Epipolis laser in-situ keratomileusis: an evolving surface ablation procedure for refractive corrections

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Purpose of review
The aim of this article is to provide an update on epipolis laser in-situ keratomileusis – an alternative surface photorefractive surgical technique for the correction of myopia.
Recent findings
In-vivo studies on animal models provide evidence that the replacement of the epithelial sheet on an ablated cornea can control corneal wound healing. Preliminary clinical data confirm that epipolis laser in-situ keratomileusis can provide excellent long-term visual and refractive results. The problems of late visual rehabilitation and postoperative pain, however, have not yet been fully addressed.
Summary
Being a recently introduced surgical photorefractive technique for ametropias correction, epipolis laser in-situ keratomileusis is a fast evolving area of interest for refractive surgeons.

Keywords
Epi-laser in-situ keratomileusis, laser epithelial keratomileusis, surface ablations

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Abbreviations

LASEK	laser epithelial keratomileusis
LASIK	laser in-situ keratomileusis
PRK	photorefractive keratectomy

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Introduction

Despite the fact that laser in-situ keratomileusis (LASIK) remains the undisputed leading photorefractive procedure worldwide recent surveys suggest that surface procedures are gaining ground amongst refractive surgeons [1].

Due to its limitations, mostly concerning postoperative pain and the well recognized risk of haze, conventional photorefractive keratectomy (PRK) is gradually being replaced by modified surface treatments that comprise the replacement of corneal epithelium onto the ablated stroma. Although not yet documented in the clinical setting, the replaced epithelium is expected to act as corneal wound healing modulator after the procedure.

Epipolis-LASIK is a recently described [2] photorefractive procedure that comprises the replacement of the mechanically separated epithelial sheet onto the ablated corneal stroma. The main difference to laser subepithelial keratomileusis (LASEK) is the means of epithelial sheet separation that is achieved mechanically without requiring prior corneal preparation with alcohol.

The rationale of preserving the epithelial sheet for surface treatments

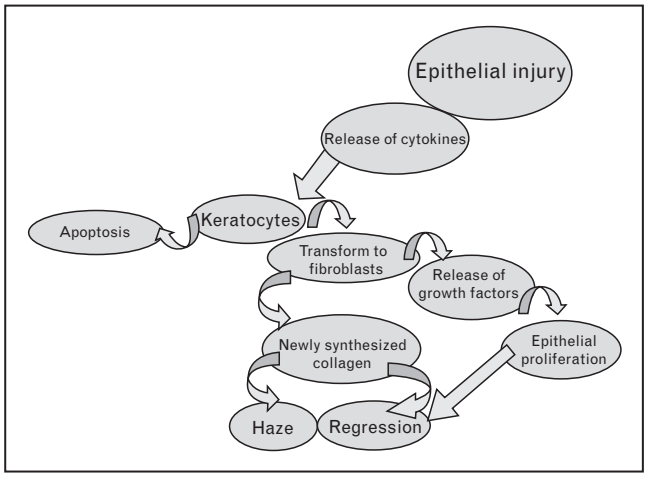
The wound healing responses following PRK occur at the stromal epithelial interface as a result of interactions between the regenerating epithelium and stromal keratocytes in response to injury [3,4].

The first stage of wound healing of the cornea after any surface treatment is epithelial migration, followed by epithelial hyperplasia and subsequent stromal regeneration. Cytokines secreted by the regenerating epithelium activate the process of keratocyte apoptosis and their transformation to myofibroblasts initiates the healing cascade that results in corneal haze and regression of the refractive effect, which have been related to surface photorefractive corrections (Fig. 1).

In-vivo studies in different animal models have confirmed that the replacement of an epithelial sheet onto the ablated cornea can modulate the corneal wound healing.

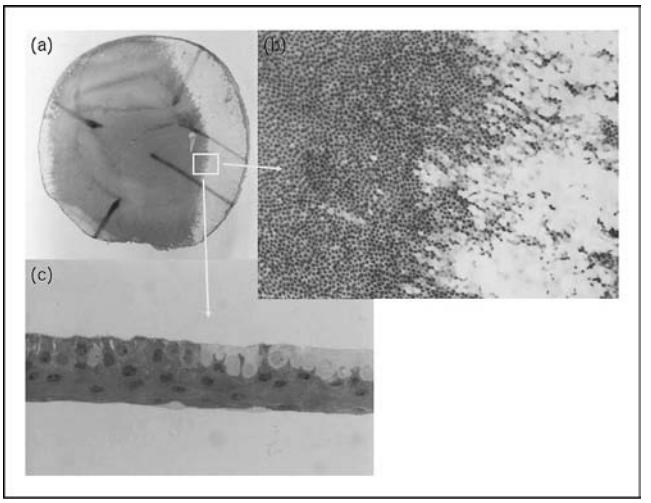
Lee *et al.* [5] reported reduced superficial keratocyte apoptosis in the central stroma of the leghorn chick

Figure 1 Inflammatory cascade that results in haze and regression after conventional PRK



The repositioning of the epithelial flap is expected to block the pathway at the level of cytokine interaction with the stroma keratocytes.

Figure 2 Trypan blue is a vital stain that is retained from traumatized cells



Optical photograph of a human epithelial sheet (basal surface) stained with trypan blue (a). Traumatized basal cells that retain the stain in this specimen are mostly located at the central part and lower part of the sheet. Unstained areas correspond to the upper part of the sheet (b) Detail of the interface between stained and unstained areas. Optical microscopy (c) of the borders between traumatized (whitish) and non-traumatized (bluish) areas of the sheet reveals cell trauma only to the layer of basal cells.

cornea 4 h after LASEK as compared with conventional PRK. Similarly, Esquenazi *et al.* [6•] using the rabbit model showed a significant increase in keratocyte apoptosis 7 days after PRK as compared with LASEK for attempted myopic corrections of −7 diopters.

Song and Joo [7] using the Sprague–Dawley rat eye model also reported that ethanol-mediated epithelial flap repositioning induced less keratocyte loss and resulted in a slower wound healing process than after conventional mechanical scraping of the epithelium.

Although results of studies on animal models cannot be directly extrapolated to humans those reports provide supporting evidence that the replaced epithelium can modulate the wound healing cascade probably in a similar way as was shown for the application of human amniotic membrane [8], that is, providing a mechanical barrier between the tear film and the corneal stroma.

Epipolis-LASIK evolved from LASEK with the aim of separating the epithelial flap without the use of alcohol. Using an in-house designed epikeratome we have shown that the use of the epikeratome could successfully achieve epithelial separation as a sheet that could subsequently be replaced onto the corneal stroma. Comparing specimens obtained either with the use of the epikeratome or the classic Camellin's LASEK technique using alcohol, we have shown that the mechanically assisted separation cleavage plane was deeper than that of alcohol. Confirming the findings of other investigators [9–11] we have shown that alcohol assisted separations are taking place within the basement membrane whereas the use of the epikeratome can successfully separate the corneal epithelium as a sheet, preserving its basal membrane [12].

Trypan blue staining of mechanically separated human epithelial sheets (Fig. 2) showed that, similar to ethanol aided separations, mechanical separation also results in significant trauma of the sheet's basal cells (own unpublished data). As shown by transmission electron microscopy this trauma may due to the local shearing forces exerted during the separation to the basal part of the sheet by the detached hemidesmosome anchoring fibrils (Fig. 3). Transmission electron microscopy has also shown that, despite the trauma, mechanically separated epithelial cells remain morphologically close to normal at least for the first 24 h after the replacement of the sheet [13]. As evident from biomicroscopy of the operated eyes [14] the replaced cells are eventually replaced by new epithelium, that is, the migratory phase of epithelial healing is not cancelled with this modality. Even so, the epithelial sheet's replacement has the potential of reducing the risk of haze in human corneas by disturbing the time relations between epithelial migration and keratocyte activation after the ablation [15].

Surgical procedure

The operative eye is anaesthetized with topical tetracaine hydrochloride 0.5% eye drops, a sterile drape is applied and a lid speculum is inserted.

After 30 s of irrigation with iced, balanced salt solution the corneal epithelium is dried and marked with a purpose designed epipolis-LASIK marker (Duckworth and Kent,

Figure 3 Transmit ion electron photograph of the interface between traumatized and nontraumatized areas of a mechanically separated epithelial sheet

The cleavage plane remains beneath the basement membrane throughout the whole specimen part of the membrane is detached, however, causing local trauma of the basal cells due to the locally exerted shearing forces during the separation.

Baldock, UK). The epikeratome is applied onto the operative eye and the suction is activated through a foot pedal.

The advance of the oscillating blade separates the epithelium leaving a 2–3 mm nasal hinge, the suction is released and the device is removed from the eye. The epithelial sheet is reflected nasally with the use of a moistened merocell sponge to reveal the corneal stroma to be ablated.

After the application of the excimer laser ablation the cornea is irrigated with balanced salt solution and the epithelial sheet is repositioned on the ablated corneal stroma. Preoperative marks serve so that the epithelium is replaced without significant stressing. The sheet is left to dry for 2–3 min and a therapeutic contact lens is applied on the operative eye.

Although the handling of the epithelial sheet is quite different from that of the stromal LASIK flap, the use of the epikeratome has a short learning curve for experienced refractive surgeons and provides an automated and fast modality for the separation of the epithelial sheet.

Postoperative treatment includes anti-inflammatory eye drops (diclofenac sodium 0.1%; CIBA Vision Ophthalmics, Duluth, Georgia, USA) for 2 days and combined eye drops of tobramycin dexamethasone (Tobradex, Alcon, Fortworth, Texas, USA) until the removal of the lens on the day of reepithelization. After the removal of the lens fluorometholone (FML, Allergan, Irvine, California, USA) eye drops are prescribed four times daily in a tapered dose for 5 weeks.

Epipolis-laser in-situ keratomileusis: Crete clinical experience

All eyes in our setting were operated with the Centurion SES epikeratome (Norwood Abbey EyeCare, Australia) and the Wave Allegretto (Wavelight, Enlagen, Germany) laser platform.

The mean time of epithelial healing in more than 500 eyes that have been operated on in Crete up to date is around 5 days, ranging from 3 to 7 days. The epithelial healing is complete by day 5 in the vast majority of the operated eyes .The lenses are removed on the third day after the treatment in less than 10% of the operated eyes.

The overall mean pain scores at the operation day remain below the level of burning feeling. A small percentage of about 10–15% of the operated patients, however, still report burning feeling or worse during the first two postoperative hours. The records show that this percentage decreases with time from surgery and less than 3% of the patients need oral analgesics or are prescribed eye drops of diluted topical anaesthetic (20% tetracaine in natural tears) to control pain. By the third day after the treatment a small minority of patients may complain of mild discomfort as a new symptom. In those cases the symptoms are mild and do not require any further medication than is standard.

As reported in our preliminary report of 3 months results after epipolis-LASIK on 44 eyes the visual rehabilitation after the procedure is quite slow with only 48% of the eyes having unaided vision of 20/40 or better on day 1 after the procedure [14]. A larger series of 234 eyes confirmed this result reporting 53% of eyes having 20/40 or better on day 1 increased to 78% on the day of re-epithelization. Follow-up in the same series showed that vision improved even at 6 months after the procedure with refractive stabilization by the third month interval. At 1 year postoperatively, more than 50% of the eyes gained lines of best-corrected visual acuity. The contrast sensitivity testing in four different spatial frequencies was found equal to or better than baseline at 1 year after the procedure (Katsanevaki *et al.*, 1-year clinical results after epipolis-LASIK for myopia, data under review).

Complications

The epithelial separation was complicated in almost 3% of the eyes treated with the first generation separators. In those eyes the cleavage plane of the separation was uneven, including a strip of corneal stroma within the epithelial sheet.

In eyes with inadvertent stromal penetration outside the treatment zone the operation was completed at the same

session reversing to PRK with additional application of 0.02% mitomycin C for 12 s after the completion of the ablation.

In cases for which the crease implicated the treatment zone, the separated tissue was carefully replaced onto the corneal surface and the operation was postponed for a later date. The eyes were followed daily and received standard topical medication until the completion of surface healing. After the refractive stabilization of the eyes as shown by manifest refraction and consecutive corneal topographies in 1-month intervals after the incident, the eyes were treated with LASIK.

All the complicated eyes were followed for at least 1 year. At the last follow-up visit, all eyes are within 0.5 D of attempted correction without any line loss of best-corrected visual acuity (data to be submitted).

Evolution of epi-laser in-situ keratomileusis

The Centurion SES epikeratome operates under suction with forward oscillation of a blunt polymethyl methacrylate separator. The occurrence of inadvertent stromal incursion during epithelial separation with the first generation separators has led to optimization of the epikeratome's settings. The manufacturer redesigned the angle of the separator to be blunter and adjusted the recommendations for other parameters raising the oscillation rate from 10 800 to 12 000 rpm, lowering the speed of head advancement from 4 to 2 mm/min and raising the vacuum pressure from 630 to 640 mmHg. These changes eliminated the incidence of stromal incursions but resulted in high incidence of free sheets that were reported from different users of a specific epikeratome to a percentage of about 30% of the cases. Although free capping is not considered a significant complication in terms of safety and in the vast majority of free caps epithelial replacement is possible, third generation separators are currently under investigation aiming to achieve ideal epithelial separations in all eyes.

Apart from Norwood, other major microkeratome manufacturers have recently presented modified versions of microkeratome units that utilize proprietary blades for epithelial separations to be used as epikeratomes. The separation results that have been reported up to date are excellent but due to their relatively recent launch there are currently no peer-reviewed studies in the literature.

Conclusion

Due to the technique's relatively recent debut as well as the considerable cost to obtain appropriate instrumentation peer-reviewed clinical results currently available are limited to the experience from the University of Crete [14] birthplace of epipolis-LASIK [2,12].

The increasing number of papers presented in international refractive meetings, however, as well as the recent epipolis–keratome launch by almost all major microkeratome manufacturing companies reflect the interest of the refractive community on the possible clinical benefits that epipolis-LASIK may offer.

As shown by the initial experience of the technique there are still remaining problems that have not yet been addressed. Epipolis-LASIK is not a pain free procedure: a certain percentage of treated patients complain of pain, especially within the first couple of hours after the procedure.

Furthermore, the visual rehabilitation is slow. Clinical data show that much like after any other surface ablation procedure unaided vision on the day of reepithelization, that is almost a week after the procedure, does not reach 20/20 in all eyes [14].

Long-term results, however, show evidence of excellent visual and refractive outcomes. In combination with the use of the latest generation laser platforms, epipolis-LASIK in the long term provides elimination of corneal haze, a significant percentage of eyes that gain lines of best corrected vision and unaffected contrast sensitivity. Furthermore, as any other surface ablation approach, it minimizes the risk of corneal destabilization and iatrogenic ectasia.

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 419)

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