Diclofenac-induced Acute Corneal Melt After Collagen Crosslinking for Keratoconus

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INTRODUCTION

Corneal collagen crosslinking with riboflavin is a new treatment modality applied to strengthen the cornea in eyes with progressive keratoconus in which the corneal thickness is more than 400 μm. This treatment involves central epithelial debridement and application of riboflavin drops to the cornea followed by its exposure to low-dose ultraviolet A light. The photoactivated riboflavin enhances corneal strength and integrity by increasing collagen crosslinking. In this report, we highlight a rare and paradoxic vision-threatening complication of crosslinking treatment, which defeats the very purpose of the treatment.

CASE REPORT

A 19-year-old male patient had been using rigid gas-permeable lenses for keratoconus in both eyes. Progression of keratoconus was documented in both eyes by serial topography and refractive error over a period of 2 years. There was no history of ocular allergy or dryness. He underwent bilateral corneal collagen crosslinking treatment for progressive keratoconus.

After topical proparacaine anesthesia, central 8-mm epithelial debridement was done. A solution of 0.1% riboflavin (Ricrolin; SOOFT) was applied to the cornea every 5 minutes for 25 minutes. The central 8.0 mm of the cornea was then irradiated with ultraviolet A light (VEGA crosslinker; CSO Ophthalmic) with a wavelength of 370 nm and an irradiance of 3 mW/cm². During the 25 minutes of irradiation, drops of riboflavin solution were applied to the cornea every 5 minutes to sustain the required concentration of riboflavin and to prevent desiccation of the cornea.

Postoperatively, the patient was advised to use diclofenac 0.1% eyedrops (Voveran Ophthalm; Novartis Pharma) 5 times a day, ofloxacin 0.3% with dexamethasone 0.1% eyedrops (Ofto-DM; Sunways) 4 times a day, and carboxymethylcellulose 0.5% eyedrops (Refresh tears; Allergan India) 4 times a day in both eyes. He was also advised to use proparacaine 0.5% eyedrops (Paracain; Sunways) as needed to manage pain and on inquiry, the patient reported using these drops approximately 3 times a day.

He was referred to us 1 week after the crosslinking procedure with redness, watering, pain, and loss of vision in his right eye. Examination of the right eye revealed diffuse conjunctival congestion, central corneal melt with severe thinning (5 mm × 5 mm) and perforation (2 mm) with adjacent corneal edema (Fig. 1). Corneal sensation, lid margins, and tear film were normal in both eyes. The anterior chamber was flat and there was a brisk leak on Seidel's test. Visual acuity was perception of light with accurate projection in all quadrants. The left eye had keratoconus but was otherwise normal.

The patient was advised to discontinue the medications prescribed earlier and was started on 100 mg oral doxycycline twice a day, moxifloxacin 0.5% eyedrops (Mifulox; Sun Pharma) 4 times a day, and carboxymethylcellulose 0.5% eyedrops (Refresh tears; Allergan India) 4 times a day. He underwent a temporary cyanoacrylate glue application with a bandage contact lens under topical anesthesia. The bandage lens fit was not satisfactory as a result of an ectatic contour so the patient was advised to perform patching to avoid lens displacement. The glue application facilitated formation of the anterior chamber and allowed us to safely wait until a donor cornea was available. Five days later, therapeutic keratoplasty (8 mm × 8.5 mm) was done with optical-grade tissue. Postoperatively, prednisolone 1% eyedrops (Prednisolone; Allergan India) 6 times a day were prescribed in addition to the ongoing treatment. One month after keratoplasty, the patient had a clear graft with an uncorrected vision of 20/60 improving to 20/30 with pinhole.

Histologic evaluation of the excised button revealed a central area of stromal loss with perforation. (Fig. 2A) The surrounding epithelium showed regenerative changes with large epithelial cells,
irregular basement membrane, and loss of the Bowman’s layer. A few epithelial downgrowths were noted with apoptotic changes in the epithelial cells. The adjacent stroma showed edema, keratocyte loss, myofibroblastic transformation of keratocytes, and a few neutrophils and round cell infiltrates (Fig. 2B). The Descemet’s membrane was fragmented and had rolled in, showing loss of endothelial cells around the region of the perforation. The peripheral part of Descemet’s membrane, however, showed preserved endothelial cells. Special stains for fungus and bacteria were negative.

**DISCUSSION**

Corneal collagen crosslinking is gaining popularity as a treatment for keratoconus. The procedure is safe and no damage to the endothelium, crystalline lens, or retina has been noted, primarily because ultraviolet A transmission through the cornea is limited by the application of riboflavin drops. Stromal haze has been observed in the early postoperative period, but this usually resolves over time with the use of steroid drops. Keratocyte loss has been noted in the anterior 300 μm of the stroma immediately after the procedure and repopulation usually occurs by approximately 6 months. Histologic studies of corneas after crosslinking have documented 3 types of changes: changes in the collagen properties, alterations in the keratocyte population, and epithelial loss followed by repair.

Crosslinking has been advocated as a means to treat corneal melt and ulceration. In this case, perforation after treatment suggests a possible interplay of factors other than the treatment itself. The use of topical diclofenac and proparacaine in the presence of an epithelial defect postoperatively could have been responsible for the acute stromal melting and perforation.

Topical nonsteroidal anti-inflammatory drugs, including diclofenac sodium, have been reported to cause corneal melting and perforation postoperatively, especially in the presence of epithelial breakdown. Impairment of wound healing, neurotrophic effect resulting from the analgesic property of these drugs, and activation of matrix metalloproteinases are the suggested mechanisms. Topical anaesthetic abuse has been associated with epithelial defects, ring infiltrates, stromal melts, and perforation. This may be the result of delayed wound healing and the toxic effect on stromal keratocytes.

Although the exact chronologic events after treatment in this case could not be delineated, certain histologic changes were evident from our examination of the corneal button obtained on day 12 after treatment. These changes suggest that the central cornea sustained the maximum damage with the intense stromal loss here leading to perforation; the surrounding corneal epithelium, stroma, and endothelium showed regenerating changes. The presence of neutrophils and mononuclear cells correlates with the earlier reports of corneal melt following diclofenac use. The other eye, which was treated at the same sitting, probably re-epithelialized more rapidly and did not have any complication.

To the best of our knowledge and based on a survey of the literature, this is the first case report of a corneal perforation after corneal collagen crosslinking treatment for keratoconus. This case illustrates the need for a close follow up

**FIGURE 1.** Central corneal melting with a large perforation.

**FIGURE 2.** A, Section shows cornea with central area of perforation and folded ends of Descemet’ membrane (hematoxylin & eosin, ×100). B, The surrounding corneal stroma shows keratocyte loss, neutrophils, and myofibroblastic transformation of keratocytes (hematoxylin & eosin, ×400).
of these patients in the early postoperative period until surface re-epithelialization is complete. Use of nonsteroidal anti-inflammatory drops and topical anesthetics should be strictly avoided in the early postoperative period.

REFERENCES