Two Years Follow up Evaluating Progression of Ectasia for Keratoconus Patients Treated with Simultaneous Topography - Guided PRK Plus Cross Linking

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Abstract: This retrospective study was designed to evaluate the efficacy and safety of simultaneous topography-guided PRK plus cross linking for patients with mild to moderate keratoconus and to evaluate the stability of the cone. The patients were evaluated over two years for the progression and stability of the cone by the Allegro Pentacam Oculyzer to assess the changes of corneal curvatures (K readings) and the stability of the cone after the surgery and evaluating uncorrected distance (UDVA) and best corrected (CDVA) visual acuities. The follow-up results showed that UDVA improved from 0.4±0.3 to 0.7±0.1 and CDVA changed from 0.6±0.1 to 0.8±0.1 (P < 0.001). The keratometry value decreased from 44.1±2.2 to 41.4±1.6 D for K1, and from 46.4±2.6 to 43.5±1.7 for K2 (P < 0.001). This combined procedure offers a promising method to stabilize the corneal surface with reducing higher order aberrations so enhancing quality of vision in keratoconus patients.

Keywords: Keratoconus, Topography, Cross-Linking, PRK

1. Introduction

Keratoconus (KC) is a progressive, noninflammatory, bilateral (but usually asymmetrical) ectatic corneal disease, characterized by paraxial stromal thinning and weakening that leads to corneal surface distortion. Visual loss occurs primarily from irregular astigmatism and myopia, and secondarily from corneal scarring. Protrusion usually but not exclusively affects the axial and inferonasal cornea [1]. It is a common disease in our practice in Middle East due to consanguinity and frequent allergic conditions leading to eye rubbing. It leads to decreased vision due to distortion of the anterior corneal surface and inducing apical thinning, high irregular astigmatism, and central scarring of the cornea [1]. Several modalities such as hard contact lens (rigid gas permeable), glasses or other contact lenses e.g. Rose K are available currently for these patients [2]. All these options only correct the refractive error of the cornea and have no effect on the progression of keratoconus [2]. The only treatment that is believed to have the ability to stop or decrease the progression of keratoconus is collagen cross-linking (CXL) [3]. CXL changes the biomechanical, thermo-mechanical, and morphological properties of the cornea [4]. It increases the stiffness and rigidity of anterior corneal stroma [5], [6] and enhances corneal resistance to proteolytic enzymes by inducing photochemical cross-linking and covalent bindings between individual collagen fibers [3], [7]. CXL alone is effective in achieving a halt in progression of keratoconus, but the improvement in visual acuity that has been reported is not always sufficient for good functional vision and better quality of life [8], [9].

Topography guided Excimer laser ablation, aims to treat highly aberrated irregular corneas by improving the central corneal symmetry, without attempting to correct other spherical or optical defects thus the refraction is not always predictable but there is a marked reduction in optical aberrations leading to improvement in the quality of vision [10].

Our aim is to evaluate the effect of combined topography guided PRK and cross-linking for the progression and stability of the cone by the Allegro Pentacam Oculyzer.

2. Patients and Methods

In this retrospective study, Topo-guided PRK (Laser machine: Wave Light Allegretto Wave Eye Q) and Collagen cross-linking (UV-X Crosslinking Machine with Handle, Manufacturer: IROC, A6 Switzerland, Model: UV-x) was performed on 15 eyes. The procedure was done between March 2012 and October 2013. Five patients underwent bilateral operations with progressive keratoconus, with an age range of 18.0–31.0 years. Inclusion criteria were: Patients who were <30 years of age with confirmed keratoconus on pentacam, who had a clear cornea without opacity, central corneal thickness (CCT) >450 μm and maximum K-reading of (52D). Patients who had central corneal opacities, central cornea thickness <450 μm, a K-reading more than (52D), history of previous ocular surgery, herpetic keratitis, severe dry eyes, and connective tissue disease and those who were not able to attend 2-year follow-up visits were excluded from our study. We also excluded pregnant and lactating patients. Preoperative Keratoconus progression was assessed by Pentacam Wave Light Allegro and confirmed by serial differential corneal topography and by differential optical pachymetry analysis in all eyes included in the study and subjective Loss of vision.

A list of criteria for keratoconus progression was designed including: Thinnest point pachymetry is decreasing and /or shifting downward, Anterior and Posterior elevation is increasing, simulated K-reading (sim K) is increasing.

2.1. Pre-Operative Evaluations

Patients were examined in preoperative period, with complete Ophthalmic examinations included determining UDVA and CDVA, Slit lamp examination, dilated fundoscopy, subjective and Cycloplegic refractions (Autoref-keratometer: Shin-Nippon Accuref-K 9001) and corneal topography to evaluate anterior and posterior keratometry, apex and thinnest pachymetry, anterior chamber depth (ACD), corneal volume, average progression index (regarding corneal thickness change from center to periphery), Spheroequivalent (SE), apical keratometry (AK), apical gradient curvature (AGC), average corneal power in 4 mm and corneal asphericity (Q value) by Pentacam Wave Light Allegro Oculyzer. UDVA and CDVA were determined using the Snellen acuity chart, the data of which were analyzed using the decimal format. Central corneal zone was evaluated for simulated keratometry (Sim K), corneal astigmatism and anterior and posterior elevations and best fit sphere (BFS).

2.2. Surgical Procedure: Topography – Guided Photorefractive Keratectomy (PRK) and Collagen Cross-Linking Procedure (CXL)

The patients were prepared for the operation by placing an anesthetic drop before the operation every 2 minutes for 15 minutes and then moved into the operating room. The eyes sterilized and the eyelids speculum applied. Epithelium was removed by mechanical debridement in central 9.0 mm zone.

The ablation profile had been designed by the same surgeon each time with maximum ablation depth varied from one eye to the other depending upon the refractive error and the pachymetry. The Excimer laser was applied on the corneal stoma to treat between 25-67 μm of corneal thickness. Then application of micro sponge soaked with Mitomycin (0.02%) for 20 second was done. This was followed by irrigation with chilled BSS.

Riboflavin 0.1% in 20% dextran was administered topically every 2 min for 25 min. Thereafter the cornea was exposed to UVA light (365 nm) (2.7mj) for 25 min with an optical system at an irradiance of 3.0 mW/cm kept at 5 cm distance from the cornea. During UVA exposure, isotonic riboflavin was administered every 2 min. A bandage contact lens was placed on the cornea at the end of the procedure. Postoperatively, Gatofloxacin 0.5% (Zymar, allergen, USA), Prednisolone 0.1% (Predforte, Allergan, USA) and Diclofenac Na 0.1% (Voltaren ophtha, Novartis, USA) eye drops were administered from day one, five times daily each. The contact lens was removed 3 days later when the epithelial defect had healed. Antibiotic and corticosteroid drops were continued four times a day for 1 and 2 weeks, respectively.

2.3. Post-Operative Evaluation

Patients were examined postoperative on day 1, 3, 7, 14 and then every 2 weeks for three month and then every three month for 24 months.

Complete Ophthalmic examinations included determining UDVA and CDVA, Slit lamp examination, dilated fundoscopy, subjective and cycloplegic refractions (Autoref-keratometer: Shin-Nippon Accuref-K 9001) and corneal topography to evaluate anterior and posterior keratometry, apex and thinnest pachymetry, anterior chamber depth (ACD), corneal volume, average progression index (regarding corneal thickness change from center to periphery), Spheroequivalent (SE), apical keratometry (AK), apical gradient curvature (AGC), average corneal power in 4 mm and corneal asphericity (Q value) by Pentacam Wave Light Allegro Oculyzer. UDVA and CDVA were determined using the Snellen acuity chart, the data of which were analyzed using the decimal format. Central corneal zone was evaluated for simulated keratometry (Sim K), corneal astigmatism and anterior and posterior elevations and best fit sphere (BFS).

3. Statistical Methods

The collected data were coded, tabulated, and statistically analyzed using IBM SPSS statistics (Statistical Package for Social Sciences) software version 22.0, IBM Corp., Chicago, USA, 2013. Descriptive statistics were done for quantitative data as minimum & maximum of the range as well as Mean±SD (standard deviation) for quantitative parametric data, while it was done for qualitative data as number and percentage. Inferential analyses were done for quantitative variables

using paired t-test in cases of two dependent groups with parametric data. The correlations were done using Pearson correlation for numerical parametric data. The level of significance was taken at P value < 0.050 as significant, otherwise it was considered non-significant.

4. Results

The study comprised of 15 eyes of 10 patients with progressive mild to moderate keratoconus. Patients had postoperative visits 3, 6, 12 and 24 months after topography guided PRK and Collagen cross-linking procedure. Results from data analysis are shown in the tables. Our results showed stability of cone as depicted by early flattening of corneal diopters at 3 months. K1 and K2 significantly decreased progressively from preoperative period till 24 months with maximum flattening at 3 months period (P< 0.001) (Table 1, 2).

Table 1. K1 (diopters) changes among the studied cases, *shows that K1 significantly decreased progressively from preoperative period till 24 months.*

Time	Mean ± SD	Range	P value
3 months - preoperative	-2.0±1.1	-5.1–0.0	<0.001*
6 months - preoperative	-2.3±1.3	-5.4–0.0	<0.001*
12 months - preoperative	-2.5±1.4	-4.9–0.0	<0.001*
18 months - preoperative	-2.6±1.4	-5.1–-0.1	<0.001*
24 months - preoperative	-2.7±1.4	-5.1–-0.3	<0.001*
6 months - 3 months	-0.3±0.4	-1.5–0.1	0.082
12 months - 6 months	-0.2±0.7	-2.4–1.0	0.182
18 months - 12 months	-0.1±0.3	-0.9–0.2	0.524
24 months - 18 months	-0.1±0.1	-0.3–0.0	<0.001*

^Paired t-test, *Significant.

Table 2. K2 (diopters) among the studied cases, *shows that K2 significantly decreased progressively from preoperative period till 24 months, with maximum flattening at 3 months.*

Time	Mean ± SD	Range	P value
3 months - preoperative	-2.3±1.2	-4.4–-0.7	<0.001*
6 months - preoperative	-2.6±1.2	-4.5–-1.0	<0.001*
12 months - preoperative	-2.8±1.5	-6.2–-0.6	<0.001*
18 months - preoperative	-2.8±1.5	-6.0–-0.6	<0.001*
24 months - preoperative	-2.9±1.5	-6.1–-0.7	<0.001*
6 months - 3 months	-0.3±0.6	-2.4–0.4	0.082
12 months - 6 months	-0.2±0.6	-2.2–0.4	0.182
18 months - 12 months	0.0±0.2	-0.3–0.2	0.524
24 months - 18 months	-0.1±0.1	-0.3–0.1	<0.001*

^Paired t-test, *Significant.

UDVA significantly increased progressively from preoperative period till 24 months with maximum elevation at 3 months (p<0.001) but no significant change in CDVA from preoperative till 24 months (Table 3, 4).

Table 3. UDVA among the studied cases, *shows that UDVA significantly increased (vision improved) progressively from preoperative period till 24 months, with maximum increase at 3 months.*

Time	Mean ± SD	Range	P value
3 months - preoperative	0.4±0.3	0.0–0.9	<0.001*
6 months - preoperative	0.5±0.3	0.1–1.0	<0.001*
12 months - preoperative	0.6±0.2	0.3–1.0	<0.001*
18 months - preoperative	0.6±0.2	0.3–1.0	<0.001*
24 months - preoperative	0.6±0.3	0.3–1.0	<0.001*
6 months - 3 months	0.1±0.1	0.0–0.3	0.017*
12 months - 6 months	0.0±0.1	0.0–0.2	0.164
18 months - 12 months	0.0±0.0	0.0–0.1	0.041*
24 months - 18 months	0.0±0.0	0.0–0.0	1.000

^Paired t-test, *Significant.

Table 4. CDVA among the studied cases, *shows No significant change in CDVA from preoperative period till 24 months.*

Time	Mean ± SD	Range	P value
3 months - preoperative	0.0±0.1	-0.1–0.3	0.384
6 months - preoperative	0.0±0.1	0.0–0.3	0.136
12 months - preoperative	0.0±0.1	0.0–0.3	0.136
18 months - preoperative	0.0±0.1	0.0–0.3	0.136
24 months - preoperative	0.0±0.0	0.0–0.1	0.165
6 months - 3 months	0.0±0.0	0.0–0.1	0.164
12 months - 6 months	0.0±0.0	0.0–0.0	1.000
18 months - 12 months	0.0±0.0	0.0–0.0	1.000
24 months - 18 months	0.0±0.0	0.0–0.0	1.000

^Paired t-test, *Significant.

Difference between CDVA and UDVA decreased progressively from preoperative period till 24 months, with maximum gap (worst vision) at preoperative months and minimum gap (best vision) at 18 months onwards (Table 5).

Table 5. CDVA – UDVA gap among the studied cases, *shows that CDVA – UDVA gap decreased progressively from preoperative period till 24 months, with maximum gap (worst vision) at preoperative months and minimum gap (best vision) at 18 months onwards.*

Time	Mean ± SD	Range	P value
Preoperative	0.5±0.3	0.2–1.0	<0.001*
3 months	0.1±0.2	0.0–0.5	0.009*
6 months	0.1±0.1	0.0–0.3	0.041*
12 months	0.0±0.0	0.0–0.1	0.041*
18 months	0.0±0.0	0.0–0.0	1.000
24 months	0.0±0.0	0.0–0.0	1.000

^Paired t-test, *Significant.

The spherical equivalent values were significantly decreased postoperatively from third month till the end of study period with maximum reduction at 3, 6 months postoperative (Table 6).

Table 6. Spherical equivalent values among the studied cases, *shows significant decrease in spherical equivalent values from preoperative period till 24 months with maximum reduction in 3, 6 month postoperative.*

Time	SE					COMP.	Paired Differences		Paired Samples Test	
	Range			Mean	± SD		Mean	SD	t	P-value
Pre	-5.000	-	-0.500	-2.592	± 1.280					
Post 3Months	-2.125	-	0.250	-0.704	± 0.633	P-3M	-2.038	0.740	-10.307	<0.001*
Post 6Months	-2.125	-	-0.250	-0.948	± 0.622	P-6M	-2.053	0.817	-7.942	<0.001*

Time	SE						COMP.	Paired Differences		Paired Samples Test	
	Range			Mean	±	SD		Mean	SD	t	P-value
Post 12Months	-3.125	-	0.500	-1.185	±	1.123	P-12M	-1.553	0.734	-6.689	<0.001*
Post 24Months	-2.875	-	0.500	-1.060	±	1.086	P-24M	-1.778	0.934	-6.016	<0.001*

^Paired t-test, *Significant.

5. Discussion

Treatment of keratoconus has changed over the past decade. The aim of management has been to achieve biomechanical stability and optical efficiency of the irregular cornea. The use of rigid contact lenses may not be tolerated by significant number of patients due to discomfort or occupational limitations. Such patients with moderate to advanced disease have to resort to keratoplasty which has its own morbidity. Stabilization of corneas with ectatic disorders can be achieved with the application of CXL alone. The method is based on the absorption of UVA radiation by the cornea after the photo-sensitizer riboflavin is infused in the stroma. Despite stabilizing the cornea, the topography and visual performance of patients treated with CXL alone show minimal improvement [11]. The technique of simultaneous topo-guided PRK with cross linking has been used to treat keratoconic patients and has shown stability of cornea with visual improvement. Achieving functional vision consists of improving UDVA and CDVA and normalization of corneal topography. This is indicated by the fact that these patients are less dependent on contact lenses to achieve better postoperative visual quality.

In our study of topography guided PRK with Collagen cross-linking the keratometry value decreased from 44.1±2.2 to 41.4±1.6 D for K1 and from 46.4±2.6 to 43.5±1.7 for K2 (P < 0.001). the spherocylindrical and spherical equivalent values were significantly decreased post operatively from the preoperative values, This was coupled with marked improvement in UDVA (0.4±0.1) to (0.7±0.1) measured in decimal point system over first 3 months period which continued to improve further over 18 months period. Furthermore the progression of ectasia stopped in eyes with progressive disease at the time of presentation.

In addition a small proportion of patients who had residual refractive error were able to tolerate the soft contact lenses much better.

Study done by Sakla et al [10] had similar results of combined PRK with cross linking for a period of 1 year, as did Stjanovic et al [12]. Our study emphasizes the above results based on a longer follow up of 2 years. In addition it is emphasized with the follow up that at 3 months period the procedure offers early stability of the cone which continues to maintain and even improve over 18 months period. The study conducted by Mukherjee et al [13] with non topo-guided PRK with cross-linking showed promising results of the combined procedure. In our study with topo-guided treatments, there is improved visual outcome due to additional correction of aberrations leading to better visual outcomes and simultaneously maintaining the stability of the disease process.

6. Conclusion

Combined treatments seem to be the way to optimize the result of CXL treatment for keratoconus. To date, simultaneous topography-guided PRK combined with CXL in selected cases seems to be the most effective approach for optimum results in the treatment of keratoconic patients, as it is capable of offering functional vision with stabilization of the ectatic disorder. Further studies with longer follow-up are needed to confirm the promising results of this approach.

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