

Research Article

Our experience with Athens protocol - simultaneous topo-guided photorefractive keratectomy followed by corneal collagen cross linking for keratoconus

Shreyas Shah*, Sujatha Mohan, Mohan Rajan, Bina John, Vini Badlani

Rajan Eye Care Hospital Pvt. Ltd, No. 5, Vidyodaya 2nd Street, T. Nagar, Chennai- 600017, India

Received: 25 May 2016

Accepted: 02 June 2016

*Correspondence:

Dr. Shreyas Shah,

E-mail: shreyas091@gmail.com

Copyright: © the author(s), publisher and licensee Medip Academy. This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License, which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

ABSTRACT

Background: Corneal collagen cross linking (CXL) has become an established modality of treatment for progressive Keratoconus. Aim of the study was to analyze visual outcome, refractive status and changes in corneal curvature following simultaneous topography-guided photorefractive keratectomy (PRK) followed by corneal collagen cross-linking with riboflavin (C3R) for keratoconus in a tertiary eye care hospital.

Methods: All patients underwent manifest refraction, uncorrected visual acuity (UCVA), Best corrected visual acuity (BCVA), slit lamp examination, corneal topography, ultrasound pachymetry and fundus evaluation pre operatively. 39 eyes of 27 patients with keratoconus underwent simultaneous topo guided PRK + CXL were followed up upto 6 months.

Results: Mean UCVA improved from 0.81 log mar units pre-operatively to 0.43 log mar units at the end of 6 months. Preoperative BCVA was maintained or improved in 37 eyes (94.87%) and BCVA decreased by more than 1 line in 2 eyes (5.12%) post-operatively. The mean BCVA improved from 0.2 log mar units pre-operatively to 0.1 log mar units at the end of 6 months. The mean preoperative manifest refraction spherical equivalent reduced from $-3.1 \pm 2.3D$ to $-1.4 \pm 1.3D$ postoperatively. The mean steepest K reading decreased from $47.8 \pm 4.2D$ pre-op to $45 \pm 3.3D$ at the end of 6 month. Similarly, mean flat keratometry readings reduced significantly from $44.8 \pm 3.5D$ preoperatively to $42.2 \pm 2.8D$ at the last follow-up visit postoperatively.

Conclusions: Combined topo-guided PRK+CXL is an effective approach in treating patients with keratoconus. It biomechanically stabilizes the cornea, improves the corneal contour, reduces irregular astigmatism and offers a better quality of vision.

Keywords: PRK, Zernike compensation, Athens protocol, Corneal collagen cross linking with riboflavin

INTRODUCTION

Corneal collagen cross linking (CXL) has become an established modality of treatment for progressive keratoconus.¹⁻³ It is a minimally invasive technique which stabilizes the cornea and successfully halts the progression of keratoconus.⁴⁻⁵ However, it does not help with the visual rehabilitation in patients with keratoconus. Certain clinical studies have reported that the combined

use of corneal collagen cross linking (CXL) along with topography-guided photorefractive keratectomy (PRK) gives superior visual rehabilitation in patients with keratoconus.^{6,7} The combined procedure stabilizes the cone and it makes the cornea more regular and also helps in better contact lens fitting.

Kymionis et al reported that in simultaneous technique, where topo guided PRK was followed by CXL in 14 eyes

with progressive keratoconus, the treatment procedure was found to be effective.⁶

In response to these outcomes, Kanellopoulos et al proposed same-day simultaneous topography-guided PRK and CXL as a therapeutic intervention in patients with keratoconus.⁷ In this technique, called the *Athens protocol*, CXL is performed immediately after topography-guided PRK.

Kanellopoulos et al compared and reported that performing simultaneous topography-guided PRK and cross-linking on the same day was more effective than sequential cross-linking and PRK in cases with progressive keratoconus.⁷ Based on the rationale of the article by Kanellopoulos, we performed a prospective, nonrandomized, interventional study on 39 eyes of 27 patients with keratoconus who were subjected to simultaneous photorefractive keratectomy followed by corneal collagen cross linking with riboflavin on the same day (Athens protocol).

METHODS

In present prospective nonrandomized study, the long-term results of topography guided PRK followed by simultaneous CXL was recorded. A total of 39 eyes of 27 patients (16 women, 11 men) underwent simultaneous Photorefractive keratectomy followed by corneal collagen cross linking with riboflavin at Rajan eye care hospital (tertiary eye care hospital), Chennai, India between December 2012 and June 2014 by a single surgeon.

All patients who had clinical and topographic evidence of Keratoconus were included in the study. Patients who were older than 18 years and had thinnest pachymetry of >400 µm were included. Patients with recurrent corneal infection, corneal thinning or ectasia due to any cause other than keratoconus, corneal thickness <400µm, past history of corneal surgery, central corneal scars and pregnant or lactating women were excluded from the study.

Clinical evaluation

Each patient underwent measurement of uncorrected visual acuity (UCVA), refraction, and best corrected visual acuity (BCVA) which was recorded using Snellen visual acuity testing. BCVA and UCVA were converted to log MAR scale values for the purpose of comparison.

A slit lamp biomicroscopic examination was performed in all patients who invariably confirmed the presence of Keratoconus either by presence of Fleischer ring, central or paracentral corneal thinning, Vogt's striae and/or Munson's sign. Intra ocular Pressure was measured using Goldmann applanation tonometer and dilated fundus examination was done in all patients. Corneal topography was performed using topolyzer, (WaveLight Laser

Technologie AG, Erlangen, Germany). The following parameters were analyzed;

- Km- It characterizes the mean corneal curvatures in central 3mm area.
- Ks- It characterizes steepest meridian of the cornea in central 3mm area.
- Kf- It characterizes flattest meridian of the cornea in the central 3mm area.

For present study, keratoconus was classified on the basis of K readings into following categories using the criteria adopted in the collaborative longitudinal evaluation of keratoconus (CLEK) study⁸:-

- Mild: K Reading <48.00 D
- Moderate: K = 48-52.00 D
- Severe: K >52.00 D

Surgical procedure

A written consent was obtained according to the Declaration of Helsinki and institutional guidelines. All the procedures were performed by a single surgeon. The proprietary software in Wavelight Customized platform utilizes topographic data from Topolyzer.

The software utilizes data from eight topographies from Topolyzer and averages the data. Thus it enables the surgeon to adjust the desired post-operative corneal asphericity (chosen as zero in all cases). The software also provides the option of including tilt correction. "No Tilt" option was chosen in all cases. Zernike compensation was done in all patients to match defocus (C4) and spherical aberration (C12) keeping the refractive correction as zero. Once the adjustment of sphere, cylinder and axis was done, the treatment zone was kept at 5.5 mm in all cases. After placing the lid speculum and anaesthetizing the eye topically, the epithelium was removed by using 20% ethanol. Then the partial topography guided PRK laser treatment was done. The plan was to treat 70% of cylindrical and spherical component so as not to exceed 50µm of stromal removal. The value of 50µm as maximum ablation depth as suggested by Kanellopoulos in Athens protocol was chosen. This laser treatment was followed by corneal collagen crosslinking with riboflavin.

Corneal collagen cross linking with riboflavin

The photosensitizer, 0.1% isotonic riboflavin solution (10 mg of riboflavin-5-phosphate in 10 mL of dextran-T-500 20% solution) was applied to the de-epithelialized cornea every 3 minutes for 30 minutes. The irradiating source emitting UVA light of approximately 370 nm wavelength and 9 mW/cm² radiance at 2.5 cm was projected onto the surface of the cornea for 30 minutes placed 5 cm away from the center of the cornea. As a safety feature, the output energy intensity was checked prior to each treatment using the UV light meter that is delivered with

the system. During irradiation treatment, a drop of riboflavin solution was applied every 3 minutes to sustain the necessary concentration of riboflavin and prevent desiccation of the cornea. The cornea was kept moist with a drop of balanced salt solution every 2 minutes.

Follow up

All patients reported some degree of pain during the first day after treatment. Re-epithelialization occurred within 4 days in all patients. All cases were followed up after 1 week, 3 months and 6 months and evaluated for UCVA, BCVA, manifest refraction, keratometry (Kf, Ks, Km) topographical profile. These parameters were retrospectively collected and then statistically analyzed using paired *t* test.

Statistical analysis

Geometric visual acuity was converted to the logarithm of the minimum angle of resolution (logMAR) units, and manifest refraction was converted to manifest refraction spherical equivalent (MRSE). The Paired t-test was used to compare the logMAR visual acuity (UCVA and BCVA), MRSE, and corneal keratometry values before and after the procedure. Statistical analysis was performed using MS Excel and SPSS 20 (IBM, Armonk, NY), and a P value of <0.05 was considered significant. All the values presented statistically significant differences between preoperative and postoperative period of six months.

RESULTS

39 eyes of 27 patients (16 women, 11 men) with keratoconus were evaluated and underwent simultaneous topo guided PRK + CXL in our prospective, nonrandomized, non-controlled clinical study. No

complications, such as chronic epithelial defects, haze or infectious keratitis were reported throughout the postoperative follow-up period in the study population.

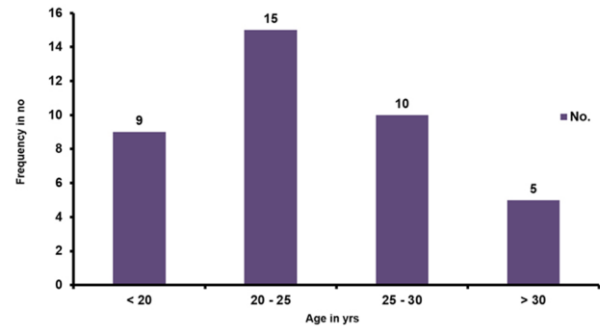


Figure 1: Age distribution.

No ocular or systemic adverse events were observed after the treatment. The age distribution in our study showed that the maximum numbers of patients (15) were in the 20-25 years age group (Figure 1) and the gender distribution in our study showed females having a higher preponderance.

Uncorrected visual acuity (UCVA)

The preoperative and postoperative (at the end of 1 week, 3 month and 6 months) uncorrected visual acuity (UCVA), expressed as logarithm of minimum angle of resolution (log MAR), were compared which showed a significant improvement in post-operative UCVA (0.8±0.3 log MAR units preoperatively to 0.4±0.2 log MAR units post operatively after 6 months follow up) (p=0.00) (Table1).

Table 1: Uncorrected visual acuity (UCVA).

	Pre-op	Post-op (1 week)	Post-op (3 months)	Post-op (6 months)
UCVA	0.8±0.3	0.6±0.3	0.5±0.3	0.4±0.2

Best corrected visual acuity (BCVA)

The preoperative and postoperative (at the end of 1 week, 3 month and 6 months) Best Corrected Visual acuity, expressed as logarithm of minimum angle of

resolution (log MAR) , were compared which showed a significant improvement in post-operative BCVA (0.2±0.1 log MAR preoperatively to 0.1±0.1 log MAR postoperatively after 6 months of follow up) (p≤0.05) (Table 2).

Table 2: Best corrected visual acuity (BCVA).

	Pre-op	Post-op (1 week)	Post-op (3 months)	Post-op (6 months)
BCVA	0.2±0.1	0.1±0.1	0.1±0.31	0.1±0.1

Manifest refraction spherical equivalent (MRSE)

The spherical equivalent of a prescription is equal to algebraic sum of the sphere and half the cylindrical value. Manifest refractive spherical equivalents and the values were compared pre operatively and at subsequent visits postoperatively. The results showed that there was a reduction in the MRSE post operatively and it was statistically significant. (-3.1±2.3 diopters (D) pre operatively to -1.4±1.3 diopters (D) at the last follow up (P<0.05) (Table 3).

Steepest keratometry value (Ks)

The steepest keratometry value (Ks) determined from the corneal topography maps was analyzed pre-operatively and post-operatively (at the end of 1 week, 3 months and 6 months). The result showed significant decrease in the steep keratometry value in the post-operative visits (P<0.05) (Table 4).

Table 3: Manifest refraction spherical equivalent (MRSE).

	Pre-op	Post-op (1 week)	Post-op (3 months)	Post-op (6 months)
MRSE	-3.1±2.3	-2.2±1.7	1.8±1.5	-1.4±1.3

Table 4: Steepest keratometry value (Ks).

	Pre-op	Post-op (1 week)	Post-op (3 months)	Post-op (6 months)
Ks	47.8±4.2	46.9±3.7	45.6±3.3	45±3.3

Table 5: Flattest keratometry value (Kf).

	Pre-op	Post-op (1 week)	Post-op (3 months)	Post-op (6 months)
Kf	44.8±3.5	43.9±3	43±2.6	42.2±2.8

Flattest keratometry value (Kf)

The flattest keratometry value (Kf) determined from the corneal topography maps was analyzed pre-operatively and post-operatively (at the end of 1 week, 3 months and 6 months). The result showed significant decrease in the flattest keratometry value in the post-operative visits (P<0.05) (Table 5).

Mean keratometry value (Km)

The mean keratometry value (Km) determined from the corneal topography maps was analyzed pre-operatively and post-operatively (at the end of 1 week, 3 months and 6 months). The result showed significant decrease in the mean keratometry value in the post-operative visits (P<0.05) (Table 6).

Table 6: Mean keratometry value (Km).

	Pre-op	Post-op (1 week)	Post-op (3 months)	Post-op (6 months)
Km	46.3±3.7	45.3±3.1	44.4±2.8	43.6±2.9

DISCUSSION

Keratoconus can be graded depending upon the extent of steepness of greatest curvature into mild (<48D), moderate (48-52D) and severe (>52D).⁹ In present study, majority of the patients (54%) fell into the mild category followed by moderate (36%), while only 10% patients had severe degree of keratoconus. The visual acuity, refractive and topographic outcomes of the PRK plus CXL procedure in eyes diagnosed with keratoconus over a follow-up of 6 months was investigated. Present results correlate with the data published by different research

groups. Study conducted by Giovanni Alessio et al¹⁰, showed that the uncorrected distance acuity improved significantly, from a mean±standard deviation of 0.63±0.36 logarithm of the minimal angle of resolution (log MAR) units to 0.19±0.17 log MAR units (P<0.05) and best distance acuity from 0.06 ± 0.08 log MAR to 0.03±0.06 log MAR (P<0.05).

Similarly, in the work conducted by Kymionis et al, the mean spherical equivalent preoperatively was -2.3±2.8 D, which was reduced significantly (P <0.001) to -1.08±2.41 D at the last post-operative follow-up examination.⁶

Kymionis GD et al also demonstrated in their study that that the mean steep and flat keratometry readings were reduced by 2.35 ($P < 0.001$) and 1.18 ($P = 0.013$) respectively at the last follow-up examination.⁶

Same-day was elected to perform simultaneous topography-guided PRK and CXL procedures in our study to reduce the morbidity of the patients. T-PRK not only flattens the corneal apex but simultaneously flattens an arcuate, broader area of the cornea away from the cone similar to a hyperopic ablation. The ablation causes some amount of steepening adjacent to the cone and effectively normalizes the cornea.

The cornea post PRK becomes flatter and less irregular in keratoconic eyes. The biomechanical stability is increased by cross linking. Removing the Bowman's layer with T-PRK followed by CXL facilitates the penetration of riboflavin into the corneal stroma in eyes with keratoconus thus enhancing cross linking.

If topography-guided PRK is performed after CXL, some portion of the cross-linked anterior cornea needs to be removed which may reduce the benefits of performing CXL.

One of the limitations of this study is that it was based on topographic data as an indirect clinical measure of the stability of the PRK plus CXL treatment over time, rather than on the knowledge of individual biomechanical corneal properties. But for obvious practical reasons, it is not feasible to measure biomechanical properties of the cornea directly with the current technological knowledge.

Another limitation of present study was the lack of control group. The existence of a control group could facilitate the comparison between CXL alone and topography-guided PRK followed by CXL. Therefore, larger, prospective and randomized, comparative studies, establishing the safety and efficacy of this treatment, and longer follow-up treatment are necessary to further validate the findings of the current study.

CONCLUSION

Present study suggests that a combined topo-guided PRK + CXL is an effective approach to not only biomechanically stabilize the cornea in keratoconus, but also to improve the corneal contour, reduce irregular astigmatism and offer a better quality of vision. The combined procedure provides better visual rehabilitation and improves vision with contact lenses and glasses by normalizing the corneal surface and reducing irregular astigmatism. It also increases functionality and eliminates the need for corneal grafting.

Thus, unlike the other treatment modalities, it not only treats the symptoms but also the cause. The positive results of this prospective, non-randomized study are quite promising and suggest the need for longer,

prospective randomized studies to evaluate the long-term safety and efficacy of such combined treatment modalities.

What was known?

Topography guided-PRK employed along with same session C3R stabilizes keratoconic corneas and provides visual rehabilitation.

What this paper adds?

- Introduction of the technique of simultaneous topography guided PRK with C3R application offers predictable results and appears to be an efficient alternative treatment modality in patients with keratoconus.
- Consistent trends towards improved visual rehabilitation, corneal flattening, and anterior-surface improvement was seen.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: Not required

REFERENCES

1. Gu SF, Fan ZS, Wang LH, Tao XC, Zhang Y, Wang CQ, et al. A short-term study of corneal collagen cross-linking with hypo-osmolar riboflavin solution in keratoconic corneas. *Int J Ophthalmol.* 2015;8:94-7.
2. Spoerl E, Huhle M, Seiler T. Induction of cross-links in corneal tissue. *Exp Eye Res.* 1998;66:97-103.
3. Jankov Ii MR, Jovanovic V, Nikolic L, Lake JC, Kymionis G, Coskunseven E. Corneal collagen cross-linking. *Middle East Afr J Ophthalmol.* 2010;17:21-7.
4. Caporossi A, Baiocchi S, Mazzotta C, Traversi C, Caporossi T. Parasurgical therapy for keratoconus by riboflavin-ultraviolet type a rays induced cross-linking of corneal collagen: preliminary refractive results in an Italian study. *J Cataract Refract Surg.* 2006;32:837-45.
5. Wollensak G. Crosslinking treatment of progressive keratoconus: new hope. *Curr Opin Ophthalmol.* 2006;17:356-60.
6. Kymionis GD, Kontadakis GA, Kounis GA, Portaliou DM, Karavitaki AE, Magarakis M, et al. Simultaneous topography-guided PRK followed by corneal collagen cross-linking for keratoconus. *J Refract Surg.* 2009;25:S807-11.
7. Kanellopoulos AJ. Comparison of sequential vs same-day simultaneous collagen cross-linking and topography-guided PRK for treatment of keratoconus. *J Refract Surg.* 2009;25:S812-8.
8. Wagner H, Barr JT, Zadnik K. Collaborative Longitudinal Evaluation of Keratoconus (CLEK) Study: methods and findings to date. *Cont Lens Anterior Eye.* 2007;30:223-32.

9. Rabinowitz YS. Keratoconus. *Surv Ophthalmol.* 1998;42:297-319.
10. 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;155:54-65.e51.

Cite this article as: Shah S, Mohan S, Rajan M, John B, Badlani V. Our experience with Athens protocol - simultaneous topo-guided photorefractive keratectomy followed by corneal collagen cross linking for keratoconus. *Int J Res Med Sci* 2016;4: 2639-44.