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Objective Assessment of Transient Corneal Haze and Its Relation to Visual Performance After Photorefractive Keratectomy (Reprint)

by Corina van de Pol (USAARL), and Koichi Soya and David G. Hwang (University of California, San Francisco)



Aircrew Health and Performance Division

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however, visual decrements were measured. As a clinical tool, the TSPC-3 hazemeter objectively measures very subtle changes in haze levels. Corneal haze appears to account for only approximately 50 percent of visual performance changes in the early healing period after photorefractive keratectomy. Other factors, namely topographic abnormalities, are more likely to be an important cause of persistent visual disturbances.

Objective Assessment of Transient Corneal Haze and Its Relation to Visual Performance After Photorefractive Keratectomy

CORINA VAN DE POL, OD, PHD, KOICHI SOYA, MD, AND DAVID G. HWANG, MD

• **PURPOSE:** Photorefractive keratectomy has the potential to cause transient corneal haze. The purpose of this study was to evaluate the relationship between transient corneal haze as measured by an objective means and high and low contrast visual performance.

• **METHODS:** In a prospective study, 44 eyes of 28 patients were examined preoperatively and at 1, 3, 6, and 12 months after photorefractive keratectomy. Five laser in situ keratomileusis and two intrastromal corneal ring segments (Intacs [KeraVision, Fremont, CA]) were included for comparison, because these procedures are not expected to cause haze. Haze was measured using a prototype objective hazemeter, TSPC-3, a modification of the Nidek EAS-1000. Visual performance was measured using high-contrast visual acuity and the Rabin Small Letter Contrast Test.

• **RESULTS:** Corneal haze was greatest at the 1-month examination and was consistent with a decrease in visual performance on both tests. Corneal haze resolved in 82% of eyes by 10 ± 4 months after photorefractive keratectomy. However, visual performance had not returned to preoperative levels in 65% and 81% of these eyes on the high-contrast visual acuity test and the Small Letter Contrast Test, respectively. Eyes that underwent laser in situ keratomileusis and Intacs did not develop corneal haze; however, visual decrements were measured.

• **CONCLUSIONS:** As a clinical tool, the TSPC-3 hazemeter objectively measures very subtle changes in haze levels. Corneal haze appears to account for only approximately 50% of visual performance changes in the early healing period after photorefractive keratectomy. Other factors, namely topographic abnormalities, are

more likely to be an important cause of persistent visual disturbances. (*Am J Ophthalmol* 2001;132:204–210. © 2001 by Elsevier Science Inc. All rights reserved.)

CORNEAL HAZE IS A POTENTIAL CONSEQUENCE OF surface excimer laser corneal ablation. Corneal haze results from the presence of incongruities in the corneal tissue, usually subepithelial and anterior stromal, which result in an increase in scattered light.^{1–6} Attempts to directly correlate corneal haze with impairment in visual performance, especially as measured by low-contrast acuity or contrast sensitivity, have been mixed. Some studies show that performance is inversely related to the amount of haze,^{2,7,8} whereas other studies show that performance deficits and haze do not progress along the same time course.^{9,10} In this study, the level of haze measured by objective means was evaluated in terms of its impact on a specific measure of visual performance, namely low-contrast visual performance on the Rabin Small Letter Contrast Test,¹¹ as well as the standard clinical measure of vision, the high-contrast visual acuity test.

The corneal stroma maintains its clarity through the regular arrangement of collagen fibrils in a lattice-type structure in lamellar sheets. It is both the spacing of the fibrils within the arrangement and the size of the collagen fibrils that influence clarity.^{12,13} Any distortion of the regularity of the corneal structure, through edema, mechanical forces, or degenerative processes such as keratoconus, results in a loss of clarity. Corneal scarring, as from inflammation or injury, is another significant cause of corneal opacification. The type III collagen that is typically present in an area of corneal haze or scarring has a larger caliber (30–50 nm) than the original type I collagen (25–30 nm).^{1,6} The larger-caliber fibrils cause a change in the form of scatter, and their irregular arrangement causes an increase in the amount of scatter.

Intraocular scatter has been proven to affect visual performance in numerous studies of aging and cataract. Forward light scatter causes a veiling glare, which can have very significant effects on contrast sensitivity. Allen and

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From the US Army Aeromedical Research Laboratory (Dr van de Pol), Fort Rucker, Alabama and the University of California, San Francisco (Drs Soya and Hwang), San Francisco, California.

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Reprint requests to Corina van de Pol, OD, PhD, Visual Sciences Branch, US Army Aeromedical Research Laboratory, PO Box 620577, Ft. Rucker, AL 36362; fax: (334) 255-6993; e-mail: corina.vandepol@se.amedd.army.mil

Vos¹⁴ and van den Berg¹⁵⁻¹⁷ found an increase in intraocular scatter with age and a strong relation of scatter to contrast sensitivity but a weak correlation of forward light scatter to high-contrast acuity. Hess and Garner¹⁸ and Hess and Carney¹⁹ evaluated the effect of edema, corneal distortion, and corneal dystrophy on the contrast sensitivity function. Edema tends to cause a diffuse clouding of the cornea, whereas granular dystrophy causes localized areas of opacity. The resulting scatter has very different impacts on the contrast sensitivity function. Edema caused an overall depression of the contrast sensitivity function, whereas a granular corneal dystrophy and keratoconus caused mid-spatial and high-spatial frequency loss and no effect on contrast sensitivity at the lower spatial frequencies.

In photorefractive keratectomy using the excimer laser, the epithelium must be removed to ablate corneal tissue and change the anterior corneal curvature. An epithelial defect measuring 6-8 mm in diameter is created using a blade or excimer laser. The laser then ablates the Bowman layer and the anterior stroma to produce the refractive effect. After the procedure, the epithelium has to regenerate to cover the "wound." All the usual healing sequelae associated with corneal abrasion take place after an ablation except that the bed of the abrasion is now stroma instead of the Bowman layer.

During healing, the anchoring fibrils of the epithelial basal cells no longer have a template to reattach to and may therefore not have the same uniformity as the original epithelial architecture.²⁰⁻²² Keratocyte activation and a change in the type and regularity of collagen present in the anterior stroma are also thought to contribute to corneal haze.^{1,23-26} Some studies show a peak in haze between 1 and 3 months, whereas others show the peak as late as 3 to 6 months.^{9,10,27} After haze peaks, there is variable resolution of the haze with time.

The objective measurement of haze is superior to subjective assessments in terms of accuracy and repeatability.^{24,28} Most studies of haze after photorefractive keratectomy have used slit-lamp observation and subjective scales in which the observer grades the presence of haze from 0 to 4, with 0 indicating no haze and 4 indicating severe haze that obscures visibility of the iris.

A few studies have incorporated objective measures of corneal haze using various instrumentations. The Scheimpflug photographic technique is a procedure that has been successfully used in human crystalline lens studies to take very accurate cross-sectional images. The major advantage of Scheimpflug over other imaging techniques is that the entire depth of the structure imaged is in focus. In 1990, Smith and associates²⁹ applied the technique to corneal analysis using computerized linear scanning densitometry to measure Scheimpflug photographs. In 1995, Soya and associates³⁰ modified an anterior segment Scheimpflug imaging system (EAS-1000; Nidek, Gamagori, Japan) to capture and analyze the cornea using

computerized densitometry of the video image. The imaging system used in the present study, prototype TSPC-3, is a further modification of the EAS-1000 in terms of anterior segment magnification and analysis programs. Similar instrumentation has already been used to assess wound healing after photorefractive keratectomy³¹ and to evaluate the transparency and barrier functions of the cornea.³²

The TSPC-3 measures back-scattered light from the cornea. However, it is forward light scatter in the eye that reduces retinal image contrast and therefore reduces contrast sensitivity.^{15,16} In a study for Nidek, the back-scattered light measured by the TSPC-3 was found to correlate to forward-scattered light for particle suspensions of sizes comparable to normal and abnormal corneal components (Soya K, unpublished data, 1997). Increases in corneal haze after photorefractive keratectomy, seen to the observer as back-scattered light, are therefore expected to correlate with decreases in visual performance resulting from forward light scatter. If measured haze is not correlated to visual performance, then corneal aberrations or other factors may be implicated.

METHODS

Photorefractive keratectomy was performed on 28 patients (44 eyes) in the Food and Drug Administration phase III trials of the NIDEK EC-5000 Excimer Laser Corneal Surgery System (Gamagori, Aichi 443, Japan; Fremont, California). Informed consent was obtained in accordance with the University of California Committee for Protection of Human Subjects and the FDA phase III trial procedures. The refractive correction procedure consisted of instillation of topical anesthetic and antibiotic preoperatively, mechanical removal of the central corneal epithelium, and ablation of the Bowman layer and the anterior stroma according to the Nidek EC-5000 algorithm. Postoperatively, topical antibiotics are instilled and a bandage contact lens applied. The patient continued to use topical antibiotics as prescribed and topical nonsteroidal anti-inflammatory drugs and/or oral analgesics as needed for pain until the epithelium had closed over the ablated area. The bandage lens was removed, topical corticosteroids added to the regimen, and topical antibiotics phased out. Corticosteroids were continued for approximately 3 months depending on the individual healing response in terms of refractive stability and haze development.

Patients were examined preoperatively ($n = 44$) for baseline and at 1 month ($n = 19$), 3 months ($n = 36$), 6 months ($n = 35$), 9 months ($n = 26$), and 12 months ($n = 17$) postoperatively. Although a larger group would have been preferred at the latest examination, a limitation in the author's timeline for this study prevented measurement of all subjects to this latest examination and is not the result of the loss of any subjects to follow-up. The data

from this examination served to determine whether any progression of haze might be evident between the 6-month and 12-month examinations. The mean refractive correction and standard deviation for the surface excimer group was -6.3 ± 1.7 diopters. Preliminary results of five laser in situ keratomileusis (mean correction, -6.8 ± 1.3 diopters; mean follow-up, 2.2 months) and two intrastromal corneal ring segments (Intacs) eyes (corrections of -2.75 and -3.25 diopters; follow-up of 9 and 2 months) are presented for comparison, because these procedures are not expected to produce central haze.

At each visit, high-contrast visual acuity was measured using a projected Snellen acuity chart, and contrast sensitivity was determined using the Rabin Small Letter Contrast Test. Both measures were completed after a manifest refraction to determine the best spectacle-corrected visual acuity. Visual acuity was recorded in log of the minimum angle of resolution (logMAR) with credit given for letters seen based on their relative value in their acuity line. Contrast sensitivity on the Small Letter Contrast Test was measured at 3.3 m with a chart luminance of 100 cd/m^2 . The letters subtended 8 minutes of arc, and the letter details subtended 1.6 minutes of arc (20/32 equivalent). The Small Letter Contrast Test chart consists of 14 rows of 10 letters each with each row decreasing 0.1 log units in contrast from top to bottom. The Small Letter Contrast Test was scored based on the number of letters correctly identified on the chart using a forced-choice procedure to determine threshold. Each correct letter is given a value of 0.01 log contrast sensitivity. The best score possible on the test is 1.30 log contrast sensitivity; the worst is -0.10 log contrast sensitivity. Because patients wore their manifest refraction in a trial frame, spectacle magnification was taken into account, especially preoperatively.

Haze was measured objectively at each visit. A prototype haze meter (TSPC-3; Nidek, Japan) based on the Scheimpflug technique was used to capture cross-sectional images of the cornea. The slit dimensions of the xenon flash slit beam were set to 0.08 by 6 mm to avoid capturing iris or peripheral corneal reflections. Cross-sections of the cornea at the 45-degree and 135-degree meridians were captured by the charge coupled device camera and digitized for analysis.

The back-scattered light from corneal haze or other optical irregularities produces areas of increased intensity in the image. The unit of measure for the intensity levels in the image is the computer-compatible tape used for recording digitized grayscale values in computerized image analysis. Corneal haze was found by tracing along the maximum intensity of the corneal cross section. The cumulative value along the central 3.5 mm of the peak intensity line for both the 45-degree and 135-degree cross section was recorded and the mean of the two meridians determined.

The progression of corneal haze was evaluated longitudinally to determine the time course and amount of haze

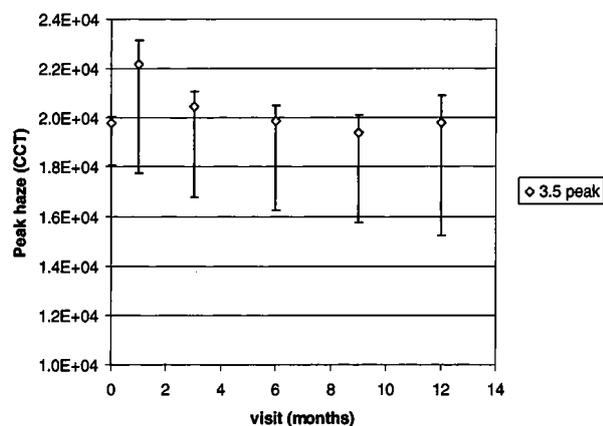


FIGURE 1. Mean values for peak haze for the 3.5-mm zone are plotted by visit. The upper bars on each point indicate standard error, and the lower bars indicate standard deviation. The unit for peak haze is a digitized measure of image intensity in the trace based on the computer-compatible tape (CCT). Peak haze is highest at 1 month and returns to baseline between 3 and 6 months.

development and recovery. The corresponding performance on the Small Letter Contrast Test and the high-contrast visual acuity test at each time interval was evaluated to determine the relative impact of corneal haze. The impact of a change in the amount of haze on visual performance was determined by evaluating the data at 1 month and at "stability," defined as the latest examination 6 or more months after surgery. Mean performance and haze measurements or mean changes from baseline are reported with the standard error of the mean, unless otherwise noted.

RESULTS

FIGURE 1 SHOWS THE MEAN HAZE MEASUREMENTS FOR THE surface excimer group at each visit. The maximum haze value occurs at 1 month and then decreases and stabilizes near preoperative levels by 3 to 6 months. The difference from preoperative values is only significant at the 1-month visit; mean increase in haze is $2.6 \text{ by } 103 \pm 870$ computer-compatible tape (paired t test = 3.12, $P = .005$). There is no significant difference in measured haze from 6 to 12 months after surgery (paired t test = 0.31, $P = .76$), indicating that corneal clarity remains relatively stable beyond 6 months.

An example case using photographs taken by the TSPC-3 hazemeter at the preoperative examination and the 1-month and 1-year postoperative examinations is provided in Figure 2. The subject represented in this figure had photorefractive keratectomy to correct -9.00 diopters of myopia. The increase in haze from baseline is evident at the 1-month examination and has completely resolved by

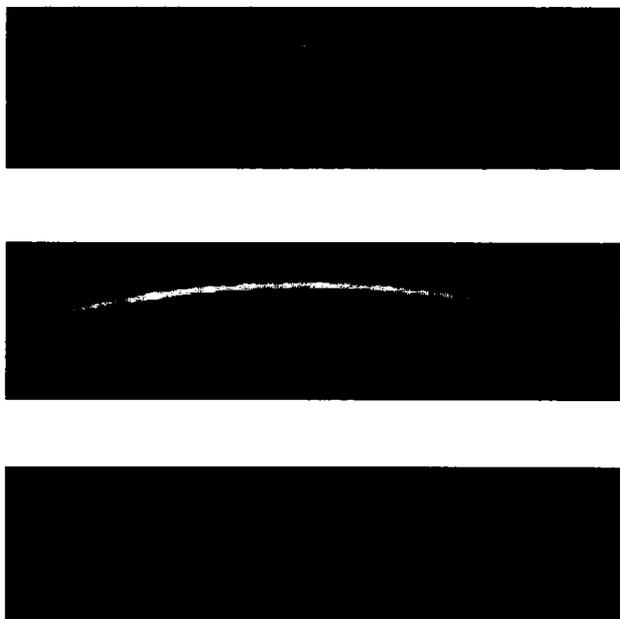


FIGURE 2. Three cross sections of one eye at three intervals. (Top) Before surgery. (Middle) One month after surgery. (Bottom) One year after surgery. The most apparent changes from before surgery to 1 month after surgery are the increase in intensity at the anterior cornea and the decrease in central corneal thickness. By 1 year after surgery, the anterior corneal haze has cleared and the only difference from before surgery is the decrease in thickness.

the 1-year examination. The only evidence of refractive surgery is the reduction in corneal thickness from baseline.

Figure 3 shows the change from baseline in visual performance in high-contrast visual acuity, and on the Small Letter Contrast Test and the change in haze at each examination for the surface excimer group. To facilitate comparison, the haze values have been converted to logHaze, and the visual performance measures have been plotted so that performance decrements correspond to negative values on the y axis. Corneal haze is maximum at the 1-month postoperative examination. This corresponds to the greatest decrement in both high-contrast visual acuity and Small Letter Contrast Test performance. At 1 month, mean performance on the high-contrast visual acuity test was decreased by 0.05 logMAR (paired t test = -2.8 , $P = .013$), and mean performance on the Small Letter Contrast Test was decreased by 0.30 log contrast sensitivity (paired t test = -5.4 , $P = .00004$). As was previously presented, haze returns to baseline by 6 months after surgery. High-contrast visual acuity and Small Letter Contrast Test score do not return to baseline at any postoperative interval in this study, however. Performance at the latest examination after stability is reached (10 ± 4 months) on the high-contrast visual acuity test remains 0.02 ± 0.01 logMAR below baseline (paired t test = -2.1 , $P = .04$) and on the Small Letter Contrast Test remains

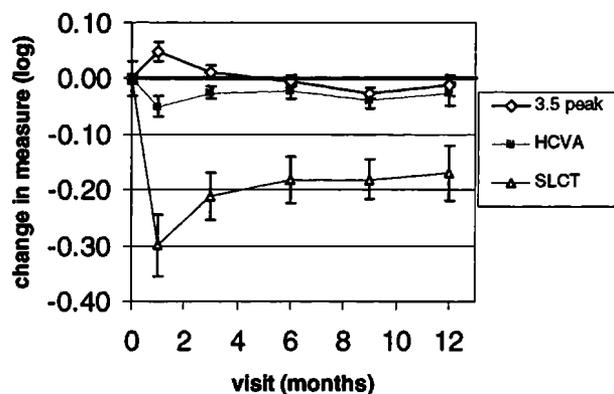


FIGURE 3. The change in the visual performance and corneal haze measures are plotted by visit. All measures are plotted in log values to ease comparison. Error bars indicate standard error, and the dark line indicates "baseline." Both high-contrast visual acuity and Small Letter Contrast Test decrease at the first month visit, whereas haze increases. The mirror-like pattern of haze versus performance seems to indicate a relationship that is strongest at 1 month. By 3 months, haze has returned to baseline, whereas the visual performance measures continue to show a deficit (only 50% recovery from the initial loss at 1 month).

0.16 ± 0.03 log contrast sensitivity below baseline (paired t test = -5.5 , $P = .000003$).

Figure 4 shows the change in corneal haze from preoperative level at the 1-month and the latest examination after stability is reached (10 ± 4 months). Fourteen of 19 eyes (74%) have an increase in haze at the 1-month examination, and only seven of 38 eyes (18%) have increased haze after the eye has stabilized. At stability, five of the seven eyes with increased haze had decreased high-contrast visual acuity and six of the seven eyes performed worse on the Small Letter Contrast Test. One of the seven eyes experienced an increase of 0.93 logHaze from preoperative level and was not plotted in the figure. The subject's cornea did not heal properly in the early postoperative period and developed a significant amount of haze and 3 diopters of myopic regression. This eye had a decrease in high-contrast visual acuity of 0.24 logMAR and a decrease in Small Letter Contrast Test score of 0.52 log contrast sensitivity. Another eye had an increase of 0.221 logHaze, which is greater than two standard deviations from the mean change in haze of -0.02 ± 0.06 logHaze. However, this eye showed improvements from baseline in both high-contrast visual acuity and Small Letter Contrast Test score by 0.06 logMAR and 0.08 log contrast sensitivity, respectively.

Eyes with a decrease in corneal haze did not show an overall improvement in visual performance. At 1 month, five of 19 eyes (26%) had a decrease in corneal haze. However, four of the five had a decrease in high-contrast visual acuity, and three of the five had a decrease in Small Letter Contrast Test performance. At stability 31 of 38

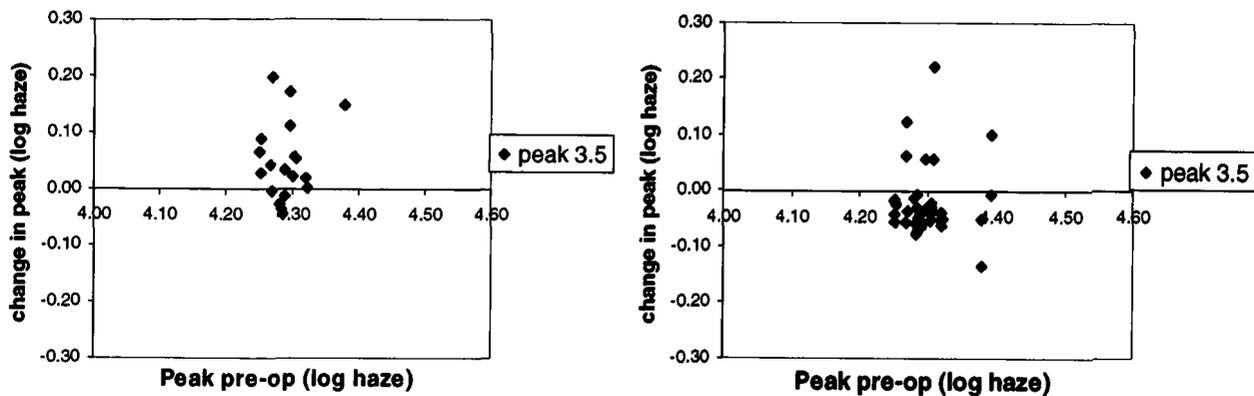


FIGURE 4. These two graphs show the change in haze from preoperative levels for both (left) the 1-month postoperative visit and (right) the latest postoperative examination. At 1 month, most eyes show an increase in haze, with a few eyes showing less haze than preoperatively. By the stability (10 ± 4 months), most eyes have less haze, with seven eyes measuring more haze than preoperatively (see text).

TABLE 1. Laser In Situ Keratomileusis and Intrastromal Corneal Ring Segments (Intacs) Results

	Change in:		
	Haze logHaze (SD)	HCVA logMAR (SD)	SLCT logCS (SD)
LASIK	0.011 (0.01)	-0.075 (0.08)	-0.358 (0.19)
Intacs	0.006 (0.01)	0.029 (0.07)	-0.192 (0.18)

LASIK = laser in situ keratomileusis.

eyes (82%) had a decrease in corneal haze with 20 and 25 of the 31 (65% and 81%) showing a decrease in high-contrast visual acuity and Small Letter Contrast Test score, respectively.

When all the eyes are considered, the change in haze is very poorly correlated to the change in visual performance. For high-contrast visual acuity, the correlations were $r = -0.13$ at 1 month and $r = -0.03$ at stability. For the Small Letter Contrast Test, the correlations were $r = .03$ at 1 month and $r = -0.01$ at stability. The highest correlation exists for the change in high-contrast visual acuity with the increase in haze at 1 month; however, the correlation is not very strong. None of the correlations are statistically significant.

Preoperative and postoperative measurements of haze were obtained for five eyes that underwent laser in situ keratomileusis and two eyes that underwent Intacs. Table 1 details the mean and standard deviations of the changes in haze and visual performance measures for the laser in situ keratomileusis and Intacs eyes. Corneal haze remains relatively unchanged from preoperative levels for both laser in situ keratomileusis and Intacs procedures. There was a decrease in high-contrast visual acuity for the laser in situ keratomileusis eyes, whereas one Intacs eye improved and the other lost high-contrast visual acuity. A

decrease in Small Letter Contrast Test performance was measured for both laser in situ keratomileusis and Intacs eyes. The performance loss after laser in situ keratomileusis was greater than for the Intacs eyes, possibly because of the higher correction for laser in situ keratomileusis eyes or differences in the procedures. Decreases in performance did not correlate with measured objective haze. Performance differences between laser in situ keratomileusis and Intacs were not evaluated in this study.

DISCUSSION

IN THIS STUDY, CORNEAL HAZE INCREASED AFTER SURFACE excimer procedures, reaching a maximum at 1 month and returning to baseline by 3. The maximum amount of haze may have occurred before or after this time interval; however, the protocol of this study limited measurements to the postoperative time intervals outlined in the Methods section. The increase in haze at 1 month correlates with the decrease in high-contrast visual acuity, although the correlation is not strong. The correlation of haze increase to Small Letter Contrast Test decrease is likewise poor. Neither did decreased haze necessarily result in improved vision. This is evidenced by three of the five eyes with decreased haze at 1 month experiencing decreased high-contrast visual acuity and Small Letter Contrast Test performance.

The relationship of haze to performance would appear clear from the plot in Figure 3 where high-contrast visual acuity and Small Letter Contrast Test performance are most affected when haze is maximum at 1 month. Because corneal haze tends to resolve to baseline between 3 and 6 months, whereas both visual performance measures fail to return to baseline, the differential in performance at 1 month versus later postoperative examinations is most likely the result of subepithelial haze. The proportion of

visual performance differential from 1 month to stability is 50% for high-contrast visual acuity and 40% for the Small Letter Contrast Test, meaning that 40% to 50% of the loss evident at 1 month is regained by the latest examination. Possible causes of the remaining visual performance decrement include induced aberrations, such as spherical aberration, coma, irregular astigmatism, or healing process residuals too small to measure using the present technique that may cause more forward scatter than back scatter.

The small number of laser in situ keratomileusis and Intacs eyes evaluated in this study had no significant change in corneal clarity, but measurable decreases in both high-contrast visual acuity and Small Letter Contrast Test performance. Factors other than corneal clarity may therefore play a role in visual changes experienced after these procedures. Further study of the optical, physiologic, and visual performance outcomes of laser in situ keratomileusis and Intacs procedures would be required to draw conclusions and are beyond the scope of this study.

Either as a result of smoothness of the ablation or suppression of the healing response using topical corticosteroids, or other factors, corneal haze mostly resolved by 3 months and had returned to baseline or better for 85% of subjects by stability (10 months \pm 4 months). If haze were the only factor affecting visual performance, then high-contrast visual acuity and Small Letter Contrast Test results would have returned to baseline at the same rate. Additionally, the six subjects who had any residual peak haze at stability would have had decreased visual performance. This is not what was found. For both of the nonsurface excimer procedures, laser in situ keratomileusis and Intacs, a performance decrement similar to that found after surface excimer procedures exists in the presence of clear corneas.

Based on the results of this study, in eyes that underwent photorefractive keratectomy with the Nidek EC-5000 excimer laser (and had an uncomplicated postoperative course), haze did not appear to be an important contributing factor to explain the presence of persistent visual disturbances. Other factors, namely topographic abnormalities, are more likely to be an important cause of these visual performance decrements.

The TSPC-3 objective hazemeter used in this study provides a quantitative measure of corneal clarity. The technique is noninvasive and takes less than 1 minute per eye to capture the two images required for analysis. Hazemeter measurements confirm that after surface excimer procedures using the Nidek EC-5000 excimer laser, the corneal response includes the development of haze. The haze is confined to the deep epithelial and anterior stromal region of the cornea, as determined by the location of the trace of the corneal cross section (Figure 2). The Nidek EC-5000 excimer laser is a scanning laser system; therefore, the timing of the appearance, location, degree, and resolution of corneal haze measured in this study may not be comparable to other laser systems that use alterna-

tive laser delivery techniques, such as broad beam or scanning spot. Additionally, the subjects in this study all underwent mechanical epithelial scrape before laser correction; alcohol epithelial scrape or laser scrape techniques may likewise result in different levels of haze.

An unexpected finding was the small group of five eyes that experienced a decrease in corneal haze at the 1-month examination. These subjects were all aged 50 to 61 years. It is possible that a higher baseline subepithelial haze resulting from the presence of dry eye or other aging factors, coupled with a possibly less aggressive healing response postoperatively, may have lead to a decrease in measured haze postoperatively. This would require further study.

There are some potential limitations in the use of the TSPC-3 hazemeter, both in its clinical application and for the purposes of this study. Although the instrument provides an objective measure of haze, the need for such a refined measure in a clinical setting is uncertain. As a clinical tool, the TSPC-3 hazemeter is able to detect very subtle changes in haze levels, which are generally difficult to measure using slit-lamp evaluation. Additionally, the instrument provides the ability to demonstrate resolution of haze to the patient and other practitioners using side-by-side comparison of corneal cross sections from various examination periods. However, if the goal of a clinical evaluation is to detect the presence of visually significant haze, the slit-lamp evaluation may in most cases be sufficient. As a research instrument in this study, the TSPC-3 was not evaluated in terms of the relationship between measured objective haze and subjective measures of haze or in terms of repeatability of measured corneal haze. Repeatability of the instrumentation has been ascertained only on suspensions of known density (Soya K, unpublished data, 1997). These aspects of the instrument may be issues for when the instrument is used in the extensive evaluation of any procedure that may produce corneal haze, albeit transient. Further studies would be needed to evaluate these parameters.

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