

Pathogenesis and management of haze after photorefractive keratectomy

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Introduction

Corneal subepithelial haze is commonly seen following photorefractive keratectomy (PRK). It is part of the normal corneal healing response after PRK.¹ Various studies have shown that corneal haze peaks at 3-6 months following PRK. There is a steady decrease in severity until 18 months post-operatively.^{2,5}

Haze is commonly described as loss of corneal transparency which may arise from scattering or diffuse refraction of light incident to structural disturbances within the ablated zone. The terminology can be confusing because haze is a subjective phenomenon that is frequently expressed by the patient. It does not necessarily refer to the loss of corneal transparency as viewed by the examiner.⁴ We believe that haze may be more accurately defined in histopathological terms as subepithelial scarring of cornea.

The degree of haze varies between individual patients. In their study of 24-month follow-up of excimer laser for myopia, Epstein *et al*⁶ observed that 96% of the eyes had a subepithelial haze of 1+ or less, while 3% of the eyes had a haze of 2+, and 1% with haze of 3+. In another study by Thompson *et al*,⁷ 89.3% of all patients were free of clinically significant haze 12 months after surgery, and no eyes suffered from marked haze. There was a tendency for early post-operative haze to diminish over time: using the VISX Excimer Laser, Machat and Maguen³ observed that corneal

haze of 2+ or more occurred in 2.3% of eyes at 3 months and decreased to 0.4% at 12 months post-operatively. Moderate to severe haze was found in 3.1% of cases at 3 months post-operatively and dropped to 2.6% at 12 months post-operatively.⁷ Seiler *et al*⁸ observed that the incidence of manifest scars after PRK depends on the attempted correction. In correction of lower myopia group (≤ -3.0 D), 0% had scar, whereas 1.1% and 17.5% of cases had manifest scars in correction of moderate myopia group (-3.1 to -6.0 D) and high myopia group (-6.1 to -9.0 D), respectively. In their 18 month follow up, Gartry *et al*⁹ reported that anterior stromal haze was maximal at 6 months and diminished thereafter. The change was detected in 92% of cases by the third month.

Pathogenesis

The variability of haze is related to the variability in wound healing responses of individual patients. In a study of wound healing response after PRK in Rhesus monkey corneas, Fantes *et al*¹ demonstrated the epithelium healed well without undergoing significant hyperplasia. However, there was a transient anterior stromal fibroplasia with production of new extracellular matrix, mainly type III collagen, type VII collagen⁹ and keratan sulfate¹⁰ which was associated with the clinical observation of haze. There was a strong correlation between the clarity of healed cornea and the absence of new collagen and epithelial hyperplasia.¹⁰

At the epithelial-stromal junction, areas of basement membrane discontinuity persists for 3 months. Discontinuity of these basement membranes was typically seen with epithelial healing over bare stroma. These irregularities at the epithelial wound junction may give the transient corneal haze.

The changes in anterior stroma were the major causes for the corneal haze. The subepithelial stromal haze appeared at 2-3 weeks after ablation and peaked by 6-8 weeks. During this time, activated fibroblasts migrated into the existing normal structures and secreted new extracellular matrix. After approximately 3 months, the number of fibroblasts decreased, and less extracellular matrix was produced, which was associated with clinical regression of haze. The irregularities in the basal epithelial cells, the vacuolation between lamellae, increased number of fibroblasts and production of extracellular matrix as a consequence of epithelial-stromal wound healing cause light scattering and corneal haze.^{1,9-13}

Malley demonstrated the presence of type VII and type III collagen in monkey corneas by indirect immunofluorescence microscopy 18 months after PRK, there were also fibronectin and laminin deposited in high quantities, which associated with an increase in size and number of keratocytes at treatment area.¹⁴ Hanna *et al* described early histochemical changes in rabbits like increased amount of type IV collagen, proteoglycans, fibronectin and laminin.¹⁵ Azar *et al*¹⁶ found that after excimer laser, the matrix metalloproteinase MMP-9 was expressed in corneal epithelium and stroma during wound closure. Another collagenase, MMP-2, was present in stroma before wounding and increased following wounding. It is possible that these proteolytic enzymes play a role in stromal remodeling in normal cornea and in scar formation and clearing post-excimer wound.¹⁶

Both clinical and histopathologic studies demonstrate individual differences in amount of haze that developed post-PRK, as there was a different biological healing response for each individual. Durrie reported 3 patterns of healing response following PRK: normal healers were those with a small amount of hyperopia and faded slowly over time; inadequate healers had minimal haze and remained hyperopic; and aggressive healers developed significant regression with subepithelial haze.¹⁷

Risk factors

The most important risk factor for the development of subepithelial scarring is the degree of intended myopic correction. Higher myopic and higher cylindrical corrections require greater treatment depths, which may explain the increased degree of subepithelial haze.^{3-5,8} Caubet observed that at 1 month, mean clinical anteriorstromal haze were 0.5, 0.74 and 1.15 in the -2, -4 and -6D myopic corrections respectively. At 3 months, mean haze were 0.73, 1.13 and 1.62; and at 18 months, they were 0.07, 0.17 and 0.83, in the -2, -4 and -6D myopic corrections respectively.

With proper surgical techniques, smoother wound contours¹⁸

and optimal intraoperative stromal hydration,³ the risk of corneal haze formation can be minimized.¹⁹ The use of a larger optical zone¹⁸ (>4.5 mm) and of multizone techniques¹⁸ tends to give less haze post-operatively. O'Brart *et al*¹⁹ investigated the effect of ablation diameter, depth and edge contour on the outcome of PRK showed that haze was significantly reduced at 1, 3 and 6 months in the 6.00mm treated eyes ($p < 0.05$). On the other hand, slow re-epithelialization and persistent epithelial defect may predispose to post-operative haze formation.²⁰

The extent of haze has also been found to be associated with younger patient age,⁵ the male sex,⁴ nitrogen flow,³ rapid steroids withdrawal,⁴ keloid former,¹⁷ pregnancy¹⁷ and dry eyes.¹⁹ Medications like acutane, amiodarone, estrogen,¹⁷ progesterone,¹⁷ may contribute to haze formation. Untreated allergic conjunctivitis has also been identified as another potential risk factor for haze and regression following PRK.²¹

Furthermore, history of previous refractive surgeries,²² such as radial keratectomy, astigmatic keratectomy and cataract surgery, may also predispose to post-operative haze development. In a multicenter trial of PRK for residual myopia after previous ocular surgery, Maloney *et al*²² found mild haze was seen in 11 of 107 eyes, moderate haze was seen in 5 of 107 eyes and marked haze in 3 of 107 eyes, i.e. there was higher incidence of corneal haze in this group of patients. The previous corneal surgery may have a propensity to scar due to fibroblast activation.

Clinical presentation and outcomes

Clinically, there are 3 major presentations of haze.³ a) faint reticular haze, which is a normal part of healing process and usually disappears over 6-12 months without interfering with vision; b) arcuate haze or scarring, which is usually in peripheral aspect of ablation and most often will resolve spontaneously with stromal remodeling; c) central dense haze or collagen plaque, which is usually visually significant, but is rare. However, if the central dense haze is persistent more than 6-12 months, retreatment is probably needed. Under slit-lamp examination, the opacities are located at subepithelial region covering the ablation zone, and they may assume several appearances: thin granules, coarse clumps, or confluent opacity.³

Results of the Summit US 6.0 mm FDA study showed that 6.8% of patients experienced loss of 2 or more lines of best spectacle-corrected visual acuity at 6 months that decreased to 1.2% at 12 months following surgery. Sixty three per cent of patients had anterior stromal reticular haze (53% trace; 7.3% mild; and 2.3% moderate) at 6 months, while 44% had trace reticular haze at 1 year following PRK.

Gartry *et al*⁶ found that best corrected visual acuity was reduced in 18% of cases; 15% lost between 1 line of best spectacle corrected visual acuity while 3% who had undergone either -6.0 or -7.0 D correction lost 2 lines. Maloney *et al*²² also showed similar relationship between

severity of haze and loss of best corrected visual acuity. A good correlation existed between haze and regression ($r=0.68$) of refraction.^{3,5}

Results of the VISX study showed that 2.3% of patients experienced loss of 2 or more lines of best spectacle-corrected visual acuity at 6 months that decreased to 2.2% at 12 months following surgery. A haze grade of 2 or greater was reported in 1.3% of patients at 3-6 months, as compared to 0.2% at ≥ 2 years following treatment.

Machet JJ³ also commented confluent haze, whether focal or diffuse, arcuate or circular, is associated with a higher risk of immediate and long term regression and loss of best corrected visual acuity related to irregular astigmatism. Other associated outcomes of clinically significant haze include decreased contrast sensitivity, and starburst phenomenon,³ which is the scattering of light around bright light sources at night. This degrades visual function and decrease contrast sensitivity. In addition, haze may lead to glare by inducing myopia through steepening the corneal curvature, reducing the effective optical zone.

Evaluation of haze

Documentation of haze development in cornea following PRK is an important aspect in evaluating the post-operative course of the procedure. Corneal haze can be graded clinically by slit-lamp microscopy.²³ The scoring system for grading corneal haze based on the VISX protocol is as follows: 0, clear, no haze; 0.5, haze, barely detectable; 1, mild, not affecting refraction; 1.5, haze, mildly affecting refraction; 2, moderate haze, refraction possible but difficult; 3, opacity prevents refraction, anterior chamber easily viewed; 4, opacity impairs view of anterior chamber; 5, unable to see the anterior chamber.

Corneal haze was also graded subjectively by Fantes *et al.*¹ According to Fantes classification, a score of 0.5+ indicates trace haze seen with careful oblique illumination by slit-lamp microscope; 1+, more prominent haze that does not interfere with visibility of fine iris details; 2+, mild obscuration of iris details; 3+, moderate obscuration of iris and lens; and 4+, completely opaque stroma in the area of ablation.

As the above methods of haze grading are subjective measurements, their accuracy and reproducibility may vary, and they are prone to inter-observer variability and bias. Objective assessment of corneal haze is important for patient follow up, and for better understanding of corneal wound healing, scarring, and pharmacological modulation. Andrade *et al.*²³ used an opacity lensometer for measuring corneal haze and reported its lack of sensitivity in measuring corneal clarity after PRK, especially with lower grade of subjective haze. Lohmann *et al.*²⁴ used a CCD (charged coupled device)-camera system fixed to a slit-lamp microscope and connected to a computer. By incorporating polarizing filters, the system could discriminate between reflected and scattered light. They found that the scattering light measured reflected well with disturbances in corneal

transparency after PRK, even in minor degrees.

Confocal microscopy may also be helpful to study corneal haze. Essepian *et al.*²⁵ showed evidence of stromal scarring in early stages of normal corneal wound healing. The degree of keratocyte elongation and subepithelial scarring slowly decreased over time, but was not normalized by 6 months after surgery. A higher frequency ultrasound biomicroscopy was used at Cornell University Medical College to study corneal wound healing and development of corneal haze. The results of studies using this method showed irregularly distributed echo hyperreflectivity that decreased over 10 weeks. The histopathological examination showed good correlation between the imaging pattern and increased keratocyte activity.²⁶

Braunstein *et al.*²⁷ used scatterometry to measure corneal light scattering in patients undergoing excimer laser surgery. Basically, it measured back-scattered light from a defined regions of cornea under standardized illumination condition. A scattering index (SI) was calculated and it showed a moderately strong positive correlation with best corrected visual acuity. Using scatterometry, Jain *et al.*²⁸ have observed that corneal light scattering is greater following surface PRK than that following laser in situ keratomileusis (LASIK).

Management

Subepithelial haze following PRK is usually transient. It generally resolves without treatment by 6 months post-operatively. Persistent haze can be managed either medically or surgically. Medical and surgical management decisions are usually based on the presence and extent of associated regression of the refractive effect.

Topical steroids is often prescribed in the first 3 months following PRK especially for myopic corrections of $>3D$, and if non-steroidal anti-inflammatory drugs (NSAIDs) are used simultaneously. There have been reports of sterile infiltrates in the cornea in patients undergoing PRK with NSAIDs used without steroids. The steroid regimen employed at the Massachusetts Eye and Ear Infirmary is: Tobradex qid until epithelium heals, followed by Fluoromethalone 0.1% qid first month, tid second month, bid third month, and qd fourth month. Steroids should be tapered sooner if the patient is hyperopic (inadequate healer).¹⁷ They are frequently used in greater frequency and concentrations if haze or significant regression are noted. Although steroids can be used to control haze, they cannot eliminate haze.¹⁹ In a study of 10 blind and 13 sighted eyes, Seiler *et al.*²⁹ showed that post-operative steroids can minimize corneal haze. In a rabbit model, post-operative steroid treatment was shown to reduce both stromal haze and thickness of subepithelial new collagen layer.³⁰ However, another study showed that steroids treatment was associated with persistence of stromal thinning.³¹ In addition, it was observed that the extent of anterior stromal haze was not influenced by the presence or absence of steroids at any stage.³² Therefore, although steroids have been shown to be helpful in controlling haze development, their long term benefits remain uncertain. The

risks of steroids complications, such as steroid-induced glaucoma, posterior subcapsular cataract, ptosis, increased risk of infection, and rebound upon withdrawal, should certainly be taken into consideration.

Topical non-steroidal anti-inflammatory drugs (NSAIDs) such as diclofenac and ketorolac have been shown to decrease corneal haze in rabbits in the early post-operative period.^{17,33} NSAIDs have been reported to have antiproliferative activity comparable to or better than that of the steroids.³³ Since diclofenac does not have the potential side effects of corticosteroids, topical NSAIDs may play an increasing therapeutic role in the future in controlling excessive fibroblast proliferation, hence reducing the development of corneal haze after excimer laser surgery. However, as NSAIDs delay epithelial wound healing, they may actually increase haze formation; which has led many investigators to limit their role to pain relief, and avoid using them for more than 24-48 hours.³⁴

Other potential medications that may have a role in the management of corneal scarring after PRK include: mitomycin C,¹¹ antioxidants,³⁵ MMP inhibitors,³⁶ plasmin- and plasminogen activator inhibitors,³⁷ and alpha 2b-interferon.³⁸ Many of these drugs are still experimental. Mitomycin C is a potent antimetabolite isolated from *Streptomyces caespitosus*. It acts by inhibiting DNA, cellular RNA and protein synthesis. It has been observed that combined topical steroids and 0.4 mg/ml mitomycin C can markedly reduce new subepithelial collagen formation and hence reduce anterior stromal scarring.¹¹ However, topical therapy with mitomycin C is not free of side effects. According to Singh series,³⁹ local side effects of mitomycin C include delayed conjunctival re-epithelialization, mild anterior-chamber inflammation, and superficial punctate keratopathy. The addition of topical steroids was helpful in minimizing these side effects. Thus, although mitomycin C may influence corneal wound healing, given the potential toxicity of this agent, further clinical trial is necessary to define its efficacy and treatment regimen.

When visually significant dense haze persists for more than 12 months despite medical interventions, surgical retreatment may become necessary. The goal of the retreatment is to achieve trace haze, and not a clear cornea, because a clear cornea usually is seen with overtreatment and significant hyperopia. The objective is to debulk haze, or transform it from clinically significant to insignificant haze, eliminate the associated refractive error and restore topography. A transepithelial approach, using combined PRK/PTK modality, in which the epithelium is ablated with a PTK approach, is almost mandatory in cases of clinically significant haze. A key to retreatment is to have a maximal optical zone. Ideally, the optic zone should be at least as large as the primary procedure. Two hundred pulses or 50 microns of epithelium ablation is recommended. The goal or the endpoint of retreatment should be about 90% of haze clearance, leaving cornea with a mottled "stromal" surface. It is ideal to leave a trace amount of residual haze because a clear cornea may mean overtreatment and leave the patient hyperopic. As a consequence, steroids withdrawal would be mandated and would lead to increased haze. When excessive

haze is still evident by the slit-lamp examination, an additional 5 to 15 microns can be ablated. Alternatively, following the ablation of the epithelium, a PRK approach can be used. Similarly, the principle is to carefully monitor the depth of ablation. Ideally, only 50-60% of associated myopia is treated to avoid full correction.⁴⁰ In conclusion, in retreatment the emphasis should be placed on the depth of ablation rather than the diopters corrected in order to avoid overtreatment.

The benefit of corneal rescraping is controversial. Meyer *et al*⁴¹ suggested long-term treatment with topical corticosteroids may be required to prevent the recurrence of haze after surgical debridement. They found that debridement alone without aggressive topical corticosteroid use resulted in rapid return of the haze.

Other surgical approaches in the management of persistent haze, such as homoplastic automated lamellar keratoplasty and penetrating keratoplasty, can also be considered when necessary.

Indisputably, the best way of managing corneal haze is to prevent it from developing. The importance of prevention cannot be overemphasized. Therefore, PRK in high myopes should be avoided if all possible. Instead, alternative approaches, such as laser in situ keratomileusis, should be considered. In performing PRK, it is important to well control the overall intraoperative hydration status of the stroma since excessive drying promotes haze formation. Likewise, control of dry eyes in the immediate post-operative period can help reduce haze in some patients.⁴² Early steroids intervention and epithelial healing can also help minimize the risk of developing corneal haze. Epithelial healing can be promoted by wearing bandage contact lens. However, care must be taken to avoid excessive movement or tightness of the contact lens. Finally, it is just as important, if not more, to keep in mind that unrealistic pre-operative expectation of PRK should always be avoided.

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