

Commentary: PACK-CXL in fungal keratitis

Corneal collagen crosslinking (CXL) was initially described as a treatment to stabilize progressive keratoconus.^[1] It halts the progression of ectasia by inducing formation of covalent bonds among collagen fibers to prevent stromal weakening. This was the rationale behind studying the effects of CXL on corneal melts of noninfectious origin in 2000.^[2] Iseli *et al.* then proceeded to evaluate the results of CXL in advanced infectious keratitis refractory to therapy and found that CXL was effective in these cases as well.^[3] Furthermore, Makdoumi *et al.* conducted a study that demonstrated CXL to be effective in early microbial keratitis.^[4] Since then, there have been multiple studies on the use of CXL in management of infective keratitis, and it has come to be known as photo-activated chromophore for infectious keratitis (PACK)-CXL.

The antimicrobial effect of CXL is due to the interaction between the ultraviolet-A (UV-A) radiation with the riboflavin acting as a chromophore. UV-A radiation itself is known to have antimicrobial properties and damages both RNA and DNA. This property is made use of when UV-A is used for disinfecting water and air. In addition, the reactive oxygen species generated during the photochemical reaction result in new covalent bonds and improve the resistance of corneal stroma against enzymatic degradation.^[5] Most of the studies till date have used the standard Dresden protocol with UV-A radiation exposure of 3 mW/cm² for 30 min.^[6] However, reports exist about the successful use of accelerated protocol using 9 mW/cm² for 10 min.^[7]

Table 1: Studies on PACK-CXL in fungal keratitis

Authors	Year	Number of eyes with fungal keratitis	Fungus	Outcome
Iseli <i>et al.</i> ^[3]	2008	2	Acremonium and <i>Fusarium</i>	Resolution of infection with scarring
Vajpayee <i>et al.</i> ^[8]	2015	20	<i>Aspergillus</i> , <i>Fusarium</i>	PACK-CXL did not have additional benefit over medical treatment in moderate mycotic keratitis
Erdem <i>et al.</i> ^[13]	2017	13	<i>Aspergillus</i> , <i>Fusarium</i>	PACK-CXL was effective in early and superficial infections, but ineffective in deep stromal infiltrates
Basaiaiwmoit <i>et al.</i> ^[14]	2018	4	<i>Aspergillus</i> , unidentified septate hyphae	PACK-CXL reduced healing time in ulcers less than 6 mm in diameter

PACK: Photo-activated chromophore for infectious keratitis; CXL: Crosslinking

The effects of PACK-CXL have been studied on various etiologies of infective keratitis. In 2013, a meta-analysis by Alio *et al.* reported that the effectiveness of CXL to reduce the corneal melt was in the following order from most to least: Gram-negative bacteria, Gram-positive bacteria, Acanthamoeba, and fungus.^[6] The poor response in fungal infections may be explained by the fact that fungal infections penetrate deeper and CXL is known to have effect in the anterior two-third of the corneal stroma. Tabibian *et al.* used PACK-CXL as a first line of treatment and found that early fungal keratitis being superficial responded well to CXL alone. The fungus isolated was *Aureobasidium pullulans*.^[7] Vajpayee *et al.* conducted a retrospective study on moderate grade mycotic keratitis and found that in these cases, addition of CXL to medical treatment did not affect the final outcome. *Aspergillus* was the most common fungus to be isolated in their study.^[8] In advanced and deep stromal fungal ulcers, CXL has been shown to be ineffective.^[9] It has been reported that use of 0.25% riboflavin has a higher fungicidal effect than 0.1% riboflavin.^[10] Özdemir *et al.* used 0.25% riboflavin and accelerated CXL protocol and showed that CXL was effective in *Fusarium* and *Candida* keratitis as well. The effect was better when PACK-CXL was combined with medical treatment.^[11]

The case reported by Thakur *et al.*^[12] shows successful resolution of a corneal fungal infiltrate at the site of phaco-tunnel. They used 0.1% riboflavin with Dresden protocol. Although the organism was not isolated, the aqueous tap was positive for fungal genome. It is possible that PACK-CXL had a synergistic effect with the already administered antifungal medical treatment. The case highlights that CXL was effective in deep fungal infiltrate when used as an adjuvant treatment. Since there are prior studies to show that deep fungal infiltrates have a poor response to CXL, it is difficult to comment whether this infection would have responded to PACK-CXL alone [Table 1]. Nevertheless, further studies on the effects of CXL on fungal keratitis are needed to understand whether deep stromal infiltrates are likely to respond well.

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