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ORIGINAL ARTICLE

ROLE OF ACCELERATED CORNEAL CROSS-LINKING IN NON-HEALING MICROBIAL KERATITIS

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ABSTRACT

Background: Non-healing microbial keratitis remains a significant threat to vision, particularly in low resource areas. Patients frequently experience delays in diagnosis and inadequate responses to standard treatments. Accelerated corneal cross linking is emerging as a promising approach to prevent irreversible blindness. The objective of this study was to evaluate the efficacy of accelerated corneal cross linking in managing non-healing microbial keratitis in a tertiary care setting.

Materials & Methods: In this prospective observational study, patients aged 18 to 70 with microbial keratitis who did not respond to antimicrobial treatment with in two weeks were included. All patients received accelerated corneal cross-linking (A-CXL) following a modified Dresden protocol. Data were collected on demographics, clinical characteristics, ulcer depth, culture results of microbes, outcomes and complications. Visual acuity (logMAR) was measured prior to the treatment, 1 month and 3 months after the surgery. IBM SPSS v-27 was used to analyze data. Paired t-test, repeated measures of ANOVA and chi-square was applied considering p-value ≤ 0.05 as significant.

Results: We enrolled 100 patients with mean age of 34.95 ± 9.537 years. Most of the 65(65%) were males. The leading risk factor was 85(85%) ocular trauma while contact lens was reported by 50(50%). Bacterial infections were predominant. Ulcer reduction was significantly noted in 85(85%) cases, with 45(45%) cases requiring keratoplasty. Mean epithelial healing time occurred at 44.2 ± 8.3 days. Visual acuity (logMAR) was noted 1.82 ± 0.61 prior to treatment but it improved to 0.94 ± 0.47 and 0.68 ± 0.45 after one and three months. ($p < 0.001$)

Conclusion: Corneal cross-linking is a safe and efficient adjunctive treatment that promotes ulcer resolution, vision recovery and symptom relief in cases of severe or treatment-resistant microbial keratitis. However, a significant number of patients still experience complications requiring additional procedures such as keratoplasty. The results encourage the adoption of accelerated corneal cross-linking in the management of saving vision.

KEY WORDS: Corneal cross-linking; Corneal ulcer; Microbial keratitis; Keratoplasty; Visual Acuity.

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INTRODUCTION

In recent years, ophthalmologists are expressing great concern regarding the rising incidence of infectious keratitis, which has been observed to manifest with increasing frequency. Microbial keratitis is a corneal infection causing permanent visual impairment, affecting individuals from bacteria, viruses, fungi, protozoa and parasites.[1-3] Treatment of advanced stages and corneal abscesses is crucial in ophthalmology, as keratitis is a major cause of preventable monocular blindness.[4] Fungal keratitis is a primary blinding disease that has become more prevalent and requiring early treatment or eye ball enucleation.[5-6] Around six million people worldwide suffer with corneal opacity, the fifth most common cause of blindness and visual impairement.[7] Annually , 1.5 to 2 million new cases occur, with microbial keratitis being endemic in some regions.[8] In china, fungual keratitis affects 40% of the population, activating the immune system and causing inflammation.[9-10] One of the Asia cornea society infectious keratitis study highlights that fungal keratitis was identified in 32.7% of patients, and bacterial keratitis was found in about 38% of cases. The most prevalent species among the detected microorganisms was fusarium, accounting for 18.3% of cases.[11]

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Ocular trauma, dry eyes, contact lens wear, eye surgery, previous illness of ocular surface, lid deformity, long term steroid use, impaired corneal sensitivity and systemic immunosuppression are among the prevalent risk factors for infectious keratitis.[12-14] Patient frequently arrive with a sudden onset of pain, conjunctival injection, photophobia and blurred vision.[15] Corneal ulcer caused by an excess of white blood cells which is originally an epithelial defect with surrounding and underlying inflammation. Usually, this ulcer results the surrounding tissue to necrotize.[15] Appropriate treatment in terms of topically administrated antimicrobial or/and antibiotics medicines must be used to treat this ocular condition. If diagnosis and initiation of adequate antimicrobial treatment are delayed, it has been estimated that only 50% of the eyes will heal with good visual outcomes.[16] A study noticed that up to 30% of infectious keratitis may have poor visual outcomes if adequate therapy is not stated right once.[17] Certain corneal ulcers provide a major issue because they are frequently resistant to conventional therapies because of antibiotic resistance.[18-19] In more severe cases, immune cells, bacteria, fungi may break down the enzymes causing corneal melting. Drug availability and eye toxicity risks complicate the treatment process requiring specific treatment strategies.[20-21]

Collagen cross linking was first used in the 1990s to treat corneal ectasia, such as keratoconus because of its potential to improve the cornea's biomechanical stability.[22-23] The method uses ultraviolet-A radiation and riboflavin to strengthen corneal collagen fibers by forming covalent bonds, corneal cross linking's applicability has evolved to include viral keratitis and corneal melting, leveraging its antimicrobial qualities and ability to repair corneal architecture, reduce inflammation and inhibit enzymatic degradation.[24-25] Its promising significance in treating resistant infectious keratitis has been highlighted by some previous studies. [26-27] The Dresden protocol has been extensively validated for various purposes.[28-29]

Accelerated protocols were developed to get around the time consuming characteristics of traditional corneal cross linking. They use high intensity UVA lamps to produce comparable therapeutic results in a shorter amount of time.[30-31] These techniques have been effective in experimental models and bacterial keratitis cases, assisting in microbial eradication while reducing the danger of corneal melting or perforation. The epithelium-off technique improves riboflavin absorption and is preferable for more severe infections, whereas the epithelium-on technique preserves the epithelium and provide less intrusive option for milder instances.[32-33]

Non-healing microbial keratitis remains a major challenge for ophthalmologists, particularly in regions where patients often present with advanced ulcers and limited access to donor corneas or surgical interventions. Despite timely and appropriate antimicrobial therapy, some cases fail to respond, resulting in persistent infection, corneal thinning or perforation. Accelerated epithelium off corneal cross linking has emerged as a promising adjuvant treatment that strengths the cornea, improves antimicrobial efficacy and promotes faster epithelial healing. Conducting this study in Karachi provides valuable insight into its clinical usefulness in a population where infectious keratitis is common and treatment options is limited. The findings may support the broader adoptions of CXL as a safe, cost effective and vision preserving option for refractory microbial keratitis in similar source limited settings. The aim of this study was to evaluate the efficacy of accelerated corneal collagen cross-linking in managing non-healing microbial keratitis.

MATERIAL AND METHODS

This prospective observational study was carried out at the Department of Opthalmology, LRBT EYE Hospital in Karachi, Pakistan, from April 2023 to April 2024. Patients with a clinical diagnosis of non-healing microbial keratitis who presented through the emergency room and out patient department were included in the study The institutional research and ethics committee granted approval and all participants gave their informed written consent before being enrolled after being fully informed about study's goal. The sample size was calculated using WHO sample size calculator considering the prevalence of re-epithelization in patients with infectious keratitis after treatment of corneal cross linking, P=75%[34] with confidence level=95% and marginal level=8.5%. The total sample size came out to be 100 patients. One hundred patients with microbial keratitis were enrolled through non probability consecutive sampling.

All patients aged between 18-70 years who were clinically diagnosed with non-healing microbial keratitis and did not show improvement after two weeks of appropriate antimicrobial therapy were included in the study. Eligible cases had a corneal ulcer diameter of ≤ 5 mm and corneal thinning or small perforations suitable for CXL. Initially, all patients received standard topical fortified antibiotic or antifungal drops before undergoing accelerated epithelium-off corneal cross linking (CXL). Patients with viral keratitis, auto immune or neutrophic ulcers, a history of ocular surface surgery within the previous three months, known riboflavin hypersensitivity and prior corneal cross linking/ keratoplasty were excluded from the study. To ensure data accuracy and dependability, missing data and lost-to-follow-up cases were not included in the final analysis.

The Dresden protocol was modified for better exposure and all patients received accelerated epithelium off corneal cross linking. To reduce

operator variability, the same skilled corneal surgeon carried out every procedure. After 10 minutes of epithelial debridement, riboflavin 0.1% drops were applied and then 10 minutes of UVA irradiation at 9 Mw/cm^2 (energy dose of 5.4 J/cm^2) was administered. Based on previous microbiological results and clinical response, patients were provided a specific course of topical antibiotics, steroids, antifungals or combination medication after the procedure.

A well organized proforma was used to collect data which included patient demographics, ocular trauma history, contact lens use, ulcer depth, microbiological culture results, use of adjuvant therapy and complication profile. The efficacy in terms of progression of corneal melting which was stopped after treatment of corneal cross linking in patients will be recorded. The other outcomes of the study were epithelium healing time, infection clearance, ulcer size reduction, need of keratoplasty, complications and improved visual acuity. Slit-lamp biomicroscopy under an optic section was used to measure the ulcer depth, which was then converted to a proportion of the overall loss of corneal thickness. Ulcers that had stromal loss of 50% or less were classified as moderate, and those that had loss of 50% or more were classified as severe. Complete epithelial closure with infiltrate resolution and no growth in ulcer size or depth was considered healing.

LogMAR scores were used to assess visual acuity before treatment, one month, three months after the surgery. Complications such as corneal haze, scarring and persistent ulcers were also recorded. IBM SPSS Version 27 were used to analyzed the data set. Frequency and percentages were used to represent the categorical variables while Mean(±SD) was used to summarized quantitative variables. Paired t-test was used to compare the means at individual time points (such as pre vs. 1 month, pre vs. 3 months and 1 months vs. 3 month). Repeated Measures of ANOVA was used to assess how logMAR visual acuity changed over the span of three time points. Chi square test was used to see the association of qualitative variables. Statistical significance was defined as a p-value of ≤0.05.

RESULTS

We enrolled 100 patients with mean age of 34.95±9.537 years. Majority of patients was males i.e 65(65%) and females was 35(35%). Majority of patients 85(85%) reported a history of ocular trauma, indicating that it was a significant contributor to their disease. Microbial culture findings revealed that bacterial infection was the most common, accounting for 60(60%) of cases, followed by mixed infections in 35(35%) and negative cultures in 5(5%). Furthermore, keratitis severity to CXL, initial ulcer depth and corneal thinning or perforation are presented in Table 1.

Table 1: shows distribution of patients' demographic and clinical profile

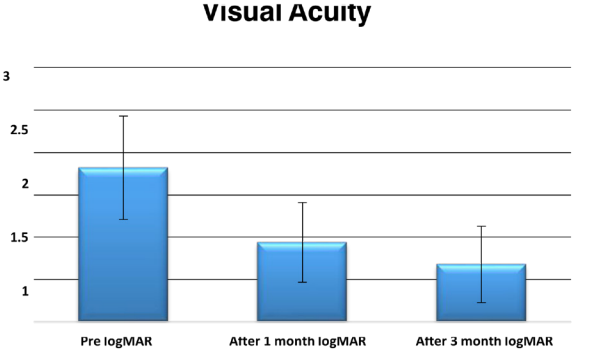
	n(%)
Age	34.95±9.537
Gender	
Male	65(65)
Female	35(35)
History of contact lense	
Yes	50(50)
No	50(50)
History of ocular trauma	
Yes	85(85)
No	15(15)
Microbial culture result	
Bacterial	60(60)
Mixed	35(35)
Negative	5(5)
Keratitis severity to CXL	
Mild	5(5)
Moderate	30(30)
Severe	65(65)
Initial Ulcer depth	
Mid stromal	50(50)
Deep stromal	50(50)
Corneal thinning or perforation presented prior to CXL	
Yes	30(30)
No	70(70)

Our clinical data shows that the average time between development of microbial keratitis and corneal crosslinking was 30.15±9.76 days. Patient had been receiving antimicrobial medication for an average of 29.70±10.14 days prior to corneal crosslinking. The average post procedure time required to achieve full epithelial healing was 44.21±8.30 days and infection resolution took 11.58±0.82 days. The detailed frequency distribution of complications, improvement in patients symptoms and patient's satisfaction are presented in Table-2.

Table 2: Shows the patient's outcome after procedure

	n(%)
Reduction in ulcer at 1 week post CXL	
Yes	85(85)
No	15(15)
Keratoplasty	
Yes	45(45)
No	55(55)
Complications Yes	45(45)
No	55(55)
Type of complication	
Corneal Haze	30(30)
Non-healing ulcer	5(5)
Scarring	5(5)
Scaring +corneal haze	5(5)
Improvement in patient symptoms	
Significant	85(85)
Moderate	15(15)
Satisfaction with treatment	
Very satisfied	40(40)
Satisfied	40(40)
Neutral	10(10)
Dis satisfied	10(10)

The visual acuity (logMAR) scores improved significantly over the time period after the procedure, using repeated measures of ANOVA ($F=1.45, 143.62$), $p<0.001$. Visual acuity significantly and steadily improved after the intervention across the three time points i.e. pre treatment, after 1 and 3 months, as presented in Table 3.



Graph shows the changes in visual acuity following accelerated epithelium-off corneal cross- linking

DISCUSSION

Patients receiving treatment were mostly male. About 65% patients had severe keratitis at presentation. It took 30 days on average from the start of accelerated corneal cross linking treatment to its completion. In 85(85%) of cases, ulcers resolved after treatment while 45(45%) eventually needed keratoplasty. Corneal haze accounted for 30(30%) of all complications. 80(80%) of patients reported being satisfied of their treatment and visual acuity improved significantly over the course of the three month follow-up period.

Our work contributes to the increasing amount of researches that accelerated corneal cross-linking is a promising adjuvant therapy for microbial keratitis that is difficult to treat. Studies conducted all across the world have confirmed the advantages, particularly in situations where conventional treatments have not been able to control severe infections.[35-36] This study focuses on the crucial treatment procedure for infectious keratitis, in contrast to other studies that use epithelium-on or epithelium-off protocols, showing the variation in efficacy of various approaches. One of the research found that epithelium-off accelerated corneal cross linking in microbial keratitis, reporting faster healing and improved corneal health.[37] Similarly, the study contrasted epithelium- on and epithelium-off accelerated corneal cross linking, indi-

Table 3: Shows the patient's outcome after procedure

Log Mar	Mean±SD	Mean Difference	P-value
Pre logMAR	1.82±0.61	0.88±0.75	<0.001*
After 1 month logMAR	0.94±0.47		
Pre logMAR	1.82±0.61	1.14±0.82	<0.001*
After 3 month logMAR	0.68±0.45		
After 1 month logMAR	0.94±0.47	0.26±0.23	<0.001*
After 3 month logMAR	0.68±0.45		

Paired t-test was applied.

*Statistically significant at $p<0.05$

cating that while both procedures produced excellent results, the epi-off strategy tends to provide better results in terms of healing time and corneal stability.[31] A study explored modified cross-linking strategies in purulent keratitis, with a particularly focus on an epi-off technique with a more severe infections.[4]

Our findings of 85% ulcer reduction, improved visual acuity, and high satisfaction rate are consistent with previous trials employing epi-off accelerated corneal cross linking. Li M 's study found that patients treated with epi-off accelerated corneal cross linking observed comparable rates of ulcer clearance and visual improvement; however, they also noted that epi-on procedures are more prevalent in specific clinical contexts.[37] Barac IR et al. altered corneal cross linking procedures, on the other hand, which also used the epi-off approach, demonstrated decreased keratoplasty rates and improved epithelial healing. In general, the epi-off strategy is consistently linked to better microbial control and quicker healing, as seen in our cohort.

Statistically, the results from Barac et al. showed a resolution rate of 70-80% without the need for surgical intervention, a result somewhat lower than our 85% but still within a comparable range.[31] Kasparova EA's study, which used epi-off accelerated corneal cross linking, observed similar trends in visual improvement, with corneal haze and persistent ulcers being noted as common complications, consistent with our findings. Kasparova EA's study further corroborates our results by emphasizing the role of epi-off corneal cross linking in severe infections, reporting reduced keratoplasty needs and improved corneal stability in patients treated early with this approach.[4] Based on experimental results by Marrie et al., our findings demonstrates that corneal cross-linking can prevent the spread of infections. While their research proved corneal cross linking's protective properties in an lab model, our clinical findings support its real world efficacy in treating resistant microbial keratitis particularly in areas with limited resources.[38]

In contrast to Kadavoor et al., who reported microbial keratitis as an un common side effect following corneal cross linking in individuals with keratoconus, our study does not treat this problem.[39] Our data utilized corneal cross linking for more significant, centrally situated infections whereas Wang et al. and Yuksel et al. concentrated on smaller or less severe cases, frequently in keratoconus.[40-41] Unlike Hsia et al., who advocated for randomized studies, we present real world data that corneal cross linking is more beneficial in bacterial keratitis than fungal patients, validating previous findings.[42] Furthermore, our results broadens the use of corneal cross linking to treat challenging cases of viral keratitis, whereas Nicula et al,. concentrated on keratoconus.[43] This study was limited by its single center design and small sample size, which may limit the generalizability of the findings. The lack of control group receiving simply antimicrobial medication made it difficult to determine the particular contribution of epi off –CXL. The three month follow-up time reduced the ability to examine long-term visual and structural results. Dependence on standard culture methods may have resulted in under-detection of certain infections. These factors may have influenced the interpretation and the strength of the connections. To address these limitations, future research should use larger, multicenter samples with longer follow-up periods, molecular diagnostic tools, and appropriate control groups to improve comparison. Randomized controlled trials focusing on organism-specific responses are required to better understand the appropriate timing, safety, and long-term efficacy of rapid epithelium-off corneal cross-linking in microbial keratitis.

CONCLUSION

Epithelium-off rapid corneal cross-linking is a safe and efficient supplementary treatment for microbial keratitis that does not heal, especially in severe instances when other treatments are ineffective. Our research supports its application in promoting ulcer healing, enhancing visual results, and giving patients a better chance of maintaining their vision. Further multicenter, randomized controlled trials with extended follow-up are required to optimize treatment regimens and validate the long-term efficacy of epi-off accelerated corneal cross linking in various clinical situations, even though the technique displays encouraging outcomes.

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CONFLICT OF INTEREST
Authors declare no conflict of interest.
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None declared.

AUTHORS' CONTRIBUTION

The following authors have made substantial contributions to the manuscript as under:

Conception or Design:	TS, SFR
Acquisition, Analysis or Interpretation of Data:	TS, SFR, SK, RA, ZK
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All the authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.