Effect of ablation profile on wound healing and visual performance 1 year after excimer laser photorefractive keratectomy

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Abstract

Background—Early photorefractive keratectomy ablations were of limited diameter and depth to maintain the integrity of the globe and to minimise postoperative haze. This study evaluated the effects of deeper, larger diameter wounds on refractive stability and corneal haze, and investigated the effects of ablation profile on wound healing and visual performance.

Methods—One hundred patients undergoing -3.00D and -6.00D corrections were randomised to receive 5 mm, 6 mm, or multizone treatments. The multizone treatment was 6 mm in diameter, but only the depth of the 5 mm treatment. Outcome was measured by Snellen visual acuity, residual refractive error, objective techniques for haze and halos, pupil diameter, subjective night vision, and requirement for retreatment.

Results—Overall, the results of 6 mm treatments were superior to those of 5 mm and multizone treatments: they had a smaller hyperopic shift ($p < 0.01$), a more predictable ($p < 0.001$) and stable refractive outcome, less haze ($p < 0.05$), smaller halos ($p < 0.05$), fewer subjective night vision problems, and fewer patients required retreatment.

Conclusions—Analysis of these data and a literature review of corneal wound healing demonstrated that the improved outcome associated with the 6 mm beam did not relate to the depth of ablation. The factor with greatest apparent influence on the development of haze and regression was the slope of the wound surface over the entire area of the ablation. Tapering the wound edge provided no additional benefit, and contributed to night vision problems. It is, therefore, recommended that small diameter or multizone treatments should not be used in low and moderate myopia.

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Photorefractive keratectomy (PRK) has now been the subject of clinical trials for over 5 years. One notable feature of the early studies was the variability of results between different treatment centres.^{1–9} Potential sources of variability could be divided into two main groups. The first comprised biological factors such as patient populations and varying

surgical procedures, together with environmental cofactors. The second concerned mechanical aspects, including the physical characteristics of excimer laser ablations and the differences between commercial systems. From the literature, it is difficult to determine the relative contributions of any one factor, as studies frequently differ in more than one variable, and not all variables are necessarily controlled or reported. The aim of this study was to evaluate systematically the independent effects of ablation depth, diameter, and profile on the outcome of PRK at 1 year.

In the early studies of PRK, the depth of ablation was minimised for two reasons. The first was the theoretical concern that excessive ablation would weaken the integrity of the globe.^{10–11} The second reason was the subjective impression that increasing depth of ablation was associated with greater postoperative haze.^{2,4,9,12–16}

In relation to the former, recent studies have shown that larger ablation diameters give a more predictable short term refractive outcome,¹⁷ but these larger wounds may produce greater disturbances in the structural integrity of the stroma.^{18–21} The present study investigated whether larger diameter treatment zones required more time to reach a stable outcome.

Systematic studies of haze failed to confirm a relation between haze and ablation depth^{1,2,5,22–25} and suggested that the depth of ablation was compounded by the severity of the pre-existing myopia.³ In addition, inconsistencies in the early work could have arisen from the lack of objective methods available to assess haze. The present study aimed to resolve these discrepancies by varying the ablation depth for a given dioptric correction, and by quantifying objectively corneal haze.

Many of the early studies used small diameter beams in order to minimise the depth of stroma removed.²⁶ Some commercial systems with beam diameters in the region of 4 mm were typified by relatively large initial hyperopic shifts, followed by a fairly rapid reduction in hyperopia to a plateau, which was nearest emmetropia in the lowest order corrections.^{1,3,4,8,9} In these studies, the principal visual problem postoperatively was halos around lights at night, and in 10–15% of cases this was classed as severe.^{3,4,8}

In contrast, other commercial systems with beam diameters up to 6 mm were characterised by smaller hyperopic shifts; although regression still followed moderate and higher

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order corrections.^{2 5 6} However, a major advantage seen in these studies over those with smaller diameter beams was the lower incidence and severity of visual problems at night.

Studies comparing different ablation diameters induced by a single laser suggested that night vision problems were not the result of differences between commercial lasers, but were dependent upon the diameter of ablation and patient factors.^{17 27} Therefore, the aim of the present study was to determine whether further increasing ablation diameters could improve halos without compromising refractive stability or corneal transparency.

Methods

PATIENT SELECTION

Approval for the study was granted by the ethics committee. Following extensive counselling, 100 patients were recruited from volunteers over the age of 24 years who had stable myopia of around -3.00D or -6.00D , with astigmatism of less than 1.50DC . Those with diabetes or connective tissue disorders were excluded, and the absence of ocular disease was confirmed by a full ophthalmic examination. Before entering the study, all patients gave fully informed consent.

TREATMENT GROUPS

Forty patients received -3.00D PRK and 60 patients received -6.00D PRK (demographic data in Table 1). Using a random numbers table, patients within each group were allocated randomly to the different ablation profiles: 5 mm or 6 mm in diameter for the group receiving -3.00D corrections; and 5 mm, 6 mm, or multizone treatments for patients receiving -6.00D corrections. The multizone treatment was a two stage procedure consisting of a -5.00D correction of 4.60 mm diameter, followed within 2 minutes by a concentric -1.00D correction 6 mm in diameter. This gave an ablation which was the diameter of the 6 mm treatment, but only the depth of the 5 mm treatment, and the profile was more tapered at the periphery.

The ablation profiles were compared by plotting the depth of tissue removed at 0.5 mm intervals across the diameter of the wounds, according to the commercial ablation algorithm. The aspect ratio of each wound was calculated from the ratio of the maximum wound depth to the wound diameter.

SURGICAL PROCEDURE

All patients were treated by a single surgeon during a 6 week period in August/September 1993. A single Summit Technology Omnimed excimer laser was used, with an emission wavelength of 193 nm, a fixed pulse repetition rate of 10 Hz, and a radiant exposure of 180 mJ/cm^2 . The profile of the ablation was determined by computer controlled expansion of the aperture in an iris diaphragm. The epithelium was removed manually from an area 6.5 mm in diameter, and the laser procedure was performed as described previously.³

POSTOPERATIVE REGIMEN

Postoperatively homatropine 2% and chloramphenicol 1% ointment were applied, the eye was padded overnight, then chloramphenicol 0.5% was administered four times a day for 1 week. Analgesia was provided by two tablets of Coproxamol (dextropropoxyphene hydrochloride 32.5 mg and paracetamol 325 mg) given immediately after treatment, then 6 hourly or as required for up to 3 days. No topical corticosteroids were prescribed as clinical trials have demonstrated that they confer no lasting benefit.^{16 28 29}

PREOPERATIVE AND POSTOPERATIVE EXAMINATIONS

Detailed assessment of corneal function and visual performance was made preoperatively, and postoperatively at week 1 and months 1, 3, 6, and 12. Refraction was measured by retinoscopy, subjectively with a fogging technique to accurately determine the end point, and by autorefraction (Nidek Autorefractor AR-1000). The results of these techniques were compared to determine whether the poor reliability of the autorefractor after PRK³ was improved following larger diameter treatments. The 'refractive change' was the difference between the preoperative and postoperative refraction. As emmetropia was not the aim of surgery in all cases, refractive results were expressed as 'residual refractive error', which is the difference between the actual refractive change and the intended refractive change.

Best corrected high contrast visual acuity was measured using a Snellen chart. Changes in visual acuity were expressed in terms of the number of lines on the chart lost or gained.

Corneal haze was assessed both objectively and subjectively. The objective measurement of haze was performed using equipment which has been described in detail elsewhere.³⁰ This technique uses a charge coupled device (CCD) video camera and frame grabber to record corneal slit images. The haze was quantified by computer analysis of the grey scale level of the central cornea. Linear polarising filters were used to distinguish the component of the haze that was the result of back scattered light. This measure is related to forward scattered light which may in turn degrade the retinal image.³¹

Although the objective assessment of haze provides more accurate results, haze was also

Table 1 Demographic data of the five treatment groups

Correction (D)	Treatment zone (mm)	Depth (μm)	Number of patients	Age (years) Mean (SD)	Sex (% male)	Preoperative refraction (sph equiv, D)* Mean (SD)
-3.00	5	26	21	37.0 (8.2)	38	-3.43 (0.56)
	6	42	19	35.7 (7.7)	26	-3.16 (0.28)
-6.00	5	62	20	38.7 (9.7)	40	-6.62 (0.92)
	Multizone	62	19	37.4 (9.4)	52	-6.96 (0.69)
	6	78	21	37.4 (9.8)	43	-6.67 (0.79)

*sph equiv=spherical equivalent in dioptres.

assessed subjectively to allow a more direct comparison to be made with data from other clinical centres. Subjective assessment was by slit-lamp biomicroscopy, and the intensity of the haze was graded from 0 to 4 as described previously.³

Subjective disturbance of vision at night was sought by direct questioning. Glare and halos were categorised as 'mild' if noticeable but tolerated or 'severe' if they resulted in functional disability such as prevention of driving at night or treatment of the second eye.

The halo experienced when viewing a bright target under standard conditions was measured objectively using a computer program.³² A central white disc on a dark background was displayed on a high resolution monitor. The outer edge of the halo seen around the white disc was delineated by moving a cursor centripetally along each of 12 fixed meridians until it touched the edge of the halo. The area bounded by these 12 points was calculated in square centimetres.

Apparent pupil diameter was measured preoperatively in darkness under standard conditions using an infrared pupillometer (VRB-100 binocular infrared videorefractor, Fortune Optical).

REQUIREMENT FOR RETREATMENT

At the 1 year appointment, the option of retreatment was discussed with those patients with a residual refractive error of more than -2.00D , or a haze with a scattered light component of more than 70 grey scale units (approximately grade 2). The decision of whether to retreat was based on the patient's level of satisfaction and visual requirements, as well as the advice of the surgeon tailored to each individual case.

STATISTICAL ANALYSIS

Stability of refraction between 6 months and 1 year postoperatively was assessed by the number of patients in each group whose refraction had changed by -0.25D over this period.

Comparison was made of the clinical outcome of the three treatment zones, for -3.00 and -6.00D corrections, at each time point. The χ^2 test was used for nominal data (stability of refraction, subjective haze, subjective night vision), the Wilcoxon rank sum for ordinal

data and skewed ratio data (visual acuity, objective haze, objective halo), and the unpaired Student's t test for normally distributed ratio data (residual refractive error). The predictability of the refractive outcome was analysed by calculating F values to compare the variances of the different groups. The correlation function was determined for objective halo with treatment zone, pupil size, and refractive change.

Results

WOUND PROFILE

Figure 1 shows the profiles of some of the ablations used in this study. Of the single zone treatments, the rate of change of slope of the wound surface was greatest in the -6.00D 5 mm ablation. The surface slope was less steep in larger diameter ablations (-6.00D 6 mm), and particularly lower order corrections (-3.00D 6 mm). The multizone treatment, over most of its surface, had the steepest slope of all, but this was blended to the untreated cornea by an annulus with a shallow surface slope.

CLINICAL RESULTS

Overall, the results of the 6 mm treatments were superior to those of the 5 mm and multi-zone treatments: they had a more predictable and stable refractive outcome, less haze, smaller halos, and fewer night vision problems.

Figure 1 Ablation profiles of the five treatment zones demonstrating the influence of dioptric correction and zone diameter on the rate of change of slope of the wound surface.

Figure 2 Residual refractive error for patients undergoing (A) -3.00D and (B) -6.00D corrections (mean (SE)); significance of the difference between the 5 mm and 6 mm treatments. * $p < 0.05$, ** $p < 0.01$.

Table 2 Refractive outcome 1 year postoperatively for each of the five treatment groups, expressed as the percentage of patients whose residual refractive error was close to emmetropia (within plus or minus 1.00D), or showed unacceptable overcorrection ($>+1.00D$) or undercorrection ($>-3.00D$)

Correction (D)	Treatment zone (mm)	Residual refractive error		
		Good outcome $\leq \pm 1.00D$	Poor outcome $>+1.00D$	Poor outcome $>-3.00D$
-3.00	5	71	14	5
	6	100	0	0
-6.00	5	20	20	25
	Multizone	26	11	21
	6	67	5	0

AUTOREFRACTION

Postoperatively the autorefractor readings were not helpful, and inconsistent results were obtained in all treatment groups. Therefore we have relied upon subjective refraction.

REFRACTION

Patients in both the -3.00 and -6.00D groups showed an initial overcorrection of the subjective refraction, followed by a return towards emmetropia (Figs 2A and 2B). The hyperopic overshoot was significantly smaller in both dioptric groups in the patients receiving 6 mm treatments than in those receiving either 5 mm or multizone treatments, at 1 week ($p<0.01$) and 1 month ($p<0.05$)

Figure 3 Reduction in visual acuity in terms of the number of Snellen lines lost for patients undergoing (A) -3.00D and (B) -6.00D corrections (mean (SE); significance of the difference between the 5 mm and 6 mm treatments. * $p<0.05$).

postoperatively. Thereafter, all groups showed further regression of the mean residual refractive error, to a plateau level at 3 months. Although this was nearer emmetropia in the 6 mm groups, the difference was not significant.

The predictability of the refractive outcome was significantly greater in the 6 mm groups than the 5 mm ($p<0.001$) and multizone ($p<0.01$) groups. This is demonstrated by comparison of the size of the standard error bars (Fig 2) and the proportion of patients within plus or minus 1.00D of the intended refraction (Table 2).

Stability of refraction between 6 months and 1 year postoperatively was greatest in the 6 mm groups and least in the multizone group.

VISUAL ACUITY

The transient reduction in visual acuity seen at 1 week was similar in the -3.00D and -6.00D groups, regardless of beam diameter (Figs 3A and 3B). This was followed by a second drop in acuity which appeared after 3 months, and was greater in the -6.00D than in the -3.00D corrections.

By 1 year, in both -3.00D groups, mean visual acuity had improved to within half a line of preoperative levels. A similar improvement was seen for the -6.00D group with the 6 mm beam. In contrast, for the -6.00D groups with the 5 mm and multizone treatments, there was a persistent loss of one line of mean visual acuity. This was partly attributable to three and four patients respectively losing 2 or more lines of visual acuity, whereas no patients receiving 6 mm corrections had such a loss (Table 3).

OBJECTIVE HAZE

The CCD monitoring system showed that in all patients corneal transparency was reduced at 1 week. This appeared to be at the level of the epithelium or immediately below the epithelium, and was of similar severity in all treatment groups. It resolved by 1 month postoperatively (Figs 4A and 4B).

Over the next 3 to 6 months there was a more prolonged loss of transparency as corneal haze developed. When data from all the treatment groups were pooled, this was maximal at 6 months. If patients with high haze (greater than 1 SD above the mean) were excluded from the analysis, the second peak loss of transparency occurred at 3 months in the majority of patients.

Disturbances in both reflected and scattered light were significantly greater in the -6.00D than the -3.00D groups. The haze in the 6 mm groups was significantly less intense than in the 5 mm ($p<0.05$ to 0.01) and multizone ($p<0.05$) groups, and also appeared to be less prolonged. By 1 year, the mean haze had markedly reduced in all groups, although it still remained greater in the 5 mm ($p<0.01$ to 0.05) and multizone groups than in the 6 mm groups.

Table 3 Complication rates 1 year postoperatively for each of the five treatment groups, expressed as the percentage of patients with loss of visual acuity or night vision problems. Severe haze as assessed by subjective means is recorded so these results can be compared with those of other published studies

Correction (D)	Treatment zone (mm)	Lost lines of Snellen visual acuity		Subjective night vision problems		Subjective haze $\geq 2+$
		≥ 1 Line	≥ 2 Lines	Mild	Severe	
-3.00	5	33	10	19	0	10
	6	26	0	10	0	0
-6.00	5	55	15	10	5	25
	Multizone	53	21	24	14	21
	6	33	0	14	0	0

SUBJECTIVE HAZE

Within the first postoperative month, the majority of patients developed haze of grades 0.5 or 1 in severity. At 3 and 6 months a minority of patients had developed more severe haze (grades 2 to 4). This was more common after -6.00D than -3.00D corrections, and in the 5 mm and multizone groups.

By 1 year the haze tended to improve, with about one third of patients achieving clear corneas. However, there were still significant numbers of patients with -6.00D corrections

who retained haze of grade 3 or 4 (25% of patients in the 5 mm group, and 20% in the multizone group). No haze of this severity was seen at 1 year in patients in the 6 mm groups (Table 3).

REQUIREMENT FOR RETREATMENT

Of the 18 patients who underwent retreatment, only one had received a 6 mm original treatment (Table 4). That patient had received a -6.00D correction, and the indication for retreatment was purely refractive. The remaining 17 patients had received either multizone (six patients) or 5 mm treatments (nine patients with -6.00D corrections, and two patients with -3.00D corrections). In the majority of these cases, the indication for retreatment was both regression and haze. The need for retreatment was five times more common in the -6.00D groups than the equivalent -3.00D groups.

SUBJECTIVE NIGHT VISION

There were no severe visual problems at night in any of the patients receiving 6 mm treatments. However, severe night vision problems did occur following -6.00D corrections in the 5 mm (one patient) and multizone (three patients) treatment groups. Mild problems were also most common in these two groups (Table 3). There was no direct correlation of subjective difficulties in night vision with pupil size.

OBJECTIVE HALO

Objective halo was maximal 1 week postoperatively, then improved over the next 3 months (Figs 5A and 5B). At all time points halos were worse in patients in the -6.00D than in the -3.00D groups. At 1 week and 1 month, halos were significantly ($p < 0.05$) greater in 5 mm and multizone treatments compared with 6 mm treatments. Halos were a greater problem in those patients with large pupil diameters.

Discussion

The excimer laser (193 nm) was introduced into ophthalmology in the early 1980s, when it was realised that it had characteristics ideally suited to performing refractive surgery.^{10 33} This laser could remove tissue with sub-micrometre precision, leaving a smooth surface with minimal damage to adjacent structures.^{34 35} The wide beam diameters allow the ablation of tissue from relatively large areas.¹⁰ Using this technique, it became possible to change the power of the cornea by the differential ablation of superficial tissue (PRK). This avoided the weakening of the globe associated with other popular refractive procedures such as radial keratotomy.^{21 36 37}

Early investigators were aware that physical aspects of the ablation may influence the biological wound healing response. The physical characteristics initially considered were pulse energy

Figure 4 Objective haze for patients undergoing (A) -3.00D and (B) -6.00D corrections. The combined reflected and back scattered values (solid lines) are an objective measure of haze as it appears to the observer. The back scattered component alone (broken lines) represents that component of the haze which interferes with the patient's vision. (Mean (SE); significance of the difference between the 5 mm and 6 mm treatments. * $p < 0.05$, ** $p < 0.01$.)

Table 4 Requirement for retreatment 1 year postoperatively for each of the five treatment groups, expressed as the percentage of patients in which the indication was for regression, haze or both

Correction (D)	Treatment zone (mm)	Indication for retreatment			Total
		Regression (RRE > -2.00D)	Haze (Sc > 70 units)	Regression and haze	
-3.00	5	5	0	5	10
	6	0	0	0	0
-6.00	5	10	5	30	45
	Multizone	0	5	26	32
	6	5	0	0	5

RRE=residual refractive error; Sc=haze measured objectively in terms of backward scattered light; 70 grey scale units is approximately equivalent to 2+ haze on subjective assessment.

and beam energy distribution, repetition rate, and area of initial ablation. In order to limit ultrastructural damage,^{22 34 38} most groups elected to use an energy which was above the ablation threshold, but below that whereby residual energy could be converted into heat. In practice this means using a system between 120–200 mJ/cm².^{39 40} At these levels, it has now been shown that there is little risk of injuring adjacent structures. The volume of tissue expelled from the surface by such energy levels has also been shown not to result in mechanical waves in the opposite direction of sufficient magnitude to damage the endothelium.^{41–43} At one time it was suggested that tangential excisions resulted in less haze than en face excisions because shock waves were not directed into the cornea⁴⁴; however, any benefit would be

offset by potential thermal damage caused by repetitive exposure of the proximal wound edge.

Pulse frequencies were initially kept low (5–10 Hz) in order to minimise cross talk between pulses and tissue heating. It has since been suggested that higher pulse repetition rates produce clearer corneas,⁴⁵ but this would require that ablation energies be further limited to avoid significant collateral heating.⁴⁶

Finally, most groups elected to use small beam diameters for the first pulses of a treatment. This was, firstly, to ease centration and, secondly, to minimise the volume of tissue ablated and therefore the shockwaves and noise generated at the beginning of the treatment. In ultrastructural studies, expanding apertures were claimed to produce better surface regularity than contracting apertures. This was considered to be because the final laser pulse was applied to the whole treatment area, and therefore the pseudomembrane was in continuity, and not disrupted by pulses to adjacent tissue.⁴⁷

The results of investigations such as these have determined some of the physical characteristics of ablations used today. However, there are other mechanical factors such as wound depth, diameter, and profile which still require investigation.

As PRK was the first technique in which tissue was permanently removed from relatively large areas of the central cornea, there was initial caution about the amount of tissue which could be safely ablated. There were two main areas of concern. Firstly, it was not known how much tissue should be left in situ to maintain the regularity and mechanical stability of the cornea after surgery. Secondly, it was possible that a larger wound would result in a greater wound healing response, which in turn might cause complications. Several studies have used ablation profiles of different shapes in order to limit the volume of tissue removed in the treatment of high myopia,^{19 20 48–52} but few so far have systematically evaluated which aspect of the wound shape accounts for the reported variations in clinical outcome.⁵³

DEPTH OF ABLATION

Initially it was considered advisable to remove minimal amounts of tissue and, where possible, to preserve elements of Bowman's layer.⁵⁴ In limiting ablations to within Bowman's layer, it was thought that the structural integrity of the cornea would be maintained, and also a smooth surface over which the epithelium could heal uniformly would be provided.¹⁰

From a mathematical model, Munnerlyn advised a maximal ablation depth of 50 µm in order to avoid the summation of irregularities in the early beams, which he suggested would become obvious with deeper treatments.²⁶ It now appears that summation of irregularities is unlikely, given the random interpulse variation in beam energy distribution. However, 50 µm was also suggested as a maximum

Figure 5 Objective halo for patients undergoing (A) -3.00D and (B) -6.00D corrections. (Mean (SE)); significance of the difference between the 5 mm and 6 mm treatments. **p*<0.05, ***p*<0.01.)

ablation depth following empirical studies of wound healing in monkeys¹² and rabbits.¹³ Corneas remained clear after ablations of 50 μm or less, but haze developed following deeper ablations. As a result of these animal studies, ablation depths in the first clinical trials were confined to the superficial one tenth of the stroma.

More recently, both experimental studies on animals and clinical observations have led to conflicting statements concerning the relation of haze to ablation depth. For example, while some animal studies suggested that postoperative haze increased with ablation depth,^{12 13 54} others showed no difference²² or the reverse relation.⁵⁵ Subjective observations of haze in clinical studies have frequently reported greater haze in patients undergoing higher order corrections,^{2 4 9 12-16} but again other studies have found little correlation with the depth of ablation.^{5-8 22-25} It has been suggested that the correlation reported in some studies may be compounded by the severity of pre-existing myopia.³ Further, the quantification of haze can be inconsistent in the absence of objective assessment techniques.³⁰ The present study was able to resolve these discrepancies, firstly, by varying ablation depth for given dioptric corrections and, secondly, by using an objective method to measure haze.

DIAMETER OF ABLATION

For a spherical correction, the diameter of a PRK treatment zone is mathematically related to its depth for a given refractive change.²⁶ Therefore, minimising the depth of ablation to conserve stroma requires that the treatment be of small diameter. The first clinical trials of excimer laser PRK used treatment zone diameters of 3.5 mm,^{4 7} 4 mm,^{3 56} 4.5 mm,^{6 9 14} or 5 mm.^{2 6 14} These produced fairly predictable refractive results, and in most patients, minimal to moderate haze. In practically all studies there were also a small number of patients in whom the haze was severe. Daytime visual performance was for the most part unaffected, but problems with vision at night were commonly recorded,^{3 4 8 9} and most patients described these as halos around lights.

Halos arose as a result of pupillary dilatation in dim illumination.^{32 57-59} Under such conditions the retinal image was degraded by unfocused light passing through the untreated zone. In support of this concept, eyes with 5 mm ablation zones experience less halo at night than eyes with 4 mm zones.²⁷ Therefore, there was interest in resolving halos by further increasing ablation diameters to an optimal level without compromising refractive stability or corneal transparency.

REFRACTIVE STABILITY

The structural integrity of the cornea is dependent upon the regular arrangement of tightly packed collagen fibres which are thought to run from limbus to limbus.^{60 61} The orientation of the fibres, with those in

adjacent lamellae running approximately perpendicular to each other, is considered to further enhance its structural stability.^{18 62} Litwin studied how the mechanical stability of the cornea was affected by ablating to successively deeper levels in fresh human cadaver eyes.¹¹ By maintaining the intraocular pressure synthetically, this study showed by photokeratoscopy that ablations of 50 and 100 μm produced corneal flattening while those of 150 μm produced central steepening. The latter result was interpreted as bowing as a result of the intraocular pressure no longer being contained by the remaining lamellae.

In the present study, the theoretical maximum ablation depth was 78 μm (the -6.00D, 6 mm group). This was the group that showed the greatest refractive stability between 6 months and 1 year, with over 50% of patients remaining within plus or minus 0.25D of their refraction at 6 months. After 6 months, no group showed a tendency towards continued regression of refraction or increasing corneal curvature on topography. These results indicate that there was no steepening of the central cornea indicative of bowing because of mechanical instability or the production of new tissue.

CORNEAL HAZE

Slit-lamp examination with subjective analysis of haze has led to the concept that haze increases with depth of ablation.^{2 4 9 12-16} This has not been sustained by objective analysis in this study, in which haze was significantly less in the 6 mm (39 or 78 μm) than the 5 mm (26 or 62 μm) and multizone (62 μm) treatments, for a given dioptric correction. Other studies have also suggested that less haze occurs following larger diameter ablations.^{7 17 23}

In the present study there were five physical variables which could affect the nature of the initial wound, and therefore the wound healing response and resultant haze. These were: the depth, the diameter, the aspect ratio, the surface slope, and the profile of the edge of the ablation zone. By reviewing the literature concerning wound healing in the cornea it has been possible to propose cellular mechanisms by which each of these factors may be exerting an effect, and evaluate their relative importance.

Ablation depth

The reduction in haze seen in the 6 mm ablations could be related to increasing ablation depth, but this seems unlikely. In the corneas of most species, the deeper collagenous layers show greater order than the superficial layers. Therefore, the wound healing tissue produced by the deeper layers may have a more regular organisation and scatter less light.^{63 64} However, this greater order occurs only in the posterior two thirds of the cornea, and would not be relevant to the results of the current study in which the maximum ablation depth was 78 μm ; although it may apply to the deeper ablations used in phototherapeutic

keratectomy.^{24 25} Deep ablations with relatively little haze are also seen following intrastromal techniques,^{22 65} but this is because stromal healing occurs without the influence of the epithelium, rather than being a direct function of depth.

Ablation diameter

Wounds of larger diameter differ from small diameter wounds in two main respects: firstly, there is a larger area of stromal ablation and, secondly, they involve more peripheral cornea. It has been suggested that stromal healing cannot take place until epithelial cover has occurred.²² If larger wounds took longer to epithelialise than small ones, this could theoretically explain why larger diameter ablations develop less haze. However, this is unlikely to be of practical importance in the present study for several reasons. Firstly, epithelial cells of peripheral origin regenerate faster than those of central origin.⁶⁶ Secondly, the rate of epithelial migration is no slower over ablated than non-ablated cornea,⁶⁷ partly due to the presence of a smooth pseudomembrane over the ablated surface.^{10 34} Thirdly, epithelial migration is rapid, with the front moving at 2.5 mm per day and complete closure being achieved by the third postoperative day in the majority of patients. Therefore, an increase in wound diameter of 1 mm would delay epithelial closure by less than half a day, which is probably clinically insignificant. Fourthly, in this study the area of epithelial debridement was the same in all patients, regardless of the ablation diameter.

It has been shown in studies of full thickness incisions, that healing in the stroma was also faster peripherally than centrally.^{68 69} If the faster healing rate in the periphery was the result of a more limited removal of damaged tissue in the early phases of wound healing, this may reduce the subsequent repair and replacement phases which result in corneal haze. However, there is little experimental or clinical evidence to suggest that the cornea scars less in the periphery than the centre. Therefore, haze is unlikely to be directly dependent on wound diameter.

Wound aspect ratio

The aspect ratio of a wound to some extent determines the type and amount of new tissue which is produced. The nature of that tissue is determined by the division and migration rates of the various cell types involved.⁷⁰ The rapid division and migration of epithelial cells enables them to cover wounds in a short amount of time. This may be followed by remodelling with limited replacement by extracellular components.^{68 69} There is a tendency for the wound healing tissue to generate a smooth surface, thus a deep narrow wound will be filled in to a greater extent than a large shallow wound, as demonstrated by radial keratotomy incisions⁶⁹ or discrete corneal ulcers.

Wound slope

Related to the aspect ratio of a wound is the slope of the wound surface. For a given algorithm, there is a greater rate of change of slope in higher order corrections and when using smaller diameter treatment zones. Both of these wound variables are associated with more severe haze. The concept of increasing haze with the steepness of the ablation surface is supported by the extreme case of square edged keratectomies in which there is loss of transparency associated with the vertical wound edges, but not the horizontal base where few collagen fibres are transected.²² Likewise, tangential excisions have less haze than those performed en face,⁴⁴ which may be because these wounds lack a vertical edge.

A possible explanation of these observations may be that the severity of haze is related to the number of adjacent collagen lamellae transected in a given area.^{34 71} Light microscopic studies of vertical incisions have demonstrated that there is a period during healing in which the keratocytes aggregate between collagen lamellae at the wound margins, disturbing its stereospatial relations.⁶⁹ In the first 3 months after PRK, haze has been shown to be associated with changes in the keratocytes beneath the ablation site. These activated cells become larger and increase in density,³¹ and may thereby also alter the spacing and regularity of the stromal collagen, particularly where transected collagen fibres now have free ends. The keratocytes exposed between transected collagen fibres at the wound edge may be the ones responsible for synthesising the sub-epithelial glycosaminoglycans which also contribute to haze.⁷³ The thickness of the epithelium (and therefore regression) may also be affected by the slope of the wound surface.

The importance of this concept can be further assessed by analysing corneal transparency as a function of the step size in a PRK wound. In laser systems using the movement of an aperture to determine the ablation profile, the wound surface has a substructure consisting of a series of steps. If the aperture moves with each pulse, the height of the steps is determined by the depth of tissue removed by a pulse (0.25 μm), and the step width is determined by the excursion of the diaphragm between pulses.

Surface smoothness was initially considered to be of importance in minimising haze.^{10 26 34 47 71} Some studies have demonstrated more severe haze in PRK wounds with a few larger steps than those which had a greater number of small steps,⁴⁵ but others have failed to confirm this.²² It has been suggested that if the steps are sufficiently small – for example, the depth of a single laser pulse (0.25 μm), no epithelial hyperplasia would occur.¹³ However, other investigators have seen transient epithelial hyperplasia³⁸ or haze^{73–75} in completely smooth wounds made by moving slits³⁸ or erodible masks.^{73–75} One problem with comparing these results was that the analysis of haze was performed at different times often by subjective means, and therefore no firm conclusions could be drawn.

Alternatively, there may be a critical step size below which changes in contour cannot be recognised by the cellular components in the system. The height or the width of the steps may be important, and wound healing may be dependent upon the aspect ratio of the steps and the size of the cells reacting to the steps.⁶¹

Edge profile

A sudden change in wound contour, as occurs at the edge of an ablation, may modulate wound healing. Such modulation may take the form of epithelial hyperplasia which tends to smooth out surface irregularities, or an exaggerated subepithelial response.¹²

In this study, the effect of edge profile was investigated independently of wound diameter or depth by using a multizone treatment. A small diameter ablation providing most of the dioptric correction was overlaid by a large diameter low dioptric correction to create a peripheral blend zone with only a gradual change in surface slope. The haze and regression which followed this multizone treatment were very similar to that resulting from the 5 mm treatment, and significantly greater than that seen with the 6 mm treatments. This aggressive wound healing may have occurred as a result of other factors which were not initially considered important. For example, 1 minute elapsed between the two portions of the multizone treatment while the laser was reprogrammed for the second stage. During this interval, surface evaporation may have occurred resulting in differential hydration across the wound site and variable rates of ablation.⁷⁶

From our data and a review of the literature on corneal wound healing, we conclude that corneal haze is not a direct function of the depth or diameter of the wound, and nor is surface smoothness of major importance within certain limits. We feel that the factor with greatest influence on the development of corneal haze is the slope of the wound surface, particularly over the centre of the ablation. It appears that tapering the wound edge in the manner performed in this study is of no additional benefit.

VISUAL ACUITY

Changes in visual acuity tended to reflect the development and resolution of corneal haze. The transient loss of transparency and acuity seen in the first week was similar in all five treatment groups. This is therefore likely to be related to epithelial irregularity on the corneal surface.

The second drop in acuity occurring after 3 months was larger in the -6.00D than the -3.00D corrections. At this time, the haze was thought to be due to keratocyte disturbances,³¹ and the subepithelial deposition of glycosaminoglycans.⁷² In the 6 mm treatment groups the subepithelial deposit tends to resolve and the mean visual acuity returns to within half a line of preoperative levels. However, in the 5 mm and multizone treatments there were a

clinically significant number of patients in whom the haze persisted causing a prolonged reduction in visual acuity.

NIGHT VISION

After PRK, visual problems at night arise from two distinct mechanisms: glare and halos.⁵⁷⁻⁵⁸ Glare is due to the forward scattering of light by corneal haze. Halos are myopic blur circles formed when the pupil dilates beyond a critical size, allowing light to pass through two or more separate refracting regions on the surface of the cornea.

The reduction in subjective night vision problems seen in the 6 mm treatment groups compared with the 5 mm groups was the result of improvements in both glare and halos. The reduction in the size of the objective halo was related to the increase in the diameter of the treatment zone. It is therefore possible that if treatment zones were enlarged sufficiently, the problem of halos could be eliminated completely. In this study, the majority of patients had a pupil diameter in darkness of less than 9 mm (mean $+2$ SD). On this basis, the smallest beam diameter required to eliminate halos would be 7.5 mm for -6.00D corrections, and even larger for higher order treatments. There is also the possibility that the use of larger diameter beams may further improve corneal haze, and with it, symptoms of glare and reduced visual acuity.

The multizone treatment was also 6 mm in diameter, but the objective halo was no better than after the 5 mm treatments. This may relate to the ablation profile. Many treatment zones consist of two portions. The optical zone is the part with the desired optical correction, and may be significantly smaller than the treatment zone (for example, 3.5 mm in a 5 mm ablation).⁷⁷ This is surrounded by the transition zone of lesser power, which connects the optical zone to the untreated cornea.⁵⁹ In the multizone treatment, the optical zone was provided by the 4.5 mm diameter component of the treatment; the 6 mm diameter component of the treatment only served to smooth the transition between the treated and untreated cornea. Nowadays, some centres are studying multizone treatments with a greater component of the correction in the larger diameter zone.

Subjective night vision following the multizone treatment was substantially worse than following the 5 mm treatment, despite producing objective halos and haze of a similar magnitude. This too may be explained by the ablation profile.⁷⁸⁻⁸² The optical zone was surrounded by the transition zone of the 4.5 mm diameter component then a 1.5 mm annulus of the 6 mm diameter component. This resulted in a wide blend zone of dioptric power between that of the optical zone and the untreated cornea. Light passing through the blend zone would be focused less sharply than that passing through the optical zone, but to a greater extent than light passing through the untreated region. It would therefore result in an intense halo of semifocused

light which could degrade the retinal image to a greater extent than a larger more diffuse halo.

If the size of a halo is related to the size of the optical zone, then the diameter of the optical zone should be increased. Seiler achieved this by using an aspheric algorithm which produced a greater power change in the mid periphery of the treatment zone than the centre, at the expense of the transition zone.⁷⁷ This resulted in a rapid change in contour at the wound edge, which could (following the discussion above) have resulted in greater peripheral haze. However, if the diameter of such an ablation is sufficiently large, and the floor in the centre is sufficiently flat, haze may be confined to the wound edge, and the central cornea may remain relatively clear and provide good vision.

ADDITIONAL BENEFITS OF LARGE DIAMETER BEAMS

This study achieved its initial aim by demonstrating that the use of larger diameter treatment zones can reduce postoperative halos without compromising corneal stability or transparency. In fact less haze occurred after 6 mm than after 5 mm treatments.

Unforeseen additional benefits of larger diameter beams were a reduction in the hyperopic shift and improved predictability of the refractive outcome.

The hyperopic shift present in the first couple of months after surgery is due to a combination of excessive central corneal flattening while the epithelium is thin, and a ring of local steepening due to the synthesis of new tissue in the periphery of the treatment zone.¹² This latter effect is probably less evident in larger ablations with more gently sloping wound edges. The resultant reduction in anisometropia may be helpful in maintaining stereopsis while waiting for treatment of the second eye.

Treatments by larger diameter beams showed better predictability of the refractive outcome, and also less variation in the severity of haze. In the past, Durrie had attributed the wide spread of data points to biological differences in wound healing.⁸³ The reduction in interindividual variation seen in the current study suggests that the physical characteristics of the ablation profile can limit the effects of biological variation.

In view of the great biological and functional benefits gained by increasing the treatment zone diameter from 5 mm to 6 mm, it will now have to be considered how much further ablation diameters will need to be increased to continue improving the clinical outcome of PRK without introducing adverse effects.

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