A Prospective Bilateral Comparison of Epi-LASIK and LASEK for Myopia

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ABSTRACT

PURPOSE: To compare the clinical and confocal microscopic results of mechanical (epi-LASIK) versus alcohol-assisted laser epithelial keratomileusis (LASEK) for the correction of myopia.

METHODS: Twenty-five patients with myopia received epi-LASIK in one eye and LASEK in the other. The difference of spherical equivalent refraction of myopia and astigmatism was less than 1.00 diopter (D) in two eyes of each case. Mechanical separation of the epithelium was performed with the Lasitome epithelial separator and alcohol-assisted separation with 25 second application of 18% alcohol. Ablation was performed with the ESIRIS laser. Patients were seen daily until epithelial closure, and at 1, 3, 6, and 12 months. Time to epithelial healing, uncorrected visual acuity (UCVA), manifest refraction, haze, and grey scale value in confocal microscopy were recorded.

RESULTS: Preoperative myopic spherical equivalent refraction was −3.95±1.49 D in the epi-LASIK and −3.91±1.39 D in the LASEK-treated eyes. The mean time to epithelial healing was slightly longer after epi-LASIK (4.86±0.64 vs 4.18±0.58 days). Of both epi-LASIK and LASEK-treated eyes, 92% achieved 20/20 or better UCVA and were within ±0.50 D of emmetropia at 12 months. The grade of haze and mean grey scale value in confocal microscopy were similar in epi-LASIK and LASEK-treated eyes at all postoperative periods. One eye treated with epi-LASIK suffered a minor stromal cut.

CONCLUSIONS: Epi-LASIK and LASEK offer effective correction of myopia with comparable results at 1 year.

Laser in situ keratomileusis (LASIK) has been the most popular procedure for treatment of refractive errors since its introduction and carries its popularity despite advances in surface ablation techniques. However, flap-related complications, corneal ectasia, and the need to retain sufficient thickness in the stromal bed have led to further research and advances in surface ablation techniques.

Laser epithelial keratomileusis (LASEK) and epipolis LASIK (epi-LASIK) are the most recent surface ablation techniques, and are referred to as “advanced surface ablations” as they probably have beneficial effects on corneal wound healing.1

Introduced in 1999 by Massimo Camellin, LASEK involves creation of an epithelial flap with 18% to 20% alcohol and repositioning of the flap over the corneal stroma after laser ablation.2,3 Preserving the epithelial sheet and replacing it over the ablated stroma has been accepted to decrease changes in stromal keratocytes and corneal wound healing.4,6 A reduced wound healing process is associated with less keratocyte apoptosis, diminished production of extracellular matrix and collagen, and reduced corneal haze.6,7 In addition, the epithelial flap serves to decrease postoperative pain, although does not eliminate it completely.8,9

Various studies have demonstrated that the epithelial cells in the LASEK flap undergo apoptosis and lose their vitality.4,10-12 The epi-LASIK technique was developed after LASEK, and it involves creation of an epithelial flap with the use of a microkeratome-like epithelial separator.1,13,14 The main motive in its development has been to avoid the toxic effects of alcohol on the epithelial flap. Epi-LASIK has been
proposed to provide a more viable epithelial sheet, better preservation of the flap morphology, and a cleavage plane underneath the basement membrane rather than within the basement membrane.\textsuperscript{1,13,14}

Hence, epi-LASIK has been introduced as a potentially superior alternative to other surface ablation techniques. The aim of the present study is to evaluate and compare the clinical and confocal microscopic findings after epi-LASIK and LASEK for correction of myopia.

\textbf{PATIENTS AND METHODS}

Twenty-five consecutive patients (5 men and 20 women) with less than 1.00 diopter (D) difference in myopic spherical equivalent refraction and astigmatism between their eyes were included in this prospective study. Mean patient age was 26.8±8.4 years (range: 19 to 47 years). The refractive error was treated with epi-LASIK in one eye and LASEK in the other eye of each patient. The odd numbered patients received epi-LASIK in the right eye and LASEK in the left eye, and vice versa in the even numbered patients.

Written informed consent was obtained from all patients. The tenets of the Declaration of Helsinki were followed throughout the study.

Inclusion criteria were at least 18 years of age, stable refraction of at least 1 year, and normal corneal topography. Daily-wear soft contact lenses were removed at least 2 weeks before the preoperative examination. Preoperative evaluation included medical history and complete ophthalmologic examination (uncorrected visual acuity [UCVA], best spectacle-corrected visual acuity [BSCVA], manifest and cycloplegic refractions, anterior segment examination, applanation tonometry, pachymetry, esthesiometry, and Schirmer testing). Patients with unstable refraction, dry eye, blepharitis, corneal disease, glaucoma, collagen vascular disease, diabetes, and topographical evidence of keratoconus were excluded.

All operations were carried out by the same surgeon (K.B.) and assistant (A.H.). All patients were treated bilaterally, with both eyes treated at the same surgical session. All procedures were performed under sterile conditions in an operating room environment. Topical proparacaine 0.5% was used to anesthetize the eyes. A drape and a lid speculum were inserted following the treatment of eyelids with 10% povidone-iodine.

In epi-LASIK–treated eyes, the epithelium was separated with the Lasitome epithelial separator (Gebauer, Neuhausen, Germany). The separator’s oscillation frequency (9000 rpm) and head-advance speed (1 mm/second) were set according to the manufacturer’s recommendations. A nasal hinged epithelial flap (9 mm, hinge 0.5 mm) was created in all eyes, and the detached epithelium was gathered nasally with an irrigating cannula.

In LASEK-treated eyes, the epithelium was incised with an 8-mm trephine placed centrally, and 18% alcohol was applied for 25 seconds. The epithelium was detached and gathered at 12 o’clock.

Laser ablation was performed with the ESIRIS excimer laser (SCHWIND, Kleinostheim, Germany). Spherical and cylindrical ablation were performed according to manifest refraction without any reduction using the SCHWIND ORK-CAM aspheric profile. The ablation diameter was 6.5 mm with a 0.75-mm transition zone in all eyes. Following the ablation, the cornea was irrigated with chilled balanced salt solution. After the epithelium was rolled to its original position, a drop of tobramycin 0.3% and dexamethasone 0.1% were instilled. The epithelial flap was allowed to dry for 2 minutes, and a cooled soft contact lens (Focus Night & Day; Ciba Vision, Duluth, Ga) was placed over the cornea with sterile forceps. The eyelid speculum and drape were removed.

Patients were examined daily until epithelial closure and at 1, 3, 6, and 12 months. Postoperative medication until epithelial closure consisted of topical tobramycin and dexamethasone five times daily. Diclofenac 50 mg was prescribed to all patients, and they were advised to take it orally once or twice per day if required.

The contact lenses were removed after epithelial closure. Topical tobramycin was discontinued following epithelial closure. Dexamethasone was administered four times daily for 1 month followed by fluorometholone 0.1% four times daily for another 1 to 2 months depending on refraction and haze level. All medications were discontinued after 3 months.

Postoperative haze was graded as follows: +0.5, barely visible corneal opacity; +1, reticular subepithelial opacities not affecting visual acuity; +2, punctuate or coalesced subepithelial opacities affecting visual acuity; +3, confluent subepithelial opacities affecting visual acuity and partially obscuring iris detail; and +4, dense opacities completely obscuring iris detail.

Grey scale value of the anterior stroma immediately beneath the epithelium was evaluated with the Confoscan 3 confocal microscope (NIDEK Technologies, Padova, Italy) at 1, 3, and 6 months.

Statistical analysis was performed using SPSS 10.0 software (SPSS, Chicago, Ill). The comparisons were done with the chi-square test for categorical variables, and t test for continuous variables. Statistical significance was considered at $P < .05$.

\textbf{RESULTS}

The mean preoperative myopic spherical equivalent refraction was $-3.95\pm1.49$ D (range: $-2.00$ to $-7.50$ D)

\begin{table}
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\begin{tabular}{|c|c|c|}
\hline
\textbf{Table 1} & \textbf{Values} & \textbf{Units} \\
\hline
Mean & -3.95 & D \\
Standard deviation & 1.49 & D \\
Range & -2.00 to -7.50 & D \\
\hline
\end{tabular}
\end{table}
in epi-LASIK–treated eyes and $-3.91 \pm 1.39$ D (range: $-2.00$ to $-7.12$ D) in LASEK-treated eyes. Mean astigmatism was $1.15 \pm 0.73$ D (range: $0.50$ to $3.25$ D) in 22 epi-LASIK–treated eyes, and $1.26 \pm 0.76$ D (range: $0.50$ to $3.75$ D) in 22 LASEK-treated eyes.

At the end of surgery, slight elongation of the epithelial flap was noted in LASEK-treated eyes. In epi-LASIK–treated eyes, this elongation was evident immediately after the flap creation with the separator, before any manual manipulation of the flap (Fig 1). On the first postoperative day, epi-LASIK–treated eyes seemed to have less epithelial edema than LASEK-treated eyes at slit lamp examination. Mean time to epithelial healing was $4.86 \pm 0.64$ days after epi-LASIK and $4.18 \pm 0.58$ days after LASEK.

No epithelial flap was lost. A small stromal cut occurred in one epi-LASIK–treated eye (Fig 2). This eye received laser ablation in the same surgical session, and achieved 20/20 UCVA, but had mild symptoms related to visual quality. Detailed questioning of the patient’s medical history revealed that the patient had suffered an epithelial trauma in this eye a few years earlier. No other postoperative complication occurred in either group.

Most patients reported mild to moderate discomfort during the first few days. Eyes with the least epithelial edema, particularly epi-LASIK–treated eyes, seemed to have more discomfort on the first postoperative day. Otherwise, epi-LASIK and LASEK-treated eyes did not differ in terms of discomfort.

Uncorrected visual acuity ranged between 20/50 and 20/25 during the first few days after epi-LASIK and LASEK. Uncorrected visual acuity showed great variation until epithelial closure, even in the same eyes on different days. Epithelial edema, extent of epithelial healing, and presence of epithelial debris under the contact lens seemed to affect UCVA during this period. Nevertheless, virtually all eyes had achieved 20/40 or better UCVA at the time of epithelial closure and contact lens removal.

At 1 month, 60% of epi-LASIK and 72% of LASEK-treated eyes achieved 20/20 or better UCVA (Table 1). At 6 months, 100% of eyes achieved 20/25 in both groups. Over 90% of eyes were within $\pm 0.50$ D of emmetropia at 6 months and maintained it at 12 months (Table 2).

No significant difference was noted in terms of haze and grey scale value (confocal microscopy) (Tables 3 and 4). No eye in either group showed more than $+1$ haze.

**DISCUSSION**

Epi-LASIK is the most recent development in surface ablation and it involves the use of a mechanical separator to create an epithelial flap. The cornea is not exposed to alcohol, and hence alcohol-related toxicity to the epithelium and underlying stroma is avoided. In addition, mechanical separation of the epithelium has been proposed to provide a more proper plane of cleavage. Pallikaris et al demonstrated that the level of separation was beneath the level of basement membrane with preserved hemidesmosomes in epi-LASIK. In the same study, the level of separation after LASEK was within the basement membrane between lamina lucida and lamina densa, which implies some damage to the basement membrane. In addition, damage to the basal epithelial cells has been observed by both light microscopic and electron microscopic evaluation in LASEK, while the basal cells were only minimally damaged after epi-LASIK. These findings suggest less damage to the basement membrane.
and basal epithelial cells after epi-LASIK than after LASEK.

In our study, the routine slight elongation of the LASEK flap was noted in the epi-LASIK–treated eyes even before any manual manipulation of the epithelial flap (see Fig 1). This may imply that despite avoiding alcohol-related toxicity to the epithelium, epi-LASIK involves some mechanical trauma to the epithelium similar to LASEK.

However, less edema was noted in epi-LASIK flaps than in LASEK flaps on the first and second postoperative days at slit lamp examination. On day 1, some epi-LASIK–treated eyes appeared almost untouched without any edema. Various groups have also noted that the epi-LASIK flap is highly transparent on the first postoperative day.1,15 This finding implies that the epithelial flap was more viable hence less edematous on the first few days after epi-LASIK. Supporting this, Katsanevaki et al16 reported that epi-LASIK flap morphology was close to normal 24 hours after surgery.

In this study, complete epithelialization lagged 0.68 days in epi-LASIK–treated eyes compared to LASEK–treated eyes, which may imply that the epithelium maintained its vitality 0.68 days longer in epi-LASIK–treated eyes before it was replaced by new epithelial cells. However, it should be noted that the epi-LASIK flap (9 mm) is larger than the LASEK flap (8 mm). The lag in epithelial healing after epi-LASIK may also be due to the larger size of the epithelial defect. Even so, the pattern of epithelial healing after epi-LASIK is similar to that after LASEK. The epithelium becomes edematous, is slowly shed, and replaced by new cells. Although it is more viable on the first few days after surgery, it is apparent that it does not survive and it does not reattach.

Most of the patients reported mild to moderate dis-
Bilateral Comparison of Epi-LASIK and LASEK/Hondur et al

comfort in both eyes during the first few days. Eyes with the least epithelial edema, particularly epi-LASIK–treated eyes, seemed to have more discomfort on the first postoperative day. Otherwise, the two techniques caused similar levels of discomfort. All patients were given oral non-steroids for pain relief. We routinely irrigate the corneas with chilled balanced salt solution at the end of ablation and cool the contact lens before placement. However, whether the practice of corneal cooling has any effect on pain relief has been controversial. On the other hand, we have observed that high Dk silicone hydrogel contact lenses provide more comfort than former low Dk hydrogel lenses (unpublished data, November 2005 to January 2006).

The results of epi-LASIK and LASEK were also similar in terms of UCVA and emmetropia (Tables 1 and 2). Uncorrected visual acuity was similar until epithelial healing and ranged between 20/50 and 20/25. At the time of contact lens removal upon complete epithelial closure, almost all eyes had achieved 20/40 or better UCVA. However, until epithelial closure neither technique could provide a consistent functional vision comparable to that after LASIK.

Afterwards, LASEK seemed to offer slightly faster improvement of UCVA. At 1 month, 72% of LASEK-treated eyes (18 eyes) achieved 20/20, whereas 60% of epi-LASIK–treated eyes (15 eyes) achieved 20/20. This difference was not statistically significant (P>.05). Similarly, in a study of 57 patients, O’Doherty et al³ reported comparable visual and refractive results after epi-LASIK and other surface ablation techniques.

Conversely, in a study of 20 eyes (20 patients) by Long et al,¹⁸ tear fluid TGF-β1 levels were found to be higher after LASEK than after epi-LASIK at 1, 3, and 5 days postoperatively. TGF-β1 level (postoperative day 1) correlated positively with the degree of haze at 1 month, which was higher after LASEK compared to epi-LASIK.

In our study, no significant difference was noted in the incidence and degree of haze between epi-LASIK and LASEK-treated eyes (Table 3). The confocal microscopic findings (grey scale value) were also similar (Table 4), which implies that the wound-healing response is similar after epi-LASIK and LASEK.

In this series of 25 cases, the only complication was a small stromal cut in an epi-LASIK–treated eye (see Fig 2). This eye achieved 20/20 UCVA, but had mild symptoms related to visual quality as the cut was in the visual axis. The stromal cut was probably due to subclinical scarring or a minor Bowman’s layer irregularity after a previous epithelial trauma. Alió et al¹⁹ reported stromal intrusion during epi-LASIK in eyes with keratoconus, previous radial keratotomy, and surface ablation. They also observed a stromal cut in an eye with a subtle and small leukoma. Detailed questioning of any previous ocular trauma and particular

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**TABLE 2**

Residual Refractive Error (Spherical Equivalent) at 3, 6, and 12 Months in Patients Who Underwent Epi-LASIK in One Eye and LASEK in the Fellow Eye

<table>
<thead>
<tr>
<th>Residual Refractive Error (Percentage of Eyes)</th>
<th>Epi-LASIK</th>
<th>LASEK</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up</td>
<td>± 0.50 D</td>
<td>± 1.00 D</td>
</tr>
<tr>
<td>3 months</td>
<td>88</td>
<td>92</td>
</tr>
<tr>
<td>6 months</td>
<td>92</td>
<td>96</td>
</tr>
<tr>
<td>12 months</td>
<td>92</td>
<td>96</td>
</tr>
</tbody>
</table>

**TABLE 3**

Incidence of Haze at 1, 3, and 6 Months in Patients Who Underwent Epi-LASIK in One Eye and LASEK in the Fellow Eye

<table>
<thead>
<tr>
<th>Incidence of Haze (Percentage of Eyes)</th>
<th>Epi-LASIK</th>
<th>LASEK</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up</td>
<td>± 0.5 D</td>
<td>± 1.00 D</td>
</tr>
<tr>
<td>1 month</td>
<td>60</td>
<td>28</td>
</tr>
<tr>
<td>3 months</td>
<td>60</td>
<td>16</td>
</tr>
<tr>
<td>6 months</td>
<td>20</td>
<td>0</td>
</tr>
</tbody>
</table>

**TABLE 4**

Grey Scale Value in Confocal Microscopic Examination at 1, 3, and 6 Months in Patients Who Underwent Epi-LASIK in One Eye and LASEK in the Fellow Eye

<table>
<thead>
<tr>
<th>Grey Scale Value</th>
<th>Epi-LASIK</th>
<th>LASEK</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up</td>
<td>± 0.50 D</td>
<td>± 1.00 D</td>
</tr>
<tr>
<td>1 month</td>
<td>130±29</td>
<td>127±29</td>
</tr>
<tr>
<td>3 months</td>
<td>112±25</td>
<td>104±24</td>
</tr>
<tr>
<td>6 months</td>
<td>93±24</td>
<td>89±24</td>
</tr>
</tbody>
</table>

*The eye with the stromal cut was disregarded.
†t test.

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*Haze in the eye with the stromal cut was disregarded.
† Chi-square test.
attention for any related signs during the preoperative anterior segment examination seem to be of vital importance in avoiding such complications.

No other postoperative complication occurred in either group. No intra- or postoperative epithelial flap loss occurred. In our LASEK practice, 25-second application of 18% alcohol has been adequate in most patients. During the present study, we did not have to reapply any alcohol beyond 25 seconds. However, we have had patients in whom flap creation was difficult with 25-second application of 18% alcohol, and we had to apply alcohol for an additional 10 to 15 seconds (unpublished data, June to September 2004). Eyes with prolonged use of contact lenses, extensive ultraviolet exposure, male gender, and young age have been associated with difficult LASEK flap creation. The automated nature of the epi-LASIK technique may be particularly useful for these eyes, for which prolonged alcohol exposure is anticipated.

In this study, no significant difference was found in clinical and confocal microscopic results of epi-LASIK and LASEK for myopia. The major motive in development of the epi-LASIK technique has been to avoid the toxic effects of alcohol on the epithelial flap and anterior stroma. Epi-LASIK has been proposed to provide better preservation of the flap morphology and a cleavage plane underneath the basement membrane rather than within the basement membrane. All of these beneficial effects are expected to enhance the viability of the epithelium. However, clinical studies have shown that the epi-LASIK flap loses its vitality, is shed off, and replaced by new cells similar to LASEK. Only, the time course of epithelial healing seems to be slightly different. No clinical or experimental modification providing the reattachment of a viable epi-LASIK flap has been developed thus far. Therefore, the theoretical advantage of enhancing epithelial flap viability for 1 to 2 days does not seem to provide any clinical benefit. In addition, the use of a microkeratome-like separator and its disposables increases the cost of surgery.

On the other hand, the exact mechanism of alcohol in LASEK flap creation has yet to be defined. Alcohol application provides separation in a plane within the basement membrane between lamina lucida and lamina densa. This plane is immediately anterior to the corneal stroma. Therefore, alcohol can be expected to have a toxic effect on the most anterior keratocytes and corneal stroma as well. However, we did not note any major difference in the anterior stroma of epi-LASIK and LASEK-treated eyes in our confocal microscopic examinations. Excimer laser correction of myopia results in ablation of the anterior stroma, which can also result in ablation and removal of possibly damaged tissue in this area.

The results of our study imply that LASEK and epi-LASIK are both effective and safe in the correction of myopia in virgin eyes. Neither technique seems to offer a major advantage to the other in clinical and confocal microscopic results.

REFERENCES

17. O’Doherty M, Kirwan C, O’Keeffe M, O’Doherty J. Postopera-


