

Comparative Study of Corneal Collagen Crosslinking (CXL) in Conjunction with Antimicrobial Agents to Antimicrobial Agents Alone in the Treatment of Infectious Keratitis

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Abstract

Purpose: To compare the outcome of corneal collagen crosslinking (CXL) in conjunction with antimicrobial agents (AMA) to antimicrobial agents alone in the treatment of infectious keratitis. **Design:** Prospective comparative clinical trial in a tertiary hospital in India. **Participants:** 40 patients with infectious keratitis randomised into two groups of 20 patients each- Group 1 and 2. **Methods:** Group 1 patients underwent CXL in addition to antimicrobial therapy. The patients in Group 2 received only antimicrobial therapy. The slit-lamp characteristics of the corneal ulceration, visual acuity, time taken for healing, and complications were documented in each group. The t-test was used for statistical analysis. P values less than 0.05 were considered statistically significant. **Results:** The mean time taken for healing in Group 1 was 44.5±11.2 days and in Group 2 was 27.65±7.79 days. Analysis of various parameters revealed that patients undergoing CXL showed slower healing duration (p=0.00). **Conclusions:** Use of CXL in conjunction with AMA lowers the risk of complications, but also slows the rate of healing of ulcers.

Keywords: Corneal collagen crosslinking, antimicrobial agents (AMA), antimicrobial resistance, infectious keratitis, riboflavin, epithelial defect.

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INTRODUCTION

Infectious keratitis is defined as “loss of corneal epithelium with underlying stromal infiltration and suppuration associated with signs of inflammation with or without hypopyon.” It is classified according to the causative organism into: Bacterial, fungal, viral and protozoal [1]. Delayed treatment of infectious keratitis can lead to significant visual loss in as many as 50% of cases [2]. Corneal infections and ocular trauma are the significant causes of corneal blindness that are often under-reported but may be responsible for 1.3 million new corneal blindness cases every year [3]. The World Health Organization classifies infectious keratitis as a “silent epidemic,” with an estimated 800,000 new cases every year in India alone [4]. The standard bacterial keratitis treatment, according to the guidelines of the American Academy of Ophthalmology, includes the use of broad-spectrum topical antibiotics. However, antimicrobial resistance (AMR) is rising at an alarming speed and the World Health Organization has published an urgent call to identify alternatives to antibiotics in its

global report on AMR [5]. With the known microbicidal effects of ultraviolet irradiation and photoactivated riboflavin together with the corneal stiffening effect, corneal collagen crosslinking (CXL) is an appealing treatment option for infectious keratitis resistant to antimicrobials or associated with corneal melting [6]. To distinguish better the use of CXL for the treatment of infectious keratitis from CXL for progressive keratoconus, the term photoactivated chromophore for infectious keratitis–corneal collagen crosslinking (PACK-CXL) was created at the ninth Cross-linking Congress in Dublin, Ireland in 2013 [7].

Infectious keratitis is a major cause of monocular blindness in developing countries. Scarring of the cornea as a result of suppurative keratitis is an important cause of preventable blindness. Surveys in Africa and Asia have confirmed this finding [8-10], and a recent report on the causes of blindness worldwide consistently lists corneal scarring second only to cataract as the major aetiology of blindness and visual

disability in many of the developing nations in Asia, Africa and the Middle East [11].

MATERIALS AND METHODS

Study Design

It was a prospective randomized clinical trial on patients with infectious keratitis attending Emergency and OPD of Regional Institute of Ophthalmology, Pt BD Sharma PGIMS, Rohtak.

Forty patients with infectious keratitis were taken for the study where all pre-existing treatment were interrupted for 24 hours and corneal scrapings for Gram's staining, KOH mount and cultures were obtained. After that, the group was randomised into 2 groups having 20 patients each - Group 1 and 2. The patients in Group 1 were treated with CXL along with antimicrobial agents and Group 2 patients were treated with antimicrobial agents alone. Visual acuity was recorded and grading of ulcer was done based on slit lamp examination. The patients were categorised into mild, moderate and severe keratitis as per the grading system proposed by Harrison SM [12].

Inclusion Criteria

All patients with infectious keratitis (more than 18 years of age) attending OPD and Emergency of Regional Institute of Ophthalmology PGIMS, Rohtak were included.

Exclusion Criteria

Patients with any kind of birth injury or congenital ocular defect causing visual deficits, underlying autoimmune diseases, history of herpetic eye disease, corneal thickness < 450µm with epithelium, thickness of involved cornea < 400µm, pregnancy or nursing mother, and those who do not consent were excluded.

Procedure

Initial Treatment

At presentation, all pre-existing treatment were interrupted for 24 hours and corneal scrapings for Gram's staining, KOH mount and cultures were obtained. After that, the group was randomised according to their presentation into 2 groups having 20 patients each. Group 1 patients were subjected to CXL followed by anti-microbial agents which consisted of fortified Vancomycin eye drops 50mg/ml and fortified Ceftazidime eye drops 50mg/ml hourly for bacterial keratitis, and Natamycin 5% eye drops hourly for fungal keratitis. Group 2 patients were subjected to the above mentioned anti-microbial agents alone.

CXL Procedure

Group 1 patients allocated to CXL (collagen crosslinking with photo activated riboflavin) were assessed and treated within 48 hours with CXL. Topical

anaesthesia was used. Thickness of the uninvolved cornea surrounding the ulcer was measured aiming for a starting thickness of no less than 450 µm. Riboflavin drops (0.1%) was instilled topically on the cornea every 2 minutes for over 30 minutes. After this, the cornea was irradiated using UV light 365 nm with an irradiance of 3Mw/cm² for 30 minutes and total dose of 5.4 J/cm² during which riboflavin was instilled every 2 minutes. After CXL treatment, antimicrobial agents were continued.

Follow up

The patients were examined daily in the first week to see for signs of improvement which included decrease in size of infiltration and epithelialization of ulcer. After that, weekly follow-up was done for the first month and subsequently it was done fortnightly for the next two months for both the groups.

Statistical Analysis

Data was analyzed with SPSS version 21 and the groups were compared using the t-test. P values less than 0.05 were considered statistically significant.

RESULTS

The age group varied from 50 to 80 years in Group 1 and 25 to 92 years in Group 2. Out of the 20 patients in Group 1, 50% were males and 50% were females. That is, out of 20 patients, there were 10 males and 10 females. In Group 2, 60% were males and 40% were females. At presentation, all the patients had complaints of pain, redness, photophobia and decreased visual acuity. There were 13 cases with central location of ulcer in the CXL group and 8 cases with central location of ulcer in Group 2. Microbiological evaluation reports were negative in 18 of 20 cases in the CXL group and 16 of 20 cases in Group 2.

- The mean time taken for healing of epithelial defect in Group 1 was 28.27±8.3 days and in Group 2, the mean time taken for complete re-epithelialisation was 16.35±6.2days. The difference between the two means was statistically significant (p=0.00) with group 2 healing faster.
- The mean time taken for start of re-epithelialization in Group 1 was 16 days and in Group 2 was 11 days (p=0.00).
- The mean time taken for stromal healing in Group 1 was 44.5±11.2 days and in Group 2 was 27.65±7.79 days. The difference between the two means was statistically significant (p=0.00) and therefore, the patients in Group 2 showed faster healing
- In Group 1, one patient had corneal perforation during the treatment whereas in Group 2, three patients developed progressive corneal thinning during the treatment.

Table 1: Showing time taken for epithelial healing in Group 1

Duration	Frequency	Percentage
1 st week	0	0
2 nd week	2	10
4 th week	7	35
8 th week	9	45
12 th week	0	0
Not healed	2	10
Total	20	100

Table 2: Showing time taken for epithelial healing in Group 2

Duration	Frequency	Percentage
1st week	0	0
2 nd week	7	35
4 th week	10	50
8 th week	0	0
12 th week	0	0
Not healed	3	15
Total	20	100

Table 3: Showing time taken for stromal healing in Group 1

Duration	Frequency	Percentage
1 st week	0	0
2 nd week	0	0
4 th week	1	5
8 th week	15	75
12 th week	2	10
Not healed	2	10
Total	20	100

Table 4: Showing time taken for stromal healing in Group 2

Duration	Frequency	Percentage
1 st week	0	0
2 nd week	0	0
4 th week	11	55
8 th week	6	30
12 th week	0	0
Not healed	3	15
Total	20	100

Table 5: Showing the complication rate in Group 1

Type of complication	Frequency	Percent
Perforation	1	5
Nil	19	95
Total	20	100

Table 6: Showing the complication rate in Group 2

Type of complication	Frequency	Percent
Corneal thinning	3	15
Nil	17	85
Total	20	100

DISCUSSION

Infectious keratitis is a leading cause of ocular morbidity and blindness worldwide [13]. It requires aggressive management to halt the disease process and reduce the extent of corneal scarring, which leads to loss of vision [14, 15]. It has been estimated that about 50% of the eyes have poor visual outcome if the diagnosis and initiation of appropriate antimicrobial treatment is delayed [2]. Long term and intensive treatment along with the emergence of antimicrobial resistant agents has led to the requirement of new approaches in the treatment of infectious keratitis [16].

Corneal collagen cross-linking (CXL) is a novel technique recently developed that was found to be effective in halting disease progression in keratoconus and infectious keratitis. The use of crosslinking for infectious keratitis was labelled as Photoactivated chromophore for infectious keratitis-corneal collagen crosslinking (PACK-CXL) at the ninth Crosslinking Conference in Dublin, Ireland in 2013 [7].

In the present study, we observed that the time taken for complete re-epithelialization was longer in patients who underwent CXL ($p=0.00$). In addition, the mean time taken for the start of re-epithelialization of the ulcer was longer in Group 1 (16 days) than in Group 2 (11 days) ($p=0.00$). Studies with larger sample sizes showed similar duration of complete re-epithelialization as observed by Panda *et al.*, (10 to 18 days) [17] and Shetty *et al.*, (21 days) [18]. However, faster healing of epithelial defect was observed by Kozobolis *et al.*, (7 days) [19] and Kymionis *et al.*, (5 days) [20] after CXL but the sample size of the two studies was small (2 cases and 1 case respectively).

The patients who did not undergo CXL had faster resolution of stromal infiltrates ($p=0.00$) in the present study. Vajpayee *et al.*, [21] conducted a retrospective comparative study in mycotic keratitis where the mean time taken for healing of ulcer was 30.85 ± 26.6 days in the patients undergoing CXL and 31.28 ± 19.97 days in the other group (0.94). They concluded that additional collagen crosslinking treatment did not have any advantage over medical management alone. In a prospective comparative trial done by Said *et al.*, the mean duration for complete healing of the ulcers was 39.76 ± 18.22 days in the CXL group and 46.05 ± 27.44 days in the control group ($p=0.68$). This study also concluded that CXL did not shorten the time of corneal healing [22].

Panda *et al.*, observed complete healing of ulcer in 21 to 35 days (3 to 5 weeks) [17] and Shetty *et al.*, in 33 days [18]. Faster resolution of stromal infiltrates was recorded by Li *et al.* (3 to 8 days) in a study done on 8 patients [23].

CONCLUSION

From the above mentioned results, it was concluded that treatment of corneal ulcers with CXL in conjunction with antimicrobials delays the onset of start of re-epithelialization of the corneal ulcer and prolongs the duration of epithelial and stromal healing as compared to use of antimicrobials alone. But the treatment may minimize or avoid severe complications as the rate of complications was lower in the patients undergoing CXL though this difference was not significant.

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