FROM THE EDITOR

Intrastromal lenticule extraction for refractive correction: Can it raise the tide for refractive surgery?

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"A rising tide lifts all boats."

—Unknown

While the practice of medicine has always been associated with continuous improvement and innovation, these forces are deeply ingrained in the field of keratorefractive surgery. Corneal refractive surgery was not born from an attempt to incrementally improve the treatment of refractive error. It arose from the audacious goal of developing a categorically different and permanent approach to correcting refractive errors. The most successful attempts have been informed by the careful consideration and keen observation of the cornea's structural and biological responses to intervention, and today corneal refractive surgery represents one of the most commonly performed and successful categories of surgery ever introduced.[1,2]

Because of the success of laser in situ keratomileusis (LASIK) and photorefractive keratectomy (PRK), the bar has been set high for new approaches to refractive surgery. Introduction of the femtosecond laser to the United States market in 2001 added additional precision and safety to the process of creating a LASIK flap.[3] Wavefront-guided,[4] wavefront-optimized, and most recently, topography-guided ablation,[5] along with accompanying enhancements in ocular registration, have all demonstrated value for improving optical outcomes and expanding capabilities for treatment customization. However, global interest in LASIK as measured by internet queries paradoxically decreased between 2007 and 2011.[6] While the timing and magnitude of the decline in the refractive surgery market was strongly associated with the global financial crisis of 2008, recovery of interest and surgical volume has lagged behind the financial recovery. There is growing consensus among industry stakeholders that concerns about complications and side effects play an important role in the slower-than-expected recovery of refractive surgery volume. Accordingly, any advance that enhances safety while still supporting excellent visual outcomes has the potential to directly address patient concerns and expand interest in refractive surgery overall.

Small-incision lenticule extraction (SMILE) is the clinical realization of earlier efforts to create an intrastromal procedure that can negate the need for creation of a nearly circumferential flap to remove underlying stromal tissue. The conceptual and scientific roots of intrastromal lenticule extraction date back to early-stage picosecond laser experiments in 1996.[7] Although improvements in the quality of stromal interfaces were observed with a switch to femtosecond lasers in 1998 experiments,[8] the first sighted human studies undergoing intrastromal treatment were not published until 2008,[9] after the VisuMax femtosecond laser was introduced for femtosecond lenticule extraction (FLEx, Carl Zeiss Meditec AG). Since then, small-incision lenticule extraction[10] has been performed in over 1 million eyes and has demonstrated largely comparable refractive results to LASIK in studies of myopia and myopic astigmatism. Treatment of hyperopia is also under active investigation.[11–13]

Bypassing the flap creation step introduces advantages, including reduced disruption of corneal sub-basal nerve density and reduced impact on corneal sensation and ocular surface symptoms.[14] Since the latter is one of the more common causes of dissatisfaction among the < 5% of LASIK patients who were dissatisfied in U.S. Food and Drug Administration early patient-reported outcomes analyses,[15] this is an important advantage, particularly for high-risk patients. Also, post-LASIK ocular surface symptoms may be related not just to incomplete postoperative re-innervation but also alterations in neural function leading to abnormal sensation.[16] Any procedure offering relative preservation of native corneal nerve morphology and function, therefore, can help address patient concerns about one important adverse outcome.

A second potential advantage to avoiding a flap is relative preservation of the anterior stromal architecture and its associated biomechanical strength. Numerous studies support theoretical and measured biomechanical advantages of a small-incision intrastromal approach over flap-based

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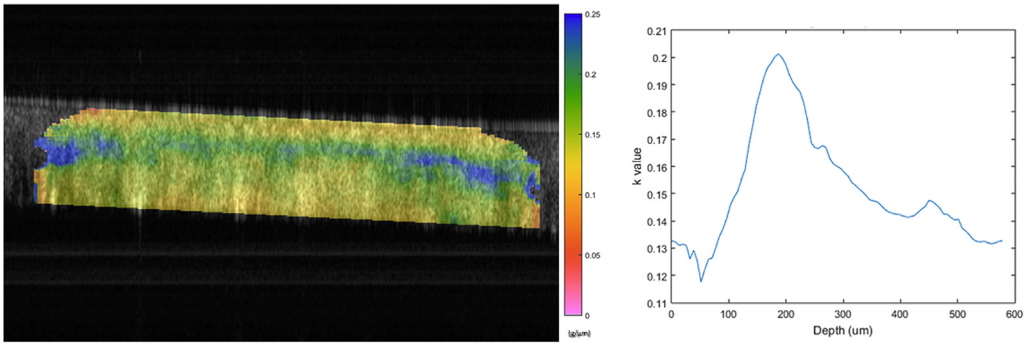

Figure 1. Optical coherence tomography elastography compressive stiffness map (*left*) and plot (*right*) as function of corneal depth in a normal human subject. Cool colors represent stiffer properties. In the plot (*right*), note low stiffness in the epithelial region (50 μm) that transitions to peak stiffness in the anterior stroma before decreasing in the posterior stroma. (Data from Other Cited Material [A])

procedures such as LASIK.[17–20] However, this should not shift clinical thresholds for whether a patient is a candidate for ablative surgery at all. Patients suspected of having an unacceptably high intrinsic risk of ectasia should not be treated any more liberally just because small-incision lenticule extraction is being considered.[21] Why? The rationale for small-incision lenticule extraction's biomechanical advantage over LASIK, which was elegantly articulated by Reinstein et al.,[17] depends in part on the assumption that the cornea in question has greater material strength in the anterior stroma. While this is true across a variety of ex vivo mechanical testing techniques and appears to follow similar trends in emerging in vivo human data from live human Brillouin microscopy[22] and optical coherence tomography elastography[23] (Figure 1), variation in the precise depth-dependent property signature is expected from patient-to-patient, even across normal eyes.[A] Furthermore, it is known that keratoconus is associated with a paucity of transverse collagen fibrils at the level of Bowman layer.[24] If selective loss or primary absence of such anterior fibrils exists in the subclinical keratoconus state and favors local anterior stromal weakness, the relative impact of small-incision lenticule extraction, LASIK, and PRK will be altered. Consistent with this hypothesis, our group is seeing early evidence of a loss or inversion of the biomechanical property gradient between the anterior and posterior stroma in keratoconic eyes.[A] While small-incision lenticule extraction will still be less structurally disruptive than LASIK due to the lower total burden of fiber disruption required, a cornea that is unexpectedly weaker in the anterior stroma than the posterior cornea might retain better stability after PRK than after LASIK or small-incision lenticule extraction because only the weakest tissue is ablated. Unfortunately, our working knowledge of the individual biomechanical makeup of a given refractive surgery candidate's corneas is currently limited, and this handicaps our ability to recommend the most structurally appropriate procedure or, in the case of small-incision lenticule extraction, to customize the cap thickness in a way that will optimize safety for a given eye's particular biomechanical signature. Progress in the development of clinical tools for depth-resolved biomechanical characterization is important for better quantifying ectasia risk and enabling more specific risk calculations.

If these approaches emphasize optimization of safety using all available options rather than pitting small-incision lenticule extraction, LASIK, and PRK as competing options, patients and practitioners alike will benefit.

While several key safety advantages have been discussed, some criticism of intrastromal lenticule extraction have included a slower visual recovery than LASIK and a tendency toward under-correction of astigmatism.[25] In this issue of the journal, Ivarsen et al. (page 1066) assess astigmatic outcomes in an 829-patient retrospective series and develop a linear regression model to predict (and potentially compensate) outcomes as a function of treatment axis and magnitude. Chiche et al. (page 1073) present a prospective nonrandomized case series comparing early visual acuity, refractive error, contrast sensitivity, objective scatter, and patient-reported outcomes in patients undergoing bilateral myopic small-incision lenticule extraction or LASIK. While LASIK boasted significantly better contrast sensitivity during the first week, better patient-reported quality of vision at 1 week, and lower objective scatter at day 1, these differences resolved by 1 month, and global patient-reported satisfaction scores were no different for the two procedures at any time point. Finally, Weng et al. (page 1080) present same-day and short-term visual outcomes comparing manual and liquid dissection techniques for small-incision lenticule extraction in a prospective randomized contralateral eye study and report greater lenticule smoothness, greater contrast sensitivity, and fewer corneal aberrations in the liquid dissection group. With these and other refinements, intrastromal lenticule extraction is uniquely positioned to appeal to refractive surgery candidates who have been standing by the sidelines awaiting a more conservative refractive surgery option.

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