 (6.9%)	
Transparent cornea	28 (84.9)	24 (82.7)	
12th month			0.99
Minimal stromal scar	2 (6.0%)	2 (7.0%)	
Transparent cornea	31 (93.9%)	27 (93.1%)	
HPMC: hydroxypropyl methylcellulose.			

the dextran-treated group and the HPMC-treated group, Rapauno et al. reported a significant BCVA improvement in the dextran-treated group in the 24th month, although there was no significant difference in the 12th month. In the same study, although there was a significant difference as flattening in K-max measurements at 1st month in the dextran-treated group, they did not find a difference at the 6th, 12th and 24th months.[15]

Significant alterations in corneal thickness have been reported after CXL. Kymionis et al.[9] reported a statistically significant intraoperative decrease of central corneal thickness measured by using ultrasound pachymetry during CXL performed with standard riboflavin and UV-A irradiation. Similarly, Mazzotta and Caragiuli[16] reported a statistically significant intraoperative reduction in corneal thinnest point value with optical coherence tomography during CXL procedure using standard riboflavin with 20% dextran. Recently, Rechichi et al.[17] reported the results of intraoperative corneal pachymetry of 30 patients undergoing accelerated CXL with HPMC and reported a non- significant intraoperative corneal thickness reduction in this group. Oltulu et al [18] compared the corneal thickness changes during surgery using riboflavin with dextran (n:13) or HPMC (n: 14) and reported that using HPMC solution resulted in a steady increase in the corneal thickness during the CXL procedure, as opposed to riboflavin with dextran. In our study, we wanted to see these variations in corneal thickness during surgery persist or not after postoperative period between riboflavin with dextran group or HPMC group but we did not determine any differences regarding the corneal thickness in 12 months of follow-up and also we have reported significantly reduced corneal thickness in both groups after CXL. Although there was a little more corneal thinning in riboflavin with dextran group in the 1st month of follow up, it came closer to the same levels with the HPMC group after the 12 nd month of postoperative period. However In the study of Thorsrud et al., after CXL using riboflavin with dextran and HPMC, they showed that corneal thickness was higher in HPMC group in the 1st month.[19]

Some of the complications of CXL have been reported in literature including corneal haze, permanent scars, and secondary infections after the procedure.[20-21-22] Raiskup et al.[23] determined the prevalence of clinically significant stromal haze as 8.6% at 1 year after CXL on 163 eyes and they also defined the advanced keratoconus as a risk factor in haze development after CXL. Greenstein et al.[24] reported that the CXL associated corneal haze was greatest at 1st month, plateaued at 3rd month, and was significantly decreased between 3rd month and 12th month. Similarly, in our study, in both groups the biomicroscopic findings reported in 1st month significantly improved in 6th month of follow-up in many of the patients. Ring like haze was the most common biomicroscopic finding in both groups in 1st month of follow up that disappeared in all cases in 6th month of follow up. On the other hand, transparent cornea was determined in more than 93% of patients in both groups, on the 12th month of follow-up. This study showed no difference in terms of complication rate between the 2 riboflavin groups after the early postoperative period. If we consider that there is a relationship between the postoperative thickness of the cornea and the complication

rate, this lack of difference between the two groups may be associated with the similar effect of these two photosensitizer on corneal thickness.

Low number of patients and lack of contrast sensitivity assessment is the main limitation of this study; moreover, 12 months of follow-up is not a very long time period.

CONCLUSION

Accelerated CXL is an effective treatment method in keratoconus. The procedure performed by using riboflavin with dextran or HPMC as photosensitizer represents similar affects in corneal parameters during the 12 months of follow-up period. Larger studies with longer follow-up periods are warranted to define the differences and similarities of these two treatment methods.

Disclosure of interest

The authors report no conflicts of interest.

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