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Original Article

Effect of PACK Corneal Cross Linking on Resistant Bacterial Keratitis

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ABSTRACT

***Background and objectives**. Corneal ulcer is a potentially blinding corneal disease that is traditionally treated with effective anti-microbial and, at times, more intrusive methods like keratoplasty. The motivation behind this study is to perceive how effective PACK corneal collagen cross-linking is in resistant corneal ulcers. Collagen cross-connecting (CXL) with UV light-initiated riboflavin is a corneal surface methodology used to treat keratoconus and corneal ectasia. It has recently been introduced for the management of infectious keratitis, particularly ulcers resistant to antimicrobial therapy or associated with corneal melting, due to the known microbicidal and corneal stiffening effects of ultraviolet irradiation and photo activated riboflavin. **Methods.** Seven eyes of seven patients with corneal ulcers included in this prospective interventional study in which patients not responding to conventional antibiotic therapy in first 7days, were treated with CXL. The procedure was performed according to the accelerated protocol CXl. **Results.** The mean age of patients was 65.7 years old (57.4 male, 42.9 female), mean ulcer size (3.6+-1.88*3.7+-1.89). Preoperative medications were continued after CXL in all cases. Microbiological exams revealed Pseudomonas aeruginosa in two cultures, in 5 of 7 eyes, progression of corneal melting was halted and complete epithelialization occurred. With mean duration of (30.3+-18.2), two eyes not responding to pack cxl and keratoplasty was needed. **Conclusion**. CXL can be considered as a promising new treatment in the management of refractory non healing bacterial keratitis with superficial stromal infiltrate.*

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INTRODUCTION

According to the World Health Organization (WHO), corneal disorders are a leading cause of vision loss and blindness. Every year, 1.5-2 millions of new cases of corneal ulcers that lead to corneal blindness [1]. To decrease the extent of corneal scarring, microbial keratitis requires vigorous treatment [2,3]. Topical antibiotics are mainstay to treat corneal ulcers. However, multidrug-resistant bacteria arouse because widespread of their use and alternate options are required [4,5]. Corneal collagen cross-linking (CXL) is a treatment that uses a photosensitizer (riboflavin) and ultraviolet (UV) radiation to promote the creation of inter- and intra-fibrillar covalent connections in the cornea. It's used to treat corneal ectasia such as keratoconus, pellucid marginal degeneration, and ectasia following refractive surgery [5]. CXL may be also useful in nonectatic problems, according to a growing number of studies [6,7].

The antibacterial effects of riboflavin photo-activation have been shown to depend on riboflavin's ability to intercalate itself between the nucleotides of DNA and RNA [8,9]. When riboflavin is triggered by light, it oxidizes guanine [10] and produces reactive oxygen species [11,12], so interferes with microbial replication and so reduces pathogen load [13], riboflavin that has been activated. Furthermore, the direct antibacterial action UVA irradiation has a potential beneficial effect (Wong, T et al., 2003; Goodrich, 2000). The term photoactivated chromophore for infectious keratitis (PACK)-CXL was invented in 2013 at the ninth cross-linking congress in Dublin, Ireland, to distinguish CXL for infectious keratitis from CXL for progressive keratoconus [14]. UVA light is also known to have a disinfectant effect. It has traditionally been used for drinking water disinfection as well as air/surface disinfection. Since the beginning of time, this method has been used to inactivate viruses, bacteria, and parasites during 1960s. Riboflavin exposed to visible or UV light could be used to inactivate the RNA-containing tobacco mosaic virus, according to Japanese researchers [15]. Several in vitro and in vivo studies have demonstrated that riboflavin and UVA are effective against a variety of pathogens [16-23]. Furthermore, crosslinking with

riboflavin and UVA could stop collagenolysis and corneal melting in severe corneal ulceration [24]. In this paper, we describe our experience with CXL in the treatment of infectious keratitis that was resistant to conventional therapy in 7 patients.

METHODS

Study design and patients

This prospective interventional case series study was conducted between June 2020 and May 2021 at Dar Altamuz private eye center included seven eyes of seven patients with bacterial corneal ulcers. Only patients included those that presented with clinical signs of bacterial corneal ulcers (proven by culture) and poorly respond to initial conventional antibiotics in first 7 days, first medical seeking and did not receive any antibiotics before visiting our clinic. Exclusion criteria were the presence of underlying autoimmune disease, other microbial keratitis instead of bacterial one, sterile corneal ulcer. Slit lamp bio microscopy was used to assess ulcer details, anterior chamber condition, and ulcer size.

Experiment

After applying topical anesthesia Benox® (benoxinate hydrochloride 0.4%), samples from edges of the corneal ulcers were taken by sterile swabs from and included in culturing kit, then placed into the prepared broth and sent for culture and sensitivity.

Initial antimicrobial therapy consisted of fortified vancomycin eye drops 50 mg/ml (to a 500 mg vial of vancomycin ,10ml of artificial tear solution added to supply 50mg\ml)and fortified ceftazidime eye drops 50 mg/ml (9.2ml of artificial tears added to avail of 1g ceftazidime powder for injection to dissolve 5ml of this solution are taken and added to5 ml of artificial tears) applied hourly in first two days then every two hours in third day after the sensitivity culture results we decided if the patient continue on fortified vancomycin or fortified ceftazidime. The treatment continued for 7 days.

One patient had history of contact lens wearer, two patients with history of trauma and two patients with previous ocular surgeries, 3 patients had dry eye and diabetic. (Details shown in table1)

After 7 days, PACK Cross-linking was done to all non-responding patients based on accelerated protocol started with putting of topical anesthesia Benox® every 5min for 30 min. then epithelial removal with blade 15 around ulcer was performed an isotonic solution of 0.1% riboflavin is then applied to the cornea every 2minutes for 20 minutes to saturate the stroma. The cornea was then exposed to UVA radiation of 365 nm wavelength with an energy density of 9 mW/cm2 for 10 minutes.

Antimicrobial treatment was continued as before after PACK- CXL treatment, and daily follow up examinations were conducted until healing was complete. Complete recovery was achieved as re-epithelialization of the corneal epithelial defect, absence of anterior chamber activity and elimination of hypopyon, stromal infiltrate is cleared.

Statistical analysis

Statistical package for social science (SPSS), version 23.0 was utilized in analysis. Categorical variables were tabulated in proportions or depicted in Pie charts or Bar charts. Measurement variables were described in mean and standard deviation (SD) as well as range values.

Table 1. Clinical data of patient with bacterial keratitis

Case	1	2	3	4	5	6	7
Ulcer dimensions in millimeters* millimeters	2.5*3	2*2	1*1	7*7	4*4	5.5*4.5	4*4
Ulcer site	Central	Central	Para-central	Central	Central	Central	Central
Hypopyon	Yes	no	no	yes	yes	yes	yes
Depth of infiltration	Anterior 1/3 of stroma	Anterior 1/3 of stroma	Anterior 1\3 of stroma	Full thickness	Middle 2\3	Near total	Anterior 1\3 of stroma
Detected microbe	PA	Enterobacter	Staph. aureus	PA	Mixed (strept. and coagulase-staph	Strep pneumonae	Staph epidermides
BCVA at presentation (Log MAR)	HM (2.3)	HM (2.3)	CF 3m (1.5)	HM (2.3)	HM (2.3)	CF 1m (1.8)	CF-1m (1.8)

BCVA at complete resolution (Log MAR)	CF 1m (1.8)	CF-3m (1.5)	6/60 (1.0)	No response	C.F 1m (1.8)	no response	6/60 (1.0)

PA-pseudomonoues aerugenosa, Strept. Streptococcus, Staph. Staphylococcus HM-hand movement, CF-counting finger, BCVA-best corrected visual acuity

RESULTS

A total of 7 patients with bacterial corneal ulcers not responding to the conventional antibiotics protocol in first 7 days received pack CXL (clinical data are shown in table 1). The age of the patients ranged from (38-85) with a mean age of 65.7 years. male to female ratio was 1.33:1 (Figure 1).

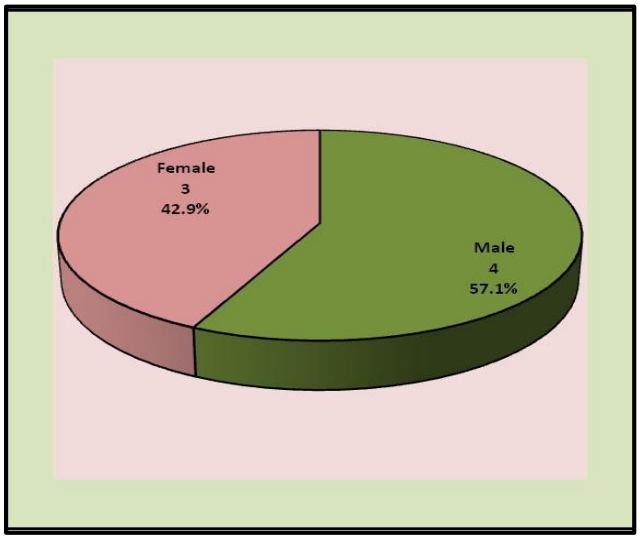

Figure 1: Distribution of study population according to gender

The best corrected distance visual acuity at presentation was 2.30+-0.35 logarithm of the minimum angle of resolution (log MAR) units, isolated causative microorganisms are shown in figure 2 with most common isolated microorganisms was staph and *Pseudomonas aerueginosa* which isolated from 2 cultures.

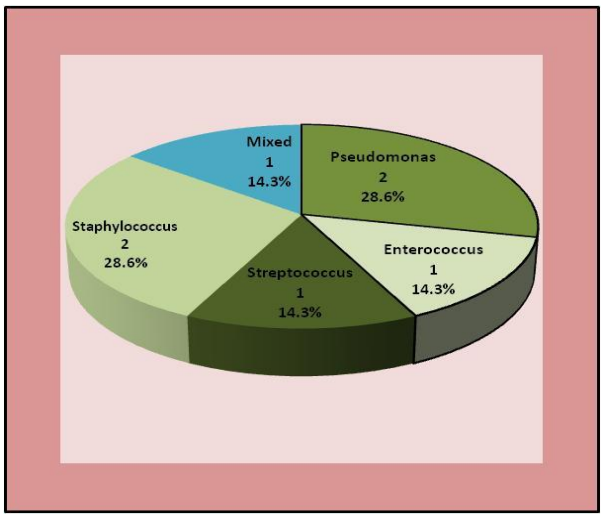

Figure 2. Distribution of study population according to culture result of microorganism

Most of cases had centrally located ulcer (6/7; 85.7%) (Figure 3), and also most had associated Hypopyon (5/7; 71.4%). All of cases had predisposing factors most frequently dry eye disease and diabetes (Figure 4).

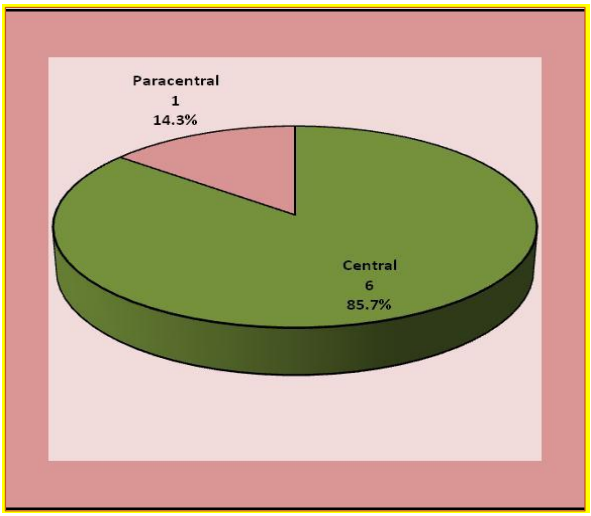

Figure 3. Location of the corneal ulcers

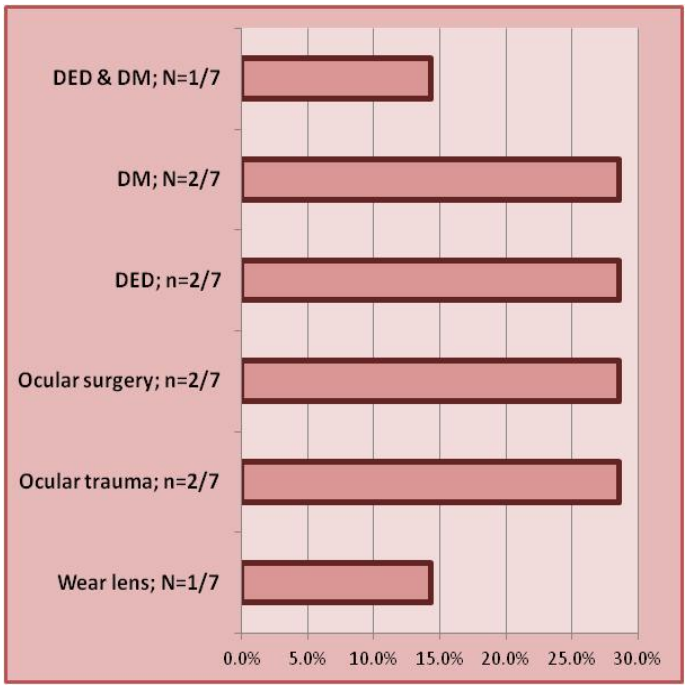

Figure 4. Ocular history in eye with microbial keratitis and history of systemic diseases
DED Dry eye disease, DM Diabetes mellitus

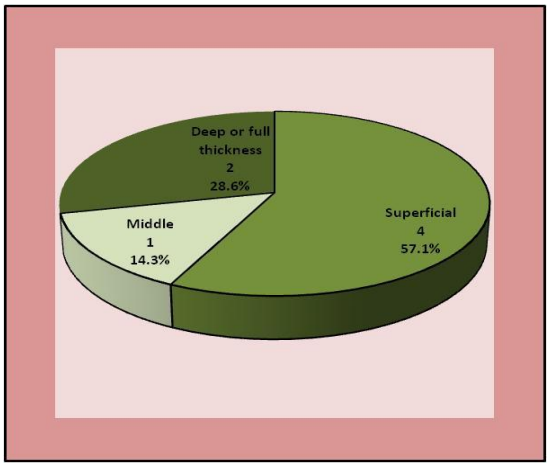

Figure 5. Distribution of study population according to depth of ulcer

The mean duration of complete healing was (22.3+-18.2), The best corrected distance visual acuity after complete healing was (1.8+- 0.62) log MAR, 2 patients not respond to pack CXL and undergo to keratoplasty (Figure 6). Best corrected visual acuity ranged from counting finger (1-3m) to hand movement at presentation, which improved to counting finger to 6/60 post CXL.

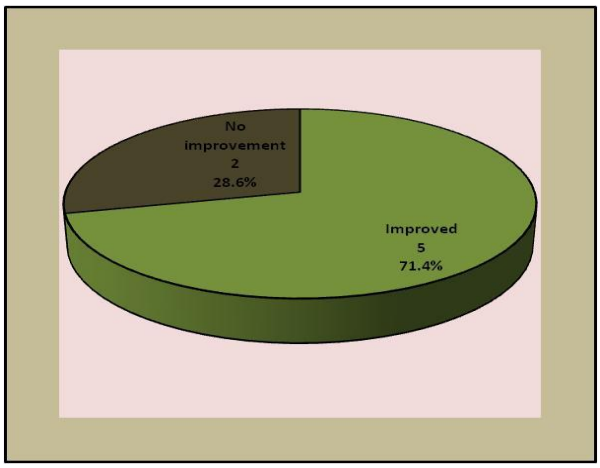

Figure 6. Distribution of study population according to improvement

DISCUSSION

This series showed promising results from CXL for treating refractory bacterial corneal ulcers except two eyes. All patients showed clinical improvement in ulcer characteristics and reported a decrease in pain and other symptoms from first day post CXL.

Regarding the use of PACK CXL as an effective technique in management of microbial keratitis, a case series of forty patients with microbial keratitis treated with CXL while receiving standard antimicrobial therapy was published by Price et al. The keratitis did not resolve in six patients according to the authors. The CXL is most effective in superficial infections and bacterial etiology [19].

Sorkhabi et al. had performed CXL on ten patients with resistant microbial corneal ulcers who had not responded adequately to maximal topical and subconjuctival antibiotic treatment. Eight cases healed with a corneal scar [25]. Shetty et al. used CXL in 15 patients with refractory bacterial or fungal keratitis and noted that two-third of bacterial and half of fungal keratitis healed [26].

A better treatment response was seen in patients with superficial corneal infiltrate involving the anterior third of the stroma. In this study, two cases with deep infections did not respond and requires additional surgical interventions.

CONCLUSION

CXL could be used as an adjuvant therapy in bacterial keratitis with superficial stromal infiltrate. This procedure has the potential to reduce the need for emergency penetrating keratoplasty. More research on a larger number of eyes, as well as randomized clinical trials comparing the safety of CXL versus conventional antibiotics, is recommended. Small portable devices may allow the comprehensive ophthalmologist to perform a PACK-CXL treatment as soon as an early infiltrate or a beginning ulcer is detected in the future.

Disclaimer

The article has not been previously presented or published, and is not part of a thesis project.

Conflict of Interest

There are no financial, personal, or professional conflicts of interest to declare.

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