



Corneal collagen cross linking after Conventional epithelial removal versus transepithelial phototherapeutic keratectomy (t-ptk) for treatment of keratoconus in females

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ABSTRACT

Background: Keratoconus (KC) is one of the most frequent disorders that affect corneal transparency. Excimer laser transepithelial phototherapeutic keratectomy (PTK), which is often applied to remove superficial corneal disease, has also been used to remove the epithelial layer prior to Corneal collagen cross-linking (CXL).

Aim: To compare the efficacy of using transepithelial PTK versus Conventional epithelial debridement prior to corneal collagen cross-linking in cases with progressive Keratoconus in females.

Patients and Methods: This was a prospective comparative investigation that was conducted on 40 female patients (80 eyes) with progressive keratoconus. Cases were separated Randomly into 2 groups. In Group (A): transepithelial phototherapeutic keratectomy was done for epithelial removal. And In Group (B): the epithelium was removed conventionally (manually).

Results: Epithelial removal via PTK results in almost the same outcomes as conventional manual debridement, for nearly all data points at all time interval, Additional, there is some evidence to suggest that phototherapeutic keratectomy improve UDVA & CDVA at the six-month interval where the phototherapeutic keratectomy group showed statistically significant improvement of the UDVA & CDVA compared to the manual debridement group.

Conclusion: Our study agreed with the opinion that transepithelial phototherapeutic keratectomy - corneal collagen cross-linking provides an efficient & secure therapeutic modality for keratoconic cases however Our results suggest that corneas with epithelial removal through t-PTK showed similar degrees of refractive and keratometric changes compared to others that was de-epithelialized manually which agreed with the retrospective comparative study of Gaster et al , On the contrary , In a study comparing different cases, Kymionis , et al found that cases who underwent t-PTK epithelial removal prior to CXL showed significant improvements in CDVA, UDVA, steep keratometry, & corneal astigmatism. However, no similar results were observed in the group of cases who had mechanical epithelium removal.

Keywords: Keratoconus; Corneal collagen cross-linking (CXL); Transepithelial phototherapeutic keratectomy (PTK); Conventional Epithelial removal.

INTRODUCTION

KC is a non-inflammatory, bilateral condition characterized by increasing corneal bulging & thinning. Because of its biomechanical instability, the cornea takes on a conical shape, resulting in irregular astigmatism & a consequent diminution of visual acuity. ¹

It usually appears in the 2nd decade of life, usually at puberty, although it has also been seen to develop sooner and later in life, and it typically advances until the 4th decade of life, when it usually stabilizes. ²

The corneal stroma, including approximately 80-90% of the total corneal thickness, contains of intricately arranged collagenous lamellae and specialized keratocytes responsible for synthesizing the stromal extracellular matrix (ECM) components. ^{3,4}

Keratoconus leads to the thinning of the corneal stroma, causing it to adopt a protruding conical shape. This change induces irregular astigmatism and myopia, resulting in vision impairment ranging from mild to severe. ⁵ It is a progressive condition, often beginning asymmetrically but eventually affecting both eyes. ⁶

Advances in diagnostic tools over the past two decades have enabled the early detection of keratoconus. The shape of the cornea is a crucial factor affecting corneal optics. ⁷

Collagen cross-linking is a procedural method involving the formation of covalent bonds among collagen fibrils within the stroma of the cornea. ⁸, In a span of 15 years, CXL has transitioned from a laboratory technique to become the preferred method for managing progressive ectasia. This procedure has demonstrated its effectiveness in stabilizing conditions, for example pellucid marginal degeneration, keratoconus, & ectasia following refractive laser surgeries, delivering favorable long-term outcomes for both adults and children. ⁹

Excimer laser t-PTK, which is applied to remove superficial corneal disease, has also been utilized to remove the epithelial layer prior to CXL. ¹⁰ The goal of t-PTK was to remove epithelial cells & smooth the anterior corneal stroma thus reduce keratoconus-induced irregular astigmatism, depending on the distinct pattern of corneal epithelium in keratoconic patients "epithelial doughnut" described by Reinstein et al ¹¹ where the central epithelial thickness in keratoconus is thinner than in normal corneas. ¹²

The purpose of this research was to compare the efficacy of applying transepithelial PTK versus Conventional epithelial debridement prior to corneal collagen cross-linking in cases with progressive Keratoconus in females.

PATIENTS AND METHODS

This was a prospective comparative research that was performed on 40 female cases (80 eyes) with progressive keratoconus.

Inclusion criteria: Female cases 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 taking including the following: (Age, complaint, and family history of keratoconus), complete ophthalmic test including Uncorrected visual acuity (UCVA), manifest refraction (detecting spherical equivalent & refractive astigmatism) & Best corrected visual acuity (BCVA). fundus examination & Slit-lamp examination.

The Pentacam Allegro Oculyzer, developed by WaveLight AG in Erlangen, Germany, utilizes Scheimpflug imaging to get precise measurements of keratometric readings, mean corneal astigmatism, and corneal thickness at the thinnest point of the cornea.

Cases were separated Randomly into 2 groups:

In Group (A): transepithelial phototherapeutic keratectomy was done for epithelial removal. And **In Group (B):** the epithelium was removed conventionally.

CXL was done to all patients (PESCHKE Trade CCL-VARIO Cross-linking Swissmed in Gdańsk, Poland. It produces UVA light with a wavelength of 370 nanometers & a power density of 18 mW/cm² for a duration of five minutes.

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) , then corneal epithelium was removed through 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 within 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/cm². 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± 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

distinctions were discovered among both group before the operation in any of the parameters (Table 1).

Table (1) pre-operative parameters, no statistically significant distinctions were discovered among both groups.

	PTK + CXL	CXL	
	preoperative	preoperative	p value
Age	26.12 ± 2.9	26.68 ± 2.82	0.384
UDVA	0.33 ± 0.08	0.35 ± 0.12	0.382
CDVA	0.55 ± 0.12	0.5 ± 0.12	0.064
Refractive values			
Spherical equivalent (D)	-3.45 ± 1.48	-3.56 ± 1.1	0.700
Cylinder (D)	-5.65 ± -0.98	-5.63 ± -0.89	0.905
Corneal thickness			
Thinnest location (μ)	493 ± 24.76	486 ± 20	0.168
Curvature values			
Mean corneal astigmatism	5.35 ± 1.74	5.5 ± 1.81	0.706
K-max (D)	58.05 ± 6.17	57.05 ± 5.83	0.458

By comparing the two groups, there was statistically significant distinction regarding UDVA & CDVA (P < 0.05) at 6-month interval, but it was statistically insignificant at 1- & 12-months post-operative (P > 0.05). There weren't statistically significant variations found among both groups regarding the spherical equivalent or the refractive astigmatism all through the study. (Table 2)

Table (2) comparison among the visual & refractive outcome of both groups throughout the follow up period.

		1 month	p-value	6 months	p-value	12 months	p-value
UDVA	PTK + CXL	0.26 ± 0.07	0.759	0.5 ± 0.1	0.041	0.55 ± 0.07	0.223
	CXL	0.25 ± 0.07		0.45 ± 0.12		0.58 ± 0.11	
CDVA	PTK + CXL	0.5 ± 0.1	0.273	0.65 ± 0.12	0.000	0.7 ± 0.1	0.163
	CXL	0.48 ± 0.11		0.55 ± 0.12		0.68 ± 0.06	
S. Eq. (D)	PTK + CXL	-3.5 ± 1.43	0.627	-2.94 ± 1.52	0.271	-2.81 ± 1.4	0.425
	CXL	-3.64 ± 1.07		-3.26 ± 1.07		-3.04 ± 1.09	

Cylinder (D)	PTK + CXL	-6.25 ± -1.07	0.112	-5.13 ± -0.89	0.214	-4.88 ± -0.89	0.214
	CXL	-5.88 ± -1.01		-5.38 ± -0.89		-5.13 ± -0.89	

There weren't statistically significant variations among both groups regarding the K max or the mean corneal astigmatism all through the study (Table 3).

Table (3) comparison between the keratometric outcomes of both groups throughout the follow up period.

		1 month	p-value	6 months	p-value	12 months	p-value
Mean corneal astigmatism	PTK + CXL	5.4 ± 1.67	0.703	4.95 ± 1.12	0.185	4.93 ± 1.13	0.334
	CXL	5.55 ± 1.83		5.4 ± 1.81		5.25 ± 1.79	
K-max (D)	PTK + CXL	58.5 ± 6.19	0.441	57.35 ± 5.93	0.705	57.05 ± 5.88	0.760
	CXL	57.45 ± 5.93		56.85 ± 5.83		56.65 ± 5.79	

There weren't statistically significant distinctions among both groups regarding the thinnest corneal location all through the follow up period (Table 4)

Table (4) comparison between the corneal thickness of both groups throughout the follow up period.

		1 month	p-value	6 months	p-value	12 months	p-value
Thinnest location (µ)	PTK + CXL	472.5 ± 22.62	0.113	480 ± 23.81	0.122	477 ± 23.33	0.121
	CXL	465 ± 19.05		472.5 ± 18.81		469.5 ± 19.29	

DISCUSSION

Our results suggest that corneas with epithelial removal through t-PTK showed similar degrees of refractive & keratometric alterations compared to others that was deepithelialized manually. epithelial removal via PTK results in almost the same outcomes as conventional manual debridement, for nearly all data points at all time interval, Additional, there is some evidence to suggest that phototherapeutic keratectomy improve UDVA & CDVA at the six-month interval where the phototherapeutic keratectomy group demonstrated statistically significant improvement of the UDVA & CDVA compared to the manual debridement group. Also PTK group showed significant improvement of the refractive astigmatism starting from the 6 months interval and all through the follow up period compared to baseline value unlike the manual group which showed significant improvement at 12 month interval (still there isn't significant distinction among the two groups at any time interval), This implies that PTK may initially induce a greater flattening impact on the cornea compared to manual debridement , that agrees with the postulation suggesting that epithelial removal through PTK ablates more stromal tissue from the centre of the cone in

keratoconic cornea according to the doughnut epithelial pattern demonstrated by **Reinstein et al.**¹¹

The findings of our study were consistent with the retrospective comparative investigation conducted by **Gaster et al.**¹³ Their research showed similar results among transepithelial phototherapeutic keratectomy - corneal collagen cross-linking & mechanical epithelial removal prior to CXL after a twenty-four-month follow-up period. However, they reported that CDVA significantly improved only in the transepithelial phototherapeutic keratectomy- corneal collagen cross-linking group in the 24-month.¹⁴

In contrast, in a study conducted by **Kymionis et al.**¹⁵, they found that patients who had t-PTK epithelial removal prior to CXL demonstrated a significant improvement in CDVA, uncorrected distance visual acuity, steep keratometry, & corneal astigmatism twelve months after the surgery. On the other hand, the group of cases who had mechanical epithelial removal didn't show similar results.

In a prospective research conducted by **Grentzelos et al.**¹⁶, it was determined that utilizing t-PTK for epithelial removal is advantageous compared to mechanical epithelium removal before CXL. This method resulted in a faster & more substantial improvement in visual, refractive, & keratometric parameters. The t-PTK group showed significant improvements in both UDVA & CDVA, as well as in keratometric values (both steep & flat), starting from the first year after surgery. These improvements were significant throughout the whole follow-up duration. Corneal astigmatism showed significant improvements from the 2nd year after the surgery. In the group that had manual epithelial removal, UDVA improved significantly, while CDVA didn't demonstrate a significant improvement after the surgery. Both the steep & flat keratometry readings showed significant improvement, but only after a period of two years of follow-up. However, there wasn't significant improvement observed in corneal astigmatism following the surgery. The manual group had a significant enhancement in keratometric readings during the 2nd following surgery year, which they regret to the ongoing long-term flattening impact of the cornea caused by CXL.^{15,17}

The distribution of corneal epithelial thickness before surgery, (which is not examined in both studies), may be the most crucial factor that could impact the outcome of t-PTK during corneal collagen cross-linking (CXL). Another potential factor that might influence the outcome of transepithelial phototherapeutic keratectomy is the laser ablation profile.¹³

Gaster et al.¹³ used the VISX Star S4 excimer laser from Advanced Medical Optics in Santa Ana, CA, while we used the Allegretto WaveLight from WaveLight Laser Technologies in Erlangen, Germany. Therefore, the difference in excimer laser platforms could provide an added reason for the different findings.

In a retrospective, comparative research conducted by **Kapasi et al.**¹⁸ it was found that the t-PTK-CXL group had better visual results compared to the conventional group at twelve months following surgery. However, significant improvement in corrected distance visual acuity was only observed in the manual group at twelve months following surgery.

CONCLUSION

Our study agreed with the opinion that transepithelial phototherapeutic keratectomy- corneal collagen cross-linking provides an efficient and secure therapeutic modality for keratoconic patients however Our results suggest that corneas with epithelial removal through t-PTK showed similar degrees of refractive and keratometric changes compared to others that was de-epithelialized manually which agreed with the retrospective comparative study of Gaster et al, On

the contrary , Kymionis, et al. found that patients who underwent t-PTK epithelial removal throughout CXL showed significant improvements in CDVA, UDVA, steep keratometry, & corneal astigmatism. However, no equivalent results were observed in the group of cases who underwent mechanical epithelium removal.

LIMITATIONS

We think that our study is limited by short follow up time (1 year), also by lack of assessment of the preoperative corneal epithelial thickness and allocation (which was not measured during any of the similar studies) although it was of high importance.

RECOMMENDATIONS

We recommend studying the corneal epithelial map and putting it into consideration when fashioning the PTK ablation profile, also we encourage novel studies with longer follow up periods.

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