Persistent Subepithelial Haze in Thin-flap LASIK

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ABSTRACT

PURPOSE: To report persistent subepithelial haze in two patients following femtosecond LASIK associated with creation of a thin flap.

METHODS: Subepithelial haze was assessed by slit-lamp photography, high-resolution Scheimpflug imaging, and corneal confocal microscopy.

RESULTS: Two patients showed distinct subepithelial haze and reduced corrected distance visual acuity at 3 months after LASIK with a thin-flap generated by a femtosecond laser. The extent of haze was documented, and haze was treated topically with steroids for up to 12 weeks. The haze was localized approximately 20 to 40 μm below Bowman's layer and dissolved slowly during the 3 months of treatment. At 6 months after surgery, uncorrected visual acuity was 20/20.

CONCLUSIONS: Subepithelial haze formation represents a new potential complication in thin-flap LASIK. [*J Refract Surg.* 2010;26:222-225.] doi:10.3928/1081597X-20090930-02

Increasing evidence demonstrates that flap thickness in LASIK plays an important role in corneal biomechanics. Accordingly, many surgeons have returned to the safety of advanced surface ablation despite the longer healing time and slower visual recovery.[1,2]

There is evidence that ultra-thin flaps (90- to 100-μm thickness), when cut with a femtosecond laser, have a lesser impact on corneal biomechanics than thicker flaps[1,2] (also J. Marshall, MD, unpublished data, 2008). For some surgeons, thin-flap LASIK or so-called sub-Bowman keratomileusis of <110-μm flap thickness[3] might represent a combination of the advantages of LASIK (quick visual recovery and minimal pain) and advanced surface ablation (less risk for ectasia, better visual outcome). In this study, we report the occurrence of a thin-flap LASIK complication in two patients in whom subepithelial haze compromised vision for up to 6 months after the procedure.

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CASE REPORTS

Case 1

The patient was a 33-year-old man with no history of ophthalmic disease. Preoperative manifest refraction in the right eye was −6.50 −0.50 × 145 and −5.50 −1.25 × 160 in the left eye. Preoperative corrected distance visual acuity (CDVA) was 20/20 in both eyes. Optical pachymetry showed a minimal corneal thickness of 503 μm in the right eye and 501 μm in the left eye. Scheimpflug examination showed no apparent abnormalities in the right cornea but rather signs of a forme fruste keratoconus in the left cornea. Therefore, the surgeon decided to perform thin-flap LASIK in the right eye and photorefractive keratectomy (PRK) in the left eye with bilateral emmetropia as the refraction target in November 2007. The flap was generated using an IntraLase FS 60-kHz femtosecond laser (Abbott Medical Optics, Irvine, Calif). The intended flap thickness was 100 μm.

The treating ophthalmologist examined the patient 1 day and 1 month after surgery and noted that the early postoperative period was uneventful. However, the patient complained of decreased distance vision and halos in both eyes. On initial slit-lamp examination at 12 weeks after surgery, a minor subepithelial haze was noted in the left cornea where surface ablation had been performed. The right eye, however, showed distinct subepithelial haze grade 1+ (Figs 1A and 1B). Corrected distance visual acuity was 20/32 with a manifest refraction of −0.75 in the right eye and 20/25 with −1.25 −0.50 × 170 in the left eye. The LASIK eye (right eye) showed no signs of flap dislocation or epithelial ingrowth but a distinct increase in subepithelial reflectivity (Fig 1C), as demonstrated by high-resolution Scheimpflug imaging (Pentacam HR; Oculus Optikgeräte GmbH, Wetzlar, Germany). Corneal confocal microscopic analysis performed at 4 months after surgery showed subepithelial hyperreflectivity at 20 to 40 μm below Bowman's layer in the right eye where thin-flap LASIK surgery had been performed. Both eyes showed activated keratocytes at a corresponding depth (Fig 2).

Therapy consisted of topical fluorometholone (FML Liquifilm; Allergan Inc, Irvine, Calif) twice daily for 8 weeks, followed by application once daily for 4 weeks. At 1 week after initiation of steroid therapy, an increase in intraocular pressure (IOP) to 24 mmHg was measured by Goldmann applanation tonometry over the center of the flap. The increase in IOP was treated with topical latanoprost (Xalatan; Pfizer Inc, New York, NY) once daily for 1 week. Subepithelial haze resolved slowly over the following 2 months and at 6 months after surgery, uncorrected distance visual acuity (UDVA) was 20/20 in both eyes.

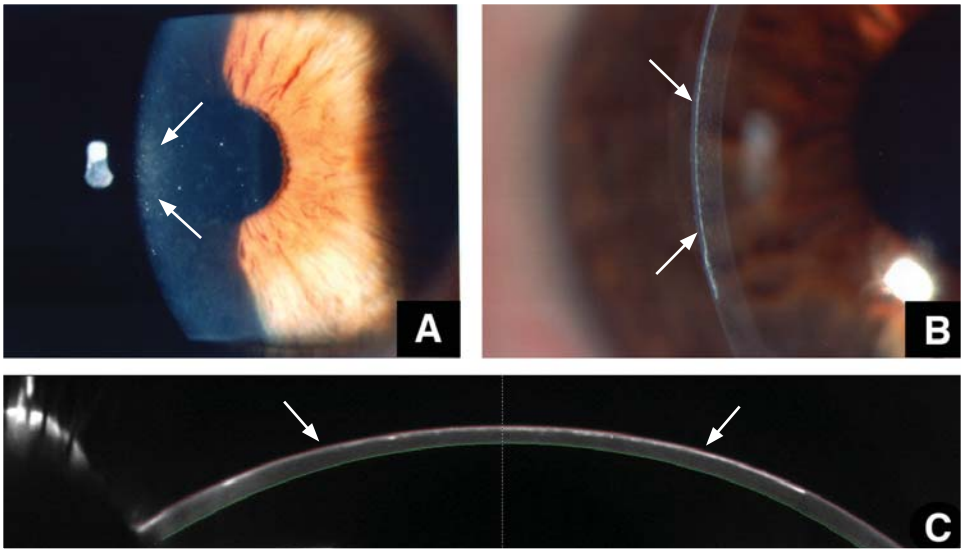

Figure 1. *Case 1.* **A, B)** Slit-lamp images of subepithelial corneal haze (arrows) in the interface between the corneal flap and wound bed of the right eye. **C)** High-resolution Scheimpflug imaging of the subepithelial haze (arrows) in the right eye.

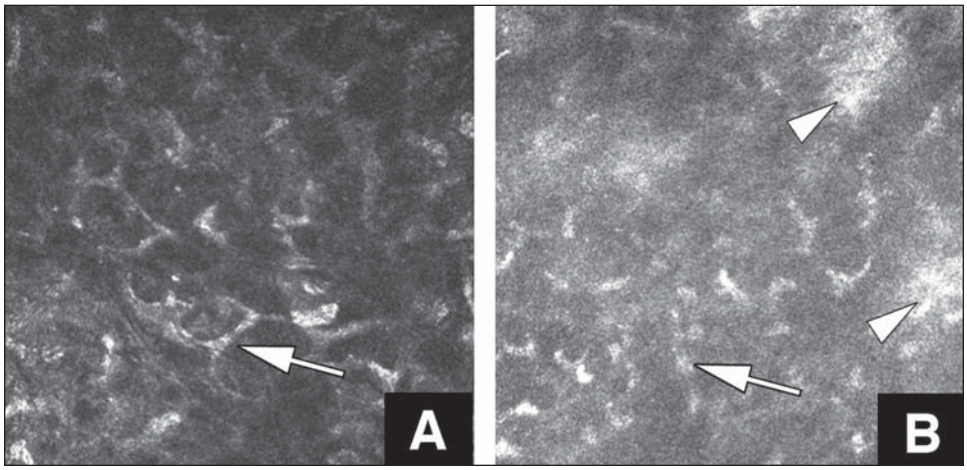

Figure 2. *Case 1.* Corneal confocal microscopic sections of the anterior corneal stroma at 20 to 40 μm below Bowman's layer. **A)** At 4 months after photorefractive keratectomy of the left eye, activated keratocytes (arrow) can be identified. **B)** At 4 months after thin-flap LASIK, the anterior stroma shows activated keratocytes (arrow) and hyper-reflective deposits corresponding to subepithelial fibrosis (arrowhead).

CASE 2

A 44-year-old man underwent bilateral LASIK for myopia in April 2008. He had no history of ophthalmic disease, and preoperative manifest refraction in the right eye was −3.75 and −3.50 in the left eye. The refraction target was bilateral emmetropia. Scheimpflug imaging of both corneas showed normal findings. In both eyes, a low energy femtosecond laser (LDV; Ziemer Ophthalmic Systems AG, Biel, Switzerland) was used to create the flap. The intended flap thickness was 110 µm. However, postoperative confocal microscopy revealed a 95-µm–thick lamella. Early postoperative healing was uneventful, but at 1-month follow-up, the patient reported increased glare in the right eye. Glare visual acuity testing was performed using a Humphrey ARK 599 (Carl Zeiss Meditec AG, Jena, Germany) with various levels of reduced letter contrast. Glare visual acuity was reduced from 20/30 preoperatively to 20/200 at 1 month. At the slit lamp, distinct subepithelial haze grade 1+ was seen (Fig 3). At the 3-month examination, the haze was again graded 1+ but decreased to 0.5+ at 6-month follow-up. Glare visual acuity in the right eye had increased to 20/50 at that time, and UDVA was 20/20 in both eyes.

DISCUSSION

Flap generation in LASIK surgery can induce unwanted corneal biomechanical changes that may lead to iatrogenic keratectasia.[4] Hence, many surgeons have returned to the safety of PRK.[1,2]

Thin-flap LASIK represents a new method where thin flaps ⩽100 µm are generated. This technique potentially combines the biomechanical safety of surface ablation with the known advantages (quick visual recovery) of LASIK.[3,5,6]

In addition, the peripheral anterior corneal stroma is stronger than the central corneal stroma.[7,8] Using shearing interferometry, Marshall[1] showed that femtosecond laser flaps had greater biomechanical stability than microkeratome-generated flaps, which tend to be thinner in the center and thicker in the periphery. Another advantage of thin-flap LASIK is the greater residu-

Figure 3. *Case 2.* Slit-lamp image of subepithelial corneal haze in the interface between the corneal flap and wound bed.

al corneal bed that lowers the risk of iatrogenic keratectasia. The tissue spared in thin-flap LASIK might even allow for higher corrections.[5,9]

Potential complications and side effects of thin-flap LASIK may include intraoperative complications such as flap tear and free cap and postoperative complications such as epithelial ingrowth, flap striae, and diffuse lamellar keratitis.[5] Only a few studies have been performed to investigate the complication rate in thin-flap LASIK. Some groups reported more intra- and postoperative complications than in thick-flap LASIK, whereas others noted less complications,[3,5] even when flap thickness was 90 µm.[6]

We report the occurrence of persistent subepithelial haze following thin-flap LASIK in two patients, a complication to our knowledge not described to date. Interestingly, experimental studies showed that femtosecond laser flaps of standard thickness (>110 µm) do not induce haze formation.[10] Rather, haze formation might only occur when proinflammatory cytokines are allowed to enter the corneal stroma, ie, after an epithelial injury.[11] In thin-flap LASIK, flaps are cut in close proximity to Bowman's layer, and the basement membrane of the corneal epithelium might be damaged. We, therefore, speculate that defects in Bowman's layer allow contact between proinflammatory epithelium-derived cytokines such as transforming growth factor β and the corneal stroma.[12] This increased cellular signaling might lead to increased keratocyte activity and the subepithelial haze observed.[13,14]

Diffuse and transient interface haze after LASIK is also observed in interface fluid syndrome. Steroid-induced elevation of IOP leads to accumulation of aqueous fluid in the interface between the flap and stromal bed.[7,15] However, we observed a transient IOP increase in case 1 only, and no signs of fluid pocket formation were detected on slit-lamp examination and Scheimpflug imaging.

Because subepithelial haze in PRK increases with the depth of treatment, an open issue is whether haze formation in thin-flap LASIK also shows an ablation depth–dependent response or an association to other risk factors that have yet to be determined. If the latter would be the case, then the use of antimetabolites such as mitomycin C or transforming growth factor β-blocking agents might be considered.

AUTHOR CONTRIBUTIONS

Study concept and design (F.H., T.S.); data collection (F.H., T.S.); interpretation and analysis of data (F.H., T.S.); drafting of the manuscript (F.H., T.S.); critical revision of the manuscript (F.H., T.S.)

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LASIK Flap Buttonhole Treated Immediately by PRK With Mitomycin C

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ABSTRACT

PURPOSE: To describe the visual outcomes of three patients who had LASIK flap buttonhole and were treated immediately with photorefractive keratectomy (PRK) and topical mitomycin C (MMC) 0.02%.

METHODS: Three patients underwent bilateral LASIK with the SCHWIND Carriazo-Pendular 90-μm head microkeratome. In all three cases, a buttonhole flap occurred in the left eye. The flap was repositioned and phototherapeutic keratectomy for 50 μm was used for epithelial removal while immediate PRK with MMC was performed to treat the buttonhole flap.

RESULTS: Three months after the procedure, uncorrected distance visual acuity and corrected distance visual acuity were 20/20 with regular topographic findings.

CONCLUSIONS: Using PRK with MMC immediately after the occurrence of a LASIK flap buttonhole may be an effective treatment. [*J Refract Surg*. 2010;26:225-228.]
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Laser in situ keratomileusis is a refractive surgical procedure with numerous advantages (fast and painless recovery, rapid visual rehabilitation, lack of subepithelial haze),[1-3] most of which are due to the creation of a corneal hinged flap. The incidence of intraoperative complications related to flap creation was reported to be 5% to 8.7% by Lin and Maloney.[4] One of the most serious flap irregularities is the buttonhole flap, with an occurrence rate of 0.3% to 2.6%.[3] A more superficial entrance of the microkeratome at the epithelium–Bowman layer interface results in the creation of a buttonhole. The uncut portion of the flap, resulting in a doughnut-shaped flap, is characteristic of this type of complication.[3] The irregular surface of the flap may provoke irregular astigmatism and decreased visual acuity, which may interfere with a patient's everyday life activities.

Different explanations have been provided to interpret the creation of a buttonhole flap. Steep corneas and partially opened eyes that may be subject to desiccation and thinning of the cornea may result in buttonhole creation. Microkeratome deficits, such as a blade defect and insufficient synchronization between the movement of the blade and microkeratome translational movement, have been suggested as probable causes. Inadequate suction, due to high astigmatism, or conjunctival incarceration may also lead to buttonhole flaps.[3]

Treatment options for buttonhole flaps depend on the severity of the complication.[5,6] Full or partial thickness flaps without epithelial ingrowth are usually managed by photorefractive keratectomy (PRK) with mitomycin C (MMC) at least 3 months after the complicated LASIK procedure. For buttonhole flaps with epithelial ingrowth around the margins, phototherapeutic keratectomy (PTK) followed immediately by PRK with MMC after a 3-month interval is considered the best approach.[7] Buttonhole flaps with stromal melt are best approached with a two-stage treatment: primary PTK followed by PRK once refractive stability is achieved.[8,9]

In this case series, we present three patients who underwent LASIK for refractive error correction, which resulted in a buttonhole formation in their left eye. Photorefractive keratectomy with MMC was performed immediately to treat the buttonhole flap.

CASE REPORTS

Case 1

A 23-year-old man presented for refractive error correction. At the time of examination, uncorrected distance visual acuity (UDVA) was counting fingers and corrected distance visual acuity (CDVA) was 20/20 in both eyes. Manifest refraction was $-5.25\ -0.25 \times 155$ in the right eye and $-5.50\ -0.25 \times 10$ in the left eye. Preoperative central corneal thickness (Corneo-Gage Plus; Sonogage, Cleveland, Ohio) was 579 µm and 574 µm in the right and left eyes, respectively. Simulated kerato-

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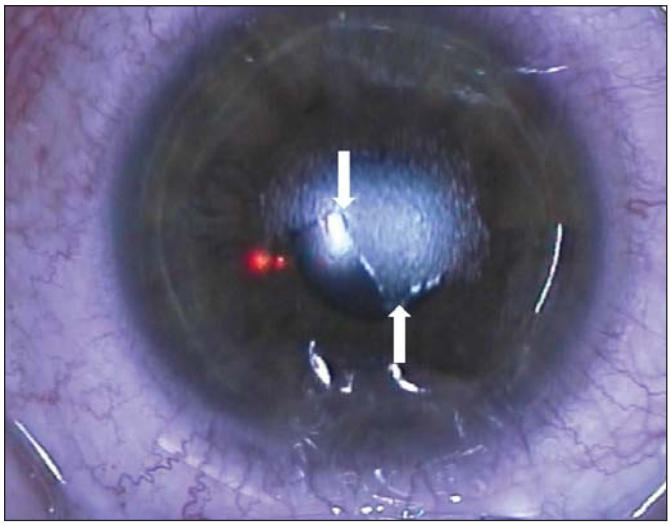

Figure 1. *Case 1.* Intraoperative photograph of the LASIK flap buttonhole.

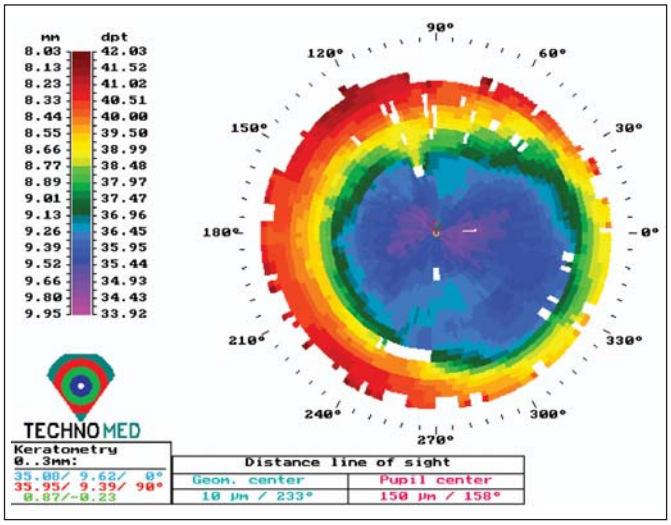

Figure 2. *Case 2.* Topography at 1 month shows an oblate corneal contour after photorefractive keratectomy with mitomycin C immediately following LASIK flap buttonhole.

metry was 41.80 diopters (D) in the right eye and 42.10 D in the left eye. During the preoperative examination, the patient reported inflammation from adenovirus 2 years prior to presentation in both eyes that was treated with topical use of cortisone drops. Slit-lamp microscopy revealed a dim spot at 5 o'clock in the right eye and two consecutive spots at 12 o'clock in the left eye with no signs of active inflammation. Complete funduscopy examination did not show any abnormalities. Taking the corneal thickness and refractive error into consideration, the surgeon (G.K.) proceeded with LASIK to correct myopia and astigmatism.

Case 2

A 30-year-old man presented for refractive error correction. At the time of examination, UDVA was counting fingers and CDVA was 20/20 in both eyes. Manifest refraction was $-5.50\ -2.25 \times 10$ in the right eye and $-6.75\ -1.50 \times 175$ in the left eye. Preoperative central corneal thickness (Corneo-Gage Plus) was 602 µm and 598 µm in the right and left eyes, respectively. Simulated keratometry was 43.10 D in the right eye and 43.40 D in the left eye. Slit-lamp microscopy revealed a subepithelial paracentral scar in the left eye. The remainder of the preoperative examination did not reveal any abnormalities. The surgeon (G.K.) proceeded with LASIK to correct myopia and astigmatism.

Case 3

A 41-year-old woman was referred for refractive error correction. At the time of examination, UDVA was counting fingers and CDVA was 20/20 in both eyes. Manifest refraction was $-1.50\ -2.25 \times 20$ in the right eye and $-6.25\ -2.25 \times 45$ in the left eye. Preoperative central corneal thickness (Corneo-Gage Plus) was 580 µm and 585 µm in the right and left eyes, respectively. Simulated keratometry was 43.43 D in the right eye and 43.86 D in the left eye. Slit-lamp microscopy revealed a clear cornea and a normal fundus. The surgeon (G.K.) proceeded with LASIK to correct myopia and astigmatism.

Buttonhole Flap Complication

For all three patients, the Carriazo-Pendular 90-µm head microkeratome (SCHWIND eye-tech-solutions, Kleinostheim, Germany) was used. In the right eye of all three patients, the flap was created successfully and flap thickness was assessed at 72 µm, 77 µm, and 76 µm, respectively. Subsequent to the right eye, a new sterilized head and blade were provided for the left eye. Intraoperatively, in all cases, a buttonhole flap occurred (Fig 1). After flap lift, the flap was immediately floated back into position. Flap alignment was checked using Gentian violet preoperative corneal markings. A 7.0-mm diameter of the corneal epithelium was removed using PTK for 50 µm. After epithelial removal, PRK with MMC was performed. A bandage soft contact lens was applied on the left eye until full re-epithelialization occurred.

Postoperative medication included diclofenac sodium 0.1% (Denaclof; Novartis, Basel, Switzerland) for 2 days as well as antibiotic/corticosteroid (tobramycin/dexamethasone) drops (Tobradex; Alcon Laboratories Inc, Ft Worth, Tex) four times daily until removal of the bandage soft contact lens. After contact lens removal, patients administered corticosteroid drops (fluorometholone 0.1%; Falcon Pharmaceuticals, Ft Worth, Tex) in the left eye, tapering the dosage over 3 weeks. Patients were

encouraged to use artificial tears at least six times per day for 6 months postoperatively.

A complete postoperative examination was performed 1 month after surgery. For all patients, UDVA was assessed at 20/20 in both eyes and CDVA was 20/20 in both eyes with manifest refraction in the left eye of +0.50 in case 1, +0.25 +0.50 × 80 in case 2, and +0.50 in case 3. On slit-lamp examination, the edges of the attempted flap in the left eye were visible. Topographic findings in the left eye revealed a uniform ablation pattern (Fig 2). At 3 months postoperatively, UDVA and CDVA remained 20/20 in both eyes and manifest refraction in the left eye was plano in case 1, +0.50 in case 2, and plano −0.50 × 30 in case 3.

DISCUSSION

An irregular flap, such as a buttonhole flap, is an intraoperative complication that may interfere with a patient's everyday activities because it might result in irregular astigmatism and loss of visual acuity. When a buttonhole occurs, good alignment between the flap buttonhole and uncut tissue is crucial to avoid epithelial ingrowth and irregular astigmatism. For that same reason, it is also necessary to meticulously clean the stromal bed. A bandage soft contact lens is positioned to ensure proper alignment.[3]

The standard procedure after buttonhole creation is to wait at least 3 months before performing a second, deeper LASIK cut. This waiting period is important to assure flap adherence. Photorefractive keratectomy over the initial complicated flap or a second, deeper microkeratome cut is usually performed at least 12 weeks after LASIK to avoid dense scar formation.[3]

Chalita et al[10] reported a patient with a LASIK flap buttonhole who underwent wavefront-guided PRK with MMC 3 months after the initial surgery. After LASIK, CDVA was 20/30; the patient suffered from monocular diplopia that could not be resolved with spectacles. Wavefront analysis revealed the presence of higher order aberrations, especially coma. Immediately, after enhancement, the patient cited an improvement of double vision symptoms and visual acuity and a decrease in higher order aberrations.

In this case series, patients underwent immediate PRK after buttonhole flap creation. Mitomycin C (0.02%) was applied with a spear for 30 seconds before the completion of the procedure to avoid postoperative corneal haze formation. Intraoperative complications occurred in the second (left) eye, while the first (right) eye underwent LASIK successfully.

Visual rehabilitation was obvious in both eyes from the first month after surgery, with regular topographies and lack of subjective symptoms (glare, halos). One month postoperatively, UDVA and CDVA were 20/20. Three months after surgery, UDVA remained 20/20 in both eyes. All patients were emmetropic although there was no adjustment in the attempted correction despite the fact that all three LASIK procedures were reversed to PRK with MMC.

Immediate treatment after LASIK flap buttonhole is a new approach that has certain advantages when compared to the established treatment methods of complicated LASIK flaps. The decision to abort the procedure and proceed with an enhancement surgery 3 months later could lead to anisometropia, patient anxiety, scar formation, epithelial ingrowth, and irregular astigmatism, which can make the retreatment challenging. Immediate treatment of the LASIK flap buttonhole may overcome those limitations.

One important advantage of immediate enhancement is patient satisfaction. Immediate visual rehabilitation and lack of subjective symptoms such as diplopia, glare, and halos can account for a successful surgical outcome. The same stands for anisometropia, which can result due to buttonhole creation in one of the two eyes treated. In addition, delaying the enhancement procedure can lead to scar formation and irregular astigmatism, which can be avoided if PRK is performed immediately.

When proceeding with immediate PRK treatment over the LASIK flap buttonhole, it is essential to remove the endothelium only by PTK and not manually because flap slippage and irregularity may occur.

Immediate enhancement of complicated LASIK flaps is a new approach, which might prove satisfactory for both patient and surgeon. Larger series of patients and longer follow-up are necessary to confirm these encouraging results.

AUTHOR CONTRIBUTIONS

Study concept and design (G.D.K., D.M.P., G.A.K., S.H.Y.); data collection (A.E.K., M.S.K., A.A.S.); drafting of the manuscript (A.E.K., G.A.K., A.A.S.); critical revision of the manuscript (G.D.K., D.M.P., M.S.K., S.H.Y.); supervision (G.D.K., S.H.Y.)

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