ARE INTRASTROMAL TREATMENTS THE FUTURE OF REFRACTIVE SURGERY?

Minimally invasive approaches have multiple advantages over earlier techniques.

BY DAN Z. REINSTEIN, MD, MA(CANTAB), FRCSC, DABO, FRCOPHTH, FEBO

The trend for all surgical procedures has been to evolve toward a minimally invasive technique, such as the robotically assisted keyhole techniques that have revolutionized many types of surgery in terms of safety, postoperative recovery, and patient perception.

Unsurprisingly, the same trend has been seen in refractive surgery—although the emphasis on safety is even higher here than in other fields, as refractive surgery is performed in patients who can already see. "It's my eyes," is a phrase that we all hear, every day, in the clinic.

AT A GLANCE

- Patients do not need a lengthy explanation about the pros and cons of LASIK versus SMILE, as they tend to be immediately attracted to the flapless nature of the procedure.
- Because SMILE leaves the cornea with greater biomechanical strength than LASIK for the same amount of vision-correcting tissue removal, it opens the possibility of safely treating higher degrees of myopia and thinner corneas.
- Challenges with the SMILE procedure include slightly slower visual recovery compared with LASIK, only one commercially available platform, and higher cost per procedure than femtosecond LASIK.
- Other intrastromal applications include cryopreservation and reimplantation of the refractive lenticule, endokeratophakia to correct hyperopia, tailored stromal expansion for patients with keratoconus, and AK incisions.

This is why early refractive surgery techniques such as keratomileusis[1] and RK[2] did not gain widespread use. Even refractive lens exchange could be included; this approach was rarely used in patients with a clear lens because the risks associated with intraocular surgery were deemed too high for such patients.

Refractive surgery eventually gained acceptance when the excimer laser was introduced to perform PRK, an approach that was seen as a less invasive and more accurate method than RK. LASIK, with the addition of the mechanical microkeratome, represented the next step in minimizing the invasiveness of the procedure by eliminating the epithelial wound of PRK. Replacing the microkeratome blade with a femtosecond laser continued the evolution, and the *bladeless* tagline was quickly taken up as a marketing differentiator to attract patients.

However, refractive surgery did not join the ranks of truly minimally invasive keyhole procedures until the introduction of small incision lenticule extraction (SMILE), which avoids the need for the corneal flap.

CONSIDER THESE PERSPECTIVES

Are intrastromal treatments the future of refractive surgery? Let us look at this question first from the perspective of our patients and then from our own perspective as surgeons.

The patient perspective. From a patient's perspective, the answer to the question is a resounding "yes." Patients do not need a lengthy explanation about the pros and cons of LASIK versus SMILE, as they tend to be immediately attracted to the flapless nature of the procedure. All that is needed is to say that both treatments remove a lens of tissue from inside the cornea, but one does it by lifting a flap and the other through a keyhole incision.

The surgeon perspective. While there is an initial attraction to the no-flap approach, surgeons also want scientific justification for preferring SMILE to LASIK. Since the intro-

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THE ART AND SCIENCE OF TITRATING INCISIONS

Patients with low mixed astigmatism at the time of cataract surgery may benefit most from intrastromal AK.

By Christopher L. Blanton, MD

Residual astigmatism after cataract surgery can serve as a major impediment to achieving a patient's refractive target. But, because not all astigmatism is equal, patients are best served by the availability of a wide range of options for astigmatism correction.

In my view, cylinder starting at 0.50 to 0.75 D must be addressed in order to give patients the best chance of achieving spectacle independence or reaching their refractive target, whatever that may be. There are several options for addressing astigmatism at the time of cataract surgery, ranging from manual corneal incisions to toric IOL implantation. For surgeons who use femtosecond lasers, there is the additional option of intrastromal astigmatic keratotomy (AK).

Venter et al reported that intrastromal AK is a viable option to reduce astigmatism ranging from 0.50 to 2.75 D of cylinder.[1] In their study of 112 eyes with low mixed astigmatism treated with nonpenetrating femtosecond laser intrastromal AK, mean distance UCVA improved from 0.18 preoperatively to 0.02 logMAR postoperatively ($P<.01$), and cylinder decreased from 1.20 D preoperatively to 0.55 D postoperatively ($P<.01$). There was a tendency toward undercorrection, so I have slightly modified the nomogram that the authors introduced.

SELECT THE RIGHT PATIENT

Before one even thinks about surgical parameters, selecting the right patients is a key factor in the success of intrastromal AK. Because AK incisions are neutral as far as myopia or hyperopia, the best results will be attained in patients who have mixed astigmatism with a plano spherical equivalent. To address astigmatism at the time of cataract surgery, it is best to perform intrastromal AK in patients who have plano spherical equivalent and at least 0.50 to 0.75 D and above of astigmatism. Although I do not have a hard cap on the maximum amount of astigmatism to address with intrastromal AK, eyes with cylinder of 2.50 D and above may obtain more predictable effects with a penetrating AK incision and/or a toric IOL.

A toric IOL is an excellent option for patients willing to pay the extra out-of-pocket expense. I typically recommend toric IOLs for patients with about 0.75 D of astigmatism or higher; however, when I have a patient who is a toric candidate but expresses hesitance about the extra charge, I also discuss intrastromal AK as an option.

THE ART OF AK

As much as intrastromal AK is a science, there is also an art to performing these incisions (Figure 1). In their study, Venter and colleagues[1] used paired symmetrical nonpenetrating intrastromal AK incisions created from 60 µm below the corneal surface

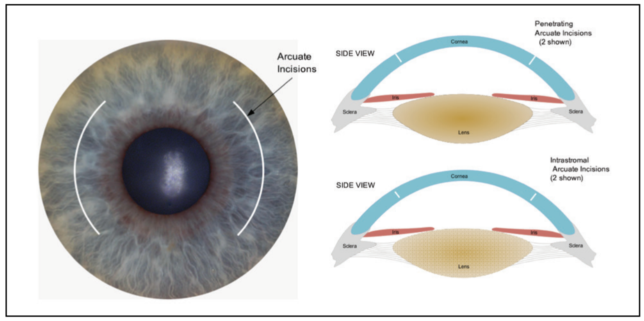

Figure 1. Illustration of AK showing penetrating (top right) and intrastromal (bottom right) incisions.

to 80% depth at a 7-mm diameter. Because the authors noted some undercorrection, I use a slightly modified approach: I add 5° to the arc length to get more effect.

It is also important when making these incisions to use a high laser energy level to ensure there is a clean, powerful incision; I make the spacing of the laser pulses tight, usually around 3 µm on both the spot and layer separation. Most nomograms center around three parameters—diameter, depth, and arc length. The arc length remains the most variable of my settings, and it is adjusted according to the amount of astigmatism in the eye.

Whereas Venter et al[1] suggested an 80% depth, other nomograms suggest a 90% depth. The theoretical advantage of a slightly deeper incision is that it will be more powerful; the drawback is that it may be more prone to perforation. A unique advantage of intrastromal AK incisions is that they can be more easily titrated by opening the incision, which can be performed at the slit lamp or in a minor procedure room. Opening the AK incision is most easily achieved if the anterior edge of the incision is left just under the Bowman layer.

There is one other variable in performing intrastromal AK: the surgical platform. In my practice, we use the iFS Advanced Femtosecond Laser (Abbott Medical Optics). I cannot say for certain whether one platform has advantages over others in terms of making AK incisions, but I can attest that, after using this laser for years to perform refractive procedures, I have a comfort level with the technology. Therefore, using it to perform intrastromal AK involved a minimal learning curve. ■

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1 OR 2 LINES

WORSE UCVA ON POSTOPERATIVE DAY 1 AFTER SMILE THAN LASIK, EQUALIZING WITH LASIK BY 2 TO 3 WEEKS POSTOPERATIVELY

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duction of SMILE and the results of the first prospective trials,[3-5] which demonstrated safety and efficacy slightly lagging behind LASIK, SMILE has gained popularity. There are now many publications demonstrating that the safety and refractive outcomes of SMILE are similar to those of LASIK.[6-17] More than 250,000 SMILE procedures have been performed worldwide, and more than 700 surgeons regularly perform it as their procedure of choice for myopia. The feasibility of the procedure has been shown by studies on the surface quality of the lenticules,[18,19] wound healing and inflammation,[20-22] and lack of impact on the corneal endothelium.[23] The accuracy of lenticule thickness parameters has been verified using very high-frequency digital ultrasound[24,25] and OCT.[26-29]

The safety of SMILE has also been demonstrated to be similar to that of LASIK,[30] and a recent publication from my center removes doubt that SMILE does equally well as LASIK for treatment of low myopia.[15] There was a question mark regarding the correction of astigmatism, as early studies reported undercorrection,[31-33] but this has been resolved by the use of a nomogram for cylindrical correction.[34]

TWO ADVANTAGES

In terms of safety, SMILE holds two major advantages over LASIK: faster dry eye recovery and an extended range of treatment due to better spherical aberration control as a result of better biomechanics. Both of these advantages stem from the nature of the opening through which the procedure is performed—a minimally invasive pocket incision—as this results in maximal retention of anterior corneal innervation and structural integrity.

Advantage No. 1: Fewer dry eye symptoms. It was expected that there would be less postoperative dry eye after SMILE: While the trunk nerves that ascend into the epithelial layer within the diameter of the cap are still severed in SMILE, those that ascend outside the cap diameter or that are anterior to the cap interface are spared. A number of studies have demonstrated lower reduction and faster recovery of corneal sensitivity after SMILE than LASIK,[35-44] with recovery to baseline in 3 to 6 months after SMILE compared with 6 to 12 months after LASIK. Some studies have also used confocal microscopy to demonstrate a lower decrease in subbasal nerve fiber density after SMILE than LASIK.[38,42,44,45]

Advantage No. 2: An extended range of treatment and spherical aberration control. The other major advantage of SMILE is its biomechanical profile, as the anterior stroma above the lenticule remains uncut (except in the location of the small incision), unlike in LASIK in which most anterior stromal lamellae are severed by the creation of the flap. Surgeons are accustomed to calculating the residual stromal thickness in LASIK as the amount of stromal tissue left under the flap, and, therefore, the first instinct is to apply this rule to SMILE. However, the actual residual stromal thickness in SMILE should be calculated as the total uncut stroma (ie, the stroma both above and below the lenticule).

It has been shown that the vertical sidecut of the flap is responsible for almost all of the change in strain due to LASIK flap creation.[46] It has also been shown that the anterior corneal stroma is the strongest part of the stroma,[47-50] due to the greater interconnectivity of collagen fibers in the anterior stroma compared with the posterior stroma, where the collagen fibers lie in parallel with each other.[51] Therefore, SMILE must leave the cornea with greater biomechanical strength than LASIK for the same amount of

The Three Phases of SMILE

By Mahipal Sachdev, MD

Phase 1: Initial docking with precise centration. During this phase, proper head position is achieved by tilting the patient's head medially to avoid nasal contact with the cone of the contact glass interface. Precise centration should be verified before the initiation of suction.

Phase 2: Femtosecond laser delivery. Femtosecond laser pulses are fired in a spiral pattern with a pulse energy of 120 to 170 nJ and a repetition rate of 500 kHz.

Phase 3: Tissue dissection and lenticule removal. The tissue disruption planes created by the laser include the posterior lenticule surface, vertical edge cut, anterior lenticule surface, and corneal sidecut (Figures 1 and 2).

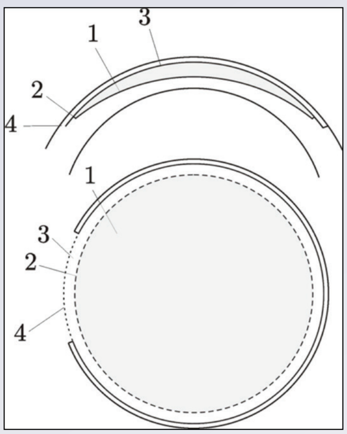

Figure 1. Cross-section of the cleavage planes created during SMILE: (1) posterior lenticule surface, (2) vertical edge cut, (3) anterior lenticule surface, and (4) corneal sidecut.

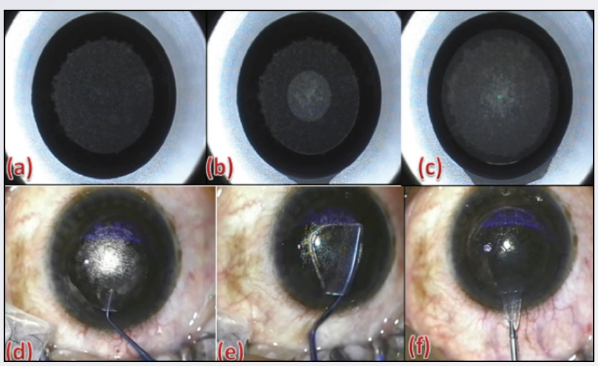

Figure 2. Surgical steps of the SMILE procedure, including laser-assisted and manual steps. Laser-assisted: posterior tissue disruption plane, or lenticule cut (A); anterior tissue disruption plane, or flap cut (B); superior flap and sidecut incision (C). Manual steps: delineation of planes (D), dissection of planes (E), and lenticule removal (F).

vision-correcting tissue removal.[52] Differences between SMILE and LASIK have also been demonstrated using finite element modeling.[53]

The first benefit of this difference is that it opens the possibility of safely treating higher degrees of myopia and thinner corneas. This is, of course, once keratoconus has been excluded, as tissue-subtraction procedures are contraindicated in eyes with asymmetric corneal biomechanics with a focal weak spot at the cone.[54] The two case reports of ectasia after SMILE have been in eyes with keratoconus on topography.[55,56]

The second benefit of the corneal biomechanical difference is that there is less induction of spherical aberration after SMILE compared with LASIK. In a recent study, colleagues and I found that SMILE, although minimally aspheric, produced similar spherical aberration induction to the highly aspherically optimized Presbyond Laser Blended Vision profile.[57] However, as the ablation depth was less for SMILE, the optical zone could be increased, meaning that less spherical aberration was induced for equivalent tissue removal, thus improving the optical quality for the patient. Our results were similar to other published studies: Three studies have shown that less aberration is induced by SMILE than LASIK,[11,12,58] and two studies showed that induction of aberrations was similar.[10,59]

ADDRESSING CONCERNS

The main disadvantage of SMILE currently is the slightly slower visual recovery experienced by some patients compared with LASIK; the day 1 postoperative visual acuity is, on average, slightly lower than on day 1 after LASIK.[6] Significant improvements have been made in this area by using different energy and spot-spacing settings,[60] although further changes to energy settings have not resulted in further improvements.[61] The difference is now approximately 1 or 2 lines of UCVA on postoperative day 1, equalizing with LASIK by 2 to 3 weeks postoperatively.

One group has described microdistortions in the Bowman layer after SMILE identified on OCT but with no clinically significant corneal striae at the slit-lamp.[62,63] These microdistortions did not have an impact on visual acuity or quality and were found to decrease over time. We have studied these central microdistortions and found that they can be minimized by appropriate centrifugal cap distension immediately at the end of the procedure to distribute redundant cap to the periphery.

Some practitioners have expressed a concern with the absence of eye tracking in the SMILE procedure. However, studies have shown this concern to be misplaced: The centration of SMILE is straightforward, and the patient essentially autocentrates the lenticule to the visual axis. Once suction has been applied, there is no need for eye tracking,

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SMILE: A BRIEF REVIEW

An example of one intrastromal procedure that can be added to the refractive surgeon's arsenal.

By Mahipal Sachdev, MD

Small incision lenticule extraction (SMILE), performed using a femtosecond laser (VisuMax; Carl Zeiss Meditec) that is capable of carving out a lenticule within the cornea, is one form of intrastromal refractive surgery. The laser energy of the VisuMax creates plasma-induced photodisruption, resulting in the formation of cleavage planes within the corneal stroma at a predetermined depth with a high degree of precision.[1] The lenticule can then be extracted from within the corneal stroma by creating and lifting a hinged flap in a procedure called femtosecond lenticule extraction (FLEX) or via the more popular SMILE procedure, in which the lenticule is extracted through a small incision.

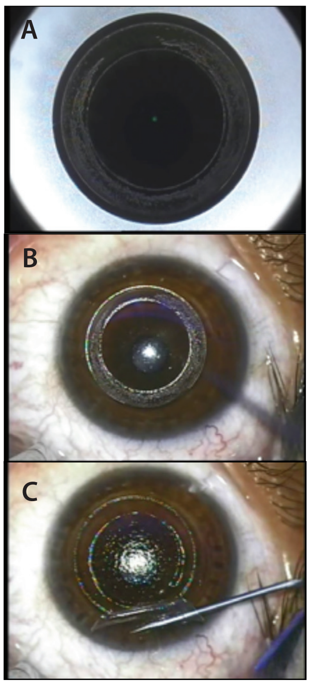

Figure 1. In Circle, a lamellar ring is created at the same depth as the existing SMILE incision, allowing the conversion of the SMILE cap into a hinged flap. The flap is then raised, and excimer laser ablation is performed.

SMILE has become an alternative to LASIK for myopic correction for many surgeons in Europe and Asia (see *The Three Phases of SMILE* on the previous page).[2,3] It is awaiting FDA approval in the United States pending the results of ongoing clinical trials. The procedure is currently available as a treatment modality for myopic correction of up to -10.00 D spherical equivalent, with a maximum astigmatic error of up to 5.00 D. The selection criteria are similar to those for LASIK. The procedure is currently not capable of hyperopic correction, although research is ongoing for this application.

MANAGING COMPLICATIONS

There are two types of complications that can be encountered intraoperatively, and each can potentially be managed successfully.

Suction loss. This occurs when the contact glass becomes detached from the cornea during the procedure.[4] The general challenge in this situation is redocking of the contact glass interface to the eye while still retaining centration. In our experience, repeating the treatment immediately is convenient and does not seem to affect the results of the procedure.

Incorrect dissection. Here, the posterior disruption plane is separated first, resulting in the lenticule being stuck to the undersurface of the cap. In our experience, when this occurs it is still possible, with some surgical dexterity, to separate the lenticule from the overlying cornea. In case this is not possible, the VisuMax allows the creation of a sidecut incision only, and it is best at this point to convert the case into a FLEX procedure by repeating a 270° to 300° sidecut incision.

SMILE OVER LASIK

Several authors have demonstrated superiority of SMILE over femtosecond LASIK in a number of measures. SMILE has been reported to result in lower degrees of induced higher-order aberrations and less reduction in corneal sensitivity than LASIK.[5,6]

Also, SMILE affects the biomechanical properties of the cornea less than LASIK.[7,8] SMILE is a flapless technique, and its effect is predicated on the new concept of tissue subtraction, which is different from tissue ablation achieved with the excimer laser in LASIK.[7,8]

ENHANCEMENT TECHNIQUE

No matter how accurate the results of SMILE, no doubt some patients will need enhancement. A recent adaptation of the VisuMax software enables enhancements of SMILE with a procedure known as *Circle* (Figure 1). With Circle, a previously created cap can be remodeled into a larger diameter hinged flap, and this can be followed by excimer laser ablation to address any residual refractive error. ■

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POCKET OR FLAP DELIVERY OF CORNEAL INLAYS: DOES IT REALLY MATTER?

Ultimately what matters is that the inlay performs safely and effectively within the cornea.

By Arthur B. Cummings, MB ChB, FCS(SA), MMed(Ophth), FRCS(Edin)

With the emergence of corneal inlays for the correction of presbyopia, there has been debate on how to implant these devices into the cornea. Of the four inlays on the market, the manufacturers of three of them recommend implanting intrastromally—in a corneal pocket—and one is designed for implantation under a flap.

The initial recommendation for the Kamra inlay (AcuFocus), which uses the pinhole effect to create depth of focus in the implanted eye, was to implant it under a 200-µm flap. However, the location for implantation was subsequently switched to an intrastromal pocket, where the device could be implanted deeper to improve its safety and efficacy. AcuFocus now recommends a pocket 200 to 250 µm deep, created with a femtosecond laser using the manufacturer's guidelines for settings to achieve the best possible pocket with the smoothest stromal bed. This setting can vary from laser to laser, and it may be that certain femtosecond lasers yield better results than others.

The Icolens (Neoptics) and the Flexivue (Presbia) are both implanted intrastromally as well, at a depth of 300 µm into the cornea. These inlays have refractive power, and they split the incoming light to create multifocality on the retina. The inlays look like a donut, with a 3.6-mm diameter. Flexivue claims there is no keratocyte activity with the implant at a depth of 300 µm, thus reducing haze and the need for biocompatibility of the material.

The Raindrop Near Vision Inlay (ReVision Optics) is the only inlay that is currently recommended to be implanted under a flap. The flap is a standard 8- to 9-mm LASIK flap created at a depth of about 30% of central corneal thickness. The flap thickness should be a minimum of 150 µm, but typically I create a 170 to 180 µm flap, depending upon the thickness of the cornea.

POCKET VERSUS FLAP

I have experience with the Kamra and the Raindrop, but not with the two PMMA devices. I have done flaps and pockets for the Kamra and flaps for the Raindrop, although it should be noted that I have not performed large numbers of procedures with either implant to date. My experience dictates that there are pros and cons to each delivery method (Table 1) but that, ultimately, what matters is that the inlay performs safely and effectively within the cornea.

Because the inlays are made out of different materials, they behave differently in the cornea. Each has its own inherent drawbacks and benefits for certain patients. For example, if a patient's refraction is naturally around -0.75 D, the Kamra is better suited; if the patient is between plano and 1.50 D, the Raindrop suits better.

My impression is that I have seen more consistent results, earlier patient satisfaction, and fewer unwanted symptoms with the Raindrop inlay. I have not seen a difference in postoperative dry eye between the two inlays. Both the Kamra and the Raindrop are straightforward to use. The hydrogel material (made of 80% water) of the Raindrop is biocompatible, works well under a flap, and should work well in a pocket, too. Variable performance was reported with the Kamra under flaps, and hence the company now endorses Kamra inlay implantation only in pockets. They have introduced the concept of planned LASIK Kamra in two steps, a procedure referred to as *PLK2*.

CONCLUSION

One important feature of all corneal inlays is that they are removable. If the patient does not like his or her outcome, or if I feel that the inlay is not being well tolerated, then I can remove it from inside the pocket or under the flap. My gut feeling is that all inlays will ultimately do better implanted intrastromally in a pocket, so I am hopeful that this will be a possibility with the Raindrop device in the future. ■

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TABLE 1. PROS AND CONS OF POCKET AND FLAP IMPLANTATION TECHNIQUES

Inlay Delivery Method	Pros	Cons
Pocket	• Less corneal tissue cut • Can go deeper where there is less keratocyte activity • Potentially less postoperative dry eye	• Inlay difficult to remove • Must have specific femtosecond laser software • Have to cut an additional flap if concurrent LASIK needed
Flap	• Can do LASIK at the same time • No special software needed • Easier to remove if needed	• Cannot go as deep into the cornea • Cuts more corneal tissue than with a pocket in an emmetropic eye • Can cause more dry eye, similar to LASIK

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as the eye is locked in place. The centration of SMILE has been shown to be similar to that achieved with LASIK using a modern eye tracker.[64,65]

SMILE FOR HYPEROPIA

Progress is also being made on extending the SMILE technique to treatment of hyperopia. Prospective studies are currently using the ReLEx femtosecond lenticule extraction[66] and SMILE[67] procedures.

Using a 6.3-mm optical zone and a 2-mm transition zone in a population of 36 eyes, our group has found that the achieved optical zone on topography was actually larger than that for LASIK using the MEL 80 (Carl Zeiss Meditec) with a 7-mm optical zone and that centration was not different from that with LASIK.[67] This difference might be due to the elimination in SMILE of two types of errors: fluence projection[68] (given that the majority of ablation is performed peripherally, these errors are increased for hyperopic LASIK compared with myopic LASIK) and truncation (ie, part of the excimer laser ablation might be applied outside the flap diameter, leading to truncation).

Analysis of a larger cohort of sighted eyes will allow investigation of refractive stability and visual outcomes in hyperopic SMILE. However, the improved optical zone observed suggests that refractive stability will be comparable to and possibly better than LASIK.

OTHER INTRASTROMAL APPLICATIONS

The ability to surgically extract an intact refractive lenticule of stromal tissue using the SMILE procedure has opened the possibility of a number of further applications. It has been demonstrated that refractive lenticules can be cryopreserved successfully for 1 month in rabbits,[69,70] and as long as 5 to 6 months in humans.[71] It has been suggested that these lenticules could be reimplanted as a method for restoring tissue in ectatic corneas or provide an opportunity for reversing the myopic correction in a patient progressing to presbyopia.[69,70] Successful reimplantation has thus far been demonstrated in rabbits.[70]

There is also the potential for implanting an allogenic lenticule obtained from a myopic donor patient into a hyperopic patient to correct hyperopia, as originally proposed by Jose I. Barraquer, MD, in 1980.[72] The first such *endokeratophakia* procedure was performed in 2012,[73] and larger series have since been reported.[71,74] The feasibility of the procedure has been demonstrated, as corneal clarity has been maintained; however, unintended posterior surface changes have resulted in undercorrection of the effect in attempted very high corrections.

Allogenic lenticules have also been used in patients with advanced keratoconus in whom the cornea was too thin for CXL.[75] In this procedure, termed *tailored stromal expansion*, a myopic SMILE lenticule is placed onto the stroma after epithelial debridement so that the thickest part of the lenticule lies over the thinnest part of the stroma, and the CXL procedure is carried out.

Another area where intrastromal laser treatment is being used is in the creation of astigmatic keratotomy (AK) incisions.[76] Use of the femtosecond laser enables the dimensions of the AK incision to be precisely controlled, and it introduces the potential for creating different incision shapes (*Editor's Note: See* The Art and Science of Titrating Incisions).

Most important, the incision can be performed either completely within the stroma or to include the Bowman layer, but without perforating the epithelium. As with all minimally invasive procedures, the main benefit is to greatly minimize risk, particularly in this case, as there is no wound whatsoever.

CONCLUSION

The development of SMILE, a flapless intrastromal keyhole keratomileusis procedure, has introduced a minimally invasive method for corneal refractive surgery. The visual and refractive outcomes of the procedure have been shown to be similar to those of LASIK, and there is increasing evidence for benefits of SMILE over LASIK because the anterior stroma is left intact. This leads to faster resolution of dry eye symptoms, faster recovery of corneal innervation, better spherical aberration control, and the potential for extending the treatable range of refractive error. Femtosecond lasers have also enabled new intrastromal procedures to be developed, including lenticule implantation, arcuate incision creation, and intrastromal implantation of corneal inlays *(Editor's Note: See* Pocket or Flap Delivery of Corneal Inlays: Does It Really Matter?*).* ■

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