ORIGINAL ARTICLES

Excimer laser treatment of corneal surface pathology: a laboratory and clinical study

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Abstract

The argon fluoride excimer laser emits radiation in the far ultraviolet part of the electromagnetic spectrum (193 nm). Each photon has high individual energy. Exposure of materials or tissues with peak absorption around 193 nm results in removal of surface layers (photoablation) with extremely high precision and minimal damage to non-irradiated areas. This precision is confirmed in a series of experiments on cadaver eyes and the treatment of 25 eyes with anterior corneal disease (follow-up 6 to 30 months). Multiple zone excimer laser superficial keratectomy is considered the treatment of choice for rough, painful corneal surfaces. All patients in this group were pain-free postoperatively. Where good visual potential exists, ablation of a single axial zone is recommended and results in improved visual acuity and reduction of glare. A hyperopic shift was noted in this group.

The potential of excimer lasers in ophthalmic surgery was first suggested in 1983¹ following their successful industrial application in etching highly precise patterns into plastics.¹⁻⁵ A distinct advantage of argon fluoride excimer laser radiation (193 nm) is that there is no significant damage beyond exposed areas. Ultrastructural examination of corneal excisions in animal models confirmed that these could be produced with a very high degree of accuracy and control. Damage to adjacent unexposed tissue was limited to 300 nm beyond the boundary of the zone of ablation.⁶⁻⁹ In non-perforating excisions of varying depths endothelial damage was noted only when the base of the excision was within 40 μ m of Descemet's membrane, which is similar to but less extensive than diamond knife incisions.^{6,8,10,11} Furthermore, excisions can be controlled precisely, in terms of uniformity along the length of a single cut, reproducibility between cuts, and in anticipated cut depth (accuracy $\pm 3\%$, diamond knife incisions $\pm 12\%$). The first clinical application was therefore the correction of astigmatism with T-cut excisions.¹²

The nature of corneal damage induced by excimer radiation at 193 nm is unique, because it results from an extremely high photon energy and high peak power. At this wavelength each photon has an energy of 6.4 electron volts, and, as this exceeds the binding voltage of carbon-carbon bonds, a single absorbed photon may lead

to bond breakdown.¹³ Ultraviolet radiation in this spectral domain does not propagate well in air, and at any biological interface the photons are virtually all absorbed within a few microns of the surface. Thus, with each laser pulse a layer of tissue only a few molecules thick will be ablated from the surface. Tissue damage induced by other clinical lasers is achieved by concentrating laser energy into a focused point. However, the excimer laser beam has a large cross sectional area, and since every photon in the beam has the potential to produce tissue change the entire cross section can be utilised. The 1 cm by 2 cm rectangular profile is adjusted by cylindrical quartz lenses, and the resultant square beam profile becomes circular by passing the emergent beam through an aperture.⁹ This facility to photoablate large areas of cornea permits selective removal of tissue to induce a refractive change (photorefractive keratectomy - PRK).^{9,14-18}

For PRK and superficial keratectomy to become accepted in clinical practice an understanding of the nature and quality of wound healing is essential. Complete epithelial wound healing is necessary to re-establish the outer osmotic barrier of the cornea and optical brilliance. Studies have been undertaken to assess latency of wound healing, epithelial migration and adhesion properties, and the presence or absence of hyperplasia.¹⁹ Stromal wound healing has been examined in relation to loss or disturbance of transparency, keratocyte infiltration, and scar formation.^{14,16,20} Endothelium has been assessed in relation to potential cell loss or long-term population changes.^{19,21} Finally the putative mutagenic effects of ultraviolet radiation on the cornea have been assessed by both unscheduled DNA repair and tissue culture, coupled with enzyme poisoning techniques.^{22,23} None of these studies has highlighted areas of concern that would preclude the beginning of clinical trials with the excimer laser at 193 nm (Slaney D, personal communication).

In February 1988, on the basis of laboratory data, ethical committee approval was given to treat overt corneal lesions with the excimer laser. The aim of this study was to determine whether the laser could be used for wide area ablations to remove opacities and produce an optically smooth surface. Since photoablation occurs across the entire area exposed, with repeated pulses the original surface contour will be reproduced in the base of the ablated disc. It was necessary therefore to devise a means of smooth-

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ing an uneven surface. The simplest method of achieving this was to apply a liquid with approximately the same ablation properties as the cornea. The surface tension of the liquid would ensure that any surface irregularities would be negated. If irregularities in the corneal surface had a different ablation rate from that of the surrounding tissue – for example, the calcium deposits in band keratopathy – it would be necessary to shield underlying tissue with a liquid while the crystalline peaks underwent ablation.

This paper describes the use of the excimer laser for the production of large-area, optically smooth corneal surfaces in the laboratory and in the clinic.

Materials and methods

After ethical committee approval all clinical trials were carried out in the Department of Ophthalmology at St Thomas's Hospital, London. A Summit Technology UV200 excimer laser was used with spectral emission at 193 nm. The pulse energy resulted in a radiant exposure of 180 mJ/cm²; the pulse frequency was fixed at 10 Hz and tissue removed per pulse was 0.24 µm. The beam configuration was circular in cross section, and a number of fixed beam diameters were used between 1 and 4 mm.

EXCIMER LASER PATTERN ABLATION IN CADAVER EYES

(1) The aim of this experiment was to create an irregular surface in cadaver corneas and then to determine whether the excimer laser could smooth these irregular surfaces. Donor eyes were used within 16 hours of death and secured in a Tudor Thomas stand. Ocular rigidity was maintained by injecting normal saline into the vitreous through the pars plana. After removal of the epithelium with a hockey end blade the globe was placed directly beneath the laser aperture and the helium-neon aiming beams focused on the centre of the cornea. An area of stroma was masked by placing a piece of bent wire on the corneal surface in the path of the beam. Fifty pulses of laser energy were then directed on to the partially occluded corneal surface with a 3 mm diameter beam. This resulted in excavation of the stromal surface in areas not shielded by the wire. In areas beneath the wire, ridges of original tissue remained.

The next objective was to remove the induced pattern with the laser to restore a smooth surface across the entire ablated zone. The wire was removed and the excavated areas 'masked' with 1% or 2% hydroxypropylmethylcellulose (HPMC) or polyvinyl alcohol to prevent their further ablation. These tear substitutes have a high water content and were assumed to have similar ablation rates to corneal stroma.

(2) In this experiment the excimer laser was used to create a cylindrical excavation 1 mm in diameter and 100 µm deep. The beam diameter was then increased to 3 mm, the ablated cylinder filled with 1% HPMC, and the surrounding stromal surface carefully dried. Ablation of the stroma was continued until the surrounding

stroma had been ablated to the same depth as the original cylinder. In practice this process was monitored by changes in tissue fluorescence to be described in the results.

EXCIMER LASER SMOOTHING OF SURGICAL LAMELLAR KERATECTOMY BEDS

This experiment was designed to assess the potential of the excimer laser in combination with masking agents to smooth irregular corneal surfaces. A series of surgical lamellar keratectomies was performed on donor eyes. The initial incision was made with a disposable 6 mm trephine, and the lamellar dissection was done with a steel blade and Paufigue's knives, beginning at the base of the trephine cut. HPMC was applied to the keratectomy base and its amount and distribution adjusted, while multiple overlapping ablation zones were produced until the base was smooth.

HISTOPATHOLOGY

After laser exposure a 5 mm penetrating incision into the posterior globe was made and the eyes were immersed in fixative. The initial fixative used was 2.5% glutaraldehyde buffered in 1 M sodium cacodylate with 10 g/l calcium chloride at a final pH of 7.4. After 24 hours the corneas were prepared for light microscopy (LM) and electron microscopy (EM). Those for scanning EM were postfixed overnight in 2% osmium tetroxide buffered in 0.1 M sodium cacodylate, dehydrated through a series of ascending concentrations of acetone, and critical-point dried. Dried samples were sputter-coated with a 30 nm layer of gold before examination in a Hitachi 520 scanning electron microscope (SEM). For transmission electron microscopy (TEM) specimens were postfixed for only one hour in the osmium tetroxide solution described above, dehydrated in alcohol, and then embedded in Araldite (CY212) via epoxypropane. Sections were cut at 1 µm on glass knives for LM and on diamond knives for EM and mounted on 200 mesh copper grids, stained with uranyl acetate and lead citrate before examination in an AEI 801 transmission electron microscope.

TREATMENT OF BAND KERATOPATHY AND ALLIED SUPERFICIAL PATHOLOGIES

Twenty five patients underwent excimer laser superficial keratectomy to remove band keratopathy or to smooth roughened corneal surfaces arising from other pathology (see tables). Amethocaine 1% was instilled, a speculum inserted, and the patient taught to fixate the centre of a ring of fiberoptic lights located around the laser aperture. A beam diameter was selected to match the areas to be treated, and in some cases the size of the beam was reselected at different stages in the procedure. The effects of photoablation were assessed with the integral binocular operating microscope positioned alongside the laser aperture. Once steady fixation was achieved, the masking liquid was applied to the corneal surface and photoablation started. During the process the surgeon could vary the

site of ablation by making small movements of the patient's head. After the procedure, which lasted about 15 minutes, a mydriatic (homatropine 2% eye drops) and antibiotic (chloramphenicol 1% eye ointment) were instilled and the eye padded for 24 hours. Follow-up was daily for the first week, weekly for one month, three monthly for two further visits, and then six monthly. For the first month chloramphenicol 0.5% eye drops were used four times a day.

The surface characteristics of selected patients were examined and recorded with a prototype photokeratoscope.²⁴ In addition, while it was impossible in most cases to comment on the preoperative status of the corneal endothelium owing to superficial opacification, it was examined postoperatively at intervals via specular reflection with the slit-lamp. Refraction was carried out where possible.

Although the morphology of band keratopathy varies, we subdivided the patients into two broad categories. The first had rough, craggy deposits with varying degrees of discomfort, the second, smooth even deposits with little or no discomfort.

Two treatment regimens were undertaken. Either a single 4 mm diameter zone or a series of partially overlapping 4 mm diameter zones was ablated. The single area technique was most commonly used for smooth bands which caused impaired vision and glare and the multiple zone technique for rough, painful bands. The noise associated with laser pulses (10 Hz) was demonstrated to the patients prior to the procedure, and they were warned to expect a faint smell of burning during treatment (see below).

Results

EXCIMER LASER PATTERN ABLATION IN CADAVER EYES

(1) The bas relief pattern produced on the cornea by shielding the underlying stroma by bent wire was best demonstrated by SEM (Figs 1A, 2A). The smoothness of the ablated surface was comparable to Bowman's layer on the non-ablated ridges, and the stromal architecture was obscured by a continuous membrane-like structure. The ridges, noted to have smooth perpendicular walls, were successfully ablated to produce a homogeneous, optically smooth surface (Fig 1B). In some specimens the ablation to produce the pattern and the subsequent smoothing ablation were not coincident. This resulted in a small peripheral annulus in which the ridges could still be seen (Figs 1B, 2B).

The most suitable masking liquid was 1% HPMC, since it was easy to apply and remove and filled the declivities between surface irregularities. HPMC fluoresced a bright blue when irradiated and corneal stroma a dark blue-black. There was thus a clear indication of the three dimensional geometry of stroma undergoing ablation. When 1% HPMC flooded the surface, an even bright blue fluorescence was noted across the entire target area with each pulse. As the masking agent was ablated, corneal stromal irregularities projected through the surface of the HPMC and were ablated, as dark blue,

Figure 1 Scanning electron micrographs of the surface of human donor corneas after excimer laser irradiation. (A) The pattern created by shielding stroma with a piece of bent wire during irradiation is shown. The ablated surface adjacent to the non-ablated ridges (arrowed) is smooth and the ridges themselves are sharply demarcated. The sides of these ridges are perpendicular as is the edge of the ablated zone. (B) A pattern similar to that in (A) has now been ablated leaving an almost totally smooth surface. A small peripheral annulus indicates that there has been a slight shift in the position of the eye prior to the final smoothing ablation. (Bar=500 μ m.)

Figure 2 High power scanning electron micrographs of the ridges created and removed by excimer laser irradiation (A) Shows the magnitude and edge quality of the ridge seen in Fig 1. (B) Shows the residual portion of a ridge (fine arrows) after a smoothing procedure. The ablation depth involved in generating the initial pattern (closed arrow) and that involving its removal (open arrow) can be clearly distinguished as a result of displacement of the globe between the two procedures. (Bar=100 μ m.)

almost black, 'islands' within the bright blue HPMC fluorescence. As ablation proceeded, so the pattern and surrounding masking agent were removed until a common depth was reached, at which point HPMC once again spread throughout the 3 mm zone, indicated by homogeneous bright blue fluorescence. Further ablation beyond the original depth of 10–12 μm removed the little remaining HPMC, and the entire area appeared dark blue-black, with each pulse confirming that the pattern had been completely removed. If further pulses were applied, then the 3 mm zone of ablation was uniformly increased in depth (Fig 1B). With relief patterns in excess of 30 μm it was more difficult to achieve uniform smoothness because of a meniscus effect where the masking agent met the vertical sides of the pillars of non-ablated tissue. It was found that blotting the edges with cellulose (Weck-cell) sponges reduced this effect.

(2) In this experiment a 1 mm diameter cylinder of corneal stroma was ablated and filled with HPMC. On ablating the area around the cylinder there was differential fluorescence – the central spot (HPMC) bright blue, the surrounding stroma dark blue-black. The end-point was reached when the blue spot disappeared and the entire area of ablation became uniformly black – that is, the surrounding stroma had been ablated to exactly the same depth as that of the original cylinder. The number of pulses required for these two processes was similar.

EXCIMER LASER SMOOTHING OF SURGICAL LAMELLAR KERATECTOMY BEDS

Scanning electron microscopy of the base and walls of a surgical lamellar keratectomy showed surfaces with a marked degree of destruction and dissociation of cellular and extracellular components. The walls of such sites showed stratification with alternate layers of compression and shearing. There was an annulus in which epithelial cells were wiped off Bowman's layer because the surface tissue was displaced and compressed against the barrel of the trephine and debrided as the trephine rotated. The floor never displayed a cleavage plane and always consisted of ripped, torn lamellae and displaced ruptured keratocytes (Fig 3A).

Figure 3 Scanning electron micrographs of the corneal surface subsequent to (A) surgical lamellar keratectomy; (B) and (C) excimer laser irradiation. (A) The bed of a lamellar keratectomy showing rough, disorganised and torn tissue. (Bar=50 μm .) (B) A surgical lamellar keratectomy bed smoothed by excimer laser irradiation. The surface has a confluent membrane-like quality seen as wrinkles and folds produced during preparation for scanning electron microscopy. (Bar=50 μm .) (C) A lamellar keratectomy bed smoothed by application of multiple overlapping zones of excimer laser radiation. The slight discontinuities between different zones are seen as variations in ablation depth and defined by arcuate boundaries (arrowed). (Bar=500 μm .)

The most appropriate method of smoothing lamellar beds was achieved by frequently applying small amounts of masking agent and constantly readjusting local distribution with cellulose (Weck-cell) sponges. This enabled removal of multiple small surface perturbations without unnecessary removal of deeper stroma. The resultant surface was smooth, with some wrinkles and folds suggesting a surface membrane (Fig 3B). Multiple overlapping ablation zones were used to smooth the entire keratectomy base (Fig 3C). Zones already smoothed

Table 1 Rough band keratopathy treated by several overlapping ablation zones

No.	Sex	Age	Band type	Aetiology	Preop. symptoms	VA	Postop. symptoms	Follow-up		
								VA	Time (months)	Comment
1	F	49	Rough surface very irregular	Increased serum Ca^{++}	Pain, photophobia decreased VA	6/36	Asymptomatic	6/12	30	Band recurred after 18 months
2	M	45	Rough, very irregular	Trauma	Pain	PL	Asymptomatic	PL	30	Stable
3	M	50	Rough, raised, thick band	Trauma	Pain	NPL	Asymptomatic	NPL	30	Stable
4	M	34	Rough, irregular disrupted ant. seg	High myope, failed retinal detachment surgery	Irritable, red, pain on blinking	PL	Asymptomatic, pleased with cosmesis	PL	14	Stable
5	F	66	Central, proud Ca^{++} plaque	Keratitis due to herpes simplex virus	Pain, decreased VA	CF	Asymptomatic, (occasional ache)	6/36	14	Stable
6	F	72	Classic band	Herpes zoster	Pain, epiphora decreased VA	6/24	Asymptomatic	6/18	12	Stable
7	F	33	Islands of Ca^{++} (previous edetic acid treatment)	Uveitis (childhood)	Poor cosmesis, minimal discomfort	NPL	Unchanged	NPL	10	Highly mobile eye during treatment (surgery abandoned)
8	F	78	Central Ca^{++} area and diffuse Ca^{+++} surround	HSV keratitis	Pain, epiphora, decreased VA	CF	Asymptomatic, slight increase in VA	4/60	10	Stable

VA=visual acuity. (N) PL=(no) perception of light. CF=counting fingers. HSV=herpes simplex virus.

Figure 4 Case 1. Rough band keratopathy. (A) Preoperative appearance. Extensive calcium deposition is present producing a grossly uneven surface. (B) Immediate postoperative appearance. The majority of the calcium has been ablated, leaving a smooth surface. (C) Appearance five months after treatment with the excimer laser. (D) Appearance 18 months after ablation. Treated areas remain clear, but recurrence of band keratopathy has resulted in some loss of corneal transparency.

Figure 4A.

Figure 4C.

Figure 4B.

Figure 4D.

were masked with HPMC to avoid unnecessary ablation. This technique was important in establishing criteria for treating large areas of stroma in the subsequent clinical cases.

TREATMENT OF BAND KERATOPATHY AND OTHER SUPERFICIAL CORNEAL PATHOLOGY

Twenty-five patients have had excimer laser treatment of band keratopathy or superficial corneal pathology since February 1988 (Tables 1–5). The six cases reported here in detail represent the spectrum of disease and illustrate different techniques of band removal with the excimer laser.

GROUP 1. ROUGH SYMPTOMATIC (UNCOMFORTABLE) BAND KERATOPATHY

Case 1

A 49-year-old female with systemic lupus erythematosus requiring renal dialysis since 1981 had a parathyroidectomy in 1984 for primary hyperparathyroidism. Her left eye had been painful

since 1974 and was treated with artificial tears. In 1987 she had removal of band keratopathy with edetic acid (EDTA). In spite of this she still had severe pain in the left eye, aggravated by blinking, which disrupted sleep. There was extensive irregular, thickened band keratopathy with a visual acuity of 6/36. Islands of calcium protruded through unstable epithelium (Fig 4A). The right eye was normal.

In February 1988 she became the first sighted patient to undergo excimer laser superficial keratectomy (ELSK). She had multiple overlapping zones located in the central 6 mm of the cornea (Fig 4B). Approximately 300–400 pulses were delivered to each site of ablation. The procedure was pain-free. One hour later, however, she complained of some discomfort, which resolved over 36 hours when the cornea had re-epithelialised. One week later she was asymptomatic. At this stage the area of photoablation was smooth, with minimal central thinning and a faint anterior stromal haze. The acuity was 6/24 improving to 6/12 with pinhole. At five months there was early recurrence of band keratopathy (Fig 4C). By 18 months it began to cause

Figure 5 Case 2. Rough band keratopathy. (A) Preoperative appearance showing gross irregularity of the corneal surface and opacification. A large central calcium plaque is evident. (B) Postoperative appearance at one week. The large calcium deposit has been completely ablated. The patient remains asymptomatic after 18 months.

Figure 5A

Figure 5B

Figure 6 Case 3. Even, diffuse band keratopathy. (A) Appearance one year after excimer laser ablation of a single, 'on-axis' zone. The photograph was taken slightly eccentrically in order to highlight the enhanced transparency of the ablated zone against the iris. (B) Photokeratoscopic image preoperatively. (C) Appearance one month following central ablation.

Figure 6A.

Figure 6B.

Figure 6C.

discomfort. A small central epithelial erosion and faint central stromal haze were noted at this time, with the zone of ablation remaining markedly clearer than the surrounding area (Fig 4D).

Case 2

A 45-year-old male had sustained blunt trauma to his left eye at the age of 24. Band keratopathy, cataract, and glaucoma had resulted, and he underwent a series of procedures between 1984 and 1987 – corneal graft, cataract extraction with lens implant, two trabeculectomies and drainage

Figure 7A.

Figure 7B.

Figure 7C.

Figure 7 Case 4. Even, diffuse band keratopathy. (A) Preoperative appearance showing an even, diffuse band keratopathy – granular in places. (B) The appearance three months after excimer ablation of a single, central 'on-axis' zone to clear the visual axis. The increased clarity of the central ablated zone is evident, and the slight central haze represents lenticular opacity. (C) Postoperative appearance at three months utilising sclerotic scatter to highlight the clarity of the treated area. Note the remarkable clarity of this central zone (underlying lenticular opacities now being excluded).

tube insertion, and revision. He had discomfort and the vision was perception of light with poor projection. There was a dense band keratopathy and a grossly roughened corneal surface with disrupted epithelium (Fig 5A).

In August 1988 he had ELSK. The large central calcium deposit was completely ablated with HPMC to mask the surrounding tissue (Fig 2B). After re-epithelialisation he has remained asymptomatic. Eighteen months later the central corneal zone was still clear and the more peripheral band remnants were unchanged.

GROUP 2. SMOOTH BAND KERATOPATHY

Case 3

A 23-year-old West Indian male had pulmonary

Figure 8 Case 5. Even, diffuse band keratopathy. (A) Preoperative appearance showing an even band keratopathy distributed over the inferior cornea. Deep, white stromal deposits and a dense cataract can also be seen. (B) Postoperative appearance at 48 hours. The overlapping zones of ablation are clearly seen. Re-epithelialisation was complete at this stage. (C) Appearance at one year. Although the ablation zones are still clearly seen, there are signs of calcium deposition along the margins of some of the ablation sites and in the centre of two of these zones. The patient was still asymptomatic.

Figure 8A.

Figure 8B.

Figure 8C.

sarcoidosis and bilateral panuveitis, the left eye being worse than the right. Acuties were 6/6 right, hand movement left. There was a fine, even band keratopathy across the lower two thirds of the left cornea with early peripheral changes in the right eye.

Figure 9A.

Figure 9 Case 6. Dense, even band keratopathy treated with overlapping ablation zones in order to clear the entire corneal surface. (A) Preoperative appearance. A dense, even band keratopathy extends across most of the cornea. Silicone oil was present in the anterior chamber, shown by the reflex which delineates its margin underlying the 10/0 nylon sutures from previous cataract surgery. (B) Appearance three months following excimer laser ablation utilising overlapping and contiguous zones. There has been total clearance of the calcium leaving a smooth, clear cornea. Slight residual haze represents deep, pre-existing, stromal scarring.

In June 1988 he had left ELSK with a 3 mm diameter beam centred on the visual axis. Approximately 200 pulses were delivered, of which 150 were required to remove the epithelium. Re-epithelialisation was complete within 48 hours.

One year later the visual acuity had improved to 6/12, though no conclusions can be drawn from this improvement, since the panuveitis had responded to treatment (Fig 6A). The surface quality postoperatively was best demonstrated by photokeratoscopy (Figs 6B, C).

Case 4

A 72-year-old male had bilateral idiopathic evenly distributed band keratopathy (Fig 7A). He had no discomfort but complained of glare and impaired vision: 6/24 right and 6/18 left. He had a right 4 mm axial ELSK without HPMC and the appearance at three months is seen in Figs 7B and 7C. Fig 7C, using sclerotic scatter, highlights the clarity of the central cornea compared to the adjacent band keratopathy against the background of the dilated pupil. Visual acuity in the right eye improved to 6/12, but veiling glare was subjectively unchanged.

Case 5

A 32-year-old Jamaican female had been blind in the right eye (no perception of light) from childhood. The cause was unknown. The eye was very uncomfortable. The left eye was normal.

There was a moderately dense band keratopathy across the inferior two thirds of the right cornea and discrete white deep stromal deposits in the same area (Fig 8A). There was seclusio pupillae and a dense cataract. ELSK was carried out with five 3 mm diameter partially overlapping zones (Fig 8B). Within 48 hours she was asymptomatic with an intact epithelium.

One year after treatment she had occasional mild photophobia. There was a faint anterior stromal haze in areas of ablation, with evidence of recurrence of band keratopathy in the centre of these zones, with a further peripheral deposition causing irregular boundaries (Fig 8C).

Figure 9B.

Case 6

A 67-year-old male developed a dense evenly distributed band keratopathy in his right eye after retinal detachment surgery which had included injection of silicone oil (Fig 9A). He had also undergone extracapsular cataract extraction with insertion of a posterior chamber intraocular lens. Before photoablation there was only a limited view into the anterior chamber in which silicone oil was present. Vision was hand movements in the inferior field only. ELSK was undertaken for cosmetic reasons and to improve the view of the posterior segment.

Overlapping ablation zones were used to clear the cornea of band. 1% HPMC was used to mask previously ablated areas. At three months the cornea was clear, with an optically smooth surface (Fig 9B). A good view of the anterior chamber, intraocular lens and retina was obtained. As expected, there was no significant improvement in vision.

GENERAL COMMENTS

No patients reported discomfort during the procedure. Postoperatively most of them experienced some discomfort for 24–48 hours. The intensity and duration of discomfort was related to the area of ablation. All patients required oral analgesics for 24 hours. In all cases re-epithelialisation was complete by 48 hours.

Sixteen of the 25 patients had an improvement in visual acuity (Tables 1–5). The 13 patients with uneven, symptomatic (painful) corneal surface became symptom free.

Improvement in visual acuity occurred in those patients who had an even band keratopathy which responded well to photoablation with minimal or no masking. In the seven patients troubled by glare (typically eyes with good visual potential and an evenly distributed 'ground glass' band keratopathy) all were markedly improved postoperatively. Three patients in the series were pleased with the improved appearance of their eyes.

In most of the cases treated it was impossible to assess the central endothelium preoperatively owing to the overlying band keratopathy. Examination by slit-lamp specular microscopy was carried out postoperatively at various stages of the follow-up, and none of the patients was found to have any endothelial disturbance.

Discussion

Our studies have not identified any complications or undesirable findings that would preclude further investigation of the clinical use of excimer lasers in ophthalmic practice.

Excimer laser ablation is a surface phenomenon and therefore irregular surfaces cannot be levelled as a single stage procedure by irradiation. If a rough surface of homogeneous tissue is irradiated, a uniform layer of tissue will be removed with each laser pulse (Fig 10), and in order to produce a smooth surface a masking agent with a similar ablation rate to that of the target material must be used (Fig 11). A liquid more easily ablated than the surrounding tissue would have to be constantly reapplied so as not to

perpetuate surface perturbations. If the ablation rate were less than the surrounding tissue, less frequent applications would be required, and flow of the liquid between laser pulses would ensure that smoothing still occurred.

The viscosity and the surface tension of the masking agent are also of importance. If liquids have high viscosity or surface tension, they may form droplets and, on irradiation, contribute to further surface disturbances rather than smoothing. Surface tension and surface adhesion may also create problems in relation to filling deep surface excavations or those with low aspect ratios in terms of width to depth. The wetting agents selected are in clinical use and have a relatively prolonged contact with the corneal surface. All agents used were adequate for smoothing, but polyvinyl alcohol and 2% HPMC were too viscous and did not have good surface contour-following properties. 1% HPMC, however, was found to have ideal viscosity and was also convenient to apply and remove.

In the laboratory investigations it was possible to produce only models of uneven surfaces with uniform ablation rate – for example, superficial keratectomy beds. While these models are identical to some surfaces encountered clinically, as during lamellar keratoplasty or following removal of pterygia, a special case is encountered

Figure 10 The effect of excimer laser radiation on an unmasked irregular surface. (A) The unexposed surface. (B) After minimal exposure the surface irregularity is repeated deeper into the material, since a uniform layer of equal thickness is ablated across the entire exposed surface with each pulse. (C) The end result is a faithful representation of the original surface topography produced deep in the material.

Figure 11 Production of a smooth surface by excimer laser radiation. (A) The irregular surface, analogous to a rough corneal surface, is covered with a masking liquid. (B) After initial exposure to excimer laser radiation both the masking liquid and surface projections have been partially ablated, the normal stroma between projections having been shielded from unnecessary ablation. (C) The resultant smooth surface at the end of the procedure (determination of the end point is assisted by observation of a uniform fluorescence).

where surface projections are formed by inclusions, such as calcium, with a lower ablation rate than that of intervening tissue troughs (Fig 12). Surface smoothing in this case requires an adjustable 'shield' through which the calcium peaks protrude and are ablated while the troughs are protected. The shield may then be lowered to complete the smoothing process. An ablation

Figure 12 Ablation of dense calcium deposits embedded within the stroma and projecting from the surface. (A) Initial surface. Calcium deposits are shaded. (B) After excimer laser irradiation without masking. The calcium deposits, having a lower ablation rate per pulse, are barely altered from their original heights (dotted line), while the intervening exposed stroma, which has a higher ablation rate, has been unnecessarily excavated (arrows). (C) The same surface shielded with a masking liquid. (D) During ablation only exposed peaks and masking liquid are removed. (E) At the end of the procedure the surface has been smoothed. To remove the remaining calcium deposits embedded in the stroma normal corneal stroma will, of necessity, have to be removed, but its rate of removal can be regulated by further applications of masking liquid.

fluid with a slow ablation rate would be preferable for shielding. In practice, though 1% HPMC may not be optimal, it was certainly adequate as a shielding agent.

The control of the distribution of 1% HPMC during the ablation was an interactive process between manual application and removal. The closed tip size and curvature of Colibri forceps facilitated delivery of small quantities of HPMC without impairing the surgeon's view. Cellulose (Weck-cell) sponges applied to the edge of the target zone were used to remove excess liquid; however, the fluid movement thus created by capillarity was found to be too fast for accurate adjustment. We are now examining alternative sponges whose capillarity engenders less rapid fluid uptake.

All three masking agents fluoresced when irradiated, and the difference in the intensity and wavelength of fluorescence between the masking agent and the corneal substrate was helpful in monitoring the ablation process. The difference in fluorescence was best appreciated when viewing ablation of masked patterns of regular geometry. Discrimination became more difficult during ablation of masked irregular shallow surface perturbations.

It has been shown that the penetration depth of 193 nm radiation is 3–4 μm .⁸ At 248 nm it exceeds 25 μm ; and at 308 nm may be as high as 100 μm .^{25, 26} These observations support previous studies using broad band sources of radiation which showed that penetration depth increased with wavelengths between 100 nm and 400 nm.²⁷ Excimer laser radiation at 193 nm does not induce mutagenic response in cells deep to the ablation zone. This has been attributed to two aspects of the ablation process. First, that at the fluences used for clinical procedures the absorption of high energy photons results in bond breaking and ablation, and secondly that virtually no photons penetrate beyond the zone of ablation damaged cells. As a result of target fluorescence longer wavelength photons are generated which have deeper penetration and potential for DNA damage.²⁷ The fluence

associated with such secondary radiation at sites remote from the ablation surface is so low that it has been calculated to be negligible (Sliney D, personal communication). The fluorescence of the masking agent was predominantly in the short wavelength visible portion of the spectrum and was therefore not considered to be a secondary hazard.

The use of masking agents did not affect the nature of the ablated surface, since it was uniform in the pattern experiments (Figs 1B, 2B). Although we did not undertake chemical analysis of the resultant surface after ablation, the homogeneity seen in our morphological studies indicates that no chemical interactions have occurred between the masking liquid and adjacent biological tissues. All surfaces were sealed with a pseudomembrane^{6,8,9,28} as shown by wrinkling (Fig 3B), and previous studies have shown that, whatever the nature of the pseudomembrane, its existence is transitory, and it does not interfere with subsequent healing processes.¹⁴

Although preoperative visual acuity was poor in a large proportion of patients, all except four could fixate with the eye undergoing treatment. In these four patients adequate alignment was achieved with the normal eye fixating an adjustable target at one side of the laser aperture. In only one patient (case 7) was it impossible to treat the band keratopathy because of eye movement.

None of these patients detected the induced fluorescence during ablation in spite of this being clearly visible to all observers. In a further group of patients undergoing photorefractive keratectomy some were aware of a faint blue haze with each pulse. In contrast to the lack of visual stimulation auditory and olfactory sensations were notable. The patients were warned about the noise and the smell of burning, and both were demonstrated prior to the procedure by ablating paper. (The smell is a little disconcerting to some patients as it is rather like that of singed hair.) The biophysics of the smell is difficult to explain. Current concepts of ablation consider that tissue removal occurs owing to a photochemical process of bond breaking rather than a thermal event. Some workers originally considered the process to be an ultrafast thermal event with tissue loss due to massive vibrational modes breaking macromolecular bonds.²⁹ These thermal events could have resulted in 'burn-like' smells. Since the molecular fragmentation depends on wavelength, most workers now consider that ablation is a photochemical process with residual energy used to eject fragments from the surface.³ Smells must be related to airborne particles, and the similarity of smell of excimer ablated and thermally damaged biological tissue implies that similar types of particles are generated by both these processes.

Table 2 Rough band keratopathy treated with single 'on axis' ablation

No.	Sex	Age	Band type	Aetiology	Preop. symptoms	VA	Postop. symptoms	Follow-up		Comment
								VA	Time (months)	
9	F	20	Central Ca ⁺⁺ plaque	Uveitis from childhood	Poor cosmesis	NPL	Improved cosmesis	NPL	10	Epithelial ablation only required
10	F	80	Rough, central Ca ⁺⁺ deposit	Interstitial keratitis	Pain, epiphora	2/60	Marked improvement	2/60	12	Stable

Table 3 Disorders resulting in rough corneal surfaces treated by excimer ablation

No.	Sex	Age	Description	Pathology	Preop. symptoms	VA	Postop. symptoms	Follow-up		Comment
								VA	Time (months)	
11	M	27	Mucus plaque	Atopic, vernal eye disease	Pain, photophobia decreased VA	6/60	Asymptomatic	6/18	14	Re-epithelialised, no plaque recurrence
12	F	45	Rough, raised granular dystrophy	Recurrent granular dystrophy in a PK	Soreness, photophobia decreased VA	6/24	Asymptomatic	6/18	30	No recurrence
13	F	46	Extensive lattice dystrophy	Lattice dystrophy	Glare, photophobia decreased VA	6/60	Asymptomatic Marked increase in VA	6/9	6	No recurrence, no glare, hyperopic shift
14	F	46	Central raised nodules	Salzmann's	Discomfort, decreased VA	6/18	Asymptomatic	6/12	10	Stable
15	F	82	Anterior stromal scarring	Cogan's epithelial dystrophy	Decreased VA, recurrent erosion	4/60	Asymptomatic, improved VA	6/12	10	Stable. Central area treated

PK=punctate keratitis.

Table 4 Smooth surface band keratopathy treated with multiple overlapping ablation zones

No.	Sex	Age	Band type	Aetiology	Preop. symptoms	VA	Postop. symptoms	Follow-up		Comment
								VA	Time (months)	
16	F	32	Even, inferior cornea	Trauma in childhood	Discomfort	NPL	Asymptomatic	NPL	30	Stable, recurrence after 18 months (minimal)
17	M	67	Even, dense thick band	Failed RD surgery; silicon oil in AC	Glare, decreased VA	HM	Glare unchanged	CF	12	Recurrence after 6 months
18	F	81	Even, moderately dense	Idiopathic	Poor cosmesis	6/18	Good cosmesis	6/18	12	Refraction change
19	F	45	Even	Uveitis, glaucoma surgery	Decreased VA, glare	6/9	Reduced glare	6/18	12	Refraction change and irregular astigmatism
20	F	70	Even, fine	Idiopathic	Glare and decreased VA	6/36	Glare greatly improved but VA reduced	6/12	10	ECCE/IOL facilitated

AC=anterior chamber. ECCE=extracapsular cataract extraction. IOL=intraocular lens. HM=hand movements.

Table 5 Smooth surface band keratopathy treated with 'on axis' single ablation zone

No.	Sex	Age	Band type	Aetiology	Preop. symptoms	VA	Postop. symptoms	Follow-up		Comment
								VA	Time (months)	
21	M	23	Even, fine	Uveitis	Decreased VA	6/36	Improved VA	6/9	30	Cornea remains clear, refraction change
22	M	84	Even, fine	Idiopathic	Decreased VA, glare	6/24	Decreased glare Improved VA	6/12	14	Refraction change
23	F	73	Even, fine	Idiopathic	Decreased VA	6/36	Improved VA	6/18	14	Refraction change
24	F	82	Even, fine	Idiopathic	Decreased VA, glare	6/36	Reduced glare Improved VA	6/18	6	
25	F	14	Even, fine	Uveitis	Decreased VA, glare	3/60	Glare reduced, slightly improved VA	6/60	12	Cornea remains clear

Tables 1 to 5 show that postoperative progress was related to the extent of the initial pathology. Systematic analysis of the patient subsets was difficult, because there were significant variations in pathology. However, all patients with rough band keratopathy who had experienced pain preoperatively became asymptomatic (Tables 1 and 2). Most were treated with several overlapping ablation zones in order to smooth the cornea completely (Tables 1 and 2). Table 2 includes those patients who had a relatively small rough central area of band which was successfully treated with a single central ablation. In four patients visual acuity improved. Those with no improvement had extensive pathology of which the band formed only one part.

Four of the five patients with allied disorders which resulted in a rough corneal surface showed an improvement in visual acuity. Those with symptoms of soreness, pain, and photophobia were rendered asymptomatic (Table 3).

Smooth surfaced band deposition was treated with either several overlapping ablation zones (Table 4) or a single 'on-axis' ablation 4 mm in diameter (Table 5). The principal symptoms were reduced visual acuity and glare. Those patients with glare had a marked improvement which was sustained throughout the follow-up period (6 months to 2½ years). In the group treated with overlapping zones one patient showed an increase in visual acuity, one a reduced visual acuity, and the other three no significant difference. Where refraction results could be obtained, a 'plus shift' – that is, towards hypermetropia – was noted (cases 18 and 19, Table 6). In case 19 glare was markedly improved but acuity decreased. This reduction was due to irregular astigmatism because of the faceted surface generated by overlapping ablation zones. In contrast, in the group in which a central 'on-axis' zone was ablated (Table 5) visual acuity was improved in each case and glare reduced. In three of these cases a hyperopic shift was noted. In those patients in whom measurements were possible the mean hyperopic shift was 2.85 dioptres (Table 6).

From this study, which is the first reported series of corneal disease treated with an excimer laser, it is possible to put forward recommendations for selection of patients. First, for patients with rough band keratopathy the excimer laser provides successful treatment. All patients with pain and photophobia became asymptomatic (in general these eyes will have limited visual potential owing to the underlying pathology). Secondly, where the pathology is limited to the

Table 6 Refraction results before and after ablation (where applicable)

No.	Preop. VA	Refraction	Postop. VA	Refraction
18	6/18	+3.00 DS	6/18	+5.50 DS
19	6/9	Plano	6/18	+4.00 DS/-2.50 DCx 85
21	6/36	Plano	6/9	+1.50 DS
22	6/24	+1.00 DS	6/12	+4.50 DS
23	6/36	+0.50 DS	6/18	+5.00 DS/-1.75 DCx 35

anterior stroma pain relief is likely to be accompanied by an improvement in visual acuity. Thirdly, in eyes with good visual potential it is best not to clear all of the band keratopathy by using overlapping ablation zones, since, although glare will be markedly reduced, irregular astigmatism may result, which could lead to reduced visual acuity. Thus a single, axial zone of ablation should be employed. We have also shown that a hyperopic shift occurs when the central cornea is ablated, and patients should be warned about the possibility of anisometropia.

The hyperopic shift (equivalent to a myopic correction) was an unexpected finding as the smoothing procedure is not analogous to photorefractive keratectomy. This flattening of the cornea implies that some form of differential ablation must have occurred.^{9 15 17 18 30} There are several potential mechanisms that could account for this. First, if the band progressively thinned towards the visual axis, constant irradiance from the laser would effect greater ablation centrally and induce a hyperopic shift. This effect would be enhanced if the ablation rate of the band was less than stroma. In essence, if bands do have such a topography, they act rather like the lens masks currently under investigation for correcting refractive errors. Secondly, although excimer laser radiation will remove an even layer of tissue regardless of the curvature of the surface, the subsurface structure of the cornea is laminated. Removal of central portions of corneal lamellae could lead to centrifugal differential contraction and central flattening. Thirdly, the centrifugal spray of particles of debris and ablation products might be expected to shield the stroma and would theoretically provide progressively greater shielding towards the edge of the ablated zone. Fourthly, the increased obliquity of incident radiation falling on more peripheral cornea might result in a relative decrease in energy density as the edge of the ablation zone is approached. It is unlikely, however, that the degree of differential ablation encountered could arise from inhomogeneities in the excimer beam.

In conclusion, given the encouraging results, the ease with which the procedure can be performed, the patient acceptance of the procedure, and the fact that we have treated all cases on an outpatient basis, we consider excimer ablation the treatment of choice for these cases.

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