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Outcomes of Corneal Topographical Kmax readings 3 months after Corneal Cross Linkage in Keratoconus patients

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Abstract

Background and objective: **Collagen protein, which is abundant in the cornea and has a triple helix form, may be found in almost every tissue matrix in the body. Natural cross connections between monomers provide the robustness of the helical protein structure. Wollensak and his colleagues developed the Dresden Protocol, a keratoconus treatment based on Corneal Cross-Linkage. We aimed to analyse and present the findings in individuals with progressive keratoconus using topographic and refractive results after corneal collagen crosslinking treatment (CXL) (KC) after 3 months.**

Methods: **The study comprises a total of 100 patients who were diagnosed with progressive KC and who underwent CXL between 2021 and 2022 at KRL Hospital Islamabad, Pakistan. All eyes in this study had a preoperative topography within 1 month before CXL treatment and the follow-ups were conducted at 3 months interval.**

Results: **In our investigation, 100 patients were added. The average age was 24.74 years. 77% of the patients were between the ages of 12 and 25 years, while 23% were between the ages of 26 and 50 years. In our survey, males made up 84% of the population, while females made up only 16%. The right eye was afflicted in 60% of cases, whereas the left eye was impacted in 40% of the population. Grade 2 Keratoconus affected 42% of patients, whereas Grade 1 Keratoconus affected 18%. Our findings were skewed toward men and the 12−25 age group, however in our recent study, we discovered considerable KC stability 3 months after CXL.**

Conclusion: **Keratometric readings and visual acuity were stabilised or improved with CXL treatment. Keratoconus stability can be reached 3 months following the treatment, according to our findings.**

Keywords: Cornea, Topography, Tomography, Optical coherence tomography, Keratograph, Corneal cross linkage

1. Introduction

The term KERATOCONUS has a Greek derivation, with "Kerato" meaning "Cornea" and "Conus" meaning "Cone Shaped." As a result, Keratoconus means "Cone Shaped Cornea.".[1] Keratoconus affects 1 out of every 2000 persons on the planet.[1,2] Its annual incidence rates in Asian and white populations are 25/100,000 and 3.3/100,000, respectively; 10% of those afflicted have a positive family history.[1,3]

Keratoconus is a non-inflammatory chronic ectatic corneal condition that affects both eyes of the patient, producing impaired vision, myopia, and uneven astigmatism, as well as scar development.[4] Marc Amsler proposed the Amsler-Krumeich (AK) Grading Technique in 1947 as a system for properly grading illness degrees.[5]

Collagen protein, which has a triple helix shape and is plentiful in the cornea, is found in practically every tissue matrix in the body. The helical protein structure's strength is ensured by natural cross connections between the monomers. This can be accomplished using the enzyme lysyl oxidase or without enzymes through a process known as glycation, which occurs naturally as people age. UV exposure causes oxidation, which releases reactive oxygen species, which converts collagen monomers

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to cross linked polymers, making them stronger.[6] In 2003, Wollensak and his colleagues at The University of Dresden devised a therapy for keratoconus dubbed the Dresden Protocol, which was based on Corneal Cross-Linkage treatment (CXL).[7] The procedure was approved by the FDA in the United States in 2016 as the gold standard treatment for Keratoconus.[6] Under aseptic conditions and with adequate pain relief, the central 7–9 mm corneal epithelium is removed, and a solution containing 0.1% riboflavin, 10 ml of 20% dextran, and 10 mg of riboflavin-5-phosphate is applied for half an hour, followed by exposure to 370 nm UVA at an irradiance of 3mW/cm2 for another half hour.[2,7]

Keratometry analyses the centermost 3 mm curvature of the front of the cornea on two axes, one with the maximum corneal power and one with the lowest, which are referred to as K values.[8] K values are measured in Dioptres 'D' mean value is 44.7080 ± 1.3343 D.[8] Kmax is the steepest anterior corneal curve power and is widely used to aid in the diagnosis of corneal shape change, particularly keratoconus.[9] Kmax is also frequently used to assess the efficiency of corneal cross-linking.[9]

This is assessed using the Galilei G6 Lens Professional (Ziemer Ophthalmic Systems AG, Port, Switzerland), a novel anterior segment imaging technology that incorporates a twin rotating Scheimpflung camera, a placido disc topographer, and an optical coherence tomography-based scan.[10] A placido disc analyses light reflected off the anterior corneal surface as concentric rings, recording its shape.[11] A dual rotating Scheimpflung camera is a spinning camera that generates a 3D picture of the cornea by directing slit-shaped light beams at different angles across the cornea.[11]

The purpose of this study is to add to Pakistan's population-based data demonstrating corneal cross-linkage is a safe, financially acceptable, effective therapy with promising results for keratoconus patients. This treatment's research will also show better visual function and patient satisfaction.

A review of the literature revealed that the above-mentioned therapy is beneficial; Latif et al. found a mean post-corneal cross-linkage decrease of 0.7D in Kmax in all 25 patients in his research.[12] Karaca et al. observed a mean decrease in Kmax of 0.51D in group one and 0.52D in group two of his 40 patients treated with corneal cross-linkage.[13] In a Brazilian research, Kmax values were reduced by 0.68D following corneal cross-linkage in all 75 patients after three months and 0.87D after one year of therapy.[14] Another research in the Netherlands found that following corneal cross-linkage treatment, Kmax was reduced by 1D in 102 eyes in 79 patients.[15] In addition, a research in Egypt found that corneal cross-linkage treatment reduced Kmax by 1.57D in 40 keratoconus patients.[16] AlQahtani et al. reported in his study on 24 keratonconus patients that there was a mean stabilization of the Kmax after corneal cross-linkage.[2]

The Amsler-Krumeich Grading System: is as follows: patients are considered to be Grade 1 if Mean Keratometry (meanK) is < 48 D, Corneal Thickness is > 500 microns, the Spherical Equivalent (SE) is < -5D and there are No Central Corneal Scars; Grade 2 if meanK is 48–53D, Corneal Thickness is 400–500 microns, SE is −5 to -8D and No Central Corneal Scars; Grade 3 if meanK is 54–55D, Corneal Thickness is 200–400 microns, SE is > -8D and No Central Corneal Scars; and finally Grade 4 if meanK is > 55D, Corneal Thickness is < 200 microns, SE cannot be measured and there are Corneal Scars.[4]

2. Materials and methods

This prospective experimental study was conducted at the Ophthalmology OPD of the KRL Hospital, Islamabad, Pakistan between 2021 and 2022. Sample size of 100 was calculated by WHO calculator keeping anticipated population proportion of 25%, absolute precision 5%, confidence interval of 95%.

2.1. Inclusion & exclusion criteria

Inclusion criteria was determined to be any patient who falls in the first 3 grades of the AK (Amsler-Krumeich) Grading System after an initial assessment of extensive slit-lamp examination by a professional ophthalmologist. Only individuals with KC grade 3 had thickness values of less than 400 m at the narrowest location were included in the study.

An increase in the maximal keratometry (Kmax) value of at least 0.75 diopter (D) and/or an increase in the manifest cylinder of at least 0.75 D for at least two consecutive measures in the previous 1 year at a 6-month interval was used to diagnose KC progression.

Patients with a history of dry eye, eyelid abnormalities, meibomitis, blepharitis, and corneal scarring were excluded altogether from the study. Patients with uveitis, cataracts, glaucoma, or any history of such diseases were also excluded. Exclusion criteria also comprised of pregnant mothers or mothers who were lactating.

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is > 500 microns, the Spherical Equivalent (SE) is < -5D and there are No Central Corneal Scars; Grade 2 if meanK is 48–53D, Corneal Thickness is 400–500 microns, SE is –5 to -8D and No Central Corneal Scars; Grade 3 if meanK is 54–55D, Corneal Thickness is 200–400 microns, SE is > -8D and No Central Corneal Scars; and finally Grade 4 if meanK is > 55D, Corneal Thickness is < 200 microns, SE cannot be measured and there are Corneal Scars.[4]

2.2. Data collection

Data collection for the study was done by after ethical approval from the IRB committee. A detailed history from the patient & detailed ocular examination and evaluation of the patient was carried out by a senior ophthalmologist. Patient falling into the criteria of keratoconus, informed consent was taken from the patient.

Corneal Topographical scans was taken by a senior optometrist with The Galilei G6 Lens Professional (Ziemer Ophthalmic Systems AG, Port, Switzerland) and data was recorded in the performa of every patient before and 3 months after Corneal Cross-Linkage treatment. The Galilei Analysis software which is an inbuilt software in The Galilei G6 Lens Professional (Ziemer Ophthalmic Systems AG, Port, Switzerland) is used to calculate the Kmax.

2.3. Data analysis

Statistical analysis was performed using the Statistical Package IBM SPSS Statistics 26. Categorical variables (i.e. gender, stage of keratoconus) will be presented as frequency/percentage. The quantitative variables (i.e., age, Kmax) will be presented as mean.

Each variable will be compared at different times for sample at time of treatment and follow up, to appreciate the progression of disease. Chi-square test was applied & P value of <0.05 will be considered statistically significant. Odds Ratio was calculated to check the risk of disease occurrence.

3. Results

One hundred patients were added in our study. Mean age was 24.74 years.

77% of the patients were from 12 to 25 years age group whereas 23% were from 26 to 50 years age group. There were 84% male population in our study whereas females were only 16%, as described in Table 1.

60% patients had their right eye affected whereas 40% had their left eye affected. 67% patients presented to the hospital after 1 year of diagnosis & only 33% presented as early as within 6 months of diagnosis to the hospital, as described in Table 2.

42% patients had Grade 2 Keratoconus, whereas 18% patients had Grade 1 Keratoconus, as described in Table 3.

Mean Pre-Corneal K max was 54.885 whereas Post Corneal k max mean was 53.826. Risk of Pre-corneal K Max with respect to gender is 0.733 whereas Post Corneal risk has decreased to 0.644 having p value of 0.00. Pre-Corneal K Max has a risk of 2.353 to occur with respect to age whereas Post-Corneal K max has a risk of 1.719 having significant p value, as described in Table 4.

4. Discussions

Over the last decade, new and better KC therapies have been presented, with the goal of significantly lowering transplantation rates and stopping disease progression. Spoerl et al. were the first to evaluate the effects of a combination of riboflavin, a photosensitizer, with UV radiation in laboratory tests. Both pig and human corneas showed an increase in corneal stiffness in vitro.[7] Wollensak et al. then performed the first pilot clinical trial in Dresden. At follow-ups ranging from 3 to 47 months, KC progression was stopped in all 23 treated eyes. Kmax was reduced by 2.01 D on average in 16 eyes, refraction error was reduced by 1.14 D, and visual acuity improved in 15 of 22 eyes. The major findings of the study demonstrated a substantial drop in the mean value of post corneal K-max for 100 eyes included in the trial over a period of three months. Similarly, there was a lowered incidence of post-corneal Kmax (OR: 0.644, 95% CI, OR; 1.719, 95% CI) for both age and gender correspondingly. The data supported the demonstration of a favorable prognosis following corneal collagen cross-linking with riboflavin and ultraviolet A (UV-A) light in reversing keratoconus.[7]

The results of the study match those of Tiveron et al. in terms of achieving stability or achieving decrease in keratoconus incident following CXL treatment. However, they were unable to identify any statistically significant variation in keratometric

Table 1. Patient demographics.

		Frequency	Percent
Age	12–25	77	77.0
	26–50	23	23.0
Gender	Male	84	84.0
	Female	16	16.0
Total	119	100.0	

Table 2. Showing frequency of effected eye & time since diagnosis.

		Frequency	Percent
Effected Eye	Right	60	60.0
	Left	40	40.0
Time Since Diagnosis	6 months	33	33.0
	1 year	67	67.0

Table 3. Grade of keratoconus.

	Frequency	Percent
Grade 1	18	18.0
Grade 2	42	42.0
Grade 3	40	40.0

readings between male and female patients following CXL treatment. Whereas all the outcomes were statistically significant in our situation. Moreover, our results were skewed towards the male gender and towards the age group of 12–25 years. Furthermore, there was inadequate involvement of female gender in the study. A retrospective study by Kim et al. has indicated that the corneal epithelial thickness is impacted by gender and found to be greater among male children than female children.[1]

Studies have demonstrated a decline in corneal thickness with an increase in the age of the patients (2–4). There's a substantial correlation of total corneal thickness with keratoconus owing to alterations in stromal and epithelial thickness.[5] The gender difference can be explained on the basis of hormonal changes where females have 2–3 mm thinner corneas than males. The actual cause behind this is still uncertain6. These researches can give a plausible explanation for our findings.

Overall, the results proved and recommended the usefulness of CXL in the treatment of keratoconus. We found significant stability of KC 3 months following CXL in our current investigation. A systematic study by Kobashi et al. reported a reduction in Kmax value following CXL treatment for keratoconus during a follow-up period of one year.[7] However, there's not adequate substantiation free of considerable variation to sustain this agreement. The review is scarce and indicates the necessity of a randomized controlled experiment with a larger sample size and less clinical variety in order to produce useful and substantial findings.

Keratoconus is a degenerative illness that decreases vision and, in rare situations, cannot be cured readily with normal therapies. Keratoconus generally begins in the second decade of life, at adolescence, and lasts until the fourth decade, when it stabilizes. Corneal thinning produces irregular astigmatism, myopia, and conical protrusion, leading in mild to severe vision impairment and a detrimental impact on the patient's quality of life. The development of CXL treatment as a one-of-a-kind therapy for keratoconus was regarded as a watershed point in the disease's treatment. However, even two decades after CXL treatment's conception, there are still some unsolved questions.[8] While several studies have looked into the effectiveness and safety of CXL, certain studies have connected it to certain concerns, including fungal and microbial infections and corneal damage.[9–11] Although these investigations mostly consisted of case reports, other research has shown significant evidence that the safety of CXL treatment is dependent on the techniques utilized during the operation, such as the use of a light source with uniform irradiance at a wavelength of 370 nm, the removal of the epithelium to allow the diffusion of the riboflavin, which is applied 30 min before UV exposure, and a minimum corneal stroma thickness of 400 mm.[12–15]

Appropriate patient selection is recognized as a significant element that can impact CXL treatment's complications and failure rates. Patients over the age of 35 are regarded to be at a larger risk of issues, as the term suggests.[16] The majority of the patients in the study were from the age group of 12–25 years. Furthermore, the time period between the performance of the operation and diagnosis was one year for the majority of the patients, which could've introduced a possible selection bias among the results and can be regarded as a limitation of our findings.

The authors would like to note additional limitations of the study, such as the restricted sample size and lack of female gender representation. Furthermore, the three-month follow-up time may be

Table 4. Showing the risk estimate & confidence interval.

	Odds ratio	95% Confidence Interval		P Value
		Lower	Upper	
Pre- Corneal K Max with Gender	0.733	0.630	0.854	0.00
Pre- Corneal K Max with Age	2.353	1.641	3.374	0.00
Post- Corneal K Max with Gender	0.644	0.519	0.801	0.00
Post- Corneal K Max with Age	1.719	1.374	2.150	0.00

insufficient to determine the procedure's effectiveness. Because the bulk of the sample was male and the age group varied from 18 to 25 years, these variables may have had an influence on the outcomes. To corroborate the findings, a randomized experiment with a higher sample size and a longer follow-up time is essential. It would offer a better idea regarding the procedure's effectiveness.

5. Conclusions

As a result of the CXL treatment, the cornea takes on a more regular shape without affecting the corneal endothelium. We observed promising results of CXL treatment. Compared to other studies our study found significant differences in keratometric readings between male and female patients after CXL treatment. We found significant stability of KC 3 months following CXL treatment in our current investigation. Furthermore, our findings were biased towards the male gender and the age category of 12−25. Moreover, after this effective and safe procedure, we recommend longer follow-up periods and inclusion of more age groups.

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