Photo-activated chromophore for infectious keratitis cross-linking and its efficacy as a treatment modality in managing microbial keratitis

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Purpose: To assess Photo Activated Chromophore for Infective Keratitis-Cross Linking (PACK-CXL) and its efficacy as a treatment modality in managing microbial keratitis. Methods: Single Centre prospective interventional study in infectious keratitis. A total of eleven patients were taken who had corneal thickness (CT) more than 400µm. PACK-CXL was performed according to Dresden’s protocol. The response was assessed by slit lamp examination, BCVA and AS-OCT at the time of complete healing. Results: The mean visual acuity at presentation was 1.207logMAR (0.3-3) which improved to mean value of 0.53logMAR (0.3-1). Mean time taken for complete epithelization was 17.45 days (14- 30 days) and that for complete healing was 33.72 days (21- 60 days). Mean CT at the baseline was 650.5± 108µm which reduced on consecutive follow up visits. There was reduction in the symptoms in nine patients except in two. One case reported increase in symptoms with worsening increase in endoexudates and hypopyon, and the other developed drug toxicity due to topical medications. Conclusion: Patients who underwent PACK-CXL showed good and early healing, good remodelling of cornea and improved visual acuity. The recalcitrant cases became responders to the same medications after PACK-CXL. Thus, PACK-CXL works well for both fungal and bacterial keratitis.

Key words: Collagen crosslinking, corneal ulcer, fungal keratitis, keratitis, PACK-CXL

Corneal collagen cross-linking is a technique which was initially recognized as a treatment modality to halt the progression of corneal ectatic disorders, to stabilize the disease progression.[1] Recently, corneal cross-linking (CXL) has been identified for its anti-microbial effect of photo-activated riboflavin and is being explored for treating infectious keratitis.[2] The proposed mechanisms include intercalation of the chromophore with microbial nucleic acid,[3] direct damage to the pathogen cell walls by reactive oxygen free radicals,[4] and increased resistance of the cross-linked cornea to enzymatic damage.[5] There also have been various case series and studies done in different parts of the world to establish its efficacy in non-healing and recalcitrant ulcers.

Thus, photo-activated chromophore for infectious keratitis cross-linking (PACK-CXL) seems to be a promising alternative and adjunctive treatment for managing corneal ulcers and earlier resolution of infiltrates, as has been seen in various studies, especially ones having superficial infiltrates. Thus, in our study patients of corneal ulcers with superficial infiltrates and whose ulcer depth were not more than 300 µm were included.

Also, we evaluated the patients via anterior segment optical coherence tomography (AS-OCT) following PACK-CXL treatment and followed them to see the pattern of corneal changes and healing process following the treatment, and outcome of PACK-CXL in terms of healing time and safety of the procedure.

Methods

This single centre prospective interventional study was conducted after taking permission from ethical committee of Motilal Nehru Medical College, Prayagraj. It was conducted over a span of one year, from December 2019 to December 2020 in the Regional Institute of Ophthalmology, Prayagraj, a tertiary care referral centre. All the investigations and the surgical procedure were carried out after seeking informed written consent from the patient.

All the patients who exhibited clinical signs of corneal ulcer, who met the inclusion criteria were included in the study.

Inclusion criteria
1. Age >8 years
2. Patients who exhibited clinical signs of corneal ulcer, either bacterial or fungal or mixed infection in origin.
3. Minimum corneal thickness of 400 µm
4. All the patients who signed and dated consents for the procedure.
5. The patients who complied with the study procedures and were available during the course.

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Any suspected case of non-infectious keratitis, or viral keratitis, or who had descemetocele or perforated corneal ulcer or had corneal thickness less than 400 µm were excluded from the study. Also, lactating females, or patients with atopic dermatitis or eczema were excluded. A total of eleven patients (n = 11) were included in the study.

During the initial evaluation, detailed history of the patients was taken, and thorough slit-lamp examination was done. Ulcer was examined for its site, size, dimensions, infiltration, epithelial defect, hypopyon (if present), and its height and characteristic features. The ulcer scraping was obtained from the base and the margin of the ulcer. The sample was placed on a glass slide and also on a swab stick. The scraping on the glass slide was examined after placing two drops KOH solution, and the swab stick was immediately transported for culture and growth.

All the patients of the study underwent ASOCT examination carried out on Cirrus HD OCT (Model500) by Carl Zeiss Meditec, Inc. (Dublin, CA). A standardized scanning protocol was used for all cases. Serial ASOCT scans were taken at the same area of infiltration with the scanning beam running through the centre of the infiltration site at a defined axis using a 4-mm square grid. Stromal infiltration was seen as hyperreflective area with ill-defined margins corresponding to clinical corneal infiltration and infiltration thickness was measured. Corneal thickness (CT) was measured with one caliper arm on the anterior hyperreflective corneal surface, and the second arm on the posterior hyperreflective corneal endothelium measured at the site adjacent to the area of infiltration.

The operative procedure was done by the same experienced surgeon. The procedure was conducted according to the Dresden Protocol. The corneal epithelium over and surrounding 2 mm of the ulcer area was removed using a 15-number blade. Riboflavin 0.1% (Ribocross, Sunways pharma) was then instilled prior to irradiation at every 3- to 5-minute interval for 30 minutes. Thereafter UVA rays were irradiated over the cornea by CL-UVR corneal cross-linking rapid for 30 minutes with 3 mW/cm² intensity. After completing the procedure, the eye of the patient was patched. The patients were kept in the inpatient department (IPD) initially for 72 hours, and then followed up every second day for one week, and then every week until the ulcer healed. Thorough clinical examination, which included slit-lamp examination, BCVA, and ASOCT to measure corneal thickness and infiltration thickness was done to assess the response.

Results

In our study, the preceding duration of treatment, route of administration, and number of drugs used as antimicrobial therapy were variable in all the patients. And we tried to evaluate the role of PACK-CXL as adjuvant in cases where either the response to the treatment was not adequate after a week of therapy, or there were signs of progression, even within a week. Also, PACK-CXL was used in non-responding or recalcitrant cases where the patients had been on adequate local and systemic therapy but showed no signs of healing, and as a sole therapy in a small, peripherally located ulcer [Schematic 1].

The preoperative clinical characteristics of the patient are summarized in Table 1.

Schematic 1: Classification of cases according to prior treatment given

History of preceding trauma was present in all 11 cases in our study. Out of 11 patients, trauma by vegetative matter was present in five cases, trauma following sand particles going in the eye was present in two eyes of two different patients, one had history of trauma by piece of tile (stone), two had history of trauma by buffalo tail, and one had a history of applying soorma in the eyes. The duration of the symptoms before presenting to us ranged from one day to two months. Most of them presented to us within a week.

The size of the ulcer in our patients varied from 2 × 2 mm² to 7 × 6 mm², with hypopyon present in four cases. Seven patients showed KOH positivity and six were positive on culture reports; three of them showed Aspergillus and one showed Fusarium growth, while another showed Staphylococcus aureus.

Figs. 1-6 show pre- and post-operative clinical and ASOCT images. Corneal thickness (CT) and infiltration thickness (IT) was measured on ASOCT, preoperative and postoperative at each visit on days 7, 14, 21, 30, and 60. There were two cases which showed intrastromal cystic lesions [Fig. 1a clinical photograph 3b on ASOCT], which also showed similar pattern of resolution. The corneal thickness (CT) was measured by ASOCT scan adjacent to the area of infiltration and infiltration thickness was taken at the centre of infiltration site. The mean preoperative corneal thickness (CT) was 664.63 ± 118.70 µm and mean infiltration thickness (IT) was 321 ± 48.04 µm. On postoperative day 7, 14, 21, 30, and 60, the CT measured were 681.36 ± 65.69 µm, 628.63 ± 36 µm, 610.45 ± 59.32 µm, 612.90 ± 68.49 µm, and 593.81 ± 65.63 µm, respectively [Fig. 7], and the infiltration thickness (IT) measured were 300.90 ± 44.16 µm, 268.36 ± 36 µm, 279.09 ± 59.32 µm, 268.63 ± 69.49 µm, and 260.81 ± 65.63 µm [Fig. 8]. There was a progressive decline in both CT and IT measurements on each successive visit after the procedure.

The time taken for complete epithelization ranged from 14 days to 30 days with mean time being 17.45 days. In 10 out of 11 patients, the patients witnessed significant reduction in their symptoms 72 hours after PACK-CXL, along with decrease in stromal edema and surrounding infiltration. In 8 out of these 10 patients, the ulcer showed continuous regression and epithelization was complete till 14 days after the procedure, and scar tissue had developed till 21-28 days following the procedure. In case 7 with intrastromal cysts, the patient showed normal healing with no vascularization [Fig. 1a and b; 2a and b]. In the remaining 2 of the 10 patients, the epithelization and scarring took 30 days and 60 days each. The findings are summarized in Table 2 and the clinical photographs [Fig. 1a, 2a, 3a, 4a, 5a and b] and ASOCT of the corresponding photos [Figs. 1b, 2b, 3b, 4b, 6a and b] were taken.
Table 1: Demographic profile and clinical characteristics of the ulcer

| Case | Age/Sex | Laterality | History of trauma | Duration of symptoms (in days) | Previous treatment                                                                 | Ulcer site | Hypopyon |
|------|---------|------------|-------------------|-------------------------------|-----------------------------------------------------------------------------------|------------|----------|
| 1    | 65/M    | RE         | +                 | 30                            | Natamycin every hour + moxifloxacin + tobramycin every hour + oral itraconazole (200 mg) | Central    | +        |
| 2    | 40/M    | RE         | +                 | 1                             | -                                                                                 | Peripheral | -        |
| 3    | 45/M    | LE         | +                 | 4                             | Moxifloxacin every hour + natamycin eyedrops every hour                            | Peripheral | -        |
| 4    | 24/F    | RE         | +                 | 7                             | Natamycin every hour + tobramycin every hour + moxifloxacin QID                   | Central    | -        |
| 5    | 14/M    | LE         | +                 | 7                             | Natamycin + Moxifloxacin eyedrops every hour + oral fluconazole (150 mg) OD       | Central    | +        |
| 6    | 35/M    | RE         | +                 | 4                             | -                                                                                 | Central    | -        |
| 7    | 30/F    | LE         | +                 | 7                             | -                                                                                 | Central    | +        |
| 8    | 50/F    | LE         | +                 | 60                            | Moxifloxacin every hour + tobramycin every hour + oral itraconazole (200 mg) OD  | Central    | +        |
| 9    | 35/M    | LE         | +                 | 20                            | Moxifloxacin 0.5% QID + natamycin every hour                                       | Peripheral | -        |
| 10   | 45/F    | LE         | +                 | 4                             | -                                                                                 | Central    | -        |
| 11   | 42/M    | RE         | +                 | 30                            | Natamycin 5% every hour                                                           | Central    | -        |

In 1 out of 11 patients, endoexudates progressed and hypopyon increased in height 48 hours after the procedure; subsequently, he was given intrastromal and intracameral voriconazole (four injections), after which the ulcer started to heal and showed complete epithelialization and scarring over time.

There were no complications or any adverse effects observed in any of the cases and all of them responded well to the treatment and showed complete resolution.

Discussion

Clinical and microbiological evaluation

In our study, 11 patients who presented to us and met our inclusion criteria were all clinically diagnosed to have microbial keratitis. Out of these 11 patients, four had hypopyon at the time of presentation. Endoexudates were seen in two patients. Erdem et al.\cite{5} reported hypopyon in 23.07% of cases (3 patients).
Figure 3: (a and b) Preoperative clinical (a) and ASOCT (b) images of case 4

Figure 4: (a and b) Postoperative clinical (a) and ASOCT (b) images of case 4

Figure 5: (a and b) Preoperative clinical (a) and ASOCT (b) images of case 8

Figure 6: (a and b) Postoperative clinical (a) and ASOCT (b) images of case 8
whereas Idrus et al.\textsuperscript{[1]} reported hypopyon in 50\% (14 patients) of cases.

Moreover, on performing ASOCT in our patients, we found intrastromal cysts in three of the patients, which on ASOCT were seen as hyporeflective cystic spaces in the stroma of the cornea [Fig. 1a], at the site of ulcer or infiltration. The microbiological examination showed KOH positivity in seven cases, out of which four were culture positive (three showed \textit{Aspergillus} and one showed \textit{Fusarium}). In addition to this, one case with KOH negative mount showed growth of \textit{Staphylococcus aureus} when inoculated on blood agar.

Also, in our study Eight eyes of eight patients out of eleven eyes of eleven patients (72.72\%) had central corneal ulcer involving the optical zone of the cornea, and only three patients (27.27\%) had peripherally located ulcer which was concordant with the results of the study conducted by Panda et al.\textsuperscript{[6]} in which they reported central ulceration in six out of seven patients (85.71\%) and only one patient had paracentral ulcer with partial centre extension.

\textbf{Time taken for complete epithelization and healing}

In our study, ten patients showed good response. The mean time taken for complete epithelization was 17.45 days (14–30 days) and that for complete healing was 33.72 days (21–60 days). Bamdad et al.\textsuperscript{[7]} in their study observed mean duration of treatment in CXL group to be 17.2 ± 4.1 days and that in the control group to be 24.7 ± 5.5 days. Knyazer et al.\textsuperscript{[8]} showed that mean duration taken to complete epithelization was 6.5 days (5–18 days). Kozobolis et al.\textsuperscript{[9]} observed complete re-epithelization without any additional intervention in 15 patients with mean time taken for complete healing being 7.1 days (1–14 days).

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|c|c|c|}
\hline
\textbf{Cases} & \textbf{Ulcer size (H × V)} & \textbf{KOH} & \textbf{Culture (isolated organism)} & \textbf{Pain score (before/after)} & \textbf{Time to complete epithelization (in days)} & \textbf{Complete healing (in days)} & \textbf{Preop visual acuity (logMAR)} & \textbf{Final visual acuity (logMAR)} \\
\hline
1 & 6×4 & - & - & - & - & - & 3 & 0.77 \\
2 & 3×3 & - & - & - & - & - & 14 & 0.17 \\
3 & 7×5 & - & - & - & - & - & 14 & 0.17 \\
4 & 7×6 & - & - & - & - & - & 14 & 0.17 \\
5 & 6×7 & - & - & - & - & - & 14 & 0.17 \\
6 & 7×5 & - & - & - & - & - & 14 & 0.17 \\
7 & 7×6 & - & - & - & - & - & 14 & 0.17 \\
8 & 7×7 & - & - & - & - & - & 14 & 0.17 \\
9 & 7×8 & - & - & - & - & - & 14 & 0.17 \\
10 & 7×9 & - & - & - & - & - & 14 & 0.17 \\
11 & 7×10 & - & - & - & - & - & 14 & 0.17 \\
\hline
\end{tabular}
\caption{Microbiological profile and outcome}
\end{table}
Panda et al. observed that re-epithelization started in 48–72 hours and was completed in 10–18 days, and complete resolution took 3–5 weeks. Said G et al. observed the mean duration of complete healing in CXL group to be 39.76 ± 18.22 days. Wei et al. observed no fungal hyphae on In Vivo Confocal Microscopy in CXL-M group in 1.29 ± 0.30 months after antifungal medication use post PACK-CXL. The mean drugs required in CXL group were two which was lower than in group M (2.29 ± 0.47). The healing time in CXL-M group was 1.300.93 month; and that in M group was 2.21 ± 1.35 months. Thus, in all the studies, CXL accelerated the healing process and reduced the requirement for emergency procedures like penetrating keratoplasty.

**Visual acuity**

In our study, the mean visual acuity at presentation was 1.207 logMAR (0.3–3) which improved to mean value of 0.53 logMAR (0.3–1). Out of eleven subjects, the visual acuity improved in nine, and in the other two, it remained the same. In these cases, the ulcer was peripherally located and thus had no significant effect on vision. Kasetsawan et al. observed that best corrected pinhole visual acuity at day 30 improved in 8 out of 12 cases (66.7%) and in 7 out of 11 cases (63.6%) in PACK-CXL group and control group respectively with mean BPVA of 1.48 ± 0.64 logMAR in standard treatment with PACK-CXL group, and 1.20 ± 0.67 logMAR in standard treatment alone group with no significant difference in both the groups. Said G et al. reported that average corrected distance visual acuity after complete healing was 1.64 ± 0.62 logMAR in PACK-CXL group and 1.67 ± 0.48 logMAR in control group.

**Quantitative and qualitative ASOCT features**

ASOCT has become a useful tool to assess the infiltration and corneal thickness, areas of thinning quantitatively and other qualitative features more precisely.

In our study, the mean preoperative CT and IT as measured on ASOCT was 664.63 ± 118.70 µm and 321 ± 48.04 µm, respectively. On post-operative days 7, 14, 21, 30, and 60, the CT measured were 681.36 ± 65.69 µm, 628.63 ± 36 µm, 610.45 ± 59.32 µm, 612.90 ± 68.49 µm, and 593.81 ± 65.63 µm, respectively; and infiltration thickness (IT) measured were 300.90 ± 44.16 µm, 268.36 ± 36 µm, 279.09 ± 59.32 µm, 268.63 ± 69.49 µm, and 260.81 ± 65.63 µm respectively. There was a progressive decline in both CT and IT measurements on each successive visit after the procedure. The mean CT showed a slight increase on postoperative day 7 from the baseline. This might be due to the inflammation that is induced by PACK-CXL, but as our sample size is smaller, we cannot extrapolate and conclusively comment on the same.

Sharma et al. examined 50 eyes with the diagnosis of fungal keratitis (smear and culture positive) and analyzed 42 patients at the end of the study as eight eyes underwent perforation. Baseline mean IT was 321 ± 48.04 µm, which reduced on days 7, 14, 21, 28, 42 to 300.90±44.16µm, 268.36±36µm, 279.09± 59.32µm, 268.63±69.49µm, 260.81±65.63µm, respectively. In our study, it was observed that the baseline IT had a linear relationship with healing time. Konstantopoulos et al. examined four eyes of viral keratitis and thirteen eyes of fungal keratitis, and they recorded baseline maximum CT of 1490 µm and IT of 840 µm. The limitation of our study was that CT and IT values may not be representative of their true values due to surrounding tissue edema.

Also, on ASOCT, we observed intrastromal cystic spaces in three cases that resolved on healing; two eyes had intense hyperreflective area overlying the ulcer which was also seen on slit-lamp examination as epithelial plaque.

**Complications**

In our study, 10 of the 11 patients had responded well to PACK-CXL either alone (case 2) or as adjuvant in other ten cases. There was reduction in the symptoms in nine patients except in two (cases 5 and 8). One case in our study showed increase in symptoms in the form of pain, photophobia, and also increased height of hypopyon. The endoexudates increased on postoperative day 1. Thus, the patient was planned for intrastromal injection of voriconazole on second day postoperatively. The patient showed resolution of endoexudates on follow up and so, a total of four doses of intrastromal voriconazole injection were given and the patient responded well. The final BCVA after 3 months was 6/12. In case 11, corneal ulcer kept on reducing in size and the surrounding infiltration also reduced. On postoperative follow-up visit on day 14, epithelial defect appeared, measuring 3 × 4 mm, which gradually progressed. It was managed conservatively in the next 14 days. Bamdad et al. reported no complication in any case that required any additional intervention except in one patient of PACK-CXL group who required amniotic membrane transplantation after 25 days, and two patients in the control group, one of whom required amniotic membrane transplantation and the other required conjunctival flap due to persistent epithelial defect in spite of good healing, not responding to medical therapy, punctal occlusion or tarsorrhaphy. Erdem et al. observed no intraoperative complication. However, six patients (46%) had progressive corneal melting and required additional medical/surgical intervention. No perforation was reported in any of the patients. Kasetsawan et al. required therapeutic keratoplasty in two and three cases of PACK-CXL and control group, respectively, as corneal perforation occurred following uncontrolled infection. One case, each in PACK-CXL group and control group, developed endophthalmitis and therefore required evisceration. Makdoumi et al. reported no intraoperative or postoperative complication in any of his subjects.

Said G et al. reported a total complication rate of 21%. They observed corneal perforation in three patients and recurrence of infection in one patient in control group. None of the patients in PACK-CXL group had corneal perforation, but all of them developed limbitis, which resolved within five to seven days in all the cases except in one (which had acanthamoeba keratitis) that resolved in three weeks. Wei et al. reported that in CXL-M group, hypopyon was observed on postoperative day 1, but it resolved within two weeks. However, two patients in M group reported increase in the height of hypopyon, out of which one resolved and the other developed corneal perforation within a month. Total failure rate in CXL-M group was 14.29% (three eyes) and in M group was 30% (six eyes) which developed corneal perforation and required emergency keratoplasty.
Conclusion
Anterior segment optical coherence tomography (ASOCT) has become a useful tool in addition to slit-lamp examination, allowing accurate qualitative and quantitative estimation of various parameters. Also, ASOCT allows better quantitative estimation of infiltration depth and thus, the progression or resolution can be better assessed on follow-up visits. Photo-activated chromophore for infectious keratitis cross-linking (PACK-CXL) has emerged as a novel technique for the treatment of microbial keratitis. The advantages of PACK-CXL include non-invasiveness of the technique, easy to perform procedure, and good results and early recovery in terms of healing, with good patient selection, no risk of development of antimicrobial resistance, and relatively low cost. Patients who underwent PACK-CXL also showed good and early healing, good remodelling of cornea, and visual acuity also improved. The mean visual acuity before PACK-CXL was 1.207 logMAR (0.3–3) which improved to 0.53 logMAR (0.3–1). Moreover, we also observed that PACK-CXL works well for both fungal and bacterial keratitis, and also in recalcitrant and resistant cases which were not responding to the treatment given prior but became responsive to the same treatment after PACK-CXL. PACK-CXL could be a real boon where there is increasing antimicrobial resistance and cases that are not responding to conventional treatment. In our study, we observed that PACK-CXL can work well as an adjuvant therapy that accelerates the process of healing, and as a sole therapy in smaller ulcers and in the management of recalcitrant and no responding cases.

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Conflicts of interest
There are no conflicts of interest.

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