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Assessment of higher order aberrations, postoperative pain and epithelial healing time after corneal collagen cross-linking following Conventional versus laser Epithelial removal in females with progressive keratoconus

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ABSTRACT

Background: Keratoconus (KC) is a non-inflammatory, bilateral condition characterized by increasing corneal thinning & bulging due to its biomechanical instability, it is one of the most common disorders that affect corneal transparency. collagen cross-linking (CXL) has become the preferred method for managing progressive ectasia.

Aim: Assessment of higher order aberrations, post operative epithelial healing time and the severity of post-operative pain, following CXL using transepithelial phototherapeutic keratectomy (PTK) versus Conventional epithelial debridement in treatment of progressive Keratoconus in females.

Patients and Methods: This was prospective comparative research that was carried out on 40 women cases with progressive keratoconus. In Group (A): transepithelial phototherapeutic keratectomy done for epithelial removal. And In Group (B): the epithelium removed conventionally.

Results: There weren't statistically significant distinctions among both groups all through the study regarding Total HOAs, spherical and coma aberrations ($P > 0.05$). directly after the intervention and on the first postoperative day, we observed a statistically significant greater average pain level in the manual group compared to the laser group ($P < 0.05$), then the pain decreased until the fourth postoperative day, with no significant distinctions among the two groups ($p > 0.05$). Nonetheless, the manual group had a longer mean time to complete epithelial closure compared to the PTK group.

Conclusion PTK-CXL provides an efficient and secure treatment modality for keratoconic patients however there weren't statistically significant distinctions among both groups regarding higher order aberrations, still it results in less post-operative pain and rapid epithelial healing.

Keywords: Keratoconus; corneal cross linking CXL; Transepithelial phototherapeutic keratectomy (PTK); Conventional Epithelial removal, high order aberration, epithelial healing, post-operative pain.

INTRODUCTION

KC is one of the most frequent disorders that affect corneal transparency.¹ It anticipated that reported prevalence and incidence estimates would rise because of the prevalent usage of corneal topography & standard diagnostic criteria. Both sexes are susceptible to keratoconus.² From a histopathological perspective, corneas affected by keratoconus (KC) exhibit a diminished population of stromal keratocytes & a decrease in the thickness of collagenous lamellae, alongside alterations in their orientation relative to Bowman's layer.³

Additionally, evidence suggests the presence of inflammatory markers & cytokines, involving interleukins (IL-6, IL-1, IL-8), & TNF- α , in the tears of individuals with KC.^{4,5}

In the initial stages of keratoconus, patients typically do not experience any symptoms, and the condition may only be discovered incidentally by the ophthalmologist, often when the patient cannot achieve clear 20/20 vision even with corrective measures.¹

Clinical manifestations also vary according to the disease's severity. Observable signs during slit-lamp examination in moderate to advanced keratoconus may include stromal thinning, along with a conical protrusion, the presence of an iron line, totally or partially encircling the cone (known as Fleischer's ring), and fine vertical lines within the deep stroma & Descemet's membrane, termed Vogt's striae, may transiently disappear upon gentle digital pressure. Additional associated signs may comprise anterior stromal scars, epithelial nebulae, and prominent corneal nerves.⁶

Additional external signs linked to keratoconus, encompass Munson's sign which refers to a V-shaped configuration of the lower lid resulting from the ectatic cornea during downward gaze, and Rizzuti's sign is characterized by a sharply focused light beam near the nasal limbus, observed upon lateral illumination of the cornea in individuals with advanced KC.

In advanced stages, cases may sometimes experience a sudden onset of visual impairment accompanied by pain. Slit-lamp examination may reveal injection of the conjunctiva & a diffuse stromal opacity in the cornea. This condition, known as "hydrops" arises from ruptures in Descemet's membrane, allowing aqueous to enter the stroma through these ruptures. The edema can persist for an extended period of time, ranging from weeks to months, gradually declining over time. This slow reduction in edema leads to relief from pain & the removal of both redness and corneal edema. Ultimately, scarring replaces the edema.⁷

Collagen cross-linking is a procedural method involving the formation of covalent bonds among collagen fibrils within the stroma of the cornea.⁸

Corneal epithelial removal is a necessary part of the typical CXL procedure to allow the riboflavin solution to penetrate evenly into the corneal stroma. The typical approach to CXL treatment involves mechanically removing the corneal epithelium.⁹

During CXL treatment, epithelial removal can also be accomplished using alternative methods like excimer laser t-PTK. This surgical technique utilizes excimer laser ablation to remove the epithelium & refine the irregularities on the corneal surface.^{10,11}

Early research studied combining topography-guided photorefractive keratectomy (t-PRK) with CXL to improve both visual acuity (VA) and corneal stability.¹² t-PRK or wavefront-guided PRK may improve spectacle corrected distance VA (CDVA) by reducing irregular astigmatism.¹³

The aim was the assessment of higher order aberrations, post operative epithelial healing time and the severity of post-operative pain, following Corneal collagen cross-linking using transepithelial phototherapeutic keratectomy versus Conventional epithelial debridement in treatment of progressive Keratoconus in females.

PATIENTS AND METHODS

This was prospective comparative research that was carried out on 40 women cases (80 eyes) with progressive keratoconus.

Inclusion criteria: Female patients aged 18–35 years, mean central keratometric values: 48 D to 53 D, spherical equivalent up to -8 D & corneal thickness greater than four hundred micrometers.

Exclusion criteria: pregnant females and 1st year post-partum, mean central keratometric values of > 53 D), apical corneal opacity, corneal thickness less than 400 μm , spherical equivalent > -8 D, acute hydrops, presence of active or recent ocular inflammation or infection, cases with Post LASIK ectasia and patients with any other ocular disease (eg, Glaucoma, cataract, retinal disorders).

Patients were subjected to:

Full history including the following: (Age, complaint, and family history of keratoconus), complete ophthalmic test including Slit-lamp examination and fundus examination. Scheimpflug imaging with Pentacam [Allegro Oculyzer, WaveLight AG, Erlangen, Germany] to measure: total high order aberration, coma, and spherical aberrations

Cases were separated Randomly into 2 groups:

In Group (A): transepithelial phototherapeutic keratectomy done for epithelial removal. And

In Group (B): the epithelium removed conventionally.

CXL done to all patients (PESCHKE Trade CCL-VARIO Cross-linking is a medical procedure performed at Swissmed in Gdańsk, Poland. that produces UVA light with a wavelength of 370 nanometers & a power density of eighteen mW/cm^2 for a duration of five minutes.

Ocular pain was assessed an hour after the surgery on day 0, in a postoperative follow up visit at 24 hours and subsequent days until 4th day. The patient subjectively conveyed the level of eye pain, using a scale ranging from 1 to 10, with 10 indicating the most intense pain experienced.

Corneal epithelial healing time, indicated in days, was assessed through slit lamp biomicroscopy.

All patients were subjected to complete ophthalmological test at 1, 6 & 12 months, postoperatively, By Scheimpflug imaging with the Pentacam to measure: corneal aberration map (Coma, spherical and total corneal aberration).

Surgical technique

The surgeries were conducted at Roaya Eye Centre in Alexandria under aseptic conditions. In addition to the variation in epithelium removal technique, the Corneal collagen cross-linking process was same in the two groups. **In the 1st group**, Following applying topical anesthesia with BENOX (Benoxinate hydrochloride) 0.4 percent Sterile Ophthalmic Solution ten milliliters, manufactured by EGYPTIAN INT. PHARMACEUTICAL INDUSTRIES CO. (EIPICO.) in Egypt, the corneal epithelium was removed by a process using the phototherapeutic keratectomy mode of the Allegretto WaveLight excimer laser, manufactured by WaveLight Technologies in Erlangen, Germany. Transepithelial phototherapeutic keratectomy ablation was conducted inside a seven-millimeters area at a depth of fifty microns . **In the 2nd group**, the corneal epithelium was eliminated using mechanical debridement with an eight-millimeters diameter.

Following the removal of the epithelium, a solution of riboflavin (0.1 percent concentration of ten milligrams riboflavin-5-phosphate in ten milliliters of dextran-T-500 twenty percent solution) was applied to the center of the cornea every 2 minutes for a total of ten minutes. All cases will undergo corneal cross-linking using the PESCHKE Trade CCL-VARIO Cross-linking system from Swissmed, Gdańsk, Poland. This system emits UVA light with a wavelength of 370 nanometers & an intensity of 18 mW/cm^2 . Each eye will be treated for five minutes. After completing the therapy, a mixture of corticosteroid & antibiotic drops

(Tobradex; Alcon Laboratories, Inc.) was given, & a silicon hydrogel bandage contact lens was placed until complete re-epithelialization. The antibiotic & corticosteroid drops were continued five times a day until the bandage contact lens was removed. Following the extraction of the contact lens, cases were administered corticosteroid drops, antibiotic drops, & artificial tears.

Statistical analysis

SPSS v26 (IBM Inc., Chicago, IL, USA) was employed to conduct statistical analysis. The quantitative data were presented as mean \pm SD & ranges. Additionally, qualitative variables were represented as percentages & numbers. The significance of the p-value was found as follows: a P-value of less than 0.05 was considered significant, a P-value of less than 0.001 was considered highly significant, and a P-value of more than 0.05 was considered insignificant.

RESULTS

The mean age of laser group was 26.12 ± 2.9 and was 26.68 ± 2.82 In the conventional manual group, with no statistically significant distinction among their ages. No statistically significant distinction was discovered among both groups before surgery in any of the parameters (Table 1).

Table (1) pre-operative parameters, no statistically significant differences were found between the two groups.

	PTK + CXL	CXL	
	preoperative	preoperative	p value
Age	26.12 ± 2.9	26.68 ± 2.82	0.384
Aberrometric Values			
TOTAL HOAs	3.6 ± 0.6	3.58 ± 0.56	0.878
spherical aberration	1.17 ± 0.2	1.17 ± 0.24	0.926
coma aberration	2.12 ± 0.41	2 ± 0.38	0.181

On comparing the two groups, there weren't statistically significant distinction among both groups all through the study regarding Total HOAs, spherical aberration and coma aberration ($P > 0.05$) (Table 2).

Table (2) comparison between the HOAs of both groups throughout the follow up period.

		1 month	p-value	6 months	p-value	12 months	p-value
Total HOAs	PTK + CXL	3.95 ± 0.69	0.526	3.41 ± 0.57	0.496	3.3 ± 0.55	0.417
	CXL	4.05 ± 0.71		3.49 ± 0.54		3.4 ± 0.55	
spherical aberration	PTK + CXL	1.22 ± 0.2	0.054	1.03 ± 0.19	0.520	0.99 ± 0.2	1.000
	CXL	1.33 ± 0.27		1.06 ± 0.22		0.99 ± 0.23	
coma aberration	PTK + CXL	2.35 ± 0.49	0.810	2 ± 0.38	0.069	1.78 ± 0.42	0.780
	CXL	2.33 ± 0.44		1.84 ± 0.39		1.8 ± 0.38	

Cases reported more pain in the 1st postoperative hours, The pain was more intense in patients with manual epithelial removal 6.5 ± 0.24 , with a statistically significant distinction ($P < 0.05$) compared to the mean pain value reported by patients of the PTK group 9 ± 0.48 . in both

surgical techniques, there was a maximum pain peak on the first postoperative day, 7.5 ± 0.24 in the PTK group & 8.5 ± 0.24 in the conventional group, with statistically significant distinction among both groups ($P < 0.05$). There was a progressive decrease in pain until the fourth postoperative day, with very similar behavior in both groups and no statistically significant distinction among both groups ($P > 0.05$) (Table 3).

Table (3) postoperative pain in both groups

PAIN			P-value
day 0	PTK-CXL	6.50±0.24	0.000
	CXL	9.00±0.24	
day 1	PTK-CXL	7.50±0.24	0.000
	CXL	8.50±0.24	
day 2	PTK-CXL	6.50±0.24	1.000
	CXL	6.50±0.24	
day 3	PTK-CXL	3.50±0.24	1.000
	CXL	3.50±0.24	
day 4	PTK-CXL	2.50±0.24	1.000
	CXL	2.50±0.24	

The mean time to complete epithelial closure was statistically significant & longer in the manual group compared to the PTK group ($p < 0.05$). The mean time for complete epithelial closure was recorded as 2.75 ± 0.12 days for PTK eyes & 3.9 ± 0.29 days for manual group eyes (Table 4).

Table (4) Epithelial healing time in days in the two groups.

	Epithelial healing time in days	p-value
PTK + CXL	2.75 ± 0.12	0.000
CXL	3.90 ± 0.29	

DISCUSSION

Our results suggest that corneas with epithelial removal through t-PTK showed similar degrees of aberrometric alterations compared to others that was deepithelialized manually. epithelial removal via PTK results in the same outcomes as conventional manual debridement, For all data points at all time intervals.

Our results agreed with the retrospective comparative research of **Gaster et al.**¹⁴ which revealed similar outcomes among transepithelial phototherapeutic keratectomy - collagen cross-linking & mechanical epithelial removal prior to collagen cross-linking with a follow-up of twenty-four months.¹⁵

In our research, the most significant variance in the subjectively reported pain by the patient was noted directly after the intervention and on the first postoperative day, during which we

observed a higher average pain level in the manual group. Factors such as shorter duration of surgery and the lack of manipulation of the eyeball by the surgeon could account for these variances, on subsequent days, there weren't significant distinctions in subjectively reported pain among both groups with progressive decrease in pain until the fourth postoperative day and very similar behavior in both groups with no statistically significant distinctions among both groups.

Many studies have examined the issue of post-operative pain following surface refractive procedures. **Fadlallah et al.** ¹⁶ and **Aslanides et al.** ¹⁷ observed a reduction in postoperative pain following transepithelial PRK. **Aslanides et al.** ¹⁷ found no notable disparities among both groups on the 1st day postoperative, However, they noted less pain in the tPTK-PRK group by the third day following the procedure. **Luger et al.** ¹⁸ documented lower postoperative pain in patients who underwent trans-PRK in contrast to alcohol assisted PRK, along with higher levels of patient comfort intra-operatively. Conversely, **Kanitkar et al.** ¹⁹ discovered that pain following mechanical epithelial removal using alcohol was lower compared to transepithelial laser removal.

Our results revealed statistically significant difference concerning epithelial healing time with rapid complete healing in the laser group compared to the manual group, **Aslanides et al.** ¹⁷ noted that by the third day following surgery, a majority of patients in the trans-PRK group exhibited total epithelial healing, demonstrating statistically significant differences compared to the PRK group, where most patients showed epithelial healing by the fifth day post-procedure. **Fattah et al.** ²⁰ documented faster epithelial closure with trans-PRK and a reduced occurrence of corneal erosions compared to the PRK group. The primary factor contributing to the expedited recovery of the corneal epithelium in trans-PRK is that the diameter of the epithelial excision aligns with the total ablation zone, thereby diminishing the wound surface area and abbreviating epithelial closure time. ²¹

CONCLUSION

In conclusion, PTK-CXL provides an efficient and secure treatment modality for keratoconic patients however there weren't statistically significant distinctions among both groups regarding higher order aberrations, still it results in less post-operative pain & rapid epithelial healing.

LIMITATIONS

We think that our study is limited by short follow up time (1 year), Also maybe by limited sample size.

RECOMMENDATIONS

we recommend **Enlarging sample size**, also we encourage novel studies with longer follow up periods.

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