Original Article

The Effect of Topical Betamethasone Eye Drops on Postoperative Haze among Patients Undergoing Corneal Collagen Cross-Linking: a Randomized, Double Blind Placebo Controlled Study

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Abstract

Objective: To evaluate the effect of topical betamethasone eye drops on postoperative haze among patients undergoing corneal collagen cross-linking (CXL).

Patients and Methods: Patients with mild to moderate keratoconus, aged 18 to 30 years, who were a candidate for CXL treatment and had the evidence of disease progression based on topographic findings entered the present study. One eye of each patient randomly received betamethasone and topical antibiotics after CXL and the other eye received topical antibiotics and placebo in place of betamethasone. The eyes were compared regarding BCVA, UCVA, refraction, keratometric and pachymetric findings using Pentacam, as well as changes of corneal haze using confocal microscopy, before CXL as well as one month and six months after CXL.

Results: There was no difference in BCVA, UCVA, refraction, keratometric and pachymetric findings between the two groups before and six months after surgery. Based on confocal findings, the difference in light reflectance intensity between the case and control groups was statistically significant in anterior (P = 0.021) and posterior (P = 0.017) corneal stroma one month postoperatively, indicating higher haze in the placebo group. This difference was also statistically significant in anterior (P = 0.001) mid (P = 0.002) and posterior (P = 0.002) stroma six months postoperatively.

Conclusion: Betamethasone had no effect on visual acuity, refraction, keratometric and pachymetric findings six months after CXL. It reduced corneal haze in both the first and the sixth months postoperatively.

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Introduction

Keratoconus is a bilateral, non-inflammatory, progressive disease characterized by thinning of the cornea, irregular astigmatism and decreased vision [1]. The incidence of the disease is one in 2,000 and seems to be higher in Asian countries [2,3]. Although the exact cause of keratoconus is not known, gradual biomechanical weakening of the cornea secondary to corneal collagen structural changes, extracellular matrix changes, and apoptosis have been suggested as the probable mechanisms [4-6]. Involvement of patients with keratoconus in the second decade of life has a significant negative impact on their quality of life [7]. Various treatments have been proposed to control the progress of the disease and improve the patients' vision, including the use of hard contact lenses, corneal inserts and corneal transplant surgery [8,9]. A relatively new method of treatment is corneal collagen cross-linking (CXL). CXL which was introduced in 2003 by Wollensak et al., [10] modifies the mechanical properties of the cornea by using riboflavin and UV rays to create covalent bonds in the corneal stroma and increase the number of collagen bands between the strands [11]. This technique has been shown to affect corneal ectasia and to stop or even reverse its progression [12,13]. However, as with other surgical procedures, this treatment may cause some short or long term complications, such as corneal haze, corneal scar, endothelial destruction, treatment failure, sterile infiltration, and reactivation of herpes infection [7,14].

Topical treatments are used after many eye surgeries to relieve pain and inflammation, and to reduce the chance of potential complications. The use of topical corticosteroid eye drops is effective in controlling anterior segment inflammation by reducing cell infiltration, capillary dilatation, fibroblast proliferation, collagen deposition, and scarring [15]. Corticosteroid eye drops have also been shown to be useful in reducing post surgical haze in refractive surgical procedures like photorefractive keratectomy (PRK) [16,17]. Traditionally corticosteroid eye drops have been used to reduce postoperative haze in patients undergoing CXL, but in our search of English literature we did not find any previous studies evaluating its effect on post CXL haze. The present study was performed to evaluate the effect of topical betamethasone eye drops on postoperative haze among patients undergoing corneal collagen cross-linking (CXL).

Patients and Methods

This randomized, double blind, placebo controlled clinical trial included keratoconus patients referred to Torfeh Eye Hospital and Imam Hossein Medical Center, Tehran, Iran. The study was approved by the ethics committee of Shahid Beheshti University of Medical Sciences and all patients gave written consent before entering the study. The inclusion criteria were proven mild and moderate keratoconus with Kmax of less than 55 diopters, age of 18 to 30 years, BCVA of 8/10 or worse, topographic evidence of keratoconus progression such as an increase of more than 1 diopter in maximum keratometry or manifest cylinder or an increase of more than 0.5 diopter in spherical refraction over the past year, and corneal thickness of at least 400 µm. Patients with a corneal thickness of less than 400 µm, any history of eye surgery, ocular inflammation, poor epithelium repair, infection and herpetic keratitis, severe corneal scarring or opacity, neurotrophic keratopathy and severe dry eye where excluded from the present study. Also those patients with a history of systemic disease such as diabetes

and autoimmune diseases, recent contact lens use in the past 6 weeks, and pregnancy were excluded from the study. Patients who were currently using corticosteroids or had used corticosteroids in last six months for any medical condition were also excluded.

In the present study the right and left eye of the same patients randomly received either betamethasone eye drops 0.1 % (Pharmaceutical Distribution Company of Iran) as drug or Sno Tears 1.4 % eye drops (Bausch & Lomb, United Kingdom) as placebo. The drug and placebo were labeled in similar bottles by someone other than the project associates based on a randomization table.

In the pre-CXL examination, the visual acuity of patients (UCVA and BSCVA) was assessed using the visual acuity chart recommended by the Early Treatment Diabetic Retinopathy Study (ETDRS) and recorded as the logarithm of minimal angle of resolution (LogMAR). Refraction, slit lamp and fundoscopy exams were performed for all patients and intraocular pressure was measured using Goldman tonometry. Corneal topographic and pachymetry parameters were measured and recorded using a Pentacam device. Also a confocal scan of the cornea was performed to evaluate the corneal haze.

CXL surgery

After receiving a local anesthetic drop (0.5 % tetracaine) the central corneal epithelium was mechanically removed (8-9 mm) in sterile conditions and riboflavin 0.1 % eye drop was applied every 5 minutes for 30 minutes before receiving UVA radiation. Then, the UVA (mean wave length 365 ± 10 nm, 9 mW / cm 2) was delivered for 10 minutes from a 5 cm distance using a Schwind CXL-365 Vario system (SCHWIND eye-tech-solutions GmbH & Co., Kleinostheim, Germany). During the UVA radiation riboflavin 0.1 % eye drop was applied every 2.5 minutes. After completion of radiation exposure patients received topical antibiotics (0.5 % chloramphenicol), and extended-wear lenses were applied. The same procedure was repeated for both eyes.

Post surgical treatment and exams

At this stage, two identical bottles containing either betamethasone or placebo, which were randomly assigned for the right or left eye based on a randomization table, were given to the patient by a non-physician. In this way patients and the physician were unaware of which eye is receiving the drug or the placebo. These eye drops were used by patients for 25 days post surgery as follow: first 5 days every 4 hours, second 5 days every 6 hours, third 5 days every 8 hours, fourth 5 days every 12 hours, and fifth 5 days, every 24 hours. All patients also received topical antibiotic (Chloramphenicol) every 8 hours in both eyes until one day after removal of the dressing lens. Artelac Advanced Eye Drop (UK by Bausch & Lomb, UK) was also used as needed.

All patients underwent slit lamp exam one day after surgery and were re-examined 3 or 4 days after surgery. These exams were repeated weekly for the first month, every two weeks for the second month and then monthly from the third to the sixth month. In these exams patients were monitored for possible complications. Visual acuity (UCVA, BCVA), corneal topographic and pachymetry parameters as well as refraction were also assessed in the first and sixth months post surgery. Corneal haze was assessed and recorded in the first and sixth months using confocal microscopy.

In all postoperative exams close attention was given to identify possible complications of

not receiving betamethasone including severe corneal haze. If this occurred patients would be dropped from the study and treated for haze.

Sample size calculation and statistical methods

The sample size was calculated as 42 eyes in each group to detect a 10 percent difference in haze formation between the case and control groups with a type I error of 5 % and power of 90 %. The data was described as mean, standard deviation, median, range, frequency and percentage. Baseline values between the two groups were compared using paired sample t-test. Post operation values were compared when adjusted for the baseline using generalized estimating equation (GEE). SPSS version 20 (Armonk, NY: IBM Corp.) statistical program was used to analyze the results. P values less than 0.05 were considered statistically significant.

Results

A total of 43 patients with keratoconus who met the inclusion and exclusion criteria were included in the present study, of whom 23 were male (53.3 %) and 20 were female (46.5 %), with a mean age of 25 ± 4 years (Table 1).

According to the randomization table, 24 patients (55.8 %) used topical betamethasone after CXL in the right eye and placebo (artificial tears) in the left eye, and 19 patients (44.2 %) used topical betamethasone in the left eye and placebo (artificial tears) in the right eye (Table 1).

The mean uncorrected visual acuity (UCVA) in betamethasone treated and placebo treated eyes prior to CXL treatment was 0.71 ± 0.41 LogMAR and 0.74 ± 0.4 LogMAR respectively, indicating no significant difference between the two groups (Table 2). In the first month after CXL treatment, the UCVA in the betamethasone group and the placebo recipient group was 0.8 ± 0.43 LogMAR and LogMAR 0.79 ± 0.41 respectively, indicating no significant difference (Table 2). Also no significant difference in UCVA was observed in the third and sixth months (Table 2).

Table 1: The demographic findings of patients entering the study

Parameter		Value
Age	Mean ± SD	25 ± 4
	Median (range)	25 (18 to 30)
Sex	M	23 (53.5 %)
	F	20 (46.5 %)
Eye receiving betamethasone	OD	24 (55.8 %)
	OS	19 (44.2 %)

Similarly according to table 2 there was no statistically significant difference between the case and control groups regarding the BCVA, sphere, cylinder, spherical equivalent (SE), Kmin, Kmax, KImean and pachymetry readings either before treatment or 1 and 6 months after treatment.

The amount of light reflectance intensity at three levels of anterior, middle and posterior stroma according to confocal scan findings, as an indicator of haze, are shown in table 3.

As can be observed in table 3 there was no statistically significant presurgical difference of light reflectance intensity between the case and control groups in any level of corneal stroma.

One month postoperatively the difference in light reflectance intensity between the case and control groups was statistically significant in anterior (P = 0.021) and posterior (P = 0.017) corneal stroma indicating higher haze in the

Table 2: The comparison of visual findings before treatment as well as one and six months after treatment between the case and control groups

Parameter	Time	Group		Difference	95% CI		P value*
		Betamethasone	Placebo	Mean ± SD	Lower	Upper	
UCVA (LogMAR)	Before	0.71 ± 0.41	0.74 ± 0.4	- 0.03 ± 0.29	- 0.12	0.06	0.505
	1 month	0.8 ± 0.43	0.79 ± 0.41	0 ± 0.29	- 0.09	0.10	0.966
	6 months	0.73 ± 0.41	0.75 ± 0.42	- 0.02 ± 0.28	- 0.11	0.07	0.631
BCVA (LogMAR)	Before	0.25 ± 0.16	0.24 ± 0.18	0 ± 0.21	- 0.06	0.07	0.882
	1 month	0.28 ± 0.2	0.26 ± 0.22	0.01 ± 0.24	- 0.06	0.09	0.705
	6 months	0.22 ± 0.16	0.22 ± 0.19	0 ± 0.2	- 0.06	0.07	0.934
Sphere	Before	- 2.17 ± 1.93	- 1.98 ± 1.74	- 0.19 ± 1.79	- 0.75	0.36	0.491
	1 month	- 2.48 ± 2.01	- 2.09 ± 1.72	- 0.39 ± 1.54	- 0.88	0.10	0.119
	6 months	- 2.48 ± 1.99	- 2.11 ± 1.73	- 0.38 ± 1.5	- 0.85	0.10	0.121
Cylinder	Before	- 2.18 ± 1.41	- 2.47 ± 1.58	0.29 ± 1.65	- 0.22	0.80	0.257
	1 month	- 2.13 ± 1.44	- 2.54 ± 1.77	0.41 ± 1.39	- 0.03	0.86	0.068
	6 months	- 2.26 ± 1.48	- 2.6 ± 1.77	0.34 ± 1.53	- 0.15	0.83	0.164
SE	Before	- 3.26 ± 2.08	- 3.22 ± 2.13	- 0.05 ± 2.17	- 0.72	0.63	0.892
	1 month	- 3.55 ± 2.11	- 3.37 ± 2.07	- 0.18 ± 1.81	- 0.76	0.40	0.530
	6 months	- 3.61 ± 2.06	- 3.41 ± 2.06	- 0.2 ± 1.84	- 0.79	0.39	0.489
Kmin	Before	44.3 ± 2.8	44.3 ± 2.5	0.03 ± 2.46	- 0.73	0.79	0.934
	1 month	44.4 ± 2.8	44.2 ± 2.5	0.18 ± 2.35	- 0.57	0.93	0.630
	6 months	44.3 ± 2.8	44.1 ± 2.4	0.18 ± 2.33	- 0.56	0.93	0.622
Kmax	Before	47.6 ± 3.4	47.4 ± 3.3	0.16 ± 3.33	- 0.87	1.18	0.755
	1 month	47.6 ± 3.5	47.4 ± 3.2	0.15 ± 2.97	- 0.80	1.10	0.747
	6 months	47.5 ± 3.5	47.4 ± 3.2	0.15 ± 2.98	- 0.80	1.10	0.752
Kmean	Before	45.8 ± 2.9	45.7 ± 2.7	0.11 ± 2.64	- 0.70	0.92	0.786
	1 month	45.9 ± 2.9	45.7 ± 2.6	0.18 ± 2.5	- 0.61	0.98	0.642
	6 months	45.8 ± 3	45.6 ± 2.6	0.21 ± 2.53	- 0.60	1.02	0.602
Pachymetry	Before	474 ± 74	486 ± 42	- 11.21 ± 84.07	- 37.08	14.66	0.387
	1 month	480 ± 34	476 ± 43	3.1 ± 31.56	- 6.99	13.19	0.538
	6 months	484 ± 35	482 ± 42	1.65 ± 30.43	- 8.08	11.38	0.734

Before: Before surgery; 1 month: One month after CXL; 6 months: Six months after CXL

*Based on paired sample t-test when comparing baseline values between two groups and generalized estimating equation when comparing post operation values (GEE)

placebo group. Six months postoperatively the difference in light reflectance intensity between the case and control groups was statistically significant in anterior (P = 0.001) mid (P = 0.002) and posterior (P = 0.002) corneal stroma, also indicating higher haze in the placebo group.

Discussion

In the present study, the effect of betamethasone on postsurgical haze in eyes with mild to moderate keratoconus was evaluated.

The average age of patients included in this study was 25 years, which is in line with the results of other epidemiological studies

Table 3: Light reflectance intensity at three levels of anterior, middle and posterior stroma according to confocal scan findings in the case and control groups

Parameter	Time	Group		P value*
		Betamethasone	Placebo	
Anterior stroma	Before CXL	65.8 ± 13	69.7 ± 20.1	0.178
	1 month after CXL	118.7 ± 31.3	140.7 ± 63.8	0.021
	6 months after CXL	66.3 ± 12.2	78.6 ± 23.6	0.001
Mid stroma	Before CXL	45.8 ± 8.3	46.3 ± 6.8	0.564
	1 month after CXL	55.7 ± 16.6	60.7 ± 23.7	0.073
	6 months after CXL	46.6 ± 7.3	50.6 ± 9.6	0.002
Posterior stroma	Before CXL	69 ± 7.6	70.2 ± 7.4	0.282
	1 month after CXL	76.6 ± 14.9	81.5 ± 18.5	0.017
	6 months after CXL	68.5 ± 8.2	73.2 ± 9.7	0.002

* Based on paired sample t-test when comparing baseline values between two groups and generalized estimating equation (GEE) when comparing post operation values

regarding the age of keratoconus, indicating the highest prevalence of disease in the third decade of life [8]. The percentage of male patients enrolled in the present study (53.5 %) was slightly higher than female patients (46.5 %), although this difference was not statistically significant.

In our study, the increase in BCVA was 0.03 ± 0.06 and 0.02 ± 0.06 in eyes receiving betamethasone and placebo respectively, indicating no difference between the two groups regarding the improvement in BCVA. Wisse et al.,[18] in their study aimed at investigating the visual acuity predictors after receiving CXL treatment reported a mean improvement in BCVA of 0.13 LogMAR after one year of follow up. This improvement in another study by Lamy et al., [19] with a two years follow up was 0.16 LogMAR. The difference in the rate of patients' vision improvement in this study compared to other studies is probably due to the shorter follow-up period and indicates the need for further follow-up.

In the present study based on confocal findings, a significant increase in light reflectance intensity indicating increased haze was observed in the first month after CXL in both betamethasone and placebo groups and then the haze subsided at 6 months postoperatively. Similarly in a study by Greenstein et al., [20] corneal opacity showed an increase at one month after CXL and then decreased after 6 months. We observed the highest opacity at the anterior stroma followed by the posterior and mid stromal levels.

In the present study the difference in light reflectance intensity between the case and control groups was statistically significant in anterior and posterior corneal stroma one month postoperatively, indicating higher haze in the placebo group. This difference was also statistically significant in anterior, mid and posterior corneal stroma six months postoperatively. These findings indicate the usefulness of betamethasone eye drops in reducing the haze formation after CXL surgery in short term. We recommend similar studies with longer follow up to find if the effect of

betamethasone in reducing haze after CXL is still significant after longer follow up periods. To our knowledge the present study is the first study evaluating the effect of betamethasone eye drops in reducing the post CXL haze formation in English literature. One of the strengths of the present study was evaluating the haze based on confocal microscopy, which is a quantitative and accurate method, instead of simple slit lamp examination of the cornea by the examiner. This enabled a more accurate comparison of haze between the case and control groups.

Conclusion

Betamethasone had no effect on visual acuity, refraction, keratometric and pachymetric findings six months after CXL. It reduced corneal haze in both the first and the sixth months postoperatively.

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References

1. Vazirani J, Basu S. Keratoconus: current perspectives. Clin Ophthalmol. 2013;7:2019-30.
2. Gomes JA, Tan D, Rapuano CJ, Belin MW, Ambrósio Jr R, Guell JL, et al. Global consensus on keratoconus and ectatic diseases. Cornea. 2015;34(4):359-69.
3. Kok YO, Tan GF, Loon SC.Review: keratoconus in Asia. Cornea. 2012;31(5):581-93.
4. Radner W, Zehetmayer M, Skorpik C, Mallinger R. Altered organization of collagen in the apex of keratoconus corneas. Ophthalmic research. 1998;30(5):327-32.
5. Daxer A, Fratz P. Collagen fibril orientation in the human corneal stroma and its implication in keratoconus. Invest Ophthalmol Vis Sci. 1997;38(1):121-9.
6. Olivares Jiménez JL, Guerrero Jurado JC, Bermudez Rodriguez FJ, Serrano Laborda D. Keratoconus: age of onset and natural history. Optom Vis Sci. 1997;74(3):147-51.
7. Razmjoo H, Rahimi B, Kharraji M, Koosha N, Peyman A. Corneal haze and visual outcome after collagen crosslinking for keratoconus: A comparison between total epithelium off and partial epithelial removal methods. Adv Biomed Res. 2014;3:221.
8. Colin J, Velou S. Current surgical options for keratoconus. J Cataract Refract Surg. 2003;29(2):379-86.
9. Samaras KE, Lake DB. Corneal collagen cross linking (CXL): a review. Int Ophthalmol Clin. 2010;50(3):89-100.
10. Wollensak G, Spoerl E, Seiler T. Riboflavin/ ultraviolet-a-induced collagen crosslinking for the treatment of keratoconus. Am J Ophthalmol. 2003;135(5):620-7.
11. Abdolahian M, Zolghadr GH. Corneal Collagen Crosslinking for Treatment of Keratoconus. Journal of Ophthalmic and Optometric Sciences. 2017;1(4):8-14.
12. Wollensak G. Crosslinking treatment of progressive keratoconus: new hope. Curr Opin Ophthalmol. 2006;17(4):356-60.
13. Nassiri N, Azemati A. The Use of Corneal Cross-linking in Treatment of Progressive Keratoconus: a Review. Journal of Ophthalmic and Optometric Sciences. 2017;1(4):15-21.
14. Dhawan S, Rao K, Natrajan S. Complications of corneal collagen cross-linking. J Ophthalmol. 2011;2011:869015.
15. Pleyer U, Ursell PG, Rama P. Intraocular pressure effects of common topical steroids for post-cataract

inflammation: are they all the same?. Ophthalmol Ther. 2013;2(2):55-72.
16. Nien CJ, Flynn KJ, Chang M, Brown D, Jester JV. Reducing peak corneal haze after photorefractive keratectomy in rabbits: prednisolone acetate 1.00% versus cyclosporine A 0.05%. J Cataract Refract Surg. 2011;37(5):937-44.
17. Vetrugno M, Maino A, Quaranta GM, Cardia L. The effect of early steroid treatment after PRK on clinical and refractive outcomes. Acta Ophthalmol Scand. 2001;79(1):23-7.
18. Wisse RP, Godefrooij DA, Soeters N, Imhof SM, Van der Lelij A. A multivariate analysis and statistical model for predicting visual acuity and keratometry one year after cross-linking for keratoconus. Am J Ophthalmol. 2014;157(3):519-25.
19. Lamy R, Netto CF, Reis RG, Procopio B, Porco TC, Stewart JM, et al. Effects of corneal cross-linking on contrast sensitivity, visual acuity, and corneal topography in patients with keratoconus. Cornea. 2013;32(5):591-6.
20. Greenstein SA, Fry KL, Bhatt J, Hersh PS. Natural history of corneal haze after collagen crosslinking for keratoconus and corneal ectasia: Scheimpflug and biomicroscopic analysis. J Cataract Refract Surg. 2010;36(12):2105-14.

Footnotes and Financial Disclosures

Conflicts of Interest:

The authors have no conflict of interest with the subject matter of the present manuscript.