ORIGINAL ARTICLE

Infectious Keratitis Following Corneal Crosslinking: A Systematic Review of Reported Cases: Management, Visual Outcome, and Treatment Proposed

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ABSTRACT

Aim: To describe the infectious complications and the group of pathogens involved in the infection following corneal crosslinking, the visual outcome, and the treatment proposed. Methods: A Medline (National Library of Medicine, Bethesda, MD, USA) search from October 2000 to October 2013 was performed to identify all articles describing infectious keratitis following corneal crosslinking treatment. Nineteen articles were selected. Ten articles reported infectious complications of corneal crosslinking treatment were included. Nine articles were excluded, because seven described sterile keratitis, one article was in German, and one reported general complication without describing the infection complication. Results: A total number of infections reported included 10 eyes. The infectious keratitis was associated with bacteria in five eyes (50%): gram-positive bacteria in three eyes (30%) (staphylococcus epidermidis, S. aureus and streptococcus salivarius plus S. oralis, respectively) and gram-negative bacteria in two eyes (20%) (E. coli; P. aeruginosa); there was herpes virus in two eyes, fungus in two eyes (Fusarium and Microsporidium) (20%), and Acanthamoeba in one eye (10%). Conclusions: Only 10 cases of infectious keratitis following corneal crosslinking are published. The most virulent pathogens were Pseudomonas aeruginosa and Acanthamoeba. Less virulent organisms were Escherichia coli and S. epidermidis. Two cases of herpes keratitis were described, suggesting the possibility of systemic antiviral prophylaxis before corneal crosslinking treatment. The most common risk factor of infections identified was postoperative incorrect patient behavior.

Keywords: Corneal, collagen crosslinking, infectious keratitis, visual outcome, treatment

INTRODUCTION

Corneal collagen crosslinking (CXL) with riboflavin and ultraviolet-A (UVA), introduced by Wallensak et al. in 2003,1 is a non-invasive technique that changes the biomechanical properties of corneal collagen, increasing its strength by the combined action of a photosensitizing substance (riboflavin) and ultraviolet light.

This treatment is useful in arresting the progression of keratoconus.2,3 Keratoconus is a degenerative, non-inflammatory ectasia of the cornea characterized by progressive corneal protrusion and thinning, leading to irregular astigmatism and impairment in visual function that is usually bilateral.4 CXL may also be effective in the treatment and prophylaxis of iatrogenic keratectasia, resulting from laser in situ keratomileusis (LASIK) and from photorefractive keratectomy (PRK).5

The standard technique (epi-off) includes removal of the epithelium in order to expose the underlying stroma to riboflavin, which is otherwise incompletely absorbed by the epithelium because of tight junctions. The area of corneal epithelium removed has a diameter of 6.0 to 8.5 mm. A crosslinking procedure without epithelial removal could also be performed (epi-on). It would likely be less painful compared to the standard procedure.6

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CXL has been shown to stabilize progressive keratoconus with only isolated reports of side-effects like diffuse lamellar keratitis, bacterial Acanthamoeba, herpetic keratitis with iritis, development of corneal haze, and corneal melting. In the literature, there are also cases with sterile keratitis post-CXL occurring in childhood or in adulthood. Microbial keratitis after CXL is rare. Ironically, although infectious keratitis can occur after CXL, a recent metanalysis showed that CXL can also be used to treat the infectious keratitis not responding to conventional therapy. The main reason attributable to CXL efficiency is associated with the inactivation of pathogens by direct damage to bacterial DNA, the increased resistance to enzymatic degradation, and increased stromal tensile strength and rigidity of corneal collagen, which may prevent melting.

This fact suggests that the technique is itself safe and that the contamination can occur in the immediate postoperative period associated with postoperative incorrect patient behavior, delaying the time of epithelium healing. Several cases of infectious keratitis after CXL are reported but a systematic analysis of these data is missing. The aim of this study is to describe the group of pathogens involved in the infection following CXL, the visual outcome, and the treatment proposed, as well as to identify the most common risks associated with infection and the best way to manage them.

METHODS

Published journal articles were considered as the elements of study, and a specific literature search was performed in four stages:

(1) Stage 1 (Unique citations): A Medline (National Library of Medicine, Bethesda, MD, USA) search from October 2000 to October 2013 was performed to identify all articles describing infectious keratitis following CXL treatment. Keyword searches used were the terms “crosslinking” + “keratitis,” and [“Ulcerative” or “Microbial”] + “keratitis” + “crosslinking,” and “crosslinking” + “corneal complication” limited to “2000 to 2013.”

(2) Stage 2 (Article retrieval): All abstracts from the Medline searches were scrutinized to identify articles that reported clinical results. Copies of the articles were obtained, and their bibliographies were searched manually for additional articles published in peer-reviewed journals.

(3) Stage 3 (Article inclusion): Complete articles were reviewed to identify those that reported infectious complication(s) of CXL treatment. As the numbers of articles were so few, we decided to include all.

(4) Stage 4 (Article exclusion): We excluded nine articles. Among them, seven described sterile keratitis, one article was published in German, one reported complication and failure rates after CXL without describing the infection complication.

Data Abstractions and Analysis

A meticulous and systematic review of the complete articles was performed. All appropriate information regarding aspects of CXL treatment was analyzed. The primary purpose was to identify the pathogens causing the infection and the secondary end-point was the recovery of visual acuity and the treatment applied. All data were analyzed using Microsoft Excel (Microsoft Corporation, WA, USA). Patient population characteristics were recorded. Complications and their treatment were noted. There were 10 articles on this topic. According to the protocol for the Cochrane systematic meta-analysis, all of the articles included in this study were classified as level 3 evidence (non-analytical studies: case reports, case series).

RESULTS

A total of 10 articles were selected. Table 1 summarizes data items from each paper. All papers were case reports. The total number of eyes with infectious keratitis following CXL was 10. As none of the studies was analytical, comparative statistical methods could not be applied. A Vega CBM X linker (CSO, Florence, Italy) was used in one study and, in nine studies, the models of the instruments were not specified.

The standard CXL, Dresda protocol, was followed in all of the studies. The average size of epithelial debridement was 7.66 ± 0.87 mm. The most common postoperative antibacterial treatment was fluoroquinolones. This group of antibiotic was prescribed in six cases. Fluoroquinolones were associated with steroids in one case and with topical non-steroidal anti-inflammatory drugs in two cases and in the other three cases without association. Aminoglycosides were used in the other four cases. In all of these cases, the treatment was associated with steroids. In one case, it was associated with systemic treatment of paracetamol-codeine (500 mg/30 mg). In one patient, the postoperative treatment was not specified.

According to the microbiological sample results, the postoperative treatment was modified in six patients. In a case of S. epidermidis keratitis, topical beta lactam antibiotic (fortified cefazolin 50 mg/ml) following the directions of the antibiotic-sensitivity test (Kirby-Bauer disk-diffusion method), was changed to topical fluoroquinolones.
(ofloxacin 0.3%) in addition to topical aminoglycoside (fortified tobramycin 15 mg/ml). After the detection of positivity for Acanthamoeba, topical hexamidine and polymethylenebiguanide (PHMD) were added to the previous treatment with fluoroquinolones (topical levofloxacin) associated with intramuscular cephalosporin. In two patients, polymerase chain reaction (PCR) analysis of tears and corneal swab, respectively,25,27 were positive for herpes simplex virus (HSV), inducing us to discontinue topical corticosteroids and to start antiviral treatment. The identification of microsporidia spores induced us to start anthelmintic treatment (oral albendazolo),26 while the identification of fungal hyphae of Fusarium Solani induced us to prescribe topical amphotericin B drops.28

In reference to the other cases, one patient24 started topical tobramycin (14 mg/ml) and caphazolin (50 mg/ml) after identification of Escherichia coli infection, and three patients22,29,30 did not modify the postoperative treatment because the pathogens identified were sensitive to the antibiotic treatment prescribed.

A summary of the treatment is reported in Table 2. Four subjects were male and four female; in two cases, the gender was not specified. The average age was 28.6 ± 7.47 years (19–42). It was impossible to extract detailed data of VA (visual acuity) from some studies.23,28 Before the CXL treatment, the average best-spectacle corrected visual acuity (BSCVA) was 0.32 ± 0.46 (0.09–1) logMAR. At the onset of the infectious keratitis, BSCVA was 2.08 ± 0.7 (1.3–3) logMAR and, at the end of the follow-up, it was 0.68 ± 0.89 (0.04–3) logMAR. The best result was 0.04 logMAR, obtained in one patient infected with Staphylococcus epidermidis.21 The worst was 1 logMAR in patients infected with Pseudomonas aeruginosa22 and Acanthamoeba.23

The infectious keratitis was associated with bacteria in five eyes (50%): gram-positive bacteria in three cases (30%) and gram-negative bacteria in two eyes (20%); herpes virus in two cases (20%), fungus in two (20%), and Acanthamoeba in one eye (10%).

The microbiological culture was identified through BCL (bandage contact lens) and corneal scraping,21 corneal scraping for bacteria, fungi, Acanthamoeba, and herpes virus,23,24 polymerase chain reaction analysis of tear,25 or of corneal swab,27 corneal scraping submitted for Gram stain, Giemsa stain, chocolate agar, Sabouraud dextrose agar and thioglycollate broth,26 corneal scraping and potassium hydroxide mount,28 corneal swab,29 contact lens culture, and corneal scraping.30

The mean time of infection presentation after CXL was 6.50 ± 8.34 (2–30) days. The longest time was found in patients infected with Fusarium solani (30 days) and the shortest in S. Epidermis (two days).
<table>
<thead>
<tr>
<th>Authors</th>
<th>Perez Santonja21</th>
<th>Sharma22</th>
<th>Ram23</th>
<th>Pollbammer24</th>
<th>Kymionis25</th>
<th>Gautam26</th>
<th>Yuksel27</th>
<th>Garcia del Pechar28</th>
<th>Hafezi29</th>
<th>Zama30</th>
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<tbody>
<tr>
<td>Pathogens</td>
<td>S. epidermidis</td>
<td>P. aeruginosa</td>
<td>Acanthamoeba</td>
<td>E. coli</td>
<td>HSV simplex</td>
<td>HSV simplex</td>
<td>HSV simplex</td>
<td>Fusarium solani</td>
<td>S. aureus</td>
<td>S. salivarius S. oralis</td>
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<tr>
<td>Topical postoperative medication</td>
<td>Ciprofloxacin (3 times a day for 2 days)</td>
<td>Tobramycin (3 times a day)</td>
<td>Ofloxacin (3 times a day)</td>
<td>Tobramycin sulphate (3 times a day)</td>
<td>Dexamethasone (3 times a day)</td>
<td>Tobramycin (3 times a day)</td>
<td>Moxifloxacin (3 times a day)</td>
<td>Tobramycin sulphate (3 times a day)</td>
<td>Ofloxacin ointment</td>
<td>Ketorolac tromethamine 0.5% (4 times a day)</td>
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<tr>
<td>Clinical features</td>
<td>Conjunctival injection, 4 well-defined white nodules and small satellite lesions; hazy stromal infiltrate in the upper midperipheral cornea; epithelial defects overlying the infiltrates and in the central cornea; mild ACR*</td>
<td>Corneal ectasia and opacification; subtotal deep epithelial defect involving 90% of corneal depth; mild ACR*; hypopyon (1.5 mm)</td>
<td>Geographical epithelial defect; stromal edema; multiple paracentral stromal infiltrates; intact corneal epithelium; moderate ACR*</td>
<td>Conjunctival injection; corneal ulcer with a central yellow infiltrate (7.0–6.0 mm) with overlying epithelial defect involving 90% of corneal depth; mild ACR*; hypopyon</td>
<td>Conjunctival injection; central large epithelial defect (7.5–6.0 mm) with multiple coarse pinhead-size anterior stromal infiltrates, edematous and hazy intervening cornea; mild ACR*</td>
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<tr>
<td>Treatment after the culture</td>
<td>Topical: ofloxacin 0.3% (once hourly)</td>
<td>Topical: Levofoxfloxacin (4 times a day)</td>
<td>Topical: Tobramycin 14 mg/ml (4 times a day)</td>
<td>Topical: Levofloxacin (2 times a day)</td>
<td>Topical: Moxifloxacin hydrochloride 0.5% (4 times a day)</td>
<td>Topical: Moxifloxacin hydrochloride 0.5% (4 times a day)</td>
<td>Topical: Moxifloxacin hydrochloride 0.5% (4 times a day)</td>
<td>Topical: Tobramycin sulphate (every 2 hours)</td>
<td>Continued topical treatment alternating ofloxacin and garamycin drops</td>
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<td>Outcome</td>
<td>Regression of the ocular inflammation and corneal infiltrates</td>
<td>Reduction of infiltrates in size; gradual disappearance of hypopyon; residual corneal leucoma</td>
<td>Reduction of stromal infiltrates in density; avascularized stromal scar</td>
<td>Reepithelialization of geographic ulcer</td>
<td>Reduction of corneal infiltrates in size and number, disappearance of them at the end of 6 weeks, leaving a mild stromal corneal scar</td>
<td>Ulcer resolution; after 1 month postoperatively, persistence of a mild paracentral subepithelial opacity</td>
<td>Central leucoma</td>
<td>Corneal scar</td>
<td>Residual central corneal stromal haze and a subepithelial scar in a ring-like configuration</td>
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<tr>
<td>Nea transplantation</td>
<td>Corneal graft (NS for visual rehabilitation</td>
<td>Penetrating keratoplasty (PKP) for tectonic reason</td>
<td>–</td>
<td>–</td>
<td>Anterior lamellar keratoplasty for visual rehabilitation</td>
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<td>Other</td>
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R: anterior chamber reaction; NS: Not specified.
The mean time of reepithelization was clearly specified only in the two patients with Herpes virus keratitis (two days and 10 days, respectively).25,27

Varying presentations of keratitis have been reported, depending on the etiologic agent. The clinical features identified in the slit lamp examination are reported in Table 2.

Four eyes underwent penetrating or lamellar keratoplasty. Two eyes were infected with fungus,26,28 one with Acanthamoeba,23 and one with P. Aeruginosa.22 Among them, only the patient affected by Acanthamoeba needed corneal transplantation for tectonic reasons.23 The other patients only needed visual rehabilitation due to residual corneal scars. A central stromal opacity was the most frequent residual scar described in four patients. The detailed outcome is reported in Table 2.

DISCUSSION

In 1997, Spörl et al. published32 the results of their study concerning the crosslinkage in porcine eyes. The impressive clinical results initially achieved in Germany have prompted worldwide use of CXL. It’s important to consider that the post-CXL infection might be considerably underreported. Non-academic ophthalmologists rarely report complications and write articles. Furthermore, single case reports are commonly rejected by journals.

The main reasons for corneal infection after CXL can be identified in the postoperative period. The epithelial healing is the fundamental time. In some diseases, such as atopic disease and diabetes, this time is longer and the cornea is more vulnerable to infection. The use of bandage contact lenses may shorten the time to healing but increase the risk of infection associated with the manipulation of the contact lens.

The main group of pathogens reported involve bacteria, followed by herpes virus and fungal infection. A single case of Acanthamoeba was described. The most virulent pathogen was Pseudomonas aeruginosa.22 In this case, the risk was identified in excessive postoperative eye rubbing, presumably with unclean fingers, which led to the loss of a bandage contact lens. At two months, the BSCVA was 1 logMAR. Keratoplasty was planned in the future for visual rehabilitation.

Infection due to Acanthamoeba23 also had a fulminating course and corneal melting developed five days after CXL. In this case, the patient, because of the marked discharge, rinsed his eyelids aggressively with tap water. During the follow-up, the cornea perforated and therapeutic penetrating keratoplasty was performed. After two months, the patient presented with a BSCVA of 1 logMAR that improved to 0.30 logMAR with pinhole.

Less virulent organisms, such as Escherichia coli24 and Staphylococcus epidermidis,21 responded to therapy and achieved BSCVA better than 0.47 logMAR. In both cases,21,24 no patient risk was identified, probably because the infection was related to early postoperative contamination.

Polymicrobial keratitis was described associated with Streptococcus salivarius and S. oralis.12 This group has a low virulence and belongs to common commensals of the oral cavity, gastrointestinal and female genitourinary tracts. In this case, the patient admitted to cleaning the bandage contact lens in his mouth before reapplying it into his treated eye, and the break in the epithelium allowed these microbes to invade and infect his cornea. At the end of follow-up, BSCVA was 0.39 logMAR. Kymionis25 and Yüksel27 reported two cases of herpes keratitis and suggested that UVA light could be a potent stimulus to trigger/induce reactivation of latent herpes simplex virus infections. Kymionis suggests that significant corneal epithelial/stromal trauma or actual damage of the corneal nerves could be the mechanism of HSV reactivation, and the use of topical corticosteroids and mechanical trauma caused by epithelial debridement may be additional risk factors. In both cases, the patients did not have a history of previous herpetic eye disease. It will be useful to evaluate the possibility to use systemic antiviral prophylaxis before CXL treatment. The incidence of herpetic keratitis is quite low and its postoperative management permit, in both cases, the recovery of preoperative visual acuity level. At the moment, there is no evidence for the use of a systemic prophylaxis, but it would be useful to analyze this in a large and random study.

Fungal infections were associated with Fusarium solani28 and Microsporidia.26 The time of onset after CXL is quite long compared to other pathogens. In the first case, the time was four weeks after the treatment, and in the second case it was one week. The visual outcome was poor with cornea transplant indication in the Fusarium infection. In the Microsporidia case, at the end of the treatment, the BSCVA was 0.67 logMAR. Lamellar keratoplasty was suggested.

The infectious keratitis appears to be a sight-treating complication and the visual acuity resulted to be hardly reduced. Visual outcomes showed a reduction of more than half compared to the preoperative value. Several risk factors were identified through these studies. The most common was associated with irresponsible patient’s behavior. These kinds of risks will be very easy to avoid. We suggest to stress and repeat as often as possible the correct way to manage the postoperative period—to avoid touching and rubbing the eyes and definitely to wash the eye with water. On the other hand, the importance of the time of cornea healing is fundamental.
Another application is iontophoresis. This technique involves the use of aqueous solubilized compounds to render the lipophilic barrier less resistant to permeation and might offer a means to disrupt the epithelium integrity at the cornea surface. The new procedure created with the aim of increasing the safety and the patient’s comfort avoids de-epithelialization of the cornea.

To obtain this, Wollensak proposed to use riboflavin associated with benzalkonium chloride (BAC) and dextran. Others suggested using cycloextrin. Aqueous cycloextrin solutions have been shown to disrupt the epithelium integrity at the cornea surface and might offer a means to render this lipophilic barrier less resistant to permeation of aqueous solubilized compounds. Another application is iontophoresis. This technique takes advantage of the negative charge of riboflavin. The current intensity used was initially 0.2 mA and was gradually increased to 1.0 mA at an increment rate of 0.2 mA per 10 seconds with a total time of 10 min. This application permits the riboflavin to penetrate in the stroma without removing the epithelium.

Since its beginning, CXL has gained increasing popularity, and is now performed in many centers in the world. This is in part due to the ease of performing the procedure, but also, while this treatment appears simple, the sterile procedure has to be followed properly. Furthermore, the antibiotic resistance increases and the most virulent pathogens can be selected.

In conclusion, it has not been possible to define guidelines from the study published until now, because the cases are very few and all of them are case reports. On the contrary, from the analysis of these cases, is possible to derive some general suggestions, including: (1) to ensure intraoperative sterile condition; (2) to describe in detail the correct behavior after CXL treatment, evaluating if the patient understands; (3) to remember the possibility of systemic antiviral prophylaxis; (4) to evaluate the use of an epi-on CXL procedure. The application of this consideration could further reduce the risk of infectious keratitis after CXL.

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REFERENCES


DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.


