Photorefractive keratectomy with mitomycin-C for the combined treatment of myopia and subepithelial infiltrates after epidemic keratoconjunctivitis

David Alevi, MD, Allon Barsam, MA, FRCOphth, Jonathan Kruh, MD, Jessica Prince, MD, Henry D. Perry, MD, Eric D. Donnenfeld, MD

PURPOSE: To report the use of photorefractive keratectomy (PRK) with mitomycin-C (MMC) to treat concomitant myopia and visually significant infiltrates associated with epidemic keratoconjunctivitis (EKC).

SETTING: Ophthalmic Consultants of Long Island, Nassau University, Long Island, New York, USA.

DESIGN: Interventional case series.

METHODS: Consecutive patients with myopia and recalcitrant subepithelial infiltrates after EKC were treated with custom wavefront PRK (Visx S4 IR) and MMC with a target of emmetropia in all cases.

RESULTS: The study evaluated 6 eyes of 3 patients. One year after treatment, all eyes attained an uncorrected distance visual acuity of 20/20 or better. There was no recurrence of infiltrates within the ablation zone in any eye.

CONCLUSION: The use of topical MMC in conjunction with PRK to treat subepithelial infiltrates due to EKC provided good visual and refractive results.

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Excimer laser photoablation in the form of phototherapeutic keratectomy (PTK) has been used since the late 1980s to manage and treat anterior corneal pathology. The 193 nm argon-fluoride laser photochemically breaks intermolecular bonds, expelling corneal tissue in a controlled manner without thermal damage. Excimer laser photoablation can remove corneal pathology, improving visual acuity and patient comfort. Using a laser instead of conventional excisional corneal surgery may allow more controlled removal of pathological tissue by minimizing adjacent tissue damage.

Phototherapeutic keratectomy is effective in superficial corneal pathology that is present in Bowman membrane or in the anterior cornea stroma. Removing or reducing this corneal pathology allows a smoother and clearer cornea. Ablating and flattening the more central areas of the cornea with use of PTK often results in a hyperopic change in refractive error that is directly related to the depth of the ablation. This hyperopic shift is unpredictable and may diminish over time. Haze, likely secondary to deposition of new irregular collagen fibers or from light scattering by activated kerocytes in the wound, is another complication of PTK. Also, variations in the eye’s rate and ability to reepithelialize contribute to further complications, including irregular astigmatism and scarring.
Several case reports document elimination of corneal opacities followed by a recurrence in the pathology. Finally, in certain cases in which recurrence does occur, multiple treatments of PTK are necessary to reduce corneal pathology and improve patient satisfaction. Despite these potential complications, PTK has been used with much success to reduce and eliminate corneal pathology, delaying and avoiding more invasive methods including lamellar and penetrating keratoplasty.

Epidemic keratoconjunctivitis (EKC) is caused by multiple adenovirus strains and is associated with infection and inflammation of the cornea and conjunctiva. Adenovirus is a nonenveloped double-stranded DNA virus. The virus is extremely stable, being resistant to most solvents and detergents. The more virulent serotypes, such as serotypes 8 or 19, were found to be viable for up to 4 to 5 weeks on inert material. Ophthalmology offices are prone to epidemics due to contamination of instruments or hand-eye contact by ocular secretions from the infected patient. In addition, EKC has been found in hospital outbreaks, public swimming pools, and upper respiratory tract infections.

Epidemic keratoconjunctivitis is characterized by follicular conjunctivitis, papillary hypertrophy, conjunctival hemorrhage, lid edema, and chemosis. Preauricular and submandibular adenopathy may assist in the diagnosis. In severe cases, membranes or pseudomembranes may develop on the tarsal conjunctiva, which may lead to conjunctival fibrosis and symblepharon formation.

The corneal findings of EKC begin with a diffuse epithelial keratitis that stains with fluorescein and may coalesce into focal epithelial lesions approximately 1 week after infection. Subepithelial corneal infiltrates of 1.0 to 2.0 mm in diameter develop within the second or third week after conjunctival symptoms begin and diffuse epithelial keratitis is seen. These infiltrates generally develop in the center of the cornea; however, they may cover the entire corneal surface. Due to the corneal infiltrates, permanent glare or photophobia may develop; decreased visual acuity is also likely to occur as a result of irregular astigmatism and corneal opacities occluding the visual axis. Some of these visual effects may (in part) resolve spontaneously over several years and can be treated with low-dose topical corticosteroid agents. Corticosteroid therapy may require months of treatment and once discontinued, the infiltrates often reoccur. In addition, long-term corticosteroid use is associated with cataract formation and glaucoma.

Successful removal of adenoviral EKC corneal opacities using PTK and mitomycin-C (MMC) or PTK alone has been reported. There have also been reports of myopic photorefractive keratectomy (PRK) without MMC used with partial success to permanently remove the infiltrates in patients with subepithelial infiltrates. To our knowledge, the present series is the first description of the use of PRK with MMC to treat myopia and visually significant infiltrates associated with EKC.

PATIENTS AND METHODS

Patients with myopia and recalcitrant subepithelial infiltrates after EKC were treated with custom wavefront PRK (Visx S4 IR, Abbott Medical Optics); the target was emmetropia in all cases. Approximately 10 to 15 subepithelial infiltrates were observed in each patient. After informed consent and extensive discussion, each patient elected to have PRK to treat the myopia and to remove the corneal opacities. Manual epithelial debridement was performed followed by excimer ablation. After PRK with the laser, MMC 0.02% was applied for 30 seconds before the cornea was fully irrigated with a cooled balanced salt solution. Each patient had a bandage contact lens placed and was treated with gatifloxacin 0.3% 4 times a day for 6 days; ketorolac 0.5% 4 times a day for 2 days; and prednisolone acetate 1.0% 4 times a day for 1 week, 3 times a day for 1 week, 2 times a day for 1 week, and every day for 1 week. The bandage contact lens was removed 3 to 5 days after surgery. Patients were then examined 1 week and 1, 3, 6, and 12 months after treatment.

RESULTS

Six eyes of 3 patients were treated.

Case 1

A 27-year-old myopic male ophthalmology resident with a refraction of $-2.50 - 0.50 \times 110$ in the right eye and $-2.75$ in the left eye developed EKC in both eyes with visually significant subepithelial infiltrates. He had worn a soft contact lens for 7 years and was developing increased contact lens wear intolerance. Seven months before evaluation, the patient had a severe case of EKC that left him with multiple central bilateral subepithelial infiltrates. The patient was treated with a tapering dose of prednisolone acetate 1% starting at 4 times a day for 3 months without resolution of the infiltrates. After an additional 4 months without corticosteroids, the patient presented for evaluation with continued central subepithelial infiltrates and a corrected distance visual acuity (CDVA) of 20/20 in both eyes; however, he reported glare and halo that had not been present before the development of the infiltrates 40 μm beneath the epithelium. The patient had 8 to 10 infiltrates, mostly clustered around the central 6.0 mm of each cornea, with a few extending to the peripheral 9.0 mm point.

Wavefront analysis was obtainable in both eyes and matched the patient’s refraction. The decision was made to enlarge the custom wavefront ablation zone

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to 8.8 mm, which increased the depth of the ablation to 68 μm in the right eye and 77 μm in the left eye. By enlarging the ablation zone and depth of ablation, the infiltrates in the midperiphery of the cornea would also be treated. This decision was made to prevent peripheral infiltrates from causing symptoms under mesopic conditions, in which the pupil may become larger.

One year after PRK, the patient had 20/15 uncorrected distance visual acuity (UDVA) in both eyes, a refraction of plano in both eyes, no glare or halo, and clear corneas with complete resolution of all infiltrates.

Case 2

A 24-year-old myopic woman with a refraction of $-4.50 - 0.25 \times 90$ in the right eye and $-4.75 - 0.50 \times 95$ in the left eye developed EKC with visually significant infiltrates 40 μm beneath the epithelium. The infiltrates developed 2 weeks after the acute infection and were treated with a 5-month course of tapering prednisolone acetate 1.0% and then loteprednol 0.5%; this resulted in improvement of the infiltrates and a CDVA of 20/25 in both eyes. The patient also reported glare and halo. She was followed for an additional year without topical corticosteroids and had slight improvement in the infiltrates but continued to have a CDVA of 20/25 in both eyes. She had 12 to 15 infiltrates extending from the central cornea to the periphery. The glare and halo remained the same.

Photorefractive keratectomy was performed with a central ablation depth of 88 μm in the right eye and 90 μm in the left eye; the ablation zone was 8.0 mm. Two years after PRK, the patient had a UDVA of 20/20 in both eyes and a refraction of $+0.50 - 0.25 \times 90$ and $+0.25 - 0.25 \times 80$, respectively. He no longer reported glare or halo; the central cornea of each eye was clear with no infiltrates.

Case 3

A 30-year-old man with a refraction of $-8.75 - 1.25 \times 147$ in the right eye and $-7.75 - 0.50 \times 80$ in the left eye developed EKC in both eyes with visually significant infiltrates 40 μm beneath the epithelium (Figure 1). The EKC developed 7 months previously when the patient was living in Lebanon. The patient had taken several 4-week reducing courses of topical prednisolone acetate 1.0% 4 times a day since developing the viral keratitis. However, he remained symptomatic with glare despite a CDVA of 20/20 in both eyes. He had 12 to 14 infiltrates, mostly clustered around the central 5.0 mm of each cornea, with a few extending to the peripheral 10.0 mm point.

Photorefractive keratectomy was performed with a central ablation depth of 109 μm in both eyes; the ablation zone was 8.0 mm. The bandage contact lens was removed 5 days after surgery when the epithelium was almost healed (Figure 2). One year after PRK, the patient had a UDVA of 20/20 in the right eye and 20/20 in the left eye with a refraction of $+0.25$ in each eye. She no longer reported glare or halo; the central cornea of each eye was clear with no infiltrates.

DISCUSSION

All 3 patients sought refractive surgery to reduce or remove their dependence on glasses. However, the presence of subepithelial infiltrates and the glare and halo associated with them were also a concern. The decision to perform PRK rather than laser in situ...
keratomileusis (LASIK) offered the ability to remove the infiltrates rather than preserve them in the LASIK corneal flap. In addition, LASIK can reactivate subepithelial infiltrates in the area of the laser ablation. In the past, PRK treatment for residual myopia and subepithelial infiltrates without the use of MMC has had variable success, with resolution of the infiltrates centrally but recurrence in the periphery. In other cases, significant recurrences have been seen centrally in patients with subepithelial infiltrates after EKC. The recurrence is thought to be due to the natural history of the infiltrate or to the withdrawal of the corticosteroid.

The decision to perform PRK rather than PTK was based on the patients’ preexisting myopia and their desire to treat the concomitant refractive error. Photorefractive keratectomy offers greater refractive accuracy than PTK. In addition PTK in the United States can be performed with the Visx laser only and has a maximum ablation zone of 6.5 mm and no blend zone, which creates an oblate ablation profile. A maximum blend zone of 0.5 mm can be added to the Visx PTK, which decreases the effective ablation zone from 6.5 mm to 6.0 mm. Performing excimer laser ablation to treat myopia in a cornea with opacities is an off-label use of the excimer laser, and our patients were informed of this and consented appropriately. Excimer laser ablation does not always ablate at the same rate in a clear cornea as in a scarred cornea. Even though subepithelial infiltrates can be faint, they sometimes coalesce and create a large area of opacity; when this is ablated with an excimer laser, there is the potential for resultant irregularity. We did not believe that the opacities in our patients were dense enough to warrant the use of a masking agent or transepithelial PRK to prevent this potential problem.

All patients had careful evaluation of wavefront aberrometry. By selecting a custom treatment, we were also able to modify the ablation zone from 8.0 mm to 8.8 mm and ablation depth based on the patients’ refractive errors, infiltrate depths, and locations of infiltrate removal, centrally as well as in the midperiphery. However, it may not be essential to remove the peripheral infiltrates depending on the patient’s pupil size and the exact location and density of the infiltrates.

At present, there is no U.S. Food and Drug Administration–approved treatment for EKC. In general, therapy is directed to provide symptomatic relief with artificial tears and to treat the inflammation with topical corticosteroids. Several antiviral agents that have activity against adenovirus are available. Recently, ganciclovir was approved for use in the U.S., and this antiviral has in vitro and in vivo activity against adenovirus and may provide a treatment option that was not previously available.

These patients were candidates for PRK because of their stable myopic refraction with visually significant recalcitrant subepithelial infiltrates caused by EKC. In more mild cases, patients can often wait for spontaneous resolution of symptoms to avoid the risks of PRK. These risks include severe corneal haze, which has been significantly reduced with the use of smoother ablation profiles and the use of MMC; however, historically, haze may present in up to 15% of patients after surgery. In addition, patients with a high degree of myopia have less reliable refractive outcome due to the cornea’s pattern of healing after the ablation. Other less common complications after PRK include pain secondary to the epithelial defect and delayed epithelial healing. We have found that haze and scarring are very rare when PRK is combined with MMC; therefore, we do not routinely use topical steroids beyond the first month unless clinical signs indicate the need for this.

Keratocytes located within the human corneal stroma serve to organize the extracellular matrix (ECM) and to heal injury to the cornea. Studies have shown that transforming growth factor-β induces transformation of keratocytes to myofibroblasts. During times of injury, this transformation can occur, which is critical in shaping the ECM during corneal injury. A capsid of adenovirus 19 can attach to a cellular binding site, activating a signal transduction cascade that causes expression of interleukin-8 (IL-8) and monocyte chemoattractant protein-1 (MCP-1). Both IL-8 and MCP-1 are chemokines that attract proinflammatory mediators to the corneal stroma.

Although MMC was originally used as a systemic chemotherapeutic agent, topical MMC is being used with increasing frequency in ophthalmology. It has been used in glaucoma filtering surgery to prevent scarring; in pterygium surgery, in the treatment of conjunctival and corneal intraepithelial neoplasia, and in the treatment of ocular cicatricial pemphigoid.

Mitomycin-C is a modulator of corneal wound healing after PRK in animal models. Talmo et al. performed excimer laser ablation in 10 New Zealand white rabbits. The eyes were randomized to receive topical MMC 0.05%, topical steroids and topical erythromycin, steroids and erythromycin, or erythromycin alone. The medications were instilled twice daily for 14 days. Eyes receiving topical MMC 0.05%, topical steroids, and topical erythromycin had little or no subepithelial scarring. Histopathologic differences...
between the groups suggested that steroids and MMC inhibited subepithelial collagen synthesis in an additive fashion.

Schipper et al.36 examined the effect of MMC in reducing scar formation after laser PRK in rabbits. After PRK, eyes were treated with a single 5-minute application of MMC 0.04% or a balanced salt solution. Eyes treated with MMC had a significant decrease in the number of keratocytes. Scar tissue, defined as disorderly newly synthesized collagen fibrils, was absent in the MMC group. Because subepithelial collagen synthesis is an important part of scar formation in EKC, treatment with MMC may be beneficial in preventing recurrence of infiltrates after EKC.

Marcon and Rapuano37 report a case in which they successfully performed excimer laser PTK retreatment of anterior basement membrane dystrophy and Salzmann nodular dystrophy with a single intraoperative application of MMC 0.02%. They did not report complications. Six months after the procedure, the cornea showed no signs of recurrence.

The use of topical MMC has been associated with significant ocular toxicity. Complications seem to occur after prolonged topical administration in patients with contributing underlying pathology.38 Complications seen after pterygium surgery include secondary glaucoma, corneal perforation, corneal edema, iritis, pain, and photophobia.39 We apply the MMC to the central cornea and are careful not to affect the stem cells at the limbus.

The 6 eyes of our 3 patients did not have complications and maintained clear corneas without recurrence of the subepithelial infiltrates with at least 1 year of follow-up. The use of topical MMC in conjunction with PRK may prevent the recurrence of subepithelial infiltrates and help provide an excellent refractive result. Long-term follow-up and a larger cohort of patients are needed to further assess the safety and efficacy of this treatment.

**WHAT WAS KNOWN**

- Successful removal of adenoviral EKC corneal opacities using PTK and MMC or PTK alone has been reported.

- There have also been reports of myopic PRK in patients with subepithelial infiltrates without MMC used with partial success to permanently remove the infiltrates.

**WHAT THIS PAPER ADDS**

- To our knowledge, the present series is the first description of the use of PRK with MMC to treat myopia and visually significant infiltrates associated with EKC.

**REFERENCES**


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