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ORIGINAL ARTICLE

Corneal Collagen Cross Linking With Photo-Activated Chromophore for keratitis (PACK-CXL) As Adjunctive Therapy for Infectious Keratitis .

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ABSTRACT

Background : The aim of this work is to evaluate efficacy and safety of corneal collagen cross linking as adjunctive therapy for treating infectious keratitis.

Methods: This is a randomized prospective controled clinical trial. Seventy eight (78) eyes with clinically suspected infectious keratitis were enrolled in this study. The range of age of the enrolled patients was more than or equal to18 years. They were randomly classified into two groups each of 39 eyes, Group A(control group): received topical appropriate conventional broad spectrum antimicrobial therapy alone based on sensitivity reports and Group B: received combined topical appropriate conventional broad spectrum antimicrobial therapy based on sensitivity reports and corneal collagen cross linking for infectious keratitis **(PACK-CXL)**. Identification of organisms was done by lab study before treatment. Corneal healing was evaluated by corneal examination and anterior segment OCT (AS-OCT). Written informed consent was obtained from all participants and the study was approved by the research ethical committee of Faculty of Medicine, Zagazig and Cairo University. The work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Results: Complete healing and resolution (Successful treatment) was observed in 76.9 % of eyes and 97.4 % of patients in groups (A & B), respectively. They showed a statistically highly significant difference (P <0.001). Mean resolution period was 10.87±3.28 and 7.02±2 weeks in group (A & B), respectively, with statistically significant difference (P = 0.002) between both groups, being shorter in group (B).Only 2.6% of our cases had resistance to treatment in CXL compared to group A, who had 23.1% of resistance. There was no statistically significant difference between both groups as regards complications of treatment.

Conclusions: PACK-CXL is a promising , non-invasive and available treatment option. It has a synergistic effect with antimicrobial treatment that gives a good outcome results in treatment of infectious keratitis. Also, it avoids the antibiotics resistance that has become rapidly spreading worldwide.

Keywords: Corneal cross linking, PACK-CXL, infectious keratitis.

INTRODUCTION

Infectious keratitis is a serious ocular infection that can potentially lead to severe visual dysfunction and is a major cause of blindness worldwide. Most of the keratitis usually appears unilateral but there have been sporadic case reports of bilateral infectious keratitis [1].

Patients with infectious keratitis often present with marked visual loss, pain,

hypopyon and a poorly visualized posterior segment [2].

Most patients with bacterial keratitis can be cured using fortified antibiotics or fluoroquinolones without microbial identification [3]. However, inappropriate use of antibiotics may lead to bacterial resistance to the empirical regimen [4] and confusing clinical presentations, which are difficult to differentially diagnose [5].

Keratomycosis or fungal keratitis is a widely distributed fungal infection of the cornea caused by a broad spectrum of filamentous fungi and yeasts [6]. This infection could be a sight-threatening condition which may result in vision loss. There is a geographical origin-related variation in the distribution of the most common etiologies [7]. Climatic condition is another affecting factor. In tropical and subtropical regions, filamentous fungi are predominant while it is believed that in temperate climates, yeast are more frequent [8].

Despite having appropriate antimicrobial treatments for most of the pathogens implicated in infectious keratitis, clinical outcomes are often poor. Adjuvant therapies that focus on modifying the immune response to the infection thereby reducing the corneal melting and scarring which ultimately leads to poor vision, may have the greatest potential to improve clinical outcomes [9].

Techniques such as Corneal Collagen Cross-Linking (CXL), a combination treatment with ultraviolet (UVA) light and riboflavin (vitamin B2) were proposed by ***Wollensak et al.*** [10] which has become an established treatment option for improving the biomechanical stability and resisting the progression of keratoconus. Further indications for the clinical use of CXL emerged rapidly since then, including Fuch's corneal dystrophy [11] , pseudophakic bullous keratopathy as well as infectious keratitis [12].

Recently, to distinguish the use of CXL for the treatment of infectious keratitis from CXL for keratoconus, the term photoactivated chromophore for infectious keratitis (PACK)-CXL was created at the ninth cross-linking congress in Dublin, Ireland, in 2013 [13].

In this study we tried to evaluate the role of corneal cross-linking in the treatment of infectious keratitis as adjunctive therapy.

PATIENTS AND METHODS

This is a randomized prospective controled clinical trial . Seventy eight (78) eyes with clinically suspected infectious keratitis were enrolled in this study . The range of age of the enrolled patients was more than or equal 18 years. These patients were collected from the outpatient clinics and inpatient section of the Ophthalmology Department, Zagazig and Cairo University Hospitals from January 2016 to June 2019.

Patients were randomly assigned into two equal groups; Group A(control group): 39 eyes which received topical appropriate conventional broad spectrum antimicrobial therapy alone which was modified according to antibiotics sensitivity reports. **Group (B):** 39 eyes which received combined topical appropriate conventional broad spectrum antimicrobial therapy which was modified according to antibiotics sensitivity reports. and corneal collagen cross linking **(PACK-CXL).** Written informed consent was obtained from all participants and the study was approved by the research ethical committee of Faculty of Medicine, Zagazig and Cairo University. The work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Inclusion criteria: included Patients with clinically suspected infectious keratitis and confirmed by both direct smears and cultures; Central corneal thickness (CCT) of more than 400 µm with epithelium as measured by anterior segment OCT (AS-OCT) ; Infiltrates involving less than 250 µm depth of corneal thickness (up to midstromal level) and/or safety zone above the corneal endothelium without infiltrations of more than 100µm as measured by Anterior segment OCT (AS-OCT) and patients of more than 18 years.

Exclusion criteria: included perforated corneal ulcers or impending corneal perforation; Scleral involvement or corneal involvement near to limbus by 1 mm; Total corneal involvement; Evidence of endophthalmitis either clinically or by B-scan; Evidence of viral keratitis both by history or clinical examination; Known allergy to study medications; Pregnancy or lactation; Non-infectious keratitis and affected eye with no light perception.

Laboratory work up:

- The material obtained from scraping was inoculated on transport medium containing nutrient broth then sent to laboratory to be directly inoculated either on a slide for direct bacterial and fungal identification under high magnification by the microscope without stains **(called direct smear)** or on culture media as:1-Nutrient agar, blood agar and chocolate agars: for bacteria. 2- Sabouraud dextrose agar and blood agars: for fungi. 3-Non nutrient agar with E. coli overlay: for acanthamoeba.
- The growth on culture media was used to form a film stained with different stains for visualization of the different types of microbes microscopically **(called direct film).**

Treatment Protocol:

- Fourth generation fluoroquinolones (e.g. gatifloxacin and moxifloxacin) as monotherapy for bacterial keratitis.
- Voriconazole 1% or natamycin 5 % and itraconazole 1% for fungal keratitis.
- Topical anti-amoebic agents (e.g. polyhexamethylenebiguanide 0.02% or hexamidine 0.1% and aminoglycosides) for acanthamoeba keratitis.
- Treatment is modified according to results of culture and sensitivity.
- Corneal CXL was performed by de-epitheliation, riboflavin drops (Medio-Cross riboflavin–dextransolution, 0.1%) are instilled topically on the cornea every 2 minutes for a period of 30 minutes, cornea then illuminated using a Phoenix UV-A system (Peschke Meditrade GmbH, Huenenberg, Switzerland), UVA 365 nm, with an irradiance of 3 mW/cm^2 and a total dose of 5.4 J/cm^2 over 30 minutes in 2 minutes interval, then bandage contact lens is used. Modified medical treatment according to antibiotics sensitivity reports was continued after PACK-CXL.

Follow-up:

Follow up regimen: patients were evaluated daily by slit lamp for 1 week, every week for 1 month and every month for 3 months. Clinical photos using both photo slit lamp and AS-OCT were taken before and after treatment. Follow ups included reporting signs of healing as (diminished stromal infiltrates and abscess size up to complete resolution ; healing of epithelial defects together with corneal vascularization).

Statistical analysis:

The collected data were coded, entered, presented and analyzed by computer using a data base software program, Statistical Package for Social Science (SPSS) version 20. Mean ± SD, chi-square and t-test were used for determination of significance (P value). P <0.05 is considered significant.

RESULTS

This randomized prospective interventional controlled study included seventy eight (78) eyes with clinically suspected infectious keratitis and confirmed by cultures and/or smears were enrolled in this study. These patients were distributed into two groups: Group A (control group): 39 eyes received topical appropriate conventional broad spectrum antimicrobial therapy alone. They included 26 males (66.7 %) and 13 females (33.3 %). Their mean age was 58.33±13.2 years. Thirty (30) patients (76.9 %) were from rural areas, while 9 patients (23.1 %) were from urban areas **(Table 1).**

Group B: 39 eyes received same treatment as group (A) plus corneal collagen cross linking for infectious keratitis (PACK-CXL). They included 22 males (56.4 %) and 17 females (43.6 %). Their mean age was 51.71±14.9 years. Twenty two (22) patients (56.4 %) were from rural areas, while 17 patients (43.6 %) were from urban areas **(Table 1).** They showed a statistically non-significant difference (p>0.05) indicating that they were matched in age and sex.

Complete healing and resolution (Successful treatment) was observed in 76.9 % of eyes and 97.4 % of patients in groups (A & B), respectively. They showed a statistically highly significant difference (P <0.001) **(Table 4).** Mean resolution period was 10.87±3.28 and 7.02±2 weeks in group (A & B), respectively, with statistically significant difference (P = 0.002) between both groups, being shorter in group (B) **(Table 5)**. Only 2.6% of our cases had resistance to treatment in CXL compared to group A, who had 23.1% of resistance. There was no statistically significant difference between both groups as regards complications of treatment. **(Table 7).**

Table (1): Major risk factors for infectious keratitis among study groups

Risk factor	Group A		Group B		Total		χ^2	P
	N	%	N	%	N	%		
Plant trauma	18	46.2	16	41.0	34	43.6	0.287	0.59
Non plant trauma	7	18.0	8	20.5	15	19.2	0.114	0.714
Contact lens	1	2.6	2	5.1	3	3.8	0.81	0.36
Uncontrolled DM	6	15.4	8	20.5	14	17.9	0.71	0.39
Dry eye	2	5.1	2	5.1	4	5.1	0.00	1.00
Prolonged Topical steroids use	1	2.6	2	5.1	3	3.8	0.81	0.36
Ocular Surgery (Mainly corneal)	4	10.2	1	2.6	5	6.4	3.41	0.06
Total	39	100	39	100	78	100		

χ^2= Chi square, P>0.05 = Not significant. DM: diabetes mellitus.

Table (2):Best corrected visual acuity (BCVA) at the beginning of the study.

BCVA	Group A		Group B		Total		χ^2	P
	N	%	N	%	N	%		
≥ 6/60	4	10.4	2	5.2	6	7.6	0.98	0.62
CF – 6/60	1	2.6	2	5.2	3	3.8		
HMGP or worse	34	87.0	35	89.7	69	88.46		
Total	39	100	39	100	78	100		

CF= counting finger, HMGP= Hand movement good projection, P>0.05 = not significant.

Table (3): Results of culture media and direct films among study groups

Culture	Group A		Group B		Total		χ^2	P
	N	%	N	%	N	%		
G +ve bacteria	7	17.9	11	28.2	18	31.1	4.38	0.29
G –ve bacteria	4	10.3	5	12.8	9	11.5		
Acanthamoeba	1	2.6	1	2.6	2	2.6		
Fungi	24	61.5	21	53.8	45	57.7		
Mixed	3	7.6	1	2.6	4	5.1		
Total	39	100	39	100	78	100		

χ^2= Chi square, P>0.05 = Not significant.

Table (4): Outcome of treatment among study groups (Success distribution)

Outcome	Group A		Group B		Total		χ^2	P
	N	%	N	%	N	%		
Failure	9	23.1	1	2.6	10	12.8	7.34	0.007*
Success	30	76.9	38	97.4	68	87.2		
Total	39	100	39	100	78	100		

χ^2= Chi square, * P<0.01 = statistically significant.

N.B.:

- Treatment outcome was considered failed when there was no response to treatment either medical treatment alone ; with or without PACK-CXL and there were no signs of healing or resolution (as diminished infiltrates size, healing of epithelial defects and vascularization...etc) after 3 successive weeks. However, treatment outcome was considered successful when there was good response to treatment either medical treatment alone ; with or without PACK-CXL and there were signs of healing or resolution (as diminished infiltrates size, healing of epithelial defects and vascularization...etc) within 3 successive weeks.

Table (5): Duration of healing and resolution of infectious keratitis among study groups

Duration	Group A		Group B		t-test	P
	Mean	±SD	Mean	±SD		
Weeks	10.87	3.28	7.02	2.0	-6.175	0.002*

t-test = paired t-test, * P<0.01 = statistically significant.

Table (6):Best corrected visual acuity (BCVA) at the end of the study.

BCVA	Group A		Group B		Total		χ^2	P
	N	%	N	%	N	%		
≥ 6/60	4	10.4	4	10.4	8	10.4	0.32	0.89
CF – 6/60	2	5.2	3	7.6	5	6.4		
HMGP or worse	33	84.6	32	79.5	65	83.3		
Total	39	100	39	100	78	100		

CF= count finger, HM= Hand movement good projection, P>0.05 = not significant.

Table (7):Complications of treatment among study groups

Complications	Group A		Group B		Total		χ^2	P
	N	%	N	%	N	%		
No	36	92.3	38	97.4	74	94.9	2.05	0.35
Impending perforation	2	5.2	0	0.0	2	2.6		
Perforation	1	2.6	1	2.6	2	2.6		
Total	39	100	39	100	78	100		

P>0.05 = not significant.

DISCUSSION

In this study we tried to evaluate the role of corneal cross-linking in the treatment of infectious keratitis as adjunctive therapy. For this purpose we selected 78 eyes of 78 patients with clinically suspected infectious keratitis confirmed by cultures and/or smears. These patients were distributed into group A: included 39 eyes which received topical appropriate conventional broad spectrum antimicrobial therapy alone and group B: involved 39 eyes which received the same

treatment of group A combined with corneal collagen cross linking for infectious keratitis (PACK-CXL).

Group (A) included 26 males (66.7 %) and 13 females (33.3 %). Their mean age was 58.33±13.2 years. Thirty (30) patients (76.9 %) were from rural areas, while 9 patients (23.1 %) were from urban areas. Group (B) included 22 males (56.4 %) and 17 females (43.6 %). Their mean age was 51.71±14.9 years. Twenty two (22) patients (56.4 %) were from rural areas, while 17 patients (43.6 %) were from urban areas. Statistically there is insignificant difference between the two groups as regard age, sex and residence (P >0.05).

This coincides with ***Said et al.*** [13] who studied both sexes patients over 18 years of age and excluded younger than 18 years. But they oppose us in gender as they enrolled 8 men and 13 women with a mean age of 37.3 years. Also, ***Chew and Woods*** [14] found that the males to females ratio was approximately 2:1 and the mean age was 48 years, which was similar to our study. However, ***Queensland Health*** [15] reported this ratio as 1:1.

Chew and Woods [14] found also that about 80% of fungal keratitis patients were in rural areas especially that live in tropical and subtropical climates however, bacterial keratitis were nearly similar in urban and rural areas, which was similar to ***Queensland Health*** [15] study.

The risk factors in groups Aand B were vegetable (or plant) trauma was reported in 46.2% & 41.0% of patients, while non-vegetable trauma was reported in 18%& 20.5% of patients, respectively. Plant trauma was a major risk factor of fungal keratitis in our study, similar results were reported by ***Wilhelmus and Jones*** [16] who found that trauma due to plants or dirt was the risk factor in one half and 69% occurred during the hot, humid summer months.

As regard visual acuity in group A, BCVA after treatment of HMGP was reported in 33 patients (84.6 %), BCVA of CF up to 6/60 was reported in 2 patients (5.2 %) and BCVA of 6/60 or better was reported in 4 patients (10.4 %). In group B, BCVA after treatment of HMGP was reported in 32 patients (79.5 %), BCVA of CF up to 6/60 was reported in 3 patients (7.6 %) and BCVA of 6/60 or better was reported in 4 patients (10.4 %). Comparison between both groups showed a statistically insignificant difference (P >0.05).Similar to our results, ***Said et al.*** [13] found that the outcome of average corrected distance visual acuity after complete healing was 1.64 ± 0.62 logMAR in the PACK-CXL group and 1.67 ± 0.48 logMAR in the control group, they found a statistically insignificant difference (P = 0.68).This also coincides with ***Anwar et al.*** [17] who concluded that poor outcome was expected after treatment of infectious keratitis especially fungal keratitis and acanthamoeba.

Regarding the causative organisms in group (A): Fungal cultures, either filamentous fungi or yeasts, were reported in 24 patients (61.5 %). Gram positive (G +ve) bacteria were reported in 7 patients (17.9%), while Gram negative (G -ve) bacteria were reported in 4 patients (10.3 %). Mixed infectious keratitis, bacterial and fungal keratitis, was reported in 3 patients (7.6 %). Acanthamoeba was reported in only one patient (2.6 %), while in group (B): Fungal cultures, either filamentous fungi or yeasts, were reported in 21 patients (53.8 %). Gram positive (G +ve) bacteria were reported in 11 patients (28.2 %), while Gram negative (G -ve) bacteria were reported in 5 patients (12.8 %). Mixed infectious keratitis, bacterial and fungal keratitis, was reported in only 1 patient (2.6 %). Acanthamoeba was reported in only one patient (2.6 %). There showed a statistically non-significant difference between the two groups (P >0.05).

The American Academy of Ophthalmology enumerates the causes of infectious keratitis as bacterial, fungal, viral, parasitic, contact lenses, traumatic injury and vitamin A deficiency (rare). Mycotic keratitis, commonly known as fungal keratitis, accounts for approximately 44% of all cases of microbial keratitis, depending upon the geographic location. Overall, it is more common in tropical and subtropical areas. The

genera that commonly cause infection of the cornea include *Fusarium*, *Aspergillus*, *Curvularia*, *Bipolaris*, and *Candida* [18]. The high prevalence of fungal keratitis in our series (61.5%) in group (A) and (53.8%) in group (B) may be attributed to the bad hygiene especially in rural areas of our district.

Gram-positive organisms were previously thought to be the commonest causative organism [19]. This is in contrast to findings previously reported by ***Hagan et al*** [20]. and ***Stefan and Nenciu*** [21]. in more temperate climates and another study in tropical Malaysia. However, these were performed on all types of microbial keratitis regardless of etiology [22]. In the study of ***Lim et al.*** [23], no Gram-positive organisms were isolated in culture-positive eyes. *Pseudomonas aeruginosa* was the commonest Gram-negative organism isolated in their study. Similar to our study, an Indian study by ***Garg et al.*** [24] stated that Acanthamoeba keratitis accounts for 2% of microbiology-proven cases of keratitis. Trauma and exposure to contaminated water are the main predisposing factors for the disease. Association with contact lenses is seen only in small fraction of cases.

Complete healing and resolution (Successful treatment) was observed in 30 patients (76.9 %) and 38 patients (97.4 %) in groups (A & B), respectively. They showed a statistically highly significant difference (P <0.001). Mean resolution period was (10.87±3.28) and (7.02±2) weeks in group (A & B), respectively, with statistically significant difference (P = 0.002) between both groups, being shorter in group (B).

Said et al. [13]. found had shorter resolving time than us as they found the mean duration to complete healing was 39.76 ± 18.22 days in the PACK-CXL group and 46.05 ± 27.44 in the control group, however they found a statistically insignificant difference between the two groups (P = 0.68) which opposing our results.

In group B with CXL a higher successful rate was observed than group A that we used antimicrobial only without CXL. CXL seems to be have a powerful synergistic effect for treatment of infectious keratitis. In agreement with our study was the animal study by ***Rapuano et al.*** [25]. that stated that CXL has shown equal efficacy against antibiotic-sensitive and antibiotic-resistant strains of bacteria. CXL has been shown in vitro to have a strong bactericidal effect in a single treatment, and our experiments show robust bactericidal activity with a one-time treatment. In a live rabbit model, CXL has shown to decrease the size of corneal scarring and shorten healing time, as this one-time intervention replaces weeks of frequent administration of toxic antimicrobials to the ocular surface [26].

CXL had a direct antimicrobial action, in addition to direct microbial killing; CXL induces cross-linking in the extracellular matrix and enhances corneal stromal resistance [27].

In the present study, 9 patients (23.1 %) and 1 patient (2.6 %) in group (A & B) failed to respond to treatment, respectively. They showed a statistically highly significant difference (P <0.001). So, only 2.6% of our cases had resistance to treatment in CXL compared to group A, who had (23.1%) of resistance.

The use of CXL in bacterial keratitis, mainly in cases characterized by corneal melting, has been suggested before and reported as partly successful. The use of Pack-CXL technique prevented the continual melting of the cornea caused by fungal keratitis, and eventually allowed corneal transplantation and preservation of the eye's viability and function [28].

Opposing our study was the study of ***Vajpayee et al.*** [29] claimed that the practice of CXL combined with drug therapy did not increase the cure rate. After studying with 41 cases, they found that there was no significant difference between monotherapy on CXL and CXL combined with fungal regimen.

In group (A), no complications of treatment were reported in 36 patients (92.3 %), impending corneal perforation with descematocele was reported in 2 patients (5.1 %) and actual corneal perforation was

reported in 1 patient (2.6 %). In group (B), no complications of treatment were reported in 38 patients (97.4%) and actual corneal perforation was reported in 1 patient (2.6 %). Comparison between both groups showed a statistically insignificant difference (P >0.05).

These were nearly similar to ***Said et al.*** [29] who presented three patients in the control group had corneal perforation, whereas patients treated with PACK-CXL did not experience this complication.

Uddaraju et al. [30] evaluated CXL curative effect on deep matrix of fungal keratitis, just to find that CXL group had a higher perforation rate than the control group. Most of the clinical researches aim at drug-resistant infectious keratitis for trial treatment. On account of the different time antimicrobial effects and different level of the keratitis, implement CXL for advanced progressive keratitis, further aggravated the severity of keratitis, late intervention may cut down the effectiveness of CXL treatment.

CONCLUSION

PACK-CXL is an easy, available, yet effective topical cross-linking solution that could expand the reach of therapy for infectious keratitis to areas of the world without access to antibiotics or antifungals. It might be a useful adjunctive therapy for infectious keratitis together with conventional medical treatment.

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