Chapter 6

Corneal Haze

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Introduction

Corneal haze presents as a superficial opacification of the normally clear cornea leading to a transient decrease in corneal transparency after excimer laser keratectomy.[1] It primarily results as part of a postoperative healing response to PRK, LASEK, or Epi-LASIK, particularly in high corrections of myopia, hyperopia, and astigmatism. Patients are not normally aware of this haze until it begins to impact their visual acuity. Haze can cause glare at night from bright lights, which may or may not interfere significantly with vision under low light conditions. Corneal haze usually reduces and disappears spontaneously within 6 to 9 months; however, it may not disappear in all cases[2] (Figure 6-1).

What Is Corneal Haze?

Histological and immunohistochemical studies reveal that the subepithelial haze contains newly synthesized collagen such as type III collagen, type IV collagen, fibronectin, laminin, and proteoglycans.[3-5] The first stage of wound healing in the cornea after PRK is epithelial migration along the ablated stromal bed. After re-epithelialisation, epithelial hyperplasia occurs,[6-8] which is then followed by stromal regeneration. During this phase, there is an increase in the number of stromal spindle-shaped keratocytes in the subepithelial stromal layer[9] that express smooth muscle specific alpha actin (α-SM actin) and synthesis type III collagen. Transforming growth factor –β (TGF-β) has been proposed to be significant in inducing corneal stromal fibrosis after excimer laser keratectomy.[10] These activated stromal keratocytes (myofibroblasts) lay down an extracellular matrix.[11] From 1 month to a few months after PRK, the number of keratocytes tends to gradually diminish. The degree of corneal stromal haze after PRK correlates with the number of active fibroblasts and the amount of new extracellular matrix.[12]

The wound response following LASIK is quite different to that after PRK, LASEK, or Epi-LASIK. LASIK preserves corneal epithelium and Bowman's membrane, thereby reducing the effect of wound healing and problems associated with surface ablation.[13,14] Epithelial damage of the corneal flap due to severe dehydration or mechanical injury during LASIK

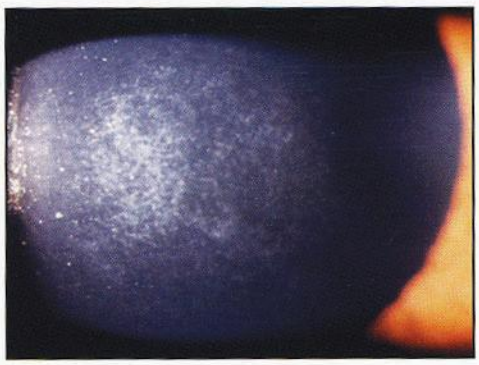

Figure 6-1. Appearance of corneal haze (grade 3.0+).

procedures can evoke excessive wound healing, leading to fibrosis or scarring. Nakamura et al hypothesized that intact epithelium is the key to the prevention of stromal haze after photoablation.[15]

Onset of Corneal Haze

In vivo investigations of the structures responsible for corneal haze after PRK reveal a subepithelial deposition of collagen and extracellular matrix that gradually develops at the epithelial-stromal junction. This starts 1 week postoperatively, increases to a peak level between 1 and 3 months, and declines slowly thereafter.[1] However, Meyer and coauthors[16] and Lipshitz and coauthors[17] define a so-called late-onset corneal haze (LOCH) as an acute haze starting 4 to 12 months after excimer laser ablation (ie, at the time regular post-PRK haze has subsided in eyes with moderate to high myopia).[1]

Causes of Corneal Haze After PRK

Patients with a larger attempted correction,[18-20] atopy, autoimmune conditions,[21] or high ultraviolet (UV) radiation exposure[1] may have a higher risk for corneal haze after excimer photoablation. Studies[1,16,17] have shown a correlation between post-PRK haze and UV-B exposure. These studies demonstrate that UV-B exposure after PRK exacerbates and prolongs the stromal healing response, manifested by increased keratocyte numbers and deposition of disorganized collagen in the anterior stroma.

Use of UV-protective eyewear should be encouraged during the first year after PRK especially in environments of high UV exposure (reflection from snow or water, high altitudes, or low latitudes).[1]

Grading Corneal Haze After PRK

Anterior stromal haze that may be associated with photorefractive keratectomy can be classified using a grading scale as follows:

- 0 = Clear; no haze
- 0.5 = Trace corneal haze
- 1.0 = Mild corneal haze not affecting refraction
- 2.0 = Moderate corneal haze with difficult refraction
- 3.0=Corneal haze preventing refraction but anterior chamber visible
- 4.0=Severe corneal haze preventing refraction and completely obscuring iris details

Prophylaxis and Treatment of Corneal Haze

- Topical anti-inflammatory drugs such as 0.1% dexamethasone (Maxidex, Alcon, Ft. Worth, Tex), 0.1% fluorometholone (FML) (Allergan, Irvine, Calif) or prednisolone acetate 1% (Prednefrin Forte, Allergan) used postoperatively can prevent the development of excessive corneal haze and should be used for at least 1 month postoperatively.[22] These drugs inhibit both early and late manifestations of the inflammatory process, including fibrin deposition, fibroblast proliferation, and collagen deposition.
- Ice packs 10 minutes pre- and post-PRK together with chilled balanced salt solution (BSS) immediately after the ablation.[23]
- Severe haze affecting functional vision can be treated using phototherapeutic keratectomy (PTK) in conjunction with Mitomycin-C (MMC).

MMC is an antibiotic with antimetabolite effects (see Chapter 10) that inhibits the proliferation of keratocytes.[24] It has been used since the 1980s systemically in cancer chemotherapy[25] where its use originated, and in ophthalmology, in cases of ocular pemphygoid and following surgical treatment of glaucoma and pterygium.[26-28] MMC at a dilution of 0.02% (0.2 mg/mL) has been used in the treatment of post-PRK haze.[29] It has no effect on normal epithelial cells of the cornea provided there is no intraoperative contact of MMC with the stem cells at the limbus. There is also the prophylactic use of MMC to prevent haze applied immediately following PRK in moderate to high myopia.[30,31]

The main causes of regression and haze are overactivity and proliferation of stromal keratocytes following laser ablation.[31,32] MMC has cytotoxic effects through inhibiting DNA synthesis. MMC on the cornea can inhibit subepithelial fibrosis through preventing the proliferation of stromal keratocytes. The effects of MMC 0.02% in preventing haze have been shown by Talamo et al[29] and Xu et al[33] in experimental models. In a study by Majmudar et al, it was concluded that the application of MMC can reduce haze following PRK where prior radial keratectomy (RK) incisions existed.[34] It can also prevent the recurrence of haze after previous surgical complications such as a buttonholed LASIK flap.[35,36] The usefulness of PRK with MMC (0.2 mg/mL) for preventing haze in high myopia was reported by Carones et al.[31] Using MMC in PRK for myopia greater than -5.00 D has been shown to be safe and effective and can reduce haze formation after surgery.[32] To reduce potential toxicity, application times have reduced from the earlier standard of 2 minutes to as little as 12 seconds.[37,38]

Case Study

In the case study presented below, we report our first experience in treating corneal haze post-PRK using PTK and 0.02% MMC as an adjunctive therapeutic agent. A 32-year-old male presented in 2001 inquiring about refractive laser surgery. He reported that he was a keen beach goer and spent a lot of time surfing while wearing soft disposable contact lenses for his high myopia. The preoperative parameters from the assessment are summarized in Table 6-1. A complete ocular health examination was unremarkable.

It can be seen from Figures 6-2A and 6-2B that the topographical appearance of the cornea was relatively normal. However, as the ultrasound pachymetry values were thinner than average (490 µm), the recommendation made was for PRK instead of LASIK. It was also recommended to treat one eye at a time, beginning with the nondominant left eye. This was to ensure that the patient gained functional vision and comfort before proceeding with the second eye. The patient was advised to leave his left contact lens out for 1 week preoperatively to minimize the chance of infection and allow stability of the corneal shape.

Table 6-1

Preoperative Parameters

Measurement	*OD*	*OS*
Manifest refraction	-9.50 DS/-0.50 DC Ax 170	-8.50 DS/-2.00 DC Ax 180
Cycloplegic refraction	-9.25 DS/-0.50 DC Ax 170	-8.00 DS/-2.00 DC Ax 180
BSCVA	20/20	20/20
U/S pachymetry	490 µm	490 µm
Simulated keratometry*	44.40/45.55 @ 80	45.08/46.61 @ 80

*Figures 6-2A and 6-2B

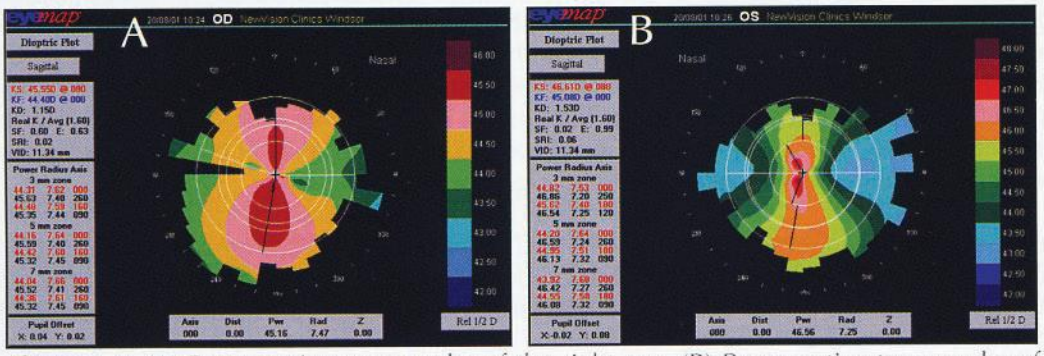

Figure 6-2. (A) Preoperative topography of the right eye. (B) Preoperative topography of the left eye.

PRK Surgery

The left eye underwent routine PRK surgery; an Amoils epithelial brush was used to remove the epithelium prior to the application of the excimer laser. The treatment programmed into the VISX STAR S2 laser (Santa Clara, Calif) was calculated using a multipass/multizone algorithm.[39] Cold BSS, Voltaren Ophtha (diclofenac sodium 5 mg/mL [Novartis, New York, NY]), and Chlorsig (chloramphenicol 5 mg/mL [Sigma Pharmaceuticals, Monticello, Iowa]) drops were subsequently used during the procedure. A bandage contact lens was applied to facilitate healing and was removed 2 days postoperatively once the epithelium had regenerated.

Postoperative topical medication was Chlorsig qid for 1 week and (once the epithelium had healed) FML (1 mg/mL) qid, tapering weekly over 1 month. Cellufresh (carmellose sodium 5 mg/mL, Allergan) lubricating drops were also used for the first month following surgery.

Postoperative Results

The results from the left surgery 6 weeks postoperatively were excellent. The patient was happy with the vision with only a minor complaint of glare at night. The results are summarized in Table 6-2. Because vision was good and there was no evidence of corneal haze at that time, arrangements were made to have PRK for the right eye. Again, the soft contact lens was removed 1 week prior to surgery. The surgical technique and postoperative topical medication were unchanged as for the left eye.

Table 6-2

Six Week Postoperative Results of Left Initial Surgery

Measurement	*OS*
UCVA	20/30++
Manifest refraction	Plano/-0.75 DC Ax 100
BSCVA	20/20
Slit-lamp	Clear cornea

Table 6-3

Postoperative Results of Both Eyes

Measurement	*OD (Postop 4 weeks)*	*OS (Postop 10 weeks)*
UCVA	20/20	< 20/200
Manifest refraction	+1.25 DS/-0.75 DC Ax 180	-5.00 DS
BSCVA	20/15	20/80+
Slit-lamp	Trace haze	Grade 1.5 to 2.0 haze
Simulated keratometry*	35.18/36.75 @ 90	39.20/40.89 @ 90
Intraocular pressure	12 mmHg	12 mmHg
U/S pachymetry	417 µm	518 µm

*Figure 6-3.

Four weeks after the right eye surgery, the patient reported that vision from his right eye was "good." However, he noted that the vision in his left eye (now 10 weeks postoperative) had deteriorated over the past few weeks. Indeed, this was confirmed by the reduced visual acuity measurements described in Table 6-3 and attributed to the appearance of corneal haze visible at the slit-lamp (Figure 6-3).

The development of corneal haze in high myopic PRK corrections has since been well-documented.[40,41] However, during this postoperative consultation the patient reported that he had been surfing extensively during the past month without wearing sunglasses despite being advised against this. The effect of UV radiation and the incidence of corneal haze after PRK has also been well-documented,[1,42] and it was concluded that this factor had contributed to the haze in this case.

Therapeutic Treatment of Corneal Haze

Over the course of the next 3 months, the patient's left eye was treated with topical anti-inflammatory agents in an effort to reduce the haze. Initial therapy was Maxidex (dexamethasone 1 mg/mL, Alcon) qid, later replaced with Pred Forte (prednisolone acetate 10 mg, Allergan) qid. When the haze had not resolved with topical therapy alone and the right eye began to show grade 0.5 haze, oral 25 mg cortisone was introduced bd.

Figure 6-3. Right and left eye topography at 2.5 months postoperatively.

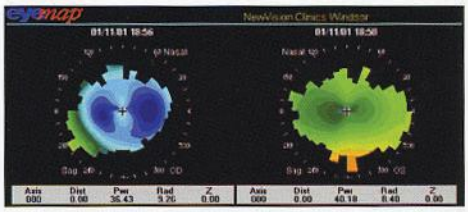

Table 6-4

Results 6 Months Following Left Initial PRK Surgery

Measurement	*OD (postop 4.5 months)*	*OS (postop 6 months)*
UCVA	20/120	< 20/200
Manifest refraction	-0.50 DS/-1.00 DC Ax 45	-9.75 DS
BSCVA	20/60	20/120
Slit-lamp	Grade 1.0 haze (diameter 5.0 mm)	Grade 3.0+ haze* (diameter 5.0 mm)

*Figure 6-1

The intraocular pressure (IOP) had initially risen to 30 mmHg as a result of the topical steroid therapy. Adjunctive topical glaucoma therapy was instigated; Diamox orally (acetazolamide 250 mg, [Lederle, Madison, NJ]) with Alphagan (brimonidine tartrate 2 mg/mL, Allergan) bd and Xalatan (latanoprost; benzalkonium chloride 0.2 mg/mL [Pfizer, New York, NY) nocte were used and the IOP returned to 16 mmHg within a few days. Xalatan was therefore used in conjunction with the steroid treatment from that point, and the IOP remained well controlled.

There was no significant improvement noted in either the vision or the appearance of the corneal haze. In fact, the left eye displayed further deterioration to a grade 3 haze, as displayed in Figure 6-1. The best-corrected acuity (BCVA) had also dropped to 20/120 in this eye. The 6-month postoperative results are summarized in Table 6-4. It should be noted that the right eye had also developed corneal haze to a lesser extent, but the unaided vision in that eye had also gradually reduced to 20/120.

Prevention of Corneal Haze Using Mitomycin-C

At this stage, the patient was restricted in his work duties because of the reduction in his vision in both eyes. He was involved in mixing paint and was required to distinguish between subtle shades of color. After extensive counseling, it was decided that surgical intervention was required.

Research through the scientific literature[31,34,43] and extensive consultation with international colleagues indicated that the use of the compound MMC could be very effective in preventing the recurrence of haze after a second surgical treatment. The risks associated with the use of MMC were researched and discussed at length with the patient.

Calculation of Residual Stromal Tissue

Once it was decided that a secondary procedure including MMC was required, the question became one of how much of the apparent myopia to treat. It cay be seen from Table 6-4

Table 6-5

Thickness of the Hyperplastic Layer of Epithelium and Haze

Calculation Of Residual Stromal Tissue For Left Eye	
Preoperative corneal thickness	490 µm
Assumed epithelium thickness	60 µm
Initial treatment depth (from VISX S2 treatment printout)	120 µm
Estimated remaining stromal tissue	310 µm
Calculation of Hyperplastic Epithelial Thickness	
Measured postoperative corneal thickness	518 µm
Estimated remaining stromal tissue	310 µm
Estimate of epithelium/haze thickness	208 µm

that there was almost 10.00 D of myopia present in the manifest refraction, which corrected the vision to only 20/120. Certainly, some of this myopia would be due to the presence of the haze on the cornea, but there was no way to determine how much. There may have also been some regression factors involved as evidenced by the epithelial hyperplasia.

It was decided to largely disregard the recurrence of the high myopia and to ablate the haze by phototherapeutic keratectomy (PTK). If required, a small amount of the myopia could be treated immediately following the PTK up to a maximum of 2.00 D. The haze reduction was to be monitored as the treatment progressed, and treatment ceased when the cornea appeared clear. This was done both objectively by observing the appearance of the cornea, and also by regular intraoperative pachymetry measurements to monitor the corneal thickness after epithelial removal and tissue ablation. A postoperative ultrasound pachymetry had previously been measured and found to be 518 µm. This was used to estimate the approximate thickness of the hyperplastic layer of epithelium and haze (Table 6-5).

PTK Surgical Technique Including Use of Mitomycin-C

As with the initial PRK procedure, the epithelium was removed with the Amoils epithelial brush. The PTK treatment was subsequently applied with a 6.0-mm circular ablation and a 0.3-mm transition zone. The frequency of the laser pulses was reduced to 6 Hz from the usual 10 Hz to allow the surgeon additional time to visualize the progressive removal of the haze.

After 45 pulses of PTK (11 µm) treatment, the procedure was paused for evaluation. There was still trace corneal haze remaining on objective examination under the laser microscope. It was decided to apply a minor myopic correction to further remove the haze and also to allow for any myopic regression that may have occurred. A treatment of -1.00 DS (63 pulses, 16 µm) within a 6.5-mm optic zone was applied at a rate of 6 Hz. The overall tissue removal was 27 µm.

Immediately following the myopic (second) treatment, the patient was evaluated at the slit-lamp. There was no discernible haze evident—at which point it was decided against any further treatment as this was deemed unnecessary and could result in overcorrection. The patient was taken back under the laser for the application of the MMC to prevent any

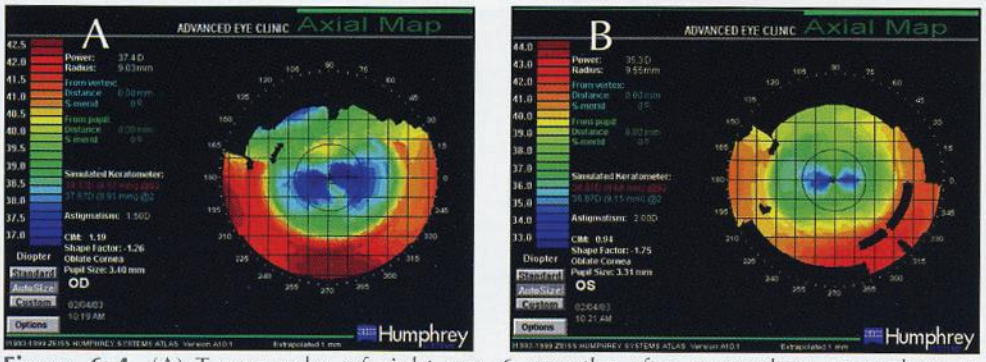

Figure 6-4. (A) Topography of right eye 6 months after secondary procedure to treat haze. (B) Topography of left eye 12 months after secondary procedure to treat haze.

future haze reformation. A Banaji shield soaked in MMC (0.02%) was applied to the cornea for 2 minutes (the recommended duration at that time). The cornea was then rinsed with 10 mL of cold BSS to flush away any remnants of MMC. As occurred after the initial surgery, a nonsteroidal anti-inflammatory drug (NSAID) was instilled, followed by a bandage contact lens and antibiotic. The contact lens was to be left in position for 2 to 3 days until corneal healing had occurred.

Postoperatively, Ciloxan (ciprofloxacin hydrochloride 3 mg/mL [Alcon]) and Predsol (minims) were prescribed qid together with Travatan (0.004% travoprost [Alcon]) nocte to keep any steroid-induced IOP rise under control.

Results Following Combined PTK/PRK With MMC

At 1 month postoperatively for treatment of haze, the results were very gratifying for both surgeon and the patient. There was a significant improvement in unaided vision, and the cornea displayed only trace haze (Figures 6-4). These results are summarized in Table 6-6.

The patient was advised to wait before considering treating the right eye for haze. This was to allow sufficient time to ensure no recurrence of corneal haze in the left had occurred and to evaluate the effectiveness of the epithelial remodelling that had occurred together with minor myopic treatment that was applied.

After 5 months (post-retreatment), it was evident that the treatment of the left eye had been successful with no noticeable haze formation and an excellent unaided vision of 20/30++. It was decided to treat the right eye in a similar fashion with a brush removal of epithelium, PTK, and minor myopic PRK.

The right eye achieved similarly excellent results as the left, and 1 month following this treatment, the patient's confidence had been restored and he had returned to full-time employment. He purchased a pair of wrap-around sunglasses that he could use during surfing and proceeded cautiously in regard to UV exposure, which included the use of a wide-brimmed hat outdoors.

Outcomes

The final review was conducted 12 months after the left eye was retreated and 7 months after the right eye was retreated. At this visit, the patient was praising the results; he was extremely pleased with his vision and level of comfort after such a frustrating but worthwhile waiting period in view of the complexity and risks of the treatment. The vision was a stable

Table 6-6

One Month Postoperative Results Following Treatment of Left Corneal Haze

Measurement	*OS*
UCVA	20/30
Manifest refraction	+0.50 DS/-1.50 DC Ax 165
BSCVA	20/30
Slit-lamp	Trace haze

Table 6-7

Results Following Treatment of Corneal Haze to Both Eyes

Measurement	*OD (postop 7 months)*	*OS (postop 12 months)*
UCVA	20/30++	20/30-
Manifest refraction	Plano / -0.75 DC Ax 45	+1.25 DS/-1.25 DC Ax 165
BSCVA	20/30++	20/20
Slit-lamp	Trace haze	Trace haze†
Simulated keratometry*	37.87/39.37 @ 92	36.87/38.87 @ 92

*Figure 6-4; †Figure 6-5

20/30 in each eye and 20/30++ binocularly, and the appearance of the cornea was relatively clear. These results are displayed in Table 6-7.

Summary

This case demonstrates the dangers of excess exposure to UV light after PRK and the effectiveness of MMC in reducing the recurrence of corneal haze following laser vision correction with PRK. It also demonstrates how the treatment of corneal epithelial remodelling plus the corneal haze without including any significant refractive treatment may contribute to reducing any residual refractive error due to haze and epithelial remodelling. In this case, the patient apparently regressed to almost 10.00 D of myopia, though this was largely excluded in the surgical treatment plan. It was expected that the myopia would resolve by the removal of the epithelial hyperplasia and haze, as indeed was the case. If not, then subsequent refractive treatment could have been applied.

Since this initial use of MMC in the clinic 5 years ago, it has been included in all primary myopic PRK treatments where the spherical equivalent is above -4.50 DS. The 0.02% solution of MMC is still used, though the duration of application has been shortened from 2 minutes to 30 seconds for primary treatments. For PRK retreatments of low refractive magnitudes after LASIK or RK, only 15 seconds application is utilized. No similar episodes have occurred over this time with PRK treatments performed with this effective adjunctive treatment.

Acknowledgments

We would like to thank our colleagues Dr. Parag Majmudar and Dr. Francesco Carones for their advice in the management of this complex case. MMC is now a routine prophylactic part of our care with PRK and high myopia in primary treatments and in retreatments over LASIK flaps.

Key Points

1. Corneal haze presents as a superficial opacification of the normally clear cornea leading to a transient decrease in corneal transparency after excimer laser keratectomy.
2. It is primarily caused as part of a postoperative healing response to PRK, LASEK, or Epi-LASIK, particularly in high corrections of myopia, hyperopia, and astigmatism.
3. Histological and immunohistochemical studies reveal that the subepithelial haze contains newly synthesized collagen such as type III collagen, type IV collagen, fibronectin, laminin, and proteoglycans
4. Patients with a larger attempted correction, atopy, autoimmune conditions, or high UV radiation exposure may have a higher risk for corneal haze after excimer photoablation.
5. Corneal haze usually reduces and disappears spontaneously within 6 to 9 months; however, it may not disappear in all cases.

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