ORIGINAL ARTICLE

EFFICACY OF TRANSEPITHELIAL ACCELERATED COLLAGEN CROSS LINKING IN STOPPING THE PROGRESSION OF KERATOCONUS

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Background: Keratoconus is a progressive ectatic disease of the cornea leading to central corneal thinning, protrusion and permanent visual impairment in untreated cases. It is affecting young children with strong association to vernal keratoconjunctivitis a common disease of Asian countries. Corneal collagen cross linkage (CXL) is standard procedure to stop progression of keratoconus. In this research article we used trans-epithelial accelerated corneal cross-linking to check its efficacy in stopping the progression of disease as quick and safe procedure with less chances of complication than standard CXL protocol. **Methods:** The study was carried out in Khyber Teaching Hospital from November 2022–October 2023. The sample size calculated was 36 with sampling technique of non-probability consecutive convenience sampling method. **Results:** The mean age of the patients was 19.157±3.53 years. Post corneal cross-linking, at 6 months follow-up showed that in 94.44% of the patients, no progression of keratoconus was noted. Improvement in vision was recorded in 44.44% of patients. A positive correlation was detected between pre- and post-treatment patients in visual acuity, keratometry and pachymetry. **Conclusion:** The trans-epithelial accelerated corneal collagen crosslinking is a safe and quick procedure for stopping the progression of keratoconus associated with less morbidity and complications.

Keywords: Corneal cross-linkage; Keratoconus

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INTRODUCTION

Keratoconus is a non-inflammatory progressive corneal ectatic disease of childhood or early adulthood, leading to progressive central corneal thinning, weakness with formation of cone shaped bulge in the cornea causing visual impairment effecting quality of life in young patients.[1] The prevalence of keratoconus is 7.5 times higher ins Asian population.[2] It typically develops during the teenage years or early adulthood. The exact cause of keratoconus is not fully understood, but it is believed that a combination of genetic and environmental factors plays a role. There is a strong association between keratoconus and vernal keratoconjunctivitis (VKC).[3] Vernal keratoconjunctivitis is common in hot weather and in region with more sunshine during summer. It is more prevalent in the subcontinent region due to extreme weather conditions.[4] While there are various treatment options available for keratoconus, such as contact lenses or corneal transplants. Collagen corneal cross-linking (CXL) has shown promising results in the treatment of progressive keratoconus.[5] This research topic aims to explore the role of transepithelial accelerated corneal cross-linking in the management of keratoconus. Corneal cross-linking is a minimally invasive treatment for keratoconus progression that involves applying riboflavin drops to the cornea and then exposing it to ultra violet-A light for a specific of time.[6] This process creates new chemical bonds between the collagen fibers in the cornea, which strengthens and stiffens the corneal collagen fibers, thus halting the progression of the disease.[7] CXL is most effective in the early stages of keratoconus with good visual acuity when the cornea is still relatively thick, and the disease has not progressed significantly. Keratoconus can have a significant impact on an individual's quality of life, as it can cause blurred vision, light sensitivity, and difficulty in driving or reading. In some cases, the disease can progress to the point where corneal transplantation is necessary.[8] Corneal transplantation is a major and expensive surgical procedure having financial burden and also associated with long term morbidity effecting quality of life of young patients. Corneal cross-linking (CXL) is a relatively new treatment for keratoconus that has shown good results in halting the progression of the disease in terms of its safety and minimum complications of the procedure.[9]

The most commonly used standard protocol for corneal cross-linkages is the Dresden protocol described by Wollensack *et al*.[10] In this procedure patients with a corneal thickness of more than 400

microns the corneal epithelium is debrided and 0.1% riboflavin 5-phosphate drops are instilled every 5 minutes for 30 minutes so that it should passes through the corneal stroma. After that the cornea is exposed to ultraviolet light of 370nm- 3 mw/cm^2 with a total of 5.4J/cm^2 energy delivered over 30 minutes. As in this procedure the corneal epithelium is removed so there is risk of corneal infection, haze, endothelium damage due to prolong UV light exposure, increase morbidity due to debrided epithelium, severe pain and sometime problem with corneal re-epithelization especially in vernal keratoconjunctivitis patients.

Transepithelial accelerated corneal collagen cross-linking (A-CXL), is another procedure for treatment of keratoconus and have many benefits in comparison to standard CXL. In transepithelial accelerated CXL the epithelium is not removed, so the patient is not at risk of epithelium related complications. It is quick, painless procedure with minimum morbidity as the patient is able to do his routine activities on the same day. The chance of endothelial toxicity is also minimum due to short exposure time. Based on Bussen-Roscoe photochemical law the amount of total energy delivered will remain the same by increasing the intensity of radiation. In transepithelial accelerated CXL 3 minutes of UV-A light exposure will be done with irradiation of 30mW/cm^2 delivering a total energy of 5.4J/cm^2 which is the same as delivered by the standard CXL procedure over 30 minutes.[11] Efficacy of transepithelial accelerated CXL has not been studied in our population.

The rationale of the study is to check the efficacy of transepithelial accelerated CXL procedure in our population as its less invasive, quick with minimum morbidity and complication with the same efficacy as standard CXL.

The objectives of the study were to identify the efficacy of transepithelial accelerated corneal cross linkages in our population in halting the progression of keratoconus.

MATERIAL AND METHODS

The study was conducted in the department of Ophthalmology of Khyber Teaching Hospital, Peshawar from 1st November 2022 to 31st October 2023. A non-probability consecutive convenience sampling technique was used for sample collection. Sample size calculated was 36 keeping the confidence level of 95% with margin of error 5% and the prevalence of the disease as 2.3%[12] using online sample size calculator.

Keratoconus was defined as progressive non-inflammatory disease of the cornea with a K-reading more than 48 diopter and corneal thickness less than 470 microns on pachymetry.

The progression of keratoconus after CXL was defined as one line drop in the best corrected visual acuity from the pre-laser visual acuity or an increase in one diopter of K-Max value after 6 months of collagen cross linkage or a decrease in corneal thickness by more than 10 microns on pachymetry[13]. The keratoconus was said to be stable if no change in the above-mentioned parameters were detected.

The inclusion criteria for transepithelial accelerated CXL were diagnosed patients of keratoconus below 20 years of age. Those above 20 years of age were followed for 6 months and after documented progression of keratoconus on corneal topography were included in the study. Patients having corneal thickness of less than 350 microns, corneal scar, acute hydrops, already underwent CXL, active corneal disease or infection, pregnant women and children of less than 8 years of age as safety profile of CXL in this age group has not been documented were excluded from the study. All the above mentioned were excluded from the study as it would have acted as confounders and would have made the study results biased.

This study was carried out in Ophthalmology department of Khyber Teaching Hospital Peshawar. Study was started after taking ethical approval from the institution ethical committee (No:449/DME/KMC). Data was collected by non-probability convenience consecutive sampling method. From all the patients written informed consent were taken. Patient data were recorded on a proforma. Patient were examined by consultant and if keratoconus is suspected, complete ophthalmic examination related to keratoconus was performed. This included visual acuity, best corrected visual acuity, subjective and objective refraction, keratometry, slit lamp examination. Patient with K-reading more than 48D on keratometry in any meridian corneal topography and Corvis ST (Corneal Visualization by Scheimflug Technology) was advised.

Once the diagnosis of keratoconus has been confirmed on corneal topography, with corneal thickness of more than 350 microns and age less than 20 years were advised trans-epithelium corneal collagen cross linking as keratoconus is progressive in this age group. Patients over 20 years of age were followed after 6 months with a fresh corneal topography to check for progression. An increase of 1 diopter changes in keratometry reading or central corneal thickness of more than 10 microns were taken as significant and patients were advised trans-epithelium corneal cross-linkage. Those with no progression after 6 months of follow ups were again followed after 6 months with a corneal topography until any progression was documented.

After transepithelial accelerated CXL patients were followed for 6 months with visual acuity, best corrected visual acuity (BCVA), K-Max (Maximum K-reading on corneal topography), pachymetry (Corneal thickness) values and were compared with pre-CXL values to look for stabilization, progression or regression of keratoconus.

Data was collected including age, gender of the patient. After confirming the diagnosis Visual acuity, best corrected visual acuity, autorefractometer, keratometry reading and manifest refraction of the patient were recorded and entered in the proforma. Keratometry reading and pachymetry reading from corneal topography were entered in the proforma along with a photocopy of the topography map to check for progression after undergoing corneal cross linkage. The patients were instilled 0.25% riboflavin drops with HPMC, dextran free (VibeX Xtra, Avedro) after every minute for 10 minutes and were exposed to ultraviolet A light radiations for 3 minutes at a dose of $30mW/cm^2$ giving a total energy of $5.4J/cm^2$. At the time of UV-A exposure time the dropping was continued. Riboflavin 0.1% with HPMC diffusion rate through cornea is twice as that of standard riboflavin. After the procedure patients were followed after 6 months with repeated corneal topography to check for any progression. All data were documented in a *proforma*.

Data was analysed using SPSS software version 26. Variables included were best corrected visual acuity, k-readings on corneal topography and corneal thickness on pachymetry. For quantitative variables mean, mode and standard deviation were calculated whereas for qualitative variables frequencies were calculated. t-test was used while making comparison between pre and post corneal cross linkages procedure. *p*-value of less than 0.05 was considered to be significant.

RESULTS

A total of 36 eyes were included of 19 patients. Two patients were having unilateral involvement with no signs of keratoconus in other eye, so treatment was offered only to one eye. The mean age was 19.157 with standard deviation of±3.53 and standard error of mean 0.810. After 6 months of accelerated transepithelial CXL, in 94.44% of the patients, no progression of keratoconus was noted and only two patients (5.56%) showed progression with increase in K-Max by one or more than one diopter. Most of the patients showed stabilization of keratometry reading and pachymetry reading after accelerated CXL. There is improvement in visual acuity and keratometry reading in 44.44% of eyes but the improvement is not statistically significant. The correlation between the pre-treatment and post-treatment best corrected visual acuity, keratometry reading and pachymetry reading was calculated showing significant positive correlation between the variables with *p*-value less than 0.05, indicating that variables are closely related as shown in the table 2. The results showed that there is statistically significant difference between the pre-treatment and post-treatment best corrected visual acuity and corneal thickness on pachymetry in accelerated corneal cross linkage (*p*-value of 0.002 and 0.000 respectively) as shown in table-3.

Table-1: Paired sample statistics

Parameters	Pre- and post-treatment	Mean	N	Std deviation	Std error of mean
Best Corrected Visual acuity	Pre-treatment	0.519	36	0.2304	0.0373
	Post-treatment	0.592	36	0.2410	0.0391
K-Max (Diopter)	Pre- treatment K-Max	52.33	36	3.746	0.607
	Post-treatment K-Max	52.24	36	3.974	0.644
Pachymetry (Microns)	Pre-Treatment pachymetry	454.052	36	34.067	5.526
	Post-treatment Pachymetry	449.605	36	34.867	5.656

Table-2: Paired sample correlation between BCVA, K-Max and pachymetry

	N	Correlation (r)	*p*-value
Pre-treatment and post-Treatment BCVA	36	0.838	0.00
Pre-treatment and post-treatment K-Max	36	0.992	0.00
Pre-treatment and post-treatment pachymetry	36	0.994	0.00

Table-3: Paired sample test of differences

	Mean	SD	Std. error Mean	95% confidence interval of Differences		T-stat	Degree of freedom (df)	*p*-value (2-tailed)
				Lower	Upper			
Pre- and post-treatment BCVA	-0.0724	0.1344	0.0218	-0.1166	-0.0282	-3.321	36	0.002
Pre- and Post-treatment K-Max	0.0842	0.5262	0.0853	-0.887	0.2571	0.986	36	0.330
Pre- and Post-treatment pachymetry	4.447	3.753	0.6089	3.213	5.681	7.303	36	0.000

DISCUSSION

Corneal cross linkage is a gold standard treatment for halting the progression of keratoconus having a success rate of over 90% in different studies. In our study progression of keratoconus was stopped in 94.44% of the individuals undergone the treatment. The basic aim of our study was to check the effect of accelerated CXL on the progression of keratoconus. There was improvement in the parameters of keratoconus but was not statistically significant and patient is not able to appreciate improvement.

The epi-off corneal cross linkage is associated with many complications including severe pain post-operatively due to corneal epithelium removal, stromal haze, poor healing of epithelium specially in vernal keratoconjunctivitis patients with limbitis. All these complications associated with epithelial removal can be avoided with trans-epithelial corneal cross linkages in which the epithelium is not removed. Accelerated corneal cross linkage procedure reduce the operative procedure time with efficacy equivalent to standard procedure. The effectiveness of standard CXL has already been established in various studies in terms of stopping progression of the disease.[14] Our study showed that accelerated CXL (A-CXL) have almost the same success rate and efficacy as that of the epi-off CXL with short operative time, early recovery and minimum risk of complications as the epithelium removal is not needed. The same findings were documented in research of Nicula C *et al* and in their article.[15]

In our research we noted some improvement in the visual acuity and the mean k Readings of patients undergone accelerated corneal cross linkages. In a study done by Salman MA *et al* found that there is stabilization and improvement in the uncorrected distant visual acuity and corrected distant visual acuity after corneal cross linkage but the improvement is not clinically significant with *p*-value less than 0.05.[16]

In our study we did not notice any complication or adverse effects of the procedure. The complications are very rare with trans epithelial accelerated corneal cross linking, if patients are selected according to the recommended corneal thickness range to avoid damage to corneal endothelium by ultraviolet light. Some transient mild adverse effects were documented by Mazzotta C *et al* but all were managed within one month of cross linking.[17] We noticed improvement in visual acuity and K-Max reading in 44.44% of patient but this difference was not statistically significant and patient is unable to appreciate this improvement. In a study by Madeira C *et al* documented an improvement in 76.66% of patients.[18] This difference in improvement can be explained due to late presentation of our patients with thinned cornea where chances of improvement are minimal. Secondly the basic purpose of CXL in keratoconus is to halt the progression of the disease which us achieved in our study in 94.44% of patients. In a randomized control trial conducted by Iqbal M and colleagues showed the progression of keratoconus in 5.4% of the patients after accelerated transepithelial corneal cross linkage.[19]

Limitations of the study:

The sample size in our study was 36, so large scale studies need to be conducted for the results to be more generalized. We follow our patients for 6 months after the cross-linking procedure, long follow up need to be done to know about the long-term efficacy of the procedure.

CONCLUSION

Trans-epithelium Accelerated corneal cross linkage is a quick, safe, painless procedure for halting the progression of keratoconus with a high success rate. The efficacy of A-CXL is the same efficacy as that of standard cross linking which is time consuming and associated with many complications.

Conflict of interest: There is no conflict of interest

AUTHORS' CONTRIBUTION

IA: Concept conceived and data analysis. NG: Data analysis. BK: Manuscript writing. JK: Data collection. FK: Data analysis and proof reading.

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