Correlation of Subepithelial Haze and Refractive Regression 1 Month After Photorefractive Keratectomy for Myopia

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ABSTRACT

PURPOSE: To relate myopic regression after photorefractive keratectomy (PRK) to subepithelial haze at the first postoperative month.

METHODS: One hundred nineteen eyes of 119 patients underwent excimer laser PRK for treatment of myopia up to -8.00 D. Eyes were examined at 1, 3, 6, 9, and 12 months after surgery. All eyes received fluorometholone 0.1% for the first 5 postoperative months in a tapered dose. Dexamethasone 0.1% qid for 1 month was prescribed to all eyes with a spherical equivalent refraction less than plano, followed by an augmented dose of fluorometholone 0.1%. Eyes with myopia greater than -0.75 D at 12 months, as well as those that had received dexamethasone at any postoperative intervalregardless of refractive outcome were considered to be regressed. Eyes that regressed and those that did not regress were compared statistically (Chi-squared statistical criterion with Yates correction) regarding haze grade.

RESULTS: Forty-seven percent (56 of 119) of eyes regressed. In 89.28% (50 of 56) of eyes, subepithelial haze grade was 1 to 2, and in 10.71% (6 of 56), subepithelial haze was graded 0 to 0.5 at 1 month. Fifty-three percent of eyes (63 of 119) did not regress and in all, subepithelial haze was graded 0 to 0.5 at the first month. The correlation between regression and haze grade 1 or more at the first postoperative month was statistically significant (*P*<.001).

CONCLUSION: Mild to marked subepithelial haze (grade 1 to 2) at the first postoperative month after PRK for myopia is strongly related to regression of initial refractive effect and increasing myopia. [*J Refract Surg* 1999;15:338-342]

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Photorefractive keratectomy (PRK) is a widespread method for correction ametropias.[1] Although PRK is a relatively safe and efficient method to correct low and moderate myopia, its predictability is dependent on the patients healing response.[2]

Partial loss of corneal clarity (haze), as judged by biomicroscopic observation, is common after PRK. The severity of haze is time dependent, with maximum haze usually noted in the first 3 months after surgery, with progressive clearing within approximately 1 year after treatment.[1]

Not uncommonly, haze is accompanied by at least partial regression of the initial effect, and this residual myopia is an indication for reoperation. Durrie and colleagues[2] have described different healing responses, associating increased haze, and myopic refractive shift with aggressive healing, in contrast to inadequate healing associated with clear corneas and residual hyperopia. The majority of patients in their study were classified as normal and had a typical healing response after PRK.[2] The possibility of modulating the wound healing response after PRK and increasing the predictability of the procedure is important.[3-9] In order to evaluate the subepithelial haze at 1 month after surgery as an early predictive factor of refractive outcome, eyes that had PRK for myopia up to -8.00 diopters (D) were retrospectively analyzed and the statistical correlation of haze at 1 month was compared to late myopic regression.

PATIENTS AND METHODS

One hundred nineteen eyes of 119 patients (60 males) underwent PRK for myopia up to -8.00 D. Patient age ranged from 20 to 37 years, (mean, 28 –

4.14 yr). Mean preoperative spherical equivalent refraction was -5.20 – -2.20 D (range, -2.50 to -8.00 D). In all eyes, attempted correction was aimed at emmetropia. An informed consent was obtained from all patients.

The preoperative ophthalmic evaluation included refraction (manifest and cycloplegic), videokeratography (to exclude patients with clinical or subclinical keratoconus and to provide baseline topographic measurements), slit-lamp microscopy, keratometry, dilated fundus examination, ultrasound pachymetry, biometry, and contrast sensitivity testing in various spatial frequencies. Eyes with known ocular surface disorders, previous ocular surgery, keratoconus, or collagen disorders were excluded.

All operations were carried out by the same surgeon according to a standard protocol using the Aesculap Meditec Mel 60a argon fluoride excimer laser system (Meditec, Heroldsberg, Germany). The clear zone was 6 mm for spherical corrections and 5.5 mm for astigmatic corrections. All patients were treated under topical anesthetic instilled before surgery (Alcaine, proparacaine hydrochloride 0.5% W/V, Alcon Couvreur, Belgium). Immediately following surgery, a bandage contact lens was applied under sterile conditions on the treated eye and was left until re-epithelialization was complete. During this period, operated eyes received the following regimen: cyclopentolate hydrochloride 1% (Cyclogyl, Alcon Couvreur, Belgium) and diclofenac sodium 0.1% (Dellimone monodose, Pharma Stulln, Germany) eye drops qid for the first 2 postoperative days and tobramycin 3mg/ml/ dexamethasone 1 mg/ml (Tobradex, Alcon Couvreur, Belgium) eye drops qid until the day of re-epithelialization. After re-epithelialization was complete, fluorometholone 1mg/ml (FML, Alcon Couvreur, Belgium) was prescribed to all patients for 5 months in a tapered dose, as follows: one drop qid for the first month, one drop tid for the second month, one drop bid for the third month, one drop once a day for the fourth month, and one drop daily for the fifth month.

Patients were examined at 1, 3, 6, 9, and 12 months. If myopic regression occurred in the first 5 months, fluorometholone 0.1% was discontinued and dexamethasone 0.1% qid was prescribed for 1 month, followed by an augmented dose of fluorometholone 0.1% (four times daily for 1 month, then tapered and discontinued over a period of 2 months) and follow-up every 2 weeks). In cases of late regression (ie, myopic shift of the patients refraction more than 0.50 D after fluorometholone discontinuation), fluorometholone 0.1% qid was reinstituted for 1 month and the patient was evaluated every 2 weeks. If no refractive changes were apparent 4 weeks after corticosteroids were prescribed, treatment was considered ineffective and was discontinued. In patients with no refractive change from the first to the third postoperative month, corticosteroids were also discontinued, under close observation. Intraocular pressure (IOP) was measured at each examination to monitor corticosteroid response. An IOP over 4 mmHg of the preoperative value or over 21 mmHg, was treated with simultaneous (during corticosteroid therapy) topical administration of beta blockers (timolol 0.5%,Temserin, Alcon Couvreur, Belgium), one drop in the evening.

Apart from refraction, uncorrected and spectacle-corrected visual acuity, tonometry, and contrast sensitivity testing, all the patients underwent slit-lamp microscopy at each examination. Haze density was graded on a predetermined scale of 0 to 4, according to the following criteria: grade 0, totally clear cornea with no opacity seen by any method of microscopic slit-lamp examination; grade 0.5, trace or faint corneal haze seen only by indirect, broad tangential illumination; grade 1, haze of minimal density seen with difficulty with direct and diffuse examination; grade 2, mild haze easily visible with direct focal slit illumination; grade 3, moderate opacity that partially obscured details of the iris; and grade 4, severe opacity that completely obscured the details of intraocular structures. According to this grading, corneas with haze grade 0 or 0.5 were considered clear.

Patients with a spherical equivalent refraction less than plano at the first month examination were considered undercorrected (not regressed) and were excluded from the study.

All eyes had complete follow-up for at least 1 year. Eyes with a final spherical equivalent refraction less than -0.75 D were considered to be regressed. Eyes that received dexamethasone at any postoperative interval, as well as those where fluorometholone was reinstituted after the fifth month, were also considered as regressed, regardless of the final refractive outcome. Subsequently, regressed (as determined above) and non-regressed eyes were statistically compared to the haze grade of the first month examination. To estimate the correlation of myopic regression at any postoperative interval with the first month haze grade, the Chi-squared statistical criterion with Yates correction was used to correlate qualitative observations. The level of statistical significance of the test was $P<.001$. The eyes were classified according to the presence or absence of haze or regression in a four-fold table (Table).

RESULTS

Fifty-six of the 119 treated eyes (47.05%) regressed during the first year of follow-up. All regressed eyes were treated with an augmented dosage of fluorometholone 0.1% or dexamethasone 0.1% according to the above mentioned protocol. The majority of regressed eyes responded to a corticosteroid therapy and 1 year after treatment, only 5 of 119 eyes (4.2%) had a residual myopia (mean spherical equivalent refraction, -1.60 – 0.675 D; range, -1.00 to -2.75 D).

In 50 of the 56 regressed eyes (89.28%), subepithelial haze grade was graded as 1 or 2 (52 treated eyes had haze grade 1 and eight eyes had haze grade 2) at the first postoperative month. This group of eyes with regression and haze was defined as group a (a=50).

In six of 56 regressed eyes (10.71%), haze was 0.5 at the first month interval. The group of regressed eyes with no haze at the first month was defined as group c (c=6). No eyes from groups a and c had a totally clear cornea (haze grade 0) at the first month.

Sixty-three of 119 treated eyes (52.94%) did not regress; 61 (51.26%) were within – 0.75 D of emmetropia although two eyes (1.28%) were overcorrected (mean spherical equivalent refraction, +2.00 D and +1.75 D, respectively).

In all non-regressed eyes, subepithelial haze was graded 0 or 0.5; 45 of 63 eyes (71.42%) had trace haze and 18 eyes (28.57%) were clear. This no haze/no regression group of eyes was defined as d (d=63).

No non-regressed eyes had a haze grade of 1 or more at the first postoperative month (b=0).

Correlation of first month haze to regression at any postoperative interval after PRK for myopia was found to be statistically significant ($P<.001$) according to the Chi-squared statistical criterion with Yates correction for small groups.

Table
Chi-squared Criterion to Classify Eyes After PRK With Respect to Presence or Absence of Corneal Haze or Refractive Regression

	Regression Group	No. eyes	No Regression Group	No. eyes	Total Group	No. eyes
Haze	a	50	b	0	a+b	50
No haze	c	6	d	63	c+d	69
Total	a+c	113	b+d	3		

Group a: Eyes with haze and regression at 1 month after surgery
Group b: Non-regressed eyes with haze 1 month after surgery
Group c: Regressed eyes with no haze at 1 month after surgery
Group d: Eyes with no haze and no regression at 1 month after surgery

DISCUSSION

Wound healing is of critical importance in correcting all corneal refractive errors. Although many studies have been published concerning wound healing response, fundamental issues regarding haze and regression, as well as the pathophysiology of these events, still remain unclear. Studies on corneal wound healing after PRK have shown epithelial hyperplasia and scarring by atypical, newly synthesized collagen. It has been suggested that haze is due to new collagen and vacuoles between intersected collagen lamellae. These vacuoles are filled with atypical glycosaminoglycans that impair the transparency of the cornea. Haze appears after the first postoperative month and becomes denser up to the third month, as activated keratocytes migrate to repair the wound.[10-18]

Epithelial hyperplasia, or the new connective tissue growth, apart from haze, was also associated with regression in some studies.[1,13,20] Although tissue regrowth is confirmed by other investigators, they suggest that corneal thickening accounts for a small fraction of regressionmostly due to structural alterations of the ablated cornea.[21] Other factors that may influence refractive outcome are the concentration of glucosaminoglycans, and especially hyaluronic acid, which can alter corneal hydration and refraction.[3]

Although not yet clear in terms of cell biology, it seems from clinical studies that there is a direct relation between haze, regression, and the depth of photoablation in PRK.[6,19] In our study, it was confirmed that there was a strong correlation between late regression and haze even at the first month after PRK, when the patient was still hyperopic.

Variation in wound healing response of individual eyes cannot be controlled, but it may be influenced by topical drugs. Various regimens such as nonsteroidal anti-inflammatory agents[22-25], interferon[8], plasmin and plasminogen activator inhibitors[7,26], collagenase inhibitors[27], and antimetabolites[28] have been proposed for the modulation of the healing response after PRK, all with poor or controversial results.

The most commonly used regimens for the postoperative control of PRK refractive outcome are corticosteroids, although there is disagreement between investigators about whether they should be used after PRK. Early clinical studies suggest that corticosteroids play a crucial role in the refractive outcome of PRK[5,29,30]; however, after initial hopeful

reports, efficacy of corticosteroids in this instance is still unclear. Other investigators have claimed that corticosteroids have no long-term effect on refraction.[26,31,32] The latter studies have either short follow-up[32], high regression in all groups, or unacceptable initial overcorrection.[31] Even studies which claim that corticosteroids are of limited value and are not justified for routine administration after PRK accept that there may be some individuals who could benefit from corticosteroids.[33]

In our study, all eyes received corticosteroids for at least 5 months; 40% were treated with augmented doses of corticosteroids because of their tendency toward myopic regression and these eyes finally achieved a satisfactory refractive outcome. The higher incidence of haze and regression or undercorrection in our study may be explained by the relatively young mean age of our patients. Since there was no control group, no conclusions can be made about long-term refractive outcome of these eyes as they were not treated aggressively with corticosteroids. Haze at 1 month proved to be a reliable predictive factor for the refractive outcome. Eyes with mild to moderate haze at the first month are likely to regress at some point during their postoperative course and corticosteroid therapy should be reserved for these eyes. The exact mechanism through which corticosteroids affect regression is not yet fully understood, as the entire procedure of regression is still unclear. Whatever the actual mechanisms, the suppressive effect of corticosteroids on the healing response would be expected during the early postoperative months when there is maximum keratocyte activity[3], however, Gartry and colleagues[6,31] have shown that topical corticosteroids do not alter the long-term refractive outcome after PRK.

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