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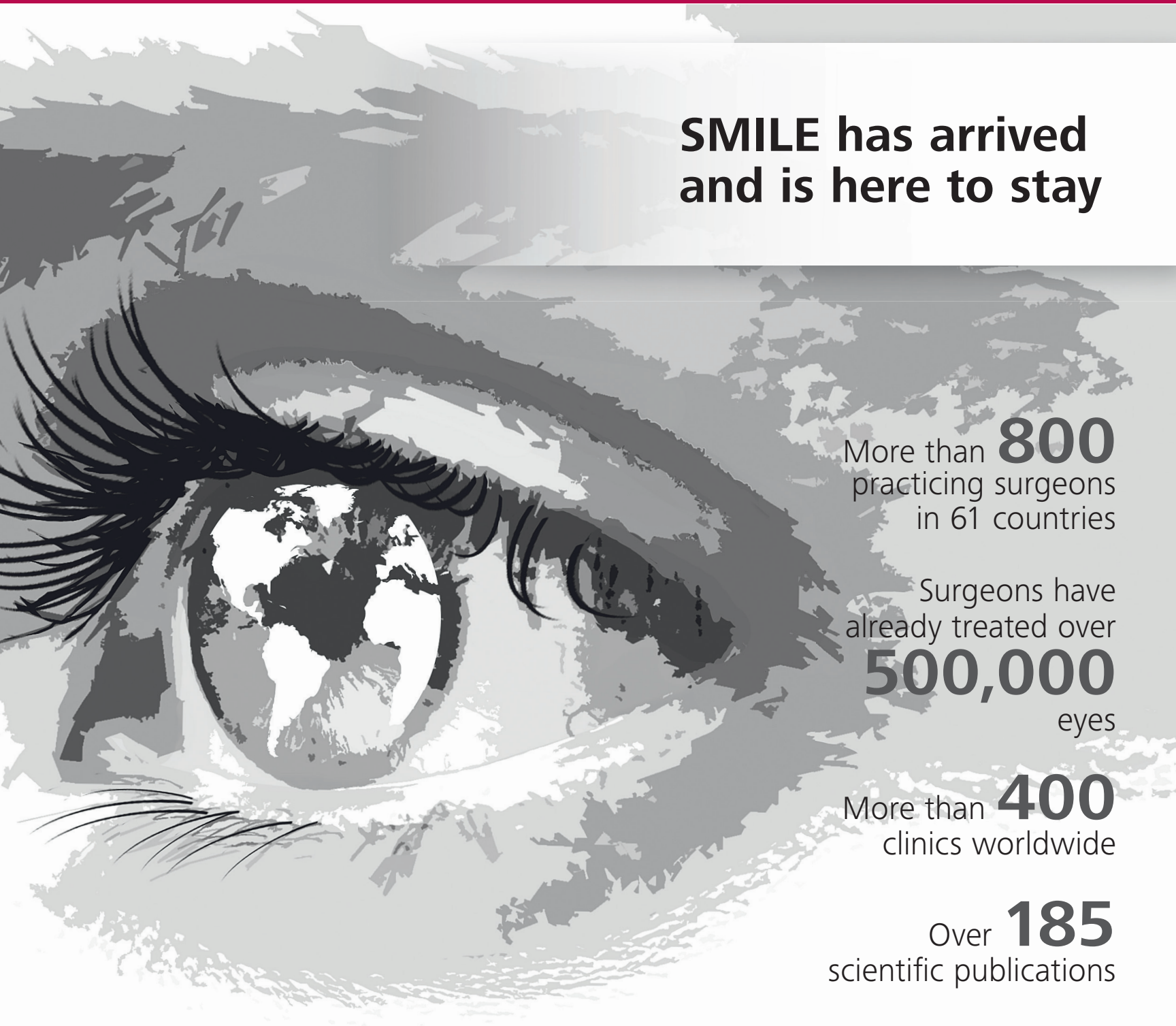

SMILE has arrived and is here to stay

More than **800** practicing surgeons in 61 countries

Surgeons have already treated over **500,000** eyes

More than **400** clinics worldwide

Over **185** scientific publications

Standing the Test of Time: SMILE Refractive Lenticule Extraction Technique

After 7.5 years and several evolutions in the procedure, SMILE continues to produce excellent and stable results.

BY RUPAL SHAH, MD

For several years now, ReLEx small incision lenticule extraction, or SMILE, has been my procedure of choice for patients who elect refractive surgery. Throughout the course of my history with this treatment, from August 2008 when I performed my first SMILE surgery, to September of that same year when I performed the first single-incision SMILE procedure in the world,[1] to current times, and through all of the improvements in the VisuMax femtosecond laser (ZEISS) technology and in the SMILE technique, I have always been impressed with the quality of results that my patients have achieved.

When I started with femtosecond lenticule extraction, or FLEx, and SMILE in 2008, the refractive lenticule extraction technique was in its infancy, and I was one of the first surgeons in the world to not only perform the technique but to experience the positive postoperative results that patients could have. Over time, as the VisuMax technology evolved, I saw my patients continue to achieve excellent postoperative results. Some of the improvements in laser technology included different scanning patterns, a higher laser head speed, and better spot spacing and energy parameters. But had the visual outcomes in some of my first patients, performed with earlier-generation VisuMax lasers, remained stable?

In an attempt to answer this question, we recently called in our first patients, many of whom were treated with SMILE more than 7 years ago, for a complete eye examination. Our motivation was to study if, like LASIK and PRK, SMILE results remained stable over time. We also wanted to find out if patient satisfaction remained high and whether patients had developed any subjective complaints over time.

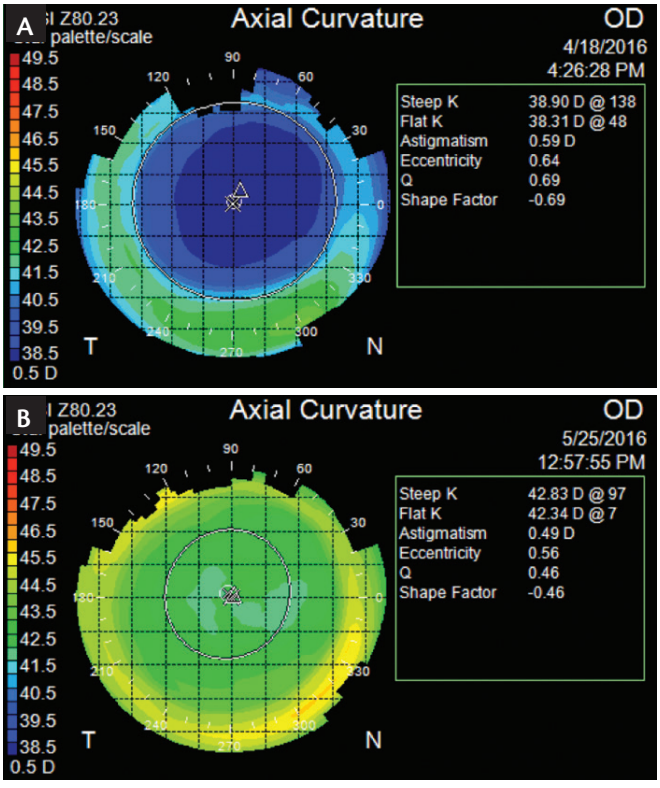

Figure 1. Topography 7.5 years after SMILE for high myopia (A). Topography 7.5 years after SMILE for low myopia (B).

BACKGROUND

The study included 30 patients with myopia (spherical equivalent, <-10.00 D) who were treated with ReLEx FLEx or ReLEx SMILE between September 2008 and May 2009. Most of the patients had undergone ReLEx SMILE with an older scanning pattern, but the cohort also included some patients who were treated with the scanning pattern we currently use.[2] In our earliest procedures, the VisuMax was only available in a 200-kHz platform, whereas the current VisuMax has a 500-kHz version.

Follow-up visits were conducted in April and May 2016. We studied BCVA, UCVA, refraction, and noninvasive tear breakup time (TBUT), and we looked at topography (Figure 1) and aberrometry (Figure 2). We also administered a subjective patient questionnaire to gauge patient satisfaction and subjective complaints.

RESULTS

Refractive stability. Among the 30 patients (60 eyes) enrolled in our study, mean spherical equivalent had increased by only 0.40 D from the 1-year postoperative visit to the 7.5-year visit. Only one

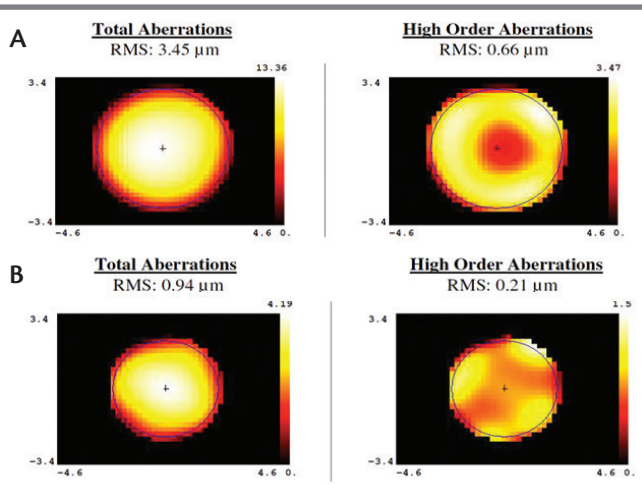

Figure 2. Aberrometry 7.5 years after SMILE for high myopia. Note the relatively low induced spherical aberration in this -10.00 D case (A). Aberrometry 7.5 years after SMILE for low myopia (B).

patient had -1.25 D spherical error in one eye and -0.75 D in the other. She had recently delivered a baby. All other patients were less than or equal to -0.75 D in both eyes after 7.5 years. In my experience, this stability is superior to that obtained after LASIK and surface ablation.

Efficacy. UCVA also remained stable over time. At 1 year postoperative, 90% of all eyes were 20/30 or better, and, at the 7.5-year visit, 63% were 20/20 or better.

Safety. Not only had safety followed the same trend as refractive stability and efficacy, but it actually improved with time. At our 7.5-year checkup, 85% of eyes had a BCVA of 20/20 or better, and 100% had a BCVA of 20/30 or better. Only one eye lost 2 lines of vision compared with the preoperative BCVA, and 40% gained 1 line of BCVA. The eye that had lost 2 lines of vision was treated with an old scan pattern.

TBUT. The Tear Stability Analysis System (Tomey), which takes serial topography images, was used to measure the TBUT. Of the 60 eyes, only four had a TBUT of less than 10 seconds. This was two eyes of one patient and one eye each in two additional patients.

Subjective satisfaction and patient complaints. All 30 patients reported that they were satisfied to very satisfied with the procedure and that they would recommend it to their friends. Although four patients reported a feeling of dryness and grittiness in their eyes and two patients reported having difficulty driving in the night, no other symptoms were reported.

CONCLUSION

By examining some of our earliest ReLEx SMILE patients more than 7 years after their procedures, we were able to show that visual results, even after so much time, were both stable and excellent. There are limitations to a study where the follow-up rate was only around 23%; however, in the population of patients who did present for follow-up, refractions were stable, and safety and efficacy were maintained. More importantly, patients remained subjectively happy with the procedure. In my mind, SMILE has withstood the test of time, and, in my practice, it continues to remain the procedure of choice for refractive correction. ■

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Spherocylindrical Hyperopic FLEx

Interim results of a prospective study.

AN INTERVIEW WITH WALTER SEKUNDO, MD, PhD

What has been your involvement with the development of the FLEx and SMILE techniques for lenticule extraction?

Along with Marcus Blum, MD, PhD, I have been involved in this pursuit from the very beginning. Together, he and I researched the idea of lifting a flap to allow the removal of an intrastromal lenticule and then developed the femtosecond lenticule extraction, or FLEx, technique using the VisuMax femtosecond laser (ZEISS) to make this possible back in 2005. As we and others knew, such a procedure had the potential to circumvent the need for incremental photoablation by an excimer laser, which for years had been the ultimate goal of corneal laser refractive surgery.

After testing with the original FLEx procedure in myopia had shown positive results, we conducted a study with the more desirable flapless form of the procedure, known as small incision lenticule extraction, or SMILE, in patients with myopia and myopic astigmatism.[1] This study showed promising outcomes at 1 year, with 88% of eyes that had a plano target achieving distance UCVA of 20/20 or better, a mean spherical equivalent of -0.19 ±0.19 D, and insignificant

changes in mean refraction between 1 and 12 months (0.08 D) and in mesopic and photopic contrast sensitivity. SMILE was launched by ZEISS in September 2011. It was clear then that the limits of this technique had not yet been reached, and investigations into expanding the SMILE technique for hyperopia were already on the agenda.

We are also in the process of going through the same iteration of studies in lenticule extraction for the treatment of hyperopia. Once we achieve positive results using the FLEx technique, we will progress to studies with the SMILE technique for hyperopic correction.

What were the early results that you and Professor Blum saw using FLEx for hyperopia, and what were the problems that you saw with the initial procedure?

The first hyperopic FLEx study was designed with a rather simple hyperopic profile.[2] In short, FLEx was performed similarly to how it was performed for myopia, but, instead of a transition zone, we used a slope so it was at the edge of the lenticule.

Unfortunately, this iteration of the procedure had a major problem: Substantial regression occurred over time. Although 1-month results were promising, by 3 months postoperatively, about 33% of patients showed signs of regression, and, by 6 months postoperatively, it had increased to about 50% of patients. This was attributed, in our opinion, to the small size of the transition zone.

Together with the Carl Zeiss Meditec AG research team, we developed a profile with a larger adjustable transition zone similar to the profiles used in last-generation excimer lasers and adapted to femtosecond laser technology. The study was then refined to include more sophisticated hyperopic profiles. This is the profile that we are using in the current study.

The current study is divided into two parts. In phase 1, we treated nine eyes with sphere only. The results of the phase 1 study, including the details of the hyperopic profile, were shared with the scientific community in a peer-reviewed publication in *Lasers and Medicine*.[3] The treatment produced similar results to hyperopia treatments with the MEL 80 and MEL 90 excimer lasers (ZEISS) and an overall undercorrection by about 0.50 D. In phase 2, which we just completed, 40 eyes with both sphere and cylinder were treated.

What can you tell us about the preliminary results of the current study?

Of the eyes included in the current study, I have treated 36 and Professor Blum has treated four. As a matter of fact, many study patients were hospital employees including several operating theater nurses and one doctor. While the profile of phase 1 was left unchanged, we improved the laser scan sequence and direction. Not only was dissection achieved easily, but we also manage to save about 6 seconds of laser treatment time despite large transition zones. A hyperopic treatment can now be performed within 30 to 32 seconds. We also corrected for the above-mentioned 0.50 D offset.

Three-month follow-up is available for all 40 eyes, and roughly one-third have accomplished successful follow-up at 6 months. Although it is too early to share 6-month results, what I can share is that, at 3 months, regression is within ±0.20 D, which is what we expected.

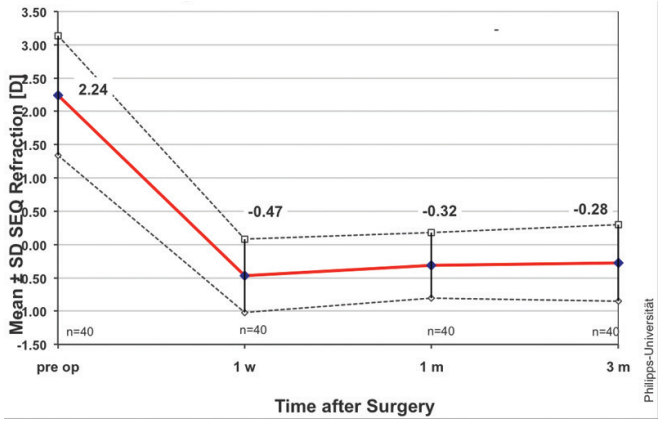

Figure 1. Attempted versus achieved spherical equivalent over time, demonstrating stability of the procedure.

I think it is still too early to say that we are getting great results, but, for the 3-month follow-up that we are able to share now, the results are promising. No eye has lost 2 lines of vision, and patients are absolutely happy. What is especially interesting is that, as mentioned earlier, the major bulk of the patients enrolled in this study work in my hospital, meaning if the results were anything but exceptional I would be hearing about it as I work with them on almost daily basis. My barber was also enrolled in the study.

Even though we do not have a nomogram for hyperopic FLEx yet, we are able to achieve good results, and that is encouraging. In the first nine eyes treated for sphere only, we saw a tendency for undercorrection of about 0.50 D. I think the reason that the eyes treated for sphere and cylinder have done so well is that we added 0.50 D on top of what we intended to treat. For instance, in an eye with 2.00 D of hyperopia, we would program the FLEx procedure to treat 2.50 D. Once we have the full follow-up data, we will work up a proper nomogram.

The 9-month results, which should be out by the end of this year, should be telling because this is when one might expect to see some regression. If they are as good as those we have seen at 3 months, then we can progress ahead into studying hyoperopic SMILE (Figure 1).

It is no secret that the hope is to move toward being able to perform this treatment with SMILE instead of FLEx. Can you share the time frame in which that might be possible?

I think as long as the 9-month results of our study are strong, and as long as the ethics committee approves of these results, it could be possible to begin clinical trials of hyperopic SMILE as early as 2017. But, for now, we are focusing on this study and the positive outcomes we have seen thus far with 3-month results need to be confirmed at the end of the study. ■

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SMILE for Hyperopia: Larger Transition Zone Produces Promising Results

An update on study results for hyperopic SMILE treatments.

BY DAN Z. REINSTEIN, MD, MA(CANTAB), FRCSC, DABO, FRCOPHTH, FEBO; AND KISHORE R. PRADHAN, MD

Treating hyperopia with the lenticule extraction technique was first investigated in 2010 in the form of femtosecond lenticule extraction, or FLEx. The initial study, published in 2012,[1] confirmed that lenticule extraction could be achieved. Although outcomes were promising, some eyes experienced a loss of CDVA and a large degree of regression, the latter of which was most likely due to the treatment's small transition zone size of between 0.2 and 1.6 mm.

Characteristics of the lenticule geometry were subsequently redesigned,[2,3] including the change to a larger 2-mm transition zone. Initial results with the new FLEx parameters in nine eyes demonstrated that the changes had succeeded in achieving larger optical zones and greater refractive stability.[4] We are currently running a parallel study with Kishore Pradhan, MD, at the Tilganga Institute of Ophthalmology in Nepal, in which the treatments are being performed as small incision lenticule extraction, or SMILE. The geometry of the SMILE parameters used in our study included a 6.3- to 6.7-mm optical zone and a 2-mm transition zone (Figure 1). Thus far, this geometry has maximized the optical zone, leaving only a small clearance (0.1–0.2 mm) between the cap diameter and the edge of the lenticule.

SIMILAR TO MYOPIC SMILE

In our experience, SMILE for hyperopia has been similar to myopic SMILE, with straightforward lenticule plane dissection and little resistance. Identifying the edges of the lenticule is slightly easier than in myopic lenticule dissections due to the thicker edge geometry of the hyperopic lenticule in comparison to the thin edge in myopia. Specifically, we have had no issues with the minimal clearance to the lenticule edge. All lenticules were successfully extracted and confirmed as being whole immediately after removal by inspection under the microscope.

The study was performed in phases. The first phase included treatment in amblyopic eyes only, followed by a second phase in sighted eyes once acceptable topographic centration and optical zone diameter had been demonstrated. Size and centration of the optical zone was assessed in 58 eyes by overlaying paracentral rings and a central grid onto the tangential curvature difference maps from the Atlas corneal topographer (ZEISS). We also repeated the analysis in a control group matched for hyperopia treated by LASIK with the MEL 80 excimer laser (ZEISS) using both 6.50- and 7-mm optical zones.[2,3]

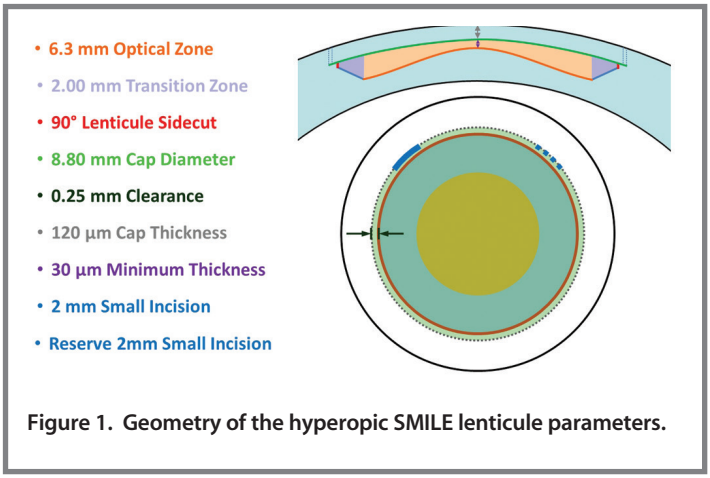

Figure 1. Geometry of the hyperopic SMILE lenticule parameters.

RESULTS

Centration. The centration offset of the functional optical zone was found to be equal for all groups (6.3- to 6.7-mm SMILE group, 0.29 ±0.21 mm; 6.5-mm LASIK group, 0.34 ±0.14 mm; and 7-mm LASIK group, 0.32 ±0.20 mm; $P>.15$), demonstrating that the centration in hyperopic SMILE was equivalent to LASIK despite the fact that an eye tracker is not used during the SMILE procedure.

Size of the optical zone. The results for optical zone size were also encouraging, as we found that not only was the mean optical zone diameter for the 6.3- to 6.7-mm SMILE group (4.99 ±0.34 mm) equivalent to the 7-mm LASIK group (4.95 ±0.23 mm; $P=.33$), but it was also larger than that of the 6.5-mm LASIK group (4.51 ±0.21 mm; $P<.01$). Optical zone size was also analyzed with axial curvature maps, in which the diameter was measured significantly larger for all groups, but the same trend was found (Figure 2).

The relatively larger optical zone achieved with the SMILE procedure also had a positive influence on the amount of induced spherical aberration. We found that the 6.3-mm SMILE procedure induced a similar low amount of spherical aberration to the 7-mm LASIK procedure and less spherical aberration than the 6.5-mm LASIK procedure (-0.52 ±0.25 µm vs -0.49 ±0.19 µm vs -0.69±0.18 µm, respectively; $P=.916$ and $P<.01$).

Visual acuity. Preliminary results are available for 31 sighted eyes

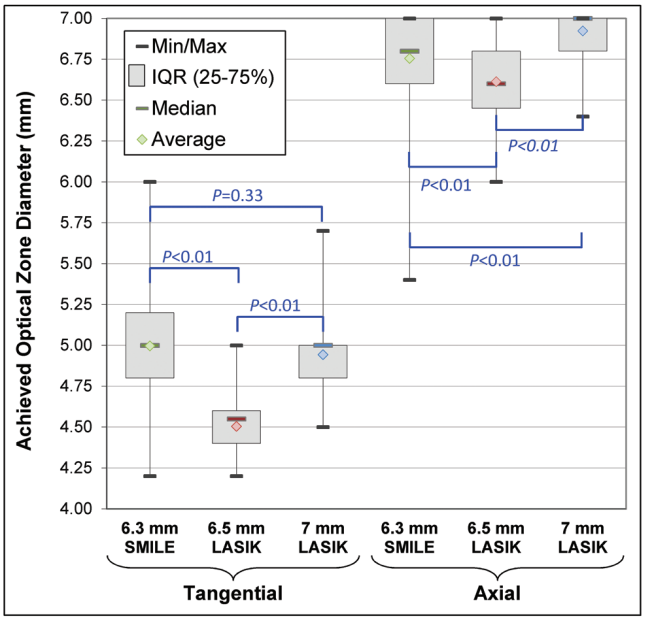

Figure 2. Box plots of the achieved optical zone diameter based on both the tangential and axial curvature difference maps for 6.3- to 6.7-mm SMILE, 6.5-mm LASIK, and 7-mm LASIK.

with a preoperative CDVA of 20/40 or better that underwent hyperopic SMILE. Although refractive and safety outcomes were compared with a LASIK control group matched for hyperopia treated, visual acuity was not compared due to the difference in preoperative CDVA.

Mean attempted spherical equivalent refraction was 5.73 ±0.80 D (range, 3.38–6.50 D) with mean astigmatism of 1.15 ±0.82 D (range, 0.00 to 2.75 D). Preoperatively, CDVA in the SMILE group was 20/32 or better in 52% and 20/40 or better in 100% of eyes. For 15 eyes in which a full correction was intended, postoperative UDVA was 20/40 or better in 87% and 20/50 or better in 100% of eyes. Mean postoperative spherical equivalent refraction relative to the intended target was -0.04 ±0.79 D (range, -2.20 to 1.88 D), with 65% of eyes within ±0.50 D and 87% within ±1.00 D. This compared favorably to predictability of 53% within ±0.50 D in the LASIK control group. There was 1 line loss CDVA in 32% of eyes in the SMILE group, but no eye lost 2 or more lines. This outcome was similar in the LASIK control group, in which there was 1 line loss CDVA in 25% of eyes, and no eye lost 2 or more lines.

CONCLUSION

SMILE with a 6.3- to 6.7-mm optical zone and a 2-mm transition zone appears to produce significantly superior outcomes to previous FLEx studies for hyperopia.[5] Compared with LASIK treatments using 6.5- and 7-mm optical zones, the superior optical zone from the new SMILE treatment might be due to eliminating fluence projection errors[6] as well as truncation errors (ie, part of an excimer laser ablation might be applied outside of the flap diameter leading to truncation). Further, given that the majority of the ablation is performed peripherally, fluence projection errors increase for hyperopic LASIK compared with myopic LASIK.

In conclusion, early refractive and visual results indicate that outcomes with the new SMILE optical zone parameters will be similar to those achieved by modern large-zone hyperopic LASIK. ■

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SMILE or LASIK: Which Alters the Cornea Less?

AN INTERVIEW WITH WALTER SEKUNDO, MD, PhD

Why is corneal biomechanics after refractive surgery such an important topic today?

First, let us define what corneal biomechanics is, and that is a study of the deformation and equilibrium of corneal tissue under the application of any force. Because corneal biomechanics affect the functional responses of the cornea, it can greatly impact quality of vision. It is an extremely important topic today because keratectasia can be the result of poor corneal biomechanics.

How do certain refractive surgery procedures affect corneal biomechanics?

Keratectasia is a rare but serious and severe complication that can occur after any type of corneal refractive surgery, as these procedures change the biomechanics of the cornea, including its structure, thickness, and fiber composition. The impact of different laser vision correction (LVC) procedures—namely, flap-based (LASIK and femtosecond lenticule extraction, or FLEx) and flapless (surface ablation and small

incision lenticule extraction, or SMILE)—on corneal biomechanical stability might differ. One study[1] has shown that the anterior cornea is stronger than the posterior cornea. Therefore, it has been postulated that, when the anterior cornea is cut or ablated—as is the case with a flap-based procedure like LASIK, but also with PRK—it weakens the cornea to a greater extent than if only the posterior cornea was cut, as it is with SMILE, which leaves the anterior cornea almost untouched, except a small incision cut of 2 to 3 mm.

Is there any concrete evidence to support this theory?

In 2013, Reinstein et al[2] used a mathematical model to demonstrate that the decrease in corneal tensile strength after SMILE was less than it was after LASIK. A literature review on in vivo studies, however, indicated that the difference between the tensile strengths of corneas after the two procedures was much less profound or even nonexistent.[3] In fact, another study showed a significant difference, and this was in eyes with high refractive errors.[4]

So, now, we are still trying to scientifically prove that the cornea remains stronger after SMILE than it is after LASIK. One problem is that only two devices on the market, the Ocular Response Analyzer (Reichert) and the Corvis-ST tonometer (Oculus Optikgeräte), can capture deformations of the cornea. However, both devices measure the deformation of the cornea after an anterior impact (air puff). In reality, the force of IOP comes from within the eye, not from outside. This makes it difficult to compare the biomechanics of a cornea after LASIK to one after SMILE in vivo. Some researchers believe that Brillon microscopy might offer a solution; however, it is too early to tell if that will be the case. Therefore, for the past 3 years, I sought to find a way to clinically test the theory that corneal biomechanics suppose to be better after SMILE than after LASIK.*

I discovered that Sabine Kling, MD, and Farhad Hafezi, MD, PhD, in Switzerland, had created a two-dimensional extensiometry device that, when a cornea is mounted onto it, it can register its stress-strain related properties. They have had good experience with this device in testing CXL protocols. We decided to collaborate on an experimental study to scientifically prove or disprove the theoretical claim that there is better corneal stability after SMILE than after a flap-based LVC procedure.

Can you discuss your study and the results?

The study was submitted to a peer-reviewed journal and was presented at the ESCRS in Copenhagen. Thus, I will give just a brief description of it. We performed the study in porcine corneas in order to control as many corneal tissue variables as possible, including age and time of death of the animal. We also treated all corneas in a single day, again in order to control the variables of the procedure.

Actually, in the preliminary study, we treated 10 porcine eyes with femtosecond lenticule extraction, or FLEx, and 10 with SMILE and compared these groups with a control group of untreated corneas. We chose FLEx over femtosecond LASIK for practical reasons: The treatment is much faster, and both procedures are flap-based, as opposed to SMILE. All treatments were set at -10.00 D. Although some differences in corneal biomechanics were noticeable between the groups, they were not statistically significant. We realized that porcine corneas are much thicker than those of humans and that we needed to treat higher corrections in order to get some comparability to human tissue. Hence, in the real study, we set the treatments at -14.00 D and increased the number of specimens to 15 in each group. This time, the difference in corneal biomechanics was statistically significant.

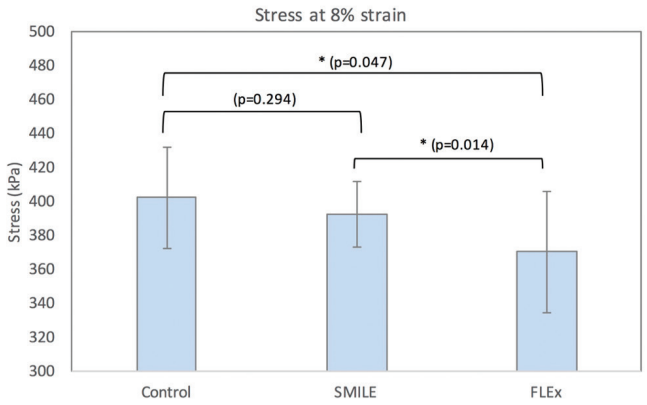

Figure 1. Corneal strength in the control, SMILE, and FLEx groups. As expected, SMILE corneas were stronger than FLEx corneas.

As expected, the control corneas were the strongest ones, followed by SMILE, and then FLEx (Figure 1). This is the first time, as far as I know, that the mathematical model calculation of Reinstein et al[2] was proven true in an experimental setting.

In terms of patient benefits, why must the cornea be as strong as it possibly can be after refractive surgery?

Keratectasia is the severest complication a patient can experience after laser refractive surgery. The stronger the cornea is, the less chance the eye has of developing keratectasia. Yes, it can still occur after SMILE; however, we now have some experimental evidence that indicates that the incidence of keratectasia after SMILE might be lower than it is after a flap-based procedure. This might give an extra safety margin and lower the probability of ectasia even further, keeping in mind, however, that the results of an experimental ex vivo study cannot be simply extrapolated to the behavior of a living human cornea. From this point of view, I think it is also important to point out that thin corneas should not be treated the same way as thick corneas and that diseased corneas, or corneas that appear to be diseased, should not be treated with any type of laser corneal refractive surgery. Just because it is not possible to perform LASIK on a cornea does not automatically mean that a SMILE procedure should be performed. In my opinion, the cornea is either good for any type of LVC or it is not. In the latter case, one should consider an entirely different approach to refractive correction, such as phakic IOLs, refractive lens exchange, or no surgery at all. ■

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Postop Tear Film Physiology and Corneal Sensation

At 3 months, eyes that underwent SMILE for myopia had better tear film characteristics and fewer dry eye symptoms than eyes that underwent myopic femto-LASIK.

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A stable tear film is essential in maintaining ocular health, visual quality, and quality of life.[1-3] Studies have shown that, although refractive outcomes after femtosecond LASIK (femto-LASIK) are excellent, patients can have ocular surface complaints such as dry eye and eye discomfort.[4,5] Such symptoms are likely due to the disruption of corneal nerves during flap creation and excimer photoablation,[6-8] which can decrease not only tear film quality and quantity but also the epithelial wound-healing process.[9] Because small incision lenticule extraction, or SMILE, does not require excimer laser photoablation or complete flap creation, there is less risk of dry eye disease postoperatively.[10]

COMPARATIVE STUDY

Study design. We recently conducted a prospective, comparative, case series study to compare tear film quality and corneal sensation in eyes that had undergone SMILE (n=100) to those that had undergone femto-LASIK (n=106). All 50 patients in the SMILE group and 53 in the femto-LASIK group returned for follow-up at 1 day, 1 week, 1 month, and 3 months postoperatively (Table 1). A major limitation in our study was that patients in the two groups were not matched by age and gender.

Tear osmolarity and lipid profile. The tear samples for osmolarity measurements were collected by placing the probe of the TearLab Osmolarity System (TearLab)[11] gently at the inferior lateral tear meniscus, taking care not to induce reflex tearing or touch the corneal surface. The tear lipid quality was evaluated with the Tearscope and the DR-1 grading system,[12] based on a 2-mm diameter observation area, by observing interference patterns of the lipid layer on the corneal surface.

Tear osmolarity was higher in the femto-LASIK group at 1 week, 1 month, and 3 months postoperatively. At the 1- and 3-month postoperative visits, corneal sensitivity, tear breakup time (TBUT), and tear lipid quality were significantly impaired in the femto-LASIK group compared with the SMILE group.

At 1 day and 1 week postoperatively, there was a high rate of signs and symptoms of dryness experienced by all patients in both groups (Table 2), with no significant differences between the two groups. However, at the 1- and 3-month follow-ups, SMILE patients experienced significantly lower symptoms of dryness (Table 2). Furthermore, 22% of patients were using artificial tears 3 months postoperatively in the SMILE group, compared with 40% in the femto-LASIK group.

A gradual improvement in corneal sensitivity, TBUT, and tear lipid layer quality was seen in both groups. This gradual change can be attributed to the healing process of the ocular surface.

TABLE 1. PATIENT DEMOGRAPHICS

	SMILE	Femto-LASIK
Age (years)	35.8 ±10.7	38.5 ±9.4
Range (years)	20–57	22–60
Gender (% female)	55	58
Race		
Asian	0	0
Black	0	0
Caucasian	50	53
Other	0	0

Corneal esthesiometry. Corneal sensitivity was measured using the contact nylon thread Luneau 12/100 mm Cochet-Bonnet esthesiometer (Luneau). Starting from 6 cm, the filament length was progressively reduced in 5-mm steps until the first response occurred. The mean of three measurements taken at the center and four at the peripheral quadrants of the cornea were used.

Visual acuity. At the 3-month postoperative visit, UDVA was not statistically different between SMILE and femto-LASIK (Figure 1).

Quality of vision. Using the Ocular Surface Disease Index, preoperatively, the mean quality of vision (QOV) score in the SMILE and femto-LASIK groups was 8.5 ±2.1 and 8.2 ±1.5, respectively. In both groups, we found a gradual improvement in patients' subjective appreciation of vision. On day 1, the QOV scores were 7.1 ±1.5 in the SMILE group and 5.2 ±2.8 in the femto-LASIK group; at month 1 and month 3, the scores in the SMILE and femto-LASIK groups improved to 9.5 ±0.4 and 8.7 ±1.2 and 9.3 ±1.1 and 9.0 ±0.7, respectively.

In short, QOV questionnaire scores improved as the symptoms of dry eye (OSDI scores) decreased. In future studies, it would be interesting to observe the actual blink rates of patients with

TABLE 2. COMPARISON OF PARAMETERS

	Pre-treatment SMILE	Pre-treatment Femto-LASIK	P value	Post-treatment SMILE (day 1)	Post-treatment Femto-LASIK (day 1)	P value	Post-treatment SMILE (1 week)	Post treatment Femto-LASIK (1 week)	P value	Post-treatment SMILE (1 month)	Post-treatment Femto-LASIK (1 month)	P value	Post-treatment SMILE (3 months)	Post-treatment F-LASIK (3 months)	P value
Tear Osmolarity (mOsm/L)	295.6 ±11.7	292.6 ±15.2	NS	318.7 ±9.7	320.1 ±12.7	NS	309.4 ±5.2	322.3 ±15.4	<.001	302.9 ±10.8	319.2 ±9.4	<.001	309.1 ±11.2	317.8 ±9.7	<.001
Esthesiometry Scale	60.1 ±3.7	62.8 ±5.8	NS	37.2 ±3.4	26.2 ±4.8	<.001	42.6 ±2.9	30.5 ±2.4	<.001	55.9 ±8.1	31.7 ±3.9	NS	56.3 ±9.1	32.9 ±9.7	NS
DR-1 Grading (1-5)	2.1 ±1.2	2.3 ±1.3	NS	3.5 ±1.5	3.5 ±1.5	NS	2.7 ±1.0	3.5 ±1.5	<.001	2.3 ±1.1	3.5 ±1.5	<.001	2.3 ±1.2	3.0 ±1.5	<.001
TBUT	6.9 ±1.4	7.3 ±1.7	NS	4.7 ±1.1	3.9 ±1.5	NS	6.2 ±2.7	4.3 ±2.3	<.001	6.5 ±1.8	5.1 ±1.5	<.001	6.7 ±1.5	5.01 ±1.3	<.001
OSDI score (0-100)	6.3 ±3.7	7.1 ±2.5	NS	22.7 ±10.7	23.9 ±12.3	NS	20.4 ±9.7	22.3 ±11.2	<.001	15.1 ±9.4	20.3 ±8.2	<.001	9.7 ±5.7	19.3 ±6.5	<.001
QOV score (1-10)	8.5 ±2.1	8.2 ±1.5	NS	7.1 ±1.5	5.2 ±2.8	NS	9.3 ±0.5	8.1 ±1.1	NS	9.5 ±0.4	8.7 ±1.2	NS	9.3 ±1.1	9.0 ±0.7	NS
Patient Satisfaction	-	-	-	-	-	-	-	-	-	97%	80%	-	100%	91%	-
Artificial Tear Use	-	-	-	-	-	-	-	-	-	15%	45%		15%	40%	-

Abbreviations: TBUT = tear breakup time; OSDI = Ocular Surface Disease Index; QOV = quality of vision; NS = not significant

refractive surgery–induced dry eye and its progression as dry eye symptoms improve.

Patient satisfaction. At 1 month, patient satisfaction was 97% in the SMILE group and 80% in the femto-LASIK group; at 3 months, it increased in both groups, to 100% and 91%, respectively.

DISCUSSION

In our study, alteration of tear film physiology and corneal sensation were observed immediately after surgery in both the SMILE and femto-LASIK groups; however, it was more prominent and prolonged in the femto-LASIK group. Findings on day 1 may not be conclusive, as postoperative medication and drops can affect results. However, at 1 week, 1 month, and 3 months, significant differences in postoperative findings were observed.

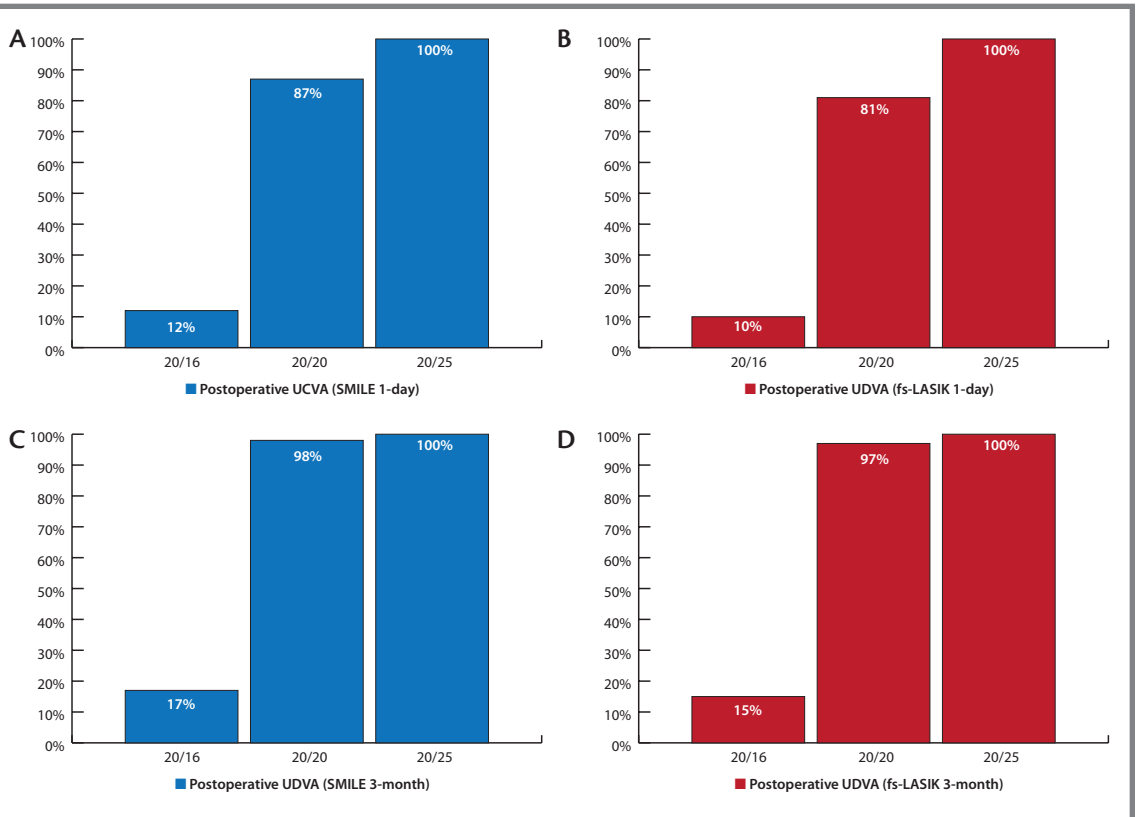

Figure 1. Comparison of UDVA: Post-SMILE (n=100 eyes) and femto-LASIK (n=106 eyes) groups on postoperative day 1 (A, B) and at postoperative month 3 (C,D).

To the best of our knowledge, this study is the first to report the comparative changes in tear lipid layer quality in SMILE and femto-LASIK patients. Our findings (Table 2) suggest that disruption in the tear lipid layer leads to increased dry eye symptoms following laser refractive surgery, which, in turn, influences optical performance. These effects are predominantly driven by corneal nerve injury, as corneal sensitivity, tear lipid quality, osmolarity, and visual acuity improved in both groups at the 3-month visit. All measures were significantly better in the SMILE group than in the femto-LASIK group, as the SMILE procedure preserves the ocular surface. Peng et al also observed that

the locally elevated evaporation of tears led to hyperosmolar spots in the tear film, which translated to epithelial irritation.[13]

With regard to corneal sensation, the findings in our study were consistent with other studies that have documented delayed normalization of corneal sensitivity in femto-LASIK patients compared with SMILE patients.[4-6,10,14-16] These other studies have shown that it can take up to 12 months for corneal sensation to reach preoperative levels. Because our assessment period was only 3 months, it is yet to be seen when corneal sensitivity, tear film osmolarity, tear lipid quality, and TBUT will rebound to preoperative levels.

CONCLUSION

The future course of this study is to help stratify preoperative SMILE and femto-LASIK. One point worth making is that surgeons can limit the risk of severe postoperative dry eye symptoms by not treating patients until dry eye symptoms improve or alternatively recommending less invasive laser refractive surgery procedures.

In our study, we found that the SMILE procedure leaves the tear film in better shape and causes less subjective dry eye symptoms compared with femto-LASIK at up to 3 months postoperatively. ■

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Keratocyte Response to ReLEx

Abnormal healing compromising the optical quality of the lamellar interface and of the remaining stroma is unlikely.

BY LEONARDO MASTROPASQUA MD; AND MARIO NUBILE, MD

Despite the great precision of excimer laser ablations, unsolved intrinsic drawbacks still persist, including surgically induced tissue damage that negatively effects stromal wound healing and triggers keratocyte changes.[1] These postsurgical corneal alterations are generally transient; however, when this is not the case, undesirable side effects and symptoms can occur. Induced keratocyte apoptosis, stromal inflammation, and less-than-optimal wound healing can cause suboptimal regression of achieved corrections and loss of corneal transparency (ie, haze).[1]

Recent studies suggest that refractive lenticule extraction, or ReLEx, due to the photodisruption mechanism and the flapless approach of the small incision lenticule extraction, or SMILE, procedure (Figure 1), may not exert the same effects on corneal keratocytes after myopic and astigmatic refractive correction as that after traditional surface ablation and LASIK techniques.

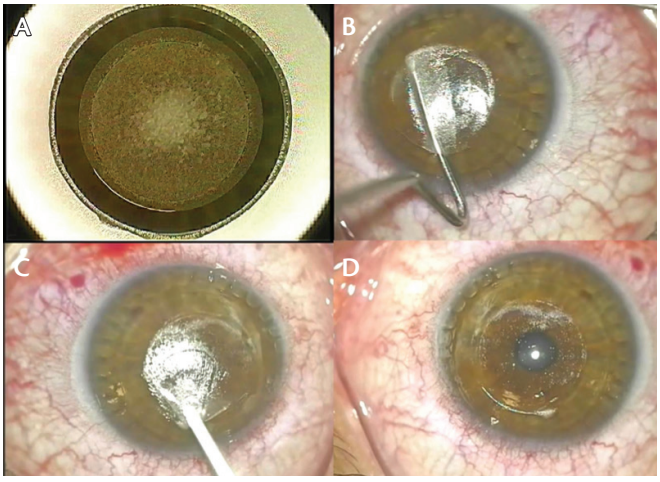

Figure 1. Surgical phases of the SMILE technique: The VisuMax femtosecond laser creates the lenticule and the sidecut incision (A); manual separation of the anterior and posterior surfaces of the lenticule with a blunt spatula (B); extraction of the lenticule through the small incision with Mastropasqua's SMILE forceps (C); and the cornea after lenticule extraction (D).

SURGICAL ANATOMY OF THE ANTERIOR STROMA

Corneal keratocytes are specialized fibroblasts that reside in the stroma. Ex vivo and in vivo studies have shown that stromal keratocyte density is higher in the anterior third of the stroma and progressively decreases in the mid and rear stroma (Figure 2). These cells, interspersed within the stroma, are composed of highly regular orthogonally arranged collagenous lamellar and extracellular matrix structures. Keratocytes produce stromal collagen and proteoglicans that play a key role in maintaining the stromal structure and transparency of the cornea.

In the unperturbed cornea, keratocytes are quiescent, but they can rapidly respond and change into repair phenotypes following injury.[2,3] Keratocytes undergo phenotypic transformations in wounds due to the influence of growth factors and cytokines, synthesizing the components necessary for corneal wound healing and tissue repair.

In surface ablation, the anterior keratocytes located within the ablation zone are destroyed. Apoptosis is induced in those located nearest the ablation interface, favoring the subsequent wound-healing cascade. In LASIK, the keratocyte and stromal healing phenomena occur at a deeper site—in the residual stromal bed, underneath the stromal flap and the ablated tissue—where the keratocyte density is lower. In ReLEx, the femtosecond laser dissection occurs without photoablation, thus inducing a different pattern of keratocyte changes and wound healing in the mid-anterior stroma, a region that is characterized to a lesser extent by apoptosis and inflammation.

Another difference between SMILE and LASIK is the greater amount of nerve fiber collateral damage and decellularization of keratocytes with the latter.[4,5] It is not yet clear whether viable keratocytes are needed to sustain corneal nerve function or vice versa; however, prolonged keratocyte apoptosis and acellularity have been observed after excimer laser–based techniques, as an extended period of postoperative denervation was observed.[4,6] Some stromal nerve fibers directly innervate stromal keratocytes. Both structures likely mediate the complex wound-healing pattern that occurs after keratorefractive laser procedures and are likely to be involved in the delicate system aimed at restoring corneal integrity, transparency, and epithelial dynamics.

IMAGING TECHNIQUES

In the past 2 decades, in vivo confocal microscopy (IVCM) has increasingly been used to acquire microscopic images of the cornea noninvasively, varying the depth of the acquisition plane. Since the cornea is normally transparent, with minimal light absorption, the axial resolution permits scanning the entire corneal thickness at high magnifications (600–1,000X) while maintaining the lateral and axial resolution within 1 to 3 µm and 5 to 10 µm, respectively.

The anatomical layers that can be identified in IVCM images include the superficial epithelium, basal epithelium, Bowman membrane, subepithelial nerve plexus, corneal stroma with resident keratocytes, deep nerve fibers, Descemet membrane, and endothelium. In vivo confocal images are oriented parallel to the objective and to the corneal surface, as opposed to the usual perpendicular corneal sections in histological specimens. Thus, observers must familiarize themselves with imaging in the coronal plane.

IN VIVO WOUND-HEALING PATTERNS: LASIK AND PRK

Stromal modification immediately after LASIK and surface ablation is dependent on the laser-tissue interaction and on the keratocyte-mediated wound-healing response; both actively influence refractive outcomes and the optical transparency of the cornea. The normal response of a cornea to photoablation is inflammation and wound healing.[7] Also, keratocyte apoptosis plays a central role in activating the wound-healing response and effects the corneal nerves, lacrimal glands, and tear film.

Keratocyte activation induced by LASIK has a shorter duration than that induced by surface ablation. Regardless of the flap-creation method, early morphological changes in keratocytes are present in the stromal tissue located below the flap, at the edge of the photoablation.[7] Keratocyte modifications induced by PRK are mostly confined in the anterior stromal layers and, in some cases, may result in abnormal collagen deposition and haze formation. Soon after the ablation, a layer in the anterior stroma (at the edge of the ablation) appears with reduced cell density. This is caused by surgically induced keratocyte death. These stromal cellular alterations can be imaged soon after surgery with confocal microscopy, at the level of the exposed stromal bed, near the limit of the photoablation. The subsequent wound-healing processes are then mediated by activated keratocytes that lead to increased collagen deposition.

It has been hypothesized that the extent of surgically induced keratocyte apoptosis, proliferation, and activation with myofibroblast functions regulates wound healing postoperatively. In LASIK, a deeper ablation level (not involving the most anterior densely distributed keratocytes) induces less intense cell activation and wound-healing phenomena. However, the presence of a new virtual space—the surgical interface—allows liquid or particles to collect and inflammatory cells to spread.

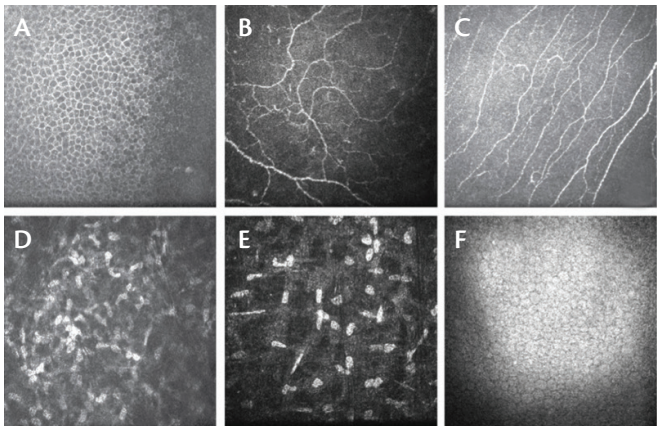

Figure 2. Images illustrating confocal microscopic anatomy of the central human corneal layers, with emphasis on visualizing nerve fibers and keratocytes: Basal epithelium (A); different pattern of subepithelial nerve plexus (B, C); high-density of anterior stromal keratocytes (D); mid-stromal keratocytes present a lower density (E); normal endothelial cell mosaic (F).

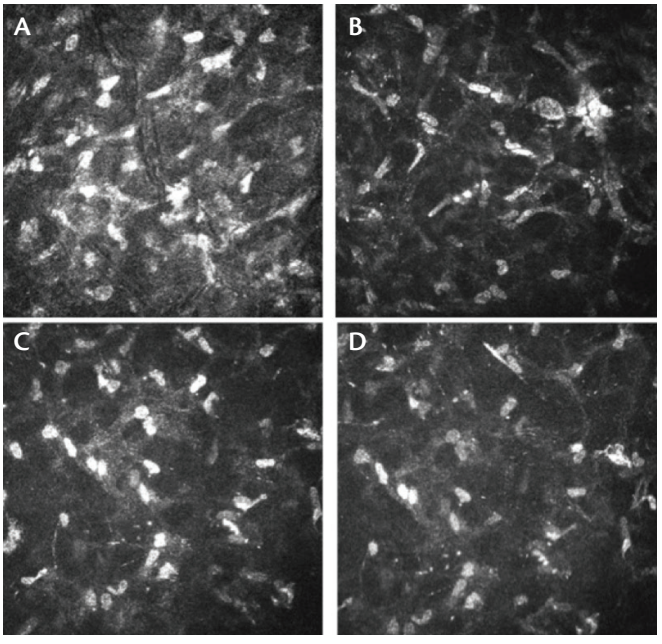

Figure 4. IVCM images showing the subinterface stromal keratocyte characteristics after SMILE and femto-LASIK: Representative confocal images of stromal layers adjacent to the interface comparing SMILE (A, B) and LASIK (C, D) at different time intervals. The stromal layers immediately below the interface (10 µm), showing greater keratocyte activation at 2 weeks postoperative. Stromal keratocyte distribution was the same at 3 months postoperatively.

IN VIVO WOUND-HEALING PATTERNS: SMILE

Just as in LASIK, in ReLEx, a stromal refractive interface remains after the lenticule is dissected and extracted. IVCM morphology of the ReLEx interface is characterized by discontinuity of the cellular architecture (Figure 3) and can be imaged microscopically as a poorly cellular layer within the anterior stroma, with variable reflective debris and particles clearly distinguishable from the other corneal layers.[8]

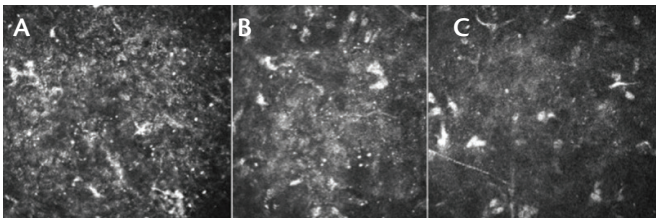

Figure 3. IVCM images of SMILE lamellar interface at different intervals after surgery: The stromal interface 1 week after SMILE, showing increased matrix reflectivity, apoptotic keratocytes, bright reflective particles, and mild edema (A); 1 month after surgery, viable keratocyte nuclei and improved reflectivity are noticeable (B); 6 months after surgery, the interface appears stable, with rare keratocytes interspersed and linear structures of regenerating nerve fibers (C). Keratocyte density remains reduced at the interface at all three time points.

A typical feature at the interface, confirmed with IVCM, is lower cellular activity and stromal remodeling with respect to the wound site.[9] Furthermore, so-called *acellular zones*, present on both sides of the interface,[9] appear thicker in the initial days after surgery, whereas keratocytes are visible closer to the interface in the following weeks.[10] The keratocyte-free layers likely represent zones undergoing apoptosis or necrosis.

KERATOCYTE RESPONSES TO SURGERY

One histological study showed that stromal keratocyte and inflammatory responses to ReLEx surgery presented a different pattern than LASIK.[11] This could be because SMILE induces less keratocyte apoptosis, proliferation, and inflammation than femtosecond LASIK (femto-LASIK).[11]

A comparison of IVCM images of the LASIK and SMILE interfaces and of stromal keratocyte changes over time are presented in Figure 4.

In ReLEx surgery, keratocyte apoptosis is mostly confined in the stromal sub-layer adjacent to the extracted lenticule. In the early postoperative period, the surrounding tissue is generally affected by minimal apoptotic/necrotic effect and inflammation. If excessive manipulation and irrigation of the interface were performed during surgery, stromal edema, with packed keratocytes within fluid cystic spaces, can be observed in IVCM images in the initial days following the procedure. These features, which may not be clearly evident at the slit lamp, can be responsible for delayed visual recovery. However, the interface and adjacent layers generally become transparent a few days after surgery, with only a mild to moderate keratocyte response generally persisting. In comparison, the response is more pronounced after excimer laser ablations (Figure 3).

In femto-LASIK, keratocyte response is affected by two sources, the laser dissection and the excimer ablation, as opposed to only one source, the laser dissection, in SMILE. The result is a greater activation of keratocytes with femto-LASIK, which is noticeable during the initial weeks after the procedure. By 3 months, keratocyte stability after femto-LASIK and SMILE are similar (unpublished data).

The minimal collateral tissue damage induced by the femtosecond laser's action on stromal tissue may be of benefit in treating residual refractive errors after keratoplasty. We have shown, by using in vivo confocal microscopy examination, that SMILE to treat residual ametropias after deep anterior lamellar keratoplasty triggers only minimal modification to the graft keratocytes and

mild and transient inflammation.[12] The occurrence of persistent keratocyte activation that may be responsible for abnormal collagen deposition and optical degradation of the interface quality in SMILE is rare and can be reversed by prolonged use of steroid eye-drops, as in excimer laser surgery.

In a recent investigation (under review), the amount of keratocyte apoptosis and stromal inflammation did not differ when comparing lower and higher myopic corrections, which is not the case in excimer laser–based techniques, such as PRK and femto-LASIK, where higher corrections correspond to a greater amount inflammation and keratocyte apoptosis and activation.

CONCLUSION

In SMILE, keratocyte apoptosis and stromal inflammation—consequently keratocyte activation and stromal wound healing—appear to be mild to moderate. Therefore, abnormal healing compromising the optical quality of the lamellar interface and of the remaining stroma is unlikely. This is substantially different than other intrastromal refractive techniques, mainly femto-LASIK. ■

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Refinements in the SMILE Procedure

Manual cyclotorsion compensation may improve postoperative outcomes in patients undergoing astigmatism correction with SMILE.

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The refractive outcome of astigmatism correction has been shown to depend upon the accuracy of the axis of treatment. Any rotational movement of the eye during treatment, otherwise known as *cyclotorsion*, can cause not only the treatment axis to shift but also undesirable postoperative results, including undercorrection and induction of aberrations.[1] Cyclotorision can be compensated for either by advanced software and eye tracking systems in laser platforms or manual markings and manual compensation.

One previous study on LASIK suggested that manual markings were equally safe and effective as automated dynamic eye trackers for cyclotorsion compensation during surgery.[2] Based on this observation, we investigated the feasibility of using limbal markings as a guide for manual compensation of intraoperative torsional errors. The prospective, interventional study was conducted in patients with significant myopic astigmatism undergoing SMILE. We also evaluated the safety, reliability, and efficacy of this technique in terms of astigmatism correction and refractive outcomes.

A total of 142 eyes were included in the study. The amount of astigmatism treated ranged from -0.75 to -5.00 D (mean, -1.82 ±0.91 D). In all eyes, irrespective of the degree of myopia, our 10% overcorrection user nomogram, based on our personal experience, was applied to both the spherical and cylindrical components of the refractive error.

The procedure was performed with a 6.5- to 7-mm optical zone and a cap thickness of 120 µm. Under topical anesthesia, with the patient looking straight ahead in the upright position, the limbus was marked in the 0º to 180º axis with an infrared transmitting dye (Viscot surgical skin marker 1436; Viscot Medical) using either a marker pen or Ganesh bubble marker (Epsilon Surgicals; Figure 1A). The patient was then positioned under the VisuMax femtosecond laser (ZEISS). As the eye was docked to thepatient interface, it was confirmed that the limbal marks extended up to 2 mm toward the center of the cornea to ensure easy visualization. The patient was then instructed to look into the green flashing fixation light, and, once proper centration was achieved, the eye was docked to the the patient interface.

After applying suction, the extent of cyclotorsion was determined using the reticule in the eyepiece or a display overlay on the treatment video. Any cylotorsion (excyclotorsion/incyclotorsion) was measured in degrees by noting the relative position of the limbal marks in relation to the 0º to 180º axis of the reticule. The contact glass was then gently rotated to align the horizontal

TABLE 1. PRE- AND POSTOPERATIVE DATA			
	Pre	2 weeks	3 months
SE (Mean SD)	-4.91±2.24	-0.212±0.38	-0.19±0.29
Range	-9.5 to -1.07	-1.5 to +1	-1.25 to +0.88
P value		0.00*	0.412
Cylinder (Mean SD)	-1.82± 0.917	-0.262± 0.358	-0.260± 0.343
Range	-5 to - 0.75	-1.5 to +1	-1.5 to +0.75
P Value		0.00*	0.939‡

SE=Spherical Equivalent, D= Diopters, SD=Standard Deviation
*Statistical significance from pre to 2 weeks postoperative
‡Statistical significance from 2 weeks to 3 month postoperative

marks on the eye to 0º to 180º axis of the reticule (Figure 1B–1D). Once both were aligned, the active laser process was started to created the refractive lenticule and a 2-mm superior incision in the regular workflow. Next, the superficial and deeper planes were identified and dissected with a blunt spatula. Once the tissue was completely dissected, it was grasped with a microforceps and extracted through the 2-mm incision. The interface was then washed with balanced saline solution.

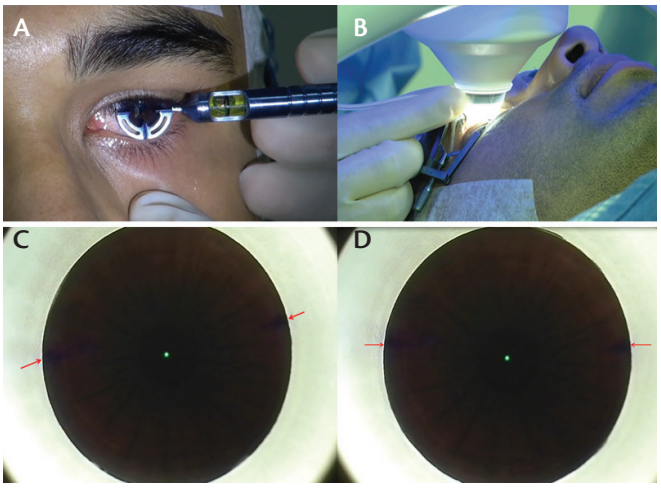

Figure 1. Preoperative limbal markings at 0º, 90º, and 180º, extending 2 mm toward the center of the cornea, made with the Ganesh Bubble marker under topical anesthesia in an upright position (A). Manual cyclotorsion compensation is achieved with gentle rotation of the cone while the tube attachment is held to the cone (B). Position of the limbal marks (red arrows) under suction ('on' condition) without cyclotorsion compensation before laser treatment, showing approximately 12º of cyclotorsion (C). Final position of the limbal marks after manual compensation of the cyclotorsion error; alignment with the horizontal axis of the eye piece reticule (D). Delivery of the laser follows.

RESULTS

All surgeries were uneventful, with no incidence of complications such as suction loss, black spots, difficulty with dissection, and incomplete separation of the lenticule due to the ink marks blocking the laser (as the used ink pen does not cause blockages). Postoperative examinations were conducted on day 1 and at 2 weeks and 3 months postoperatively.

Of the 142 eyes enrolled in the study, intraoperative cyclotorsion occurred in 66 (46.48%). Of these, 43 eyes (30.28%) showed signs of incyclotorsion from 2º to 12º degrees (mean, 5.72 ±2.88º), and the remaining 23 (16.19%) showed signs of excyclotorsion from 2º to 15º (mean, 6.43 ±3.72º).

Table 1 shows the pre- and postoperative data of all eyes included in the study. At 2 weeks postoperative, the mean astigmatism had decreased significantly (-1.82 ±0.91 and -0.262 ±0.35 D; *P*=.00). There was no significant change at 3 months (0.260 ± 0.34 D; *P*=.93), demonstrating good stability of astigmatism correction.

In terms of astigmatism correction, 91% eyes were within ±0.50 D of intended correction at 3 months postoperative, and 100% eyes were within ±1.00 D of intended astigmatism correction (Figure 2A). In all eyes, UCVA was 20/25 or better, and, in 93%, UCVA was 20/20 or better (Figure 2B). No eye lost any lines of CDVA. In fact, 57% eyes had gained 1 or more lines, demonstrating excellent safety of the procedure (Figure 2C).

With regard to achieved versus intended correction, the scatter plot showed a slight undercorrection of astigmatism (8–9%), with an average deviation of -0.13 D from the trendline (range, -0.97 to 0.62 D; Figure 2D). Although the results exhibited a fairly good accuracy of correction, individuals with higher astigmatism might better tolerate the slight undercorrection, compared to when the cylinder is overcorrected. Surgeons should consider creating and refining their own nomograms by analyzing their personal postoperative results.

We also analyzed our results with this technique by categorizing the data into two groups of low (-0.75 to -1.50 D) and high (>-1.51 D) astigmatism. We observed that the outcomes in terms of cylinder correction, predictability, and accuracy of treatment were better in eyes with high astigmatism than in eyes with low astigmatism (unpublished data). Based on the results of our study, we recommend preoperative limbal marking for all eyes with 1.00 D or more of astigmatism and manual compensation of cyclotorsion error with the technique described.

In our study, gentle rotation of the cone did not lead to loss in suction, and no complications occurred due to limbal marking when performed with the infrared transmitting ink marker.

SOURCES OF ERROR

The correct positioning of the patient and his or her head is the most important consideration and especially important in patients with a prominent nose. In such patients, the head must be turned to one side to prevent the nose from touching the contact glass. Potential sources of torsional errors during SMILE included static cyclotorsion due to change in position from upright to supine, dynamic cyclotorsion due to the nature of the laser procedure, application of suction, speculum insertion, and eye squeezing during treatment. Furthermore, previous studies on LASIK have shown that a 4º misalignment can lead to an astigmatic undercorrection of 14%; a misalignment of 6º and 16º, respectively, can cause undercorrections of a 20% and 50%, respectively.[3]

Thus, it is important to consider these intraoperative torsional errors when performing the treatment, as they may result in

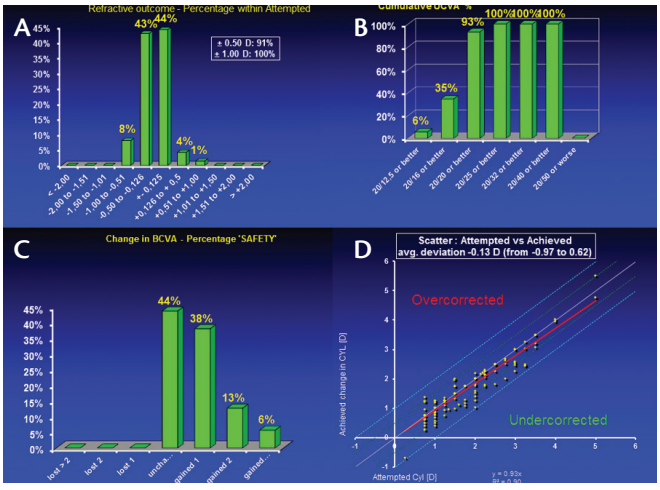

Figure 2. Predictability of astigmatism correction in eyes within ±0.50 D of intended correction (A). Cumulative uncorrected visual acuity (B). The gain or loss in lines of corrected distance visual acuity (C). Attempted vs achieved cylinder correction at 3 months following SMILE for myopic astigmatism with manual cyclotorsion compensation (D).

unsatisfactory outcomes, especially in patients with clinically significant astigmatism of 1.00 D and above.

CONCLUSION

For most cylinder treatments, a normal SMILE treatment does not require cyclotorsion compensation. However, when needed, manual compensation of cyclotorsion error may be a safe, simple, and effective approach to improve results in astigmatism correction with SMILE. In our study, this alternative to use of an active eye tracker for cyclotorsion compensation resulted in favorable outcomes in patients with myopic astigmatism.

In conclusion, combination of manual cyclotorsion compensation and application of suitable individual user nomograms may help refractive surgeons to refine their refractive outcomes and enhance satisfaction in patients with significant astigmatism undergoing SMILE. This method of cyclotorsion compensation can help to provide patients with a "wow'" factor on postoperative day 1 that is similar to that of LASIK. ■

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Post-SMILE Retreatment

An evaluation of the CIRCLE and PRK retreatment options.

BY FRANCISCO POYALES, MD; AND RICARDO PÉREZ, MD

In our practice, small incision lenticule extraction, or SMILE, has taken the place of LASIK as the technique of choice for myopia and astigmatism correction in patients with up to 7.00 or 8.00 D of these refractive errors. The reason for our switch is simple: The postoperative results that we have achieved with SMILE in these patient populations outperform those yielded by LASIK, in terms of both visual acuity and visual quality. When we started performing SMILE, we treated refractive errors of up to -10.00 D, but we gradually lowered the threshold to what we adhere to today, as we observed better results in terms of visual quality.

We still, however, have some need to treat residual refractive errors after surgery. Of the 680 SMILE procedures we performed between September 2013 and April 2016, 17 required retreatments, generating a retreatment rate of 2.5%. This represents a significant decrease from our post-LASIK and post-PRK retreatment rates, which, even accounting for the fact that we initially treated higher myopia, is about 5% in both techniques. Nowadays, we tend to create a slight overcorrection to decrease the rate of retreatments, more so in younger patients.

When a retreatment is required after SMILE, we have experience performing both PRK and a relatively new technique called CIRCLE. In our early experience with SMILE, all retreatments were performed with PRK, as CIRCLE was not yet available. Once the CIRCLE software became available, we switched to this procedure because visual recovery after PRK retreatment was much slower than that in primary PRK.

With the CIRCLE treatment software, which is part of the SMILE solution for the VisuMax femtosecond laser (ZEISS), the original SMILE cap is converted into a flap. Once the flap is lifted, an excimer

TABLE 1. RETREATMENT RATES AND STATISTICS WITH PRK AND CIRCLE			
Technique	**PRK**	**CIRCLE**	***P* value**
Number of Retreatments	7	9	
Age (years)	31.85 ±5.43	41.88 ±3.89	.002
Spherical Equivalent pre-SMILE (D)	-6.99 ±1.65	-4.76 ±1.17	.02
Astigmatism pre-SMILE (D)	-0.64 ±0.6	-0.8 ±0.42	.06
Spherical Equivalent Pre-Retreatment (D)	-1.30 ±0.42	-1.04 ±0.3	.24
Astigmatism Pre-Retreatment (D)	-0.53 ±0.54	-0.8 ±0.31	.29
Cap Depth (µm)	127 ±4.51	128 ±9.75	
Final Visual Acuity	0.91 ±0.09	0.98 ±0.01	.12
Time of Visual Recovery (Days)	243.14 ±231.74	40.87 ±14.08	.07

laser ablation is performed to correct the residual refractive error.

There are four different CIRCLE patterns available (Figure 1). Profile A, which requires a single sidecut, can be used to create a flap that had the same diameter as the original cap. However, with this approach, the diameter of the treatment area is tight to apply an extended ablation pattern with the excimer laser. In profile B, the stromal bed slightly extends below the original cap plane; in profile C, it is right above that cap plane; and, in profile D, the extension of the stromal bed is programmed to be located precisely in the cap plane. In addition to the sidecut, an internal junction cut was also made in profiles B, C, and D, in order to join the new incision plane (ie, the CIRCLE plane) with the plane of the original cap. Of these profiles, we use profile D, as recommended by ZEISS.

DATA ANALYSIS

We recently analyzed the differences in postoperative results among all patients who had underwent PRK and CIRCLE retreatment techniques after SMILE in our clinic between September 2013 and December 2015. Of these, seven were retreated with PRK and nine with the CIRCLE approach. The following parameters were analyzed in both groups: age, spherical equivalent prior to the initial SMILE surgery (pre-SMILE), pre-SMILE astigmatism, spherical equivalent prior to retreatment, astigmatism prior to retreatment, cap depth in the SMILE procedure, final visual acuity following retreatment, and time between retreatment and recovery of maximum visual acuity.

Data analysis revealed statistically significant differences in the pre-SMILE spherical equivalent as well as in patient age. Specifically, patients who had undergone the CIRCLE enhancement technique had higher average refractions and lower average ages. The reason for these differences is twofold. First, patients retreated with PRK had previously undergone SMILE during its initial implementation in our eye clinic, when higher refractive correction values of up to 10.00 D were attempted. Since this time,

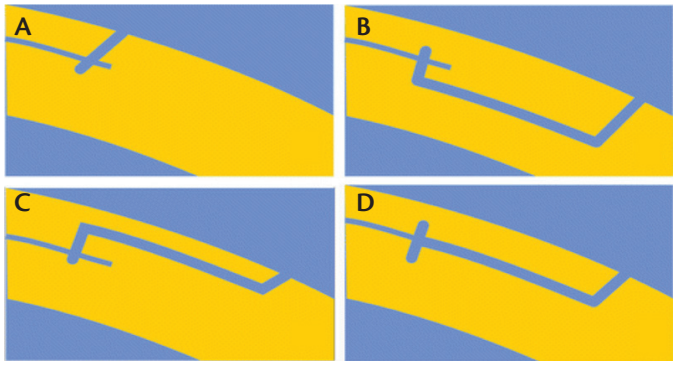

Figure 1. CIRCLE profiles. Profile A: One sidecut can be used to create a flap that had the same diameter as the original cap. Profile B: The stromal bed slightly extends below the cap plane. Profile C: The stromal bed is located right above that cap plane. Profile D: The extension of the stromal bed is located precisely in the cap plane. In profiles B, C, and D, an internal junction joins the CIRCLE plane with the plane of the original cap.

we have decreased the indications for SMILE gradually to 7.00 to 8.00 D. This means that, during the latest part of this period, retreatments were performed using CIRCLE and corresponded to patients who had, on average, lower pre-SMILE refractions. Second, age was, on average, higher among patients who underwent CIRCLE retreatment. This is because not only did we tend to use PRK more often in younger patients, but we also tried to avoid overcorrection in patients who were around 40 years of age, in order to delay the onset of presbyopia symptoms.

Even though time to visual recovery was not statistically significant between the PRK and CIRCLE retreatments, it is clinically relevant. Visual recovery in patients in the PRK retreatment group took longer than it did in patients retreated with CIRCLE. Furthermore, patients in the PRK group were more likely to develop haze than patients who undergo a primary PRK procedure. Therefore, we advise giving mitomycin C to all patients undergoing PRK retreatment, despite the fact that retreatments always involve low-refraction ablations.

CONCLUSION

At present, our technique of choice for post-SMILE enhancements is CIRCLE, because patient recovery is much quicker and less unpleasant than with PRK retreatment. We currently perform SMILE at a depth of 120 µm, and we use the same indications as we do for LASIK (ie, refractive errors that seldom exceed 7.00 to 8.00 D) in order to best avoid a potential need for retreatment with CIRCLE.

We would like to highlight the fact that PRK is also an acceptable alternative to SMILE retreatments, especially in patients with dry eye. In these specific cases, we explain to the patient about a prolonged recovery period and the instillation of mitomycin C, in our opinion, is mandatory in order to prevent postoperative haze. ■

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Tailored Stromal Expansion With SMILE Lenticules

A donor lenticule can be safely applied to thin and ultrathin corneas during CXL treatment for advanced keratoconus.

BY MAHIPAL S. SACHDEV, MD

The treatment of keratoconus, a progressive disease associated with irregular astigmatism, central corneal bulging, and progressive myopia, is far from perfected. Although the two most readily available methodologies—spectacle or contact lens correction and keratoplasty—offer patients the means for better visual acuity, neither do anything to alter the natural course of the disease.

CXL, on the other hand, is an adjunct therapy capable of increasing the mechanical and biochemical strength of the corneal tissue. Yet this treatment also has tradeoffs, including the fact that the effect of CXL is limited to the anterior 300 µm of the corneal stroma,[1,2] and that UV-A light, a crucial component of the CXL treatment, is too potent for the deep stroma, corneal endothelium, and crystalline lens. Because a corneal thickness of 400 µm is considered the safe limit to protect the endothelium and intraocular structures from the adverse effects of the UV-A irradiation, the treatment is often not advisable in a thin cornea—a frequent finding in eyes with corneal ectasia.

TAILORED STROMAL EXPANSION

Several techniques have been tried to overcome the limitations of reduced corneal thickness, including one that used hypoosmolar riboflavin to swell the cornea prior to CXL treatment.[3] Likewise, some have described the use of transepithelial CXL,[4,5] custom pachymetry-guided epithelial debridement,[6] and application of a riboflavin-soaked bandage contact lens of negligible power as possible strategies for CXL treatment in thin corneas.

We recently described a technique for stromal expansion of thin corneas that has allowed us to increase the intraoperative corneal thickness to such an extent that CXL is then possible. In our technique, the addition of donor stromal tissue with biologic and absorptive properties that are the same as those of the cornea to be treated provides an alternative approach to increase the thickness of the cornea. For a video demonstration, visit http://eyetu.be/egigo.

With tailored stromal expansion, a donor refractive stromal lenticule from a patient who had undergone myopic small incision lenticule extraction, or SMILE, is spread over the host cornea following epithelial debridement. Intraoperative pachymetry is used to ascertain the thickness of the required lenticule. The lenticule is then centered on the apex of the cone. The result is that the thickest area of the 6.2-mm lenticule corresponds with the thinnest area of the cone. Once the donor

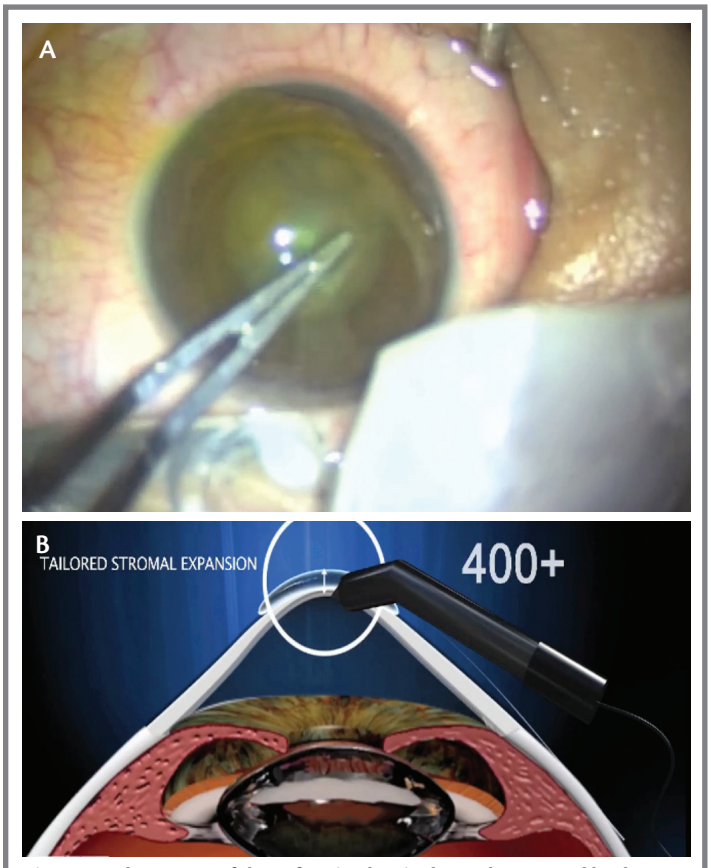

Figure 1. Placement of the refractive lenticule on the stromal bed, followed by riboflavin soakage (A). Schematic diagram shows placement of thickest portion of lenticule on thinnest point of the keratoconic cornea, by centering the refractive lenticule on the corneal apex to ensure intraoperative thickness of 400 µm (B).

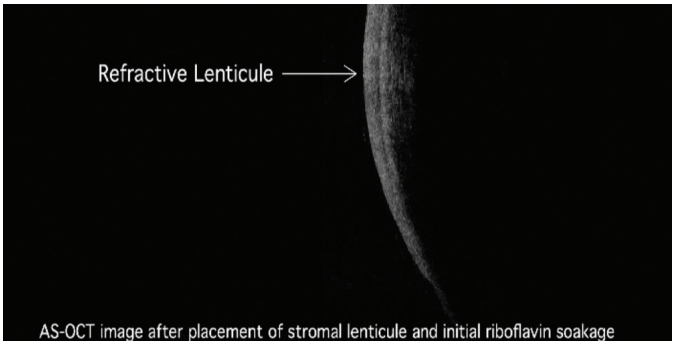

Figure 2. AS-OCT image of the well attached lenticule placed on the corneal stroma

refractive lenticule is in place, a standard CXL procedure can then be performed.

To date, we have performed tailored stromal expansion in three patients with progressive keratoconus. All patients had documented steepening on corneal topography and a corneal thickness of less than 400 µm (380, 374, and 370 µm) at the area of maximum steepening, as determined by Scheimpflug imaging.

SURGICAL TECHNIQUE

In each of the three cases of tailored stromal expansion that we have performed, the procedure was planned to coincide with a SMILE treatment in another patient with moderate myopia. Each donor refractive lenticule, with an estimated central thickness of 80 to 100 µm, was extracted in its entirety and stored in McCarey-Kaufman media until the stromal expansion procedure was to take place. Both procedures were performed in the same sitting, in adjacent operating rooms, in order to maintain sterility.

During the stromal expansion procedure, a blunt spatula was first used to debride the central 8 mm of corneal epithelium, followed by intraoperative pachymetry to determine the correct thickness of the donor lenticule. Then, placement of the thickest area of the 6.2-mm refractive lenticule was achieved by predetermining the center of the cone (Figure 1A). The relatively rough host stromal surface made it easy to spread the lenticule, and it prevented buckling.

Once intraoperative pachymetry was used to confirm that the augmented stromal thickness was more than 400 µm, CXL was performed using standard safety protocols (Figure 1B). This included instillation of one drop of riboflavin every 5 minutes for 30 minutes, followed by one drop of riboflavin every 5 minutes under UV-A radiation for the next 30 minutes. Anterior segment OCT (AS-OCT) images demonstrated a well-adhered lenticule throughout the procedure (Figure 2).

At the completion of the procedure, the donor lenticule was peeled from the stromal bed, the corneal surface was irrigated with balanced saline solution, and a bandage contact lens was applied.

Postoperatively, patients were prescribed gatifloxacin 0.3% eye drops four times daily for 7 days, loteprednol etabonate 0.5% eye drops three times daily for 7 days, and hypromellose 0.3% eye drops six times daily for 45 days. The bandage contact lens was removed on day 5.

TABLE 1. RESULTS OF TAILORED STROMAL EXPANSION

			Sim K (D)		Max K (D)		ECC (Cells/mm²)	
Patient	Sex	Indication	Preop	Postop	Preop	Postop	Preop	Postop
1	F	Prog KC	43.1/45.6	43.2/45.3	48.7	48.2	2,234	2,145
2	F	Prog KC	45.2/50.8	45.7/50.2	56.5	56.4	2,013	2,001
3	M	Prog KC	51.3/56.8	51.2/57.5	59.8	59.0	1,978	1,922

ECC = endothelial cell count; KC = keratoconus; K = keratometry; Prog = progressive; Sim = simulated

RESULTS

Of the three patients, none experience intra- or postoperative complications, and all achieved epithelial healing within 3 to 5 days of the procedure. At the 6-month follow-up, corneal stability was demonstrated on topography, and no signs of significant endothelial cell loss were seen on specular microscopy (Table 1).

Furthermore, a demarcation line ranging in depth from 250 to 280 µm was observed in all cases.

CONCLUSION

Adequate corneal thickness is one prerequisite for CXL with riboflavin and UV-A light. In addition to several other techniques that have been described to increase corneal thickness and allow us to perform CXL in patients with advanced keratoconus, we have found that tailored stromal expansion shows the most promise.

More widespread use of this technique would require long-term preservation of myopic lenticules, and long-term studies are required to further establish the efficacy and feasibility of this procedure on a larger scale. In addition to its indications for myopia and myopic astigmatism, the SMILE lenticule is fueling innovative uses in tissue-addition techniques for hyperopia[7] and keratoconus.[8] ■

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Succeeding at the Business of Refractive Surgery

Five lessons that can help a practice grow its refractive surgery volume and market share.

BY RAINER WILTFANG, MD

As most ophthalmologists practicing in Germany know, the refractive surgery market in Munich is highly competitive. With a population of about 1.5 million, there is a large pool of potential candidates who are interested in refractive surgery. Sixteen years ago, in response to the competitive market and the high demand among patients for refractive surgery, my practice opened a satellite location at the Munich Airport. Today, this center accounts for one of our 14 refractive surgery centers in Germany, and it is one of our busiest locations. This past year, more than 1,000 refractive surgeries were performed at the Munich airport location.

With our level of experience and our good understanding of how specific and important the business of refractive surgery is, we have become a leader in the market. The combination of these things has also allowed us to charge a premium for refractive surgery, which, at the moment, is around €5,000 for both eyes. Below I share five lessons learned throughout the years that have helped Smile Eyes Augenklinik become successful.

LESSONS LEARNED

Lesson No. 1: Invest in good equipment. Patients expect the best—the best doctor, the best outcomes, and the best technology. At Smile Eyes, we use the ZEISS Refractive Suite, which includes the VisuMax femtosecond laser and the MEL 90 excimer laser. We also rely on ZEISS' diagnostic technologies, like the IOLMaster. Next year, we will be refurnishing our clinic and plan on purchasing several new devices, including the OPMI Lumera microscope (ZEISS).

Lesson No. 2: Keep marketing strategies current and use tactics that are proven to work in your region and for your patient demographic. Smile Eyes is a franchise of clinics with locations in Germany and in parts of Luxembourg and Austria. We have found that it is best to tailor our marketing strategies to the location and to the patient demographic. In Munich, for instance, radio advertising works brilliantly. In this market, we purchase 17 radio spots every day on two radio stations.

In most of our other locations, however, radio advertising has not worked as well. Instead of continuing to spend money on radio spots that did not generate leads, we recently turned our attention to word-of-mouth referrals, which currently account for about 60% of all referrals. Now we rely most heavily on Internet advertising. We focus on search engine optimization, and we employ marketing strategies across various social media outlets including Facebook, Instagram, and YouTube. For instance, in some of our refractive surgery centers, we have what we call a YouTube corner. Patients are invited to provide a few comments immediately before their treatment and again immediately after. Video taping their responses and then posting them to YouTube can be a powerful marketing tool.

We no longer advertise on billboards or in newspapers and magazines; however, we do send our patients mailings, inviting them to come into the clinic for free sunglasses in the summer or ski socks in the winter, for instance.

Lesson No. 3: Tell patients about all of the procedures you offer. Our marketing and advertising efforts are targeted at generating leads for refractive surgery. We do not advertise specific treatments or procedures. Once prospective patients enter the clinic, then we explain the three treatments we offer, which are PRK, femtosecond LASIK, and small incision lenticule extraction, or SMILE, and the advantages and disadvantages of each.

Nearly 90% of patients then decide on SMILE, mainly because it is a minimally invasive procedure and, therefore, more convenient for them.

Lesson No. 4: Educate your staff. We continually educate our staff on every procedure that we offer, so that they can talk knowledgeably to prospective patients. One way we provide staff education is by holding informational meetings once every 2 months. These meetings are held after office hours, and typically include a brief presentation and a question and answer period. Updating the staff on our procedures helps to ensure that the initial contact with patients is not only pleasant but also educational.

Lesson No. 5: Do not be afraid of newer procedures. Over the past 3 years, we have continued to increase our refractive surgery volume and we have gained market share specifically because we offer the SMILE procedure. In that time, the number of LASIK surgeries we have performed has decreased, which I believe is in response to patients not being completely satisfied with the results of their procedure. Many of our patients have come to our clinic already knowing about SMILE, asking for the procedure because it is minimally invasive and flapless. If we had shied away from offering a newer procedure such as SMILE, then I believe that we would not have been able to increase our surgical volume to the extent that we have. ■

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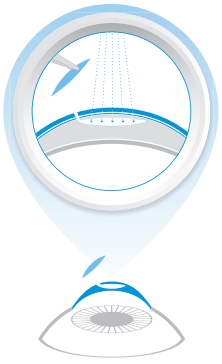
- Financial disclosure: Consultant (Carl Zeiss Meditec)

Creating vision with a SMILE.

ZEISS ReLEx SMILE

ReLEx SMILE is not approved in every country, e.g. in US FDA clinical study (IDE) is ongoing.



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