

Research Progress on Ocular Surface Changes after Femtosecond Laser Small Incision Lenticule Extraction

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Abstract

The femtosecond laser has a number of advantages, such as short pulse time, high instantaneous power, high repetition rate, low monopulse energy, and small thermal effect. Femtosecond laser-assisted small incision lenticule extraction (SMILE) is becoming the new direction in refractive surgery, and the ocular surface changes after SMILE are attracting increasingly more attention. This article reviews adverse effects, including dry eye, injury of corneal nerves, and ocular surface inflammation, occurring after SMILE. (*Eye Science* 2015; 30:48–52)

Keywords: femtosecond laser; small incision lenticule extraction; dry eye; ocular surface inflammation

Introduction

The developments in science and technology and the innovation of femtosecond laser equipment have broadened the application scope of the femtosecond laser in refractive surgery from flap creation to small incision lenticule extraction (SMILE), with significant enhancements in the accuracy, safety, and stability of refractive surgery. Dry eye is a common surgical complication of laser in situ keratomileusis (LASIK) and the primary factor leading to a decreased degree of patient satisfaction¹. The mechanism underlying dry eye is complex and multifaceted, probably including a reduction in corneal sensation and the blink reflex, decreased tear film stability secondary to corneal curvature alterations,

peripheral goblet cell injury, corneal epithelial malnutrition, use of medication or inflammation effect, etc^{2,3}. SMILE has been regarded as representing significant progress in refractive surgery. The influence of SMILE on the ocular surface structure is now capturing increasingly more attention from ophthalmologists.

Features of femtosecond laser and SMILE

Femtosecond laser produces a pulse of light with a wavelength of 1053 nm and extremely short duration of only dozens of femtoseconds (1 femtosecond=10⁻¹⁵ s). It allows a high-density spot (approximately 3 μm in diameter) to be focused on the target depth of corneal tissue and generates a stromal cavitation bubble made of carbon dioxide and water by the plasma blast. Many bubbles tightly connect and fuse into a cutting line. Thousands of cutting lines converge onto the stromal cutting surface, thereby attaining the precise cutting effect on the tissues⁴.

Femtosecond laser has been used successfully in refractive surgery since 2001, most notably in the creation of a corneal flap during LASIK refractive surgery. It has also been applied for the implantation of corneal stromal rings, astigmatic keratotomy, corneal transplantation, and cataract surgery. The introduction of the VisuMax femtosecond laser (Carl Zeiss, Germany) in 2006 significantly advanced the development of lenticule extraction. At present, the main procedures are femtosecond lenticule extraction (FLEx) and SMILE. In FLEx, a corneal pedicle flap is created by the femtosecond laser and the lens is then extracted by raising the corneal flap. In SMILE, lens extraction can be completed through a minimal arc incision (2–4 mm in diameter) without need for a corneal flap¹. SMILE is therefore a novel

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refractive surgery that not only retains the integrity of the corneal anatomical structure, but also maintains the intact structure of anterior corneal stromal layer and Bowman's membrane, which exerts the most pivotal effect on the biomechanical property of the cornea. SMILE also can reduce postoperative corneal irritation, alleviate corneal nerve injury, and ease dry eye and ocular surface inflammation and alternative complications. It is regarded as a minimally-invasive procedure.

Dry eye parameters after SMILE

Dry eye is a multifactorial disease of the tears and the ocular surface that results in discomfort, visual disturbance, and instability of the tear film, with potential incidence of ocular surface inflammation⁶. Tear film stability maintains the normal structure and function of the ocular surface epithelium and depends on normal functioning of the lacrimal gland and of the sensory and motor nerves that connect to the lacrimal gland. Disruption of tear film stability is the first factor leading to ocular surface disease. Tear film break-up time (BUT), the Schirmer I test (SI_t), and subjective grading are the most common methods for evaluating tear film stability and dry eye. Tear film stability and tear fluid secretion differ after different refractive surgeries.

Xu et al⁷. analyzed the incidence of dry eye after SMILE and LASIK and found the SI_t before SMILE and at 1, 3, and 6 months after SMILE was 17.49 ± 7.48 , 16.98 ± 6.43 , 17.46 ± 9.25 , and 17.13 ± 6.73 mm, respectively. The SI_t value was restored to the preoperative level at postoperative 3 months. The same tendency in SI_t changes was noted after femtosecond laser LASIK and SMILE. The SI_t value was gradually recovered at postoperative 6 months following LASIK flap creation with a mechanical microkeratome. The average BUT value before SMILE was 10.35 ± 3.28 s, and was steadily restored to the preoperative level at 6 months after surgery. The tendency of BUT changes was similar after femtosecond laser LASIK and LASIK using a mechanical microkeratome. The mean subjective rating score was the highest after SMILE.

In this study, the symptoms of dry eye occurred after SMILE, femtosecond laser LASIK, and me-

chanical microkeratome LASIK, but dry eye was less severe after SMILE than after LASIK. Li et al⁸. found that SMILE restored BUT to the preoperative level at postoperative 6 months after SMILE, whereas BUT was still lower than the preoperative level 6 months following femtosecond laser LASIK. The subjective symptoms of dry eye were alleviated at postoperative 1 month after SMILE and femtosecond laser LASIK, and the subjective symptoms after SMILE were less serious. Sekundo et al². found that corneal fluorescence staining and dry eye symptoms were less severe after SMILE than after FLEX, suggesting advantages of SMILE. Lemp et al⁹. recommended tear osmolarity as a novel reliable parameter for the diagnosis and classification of dry eye. Compared with alternative tests, tear osmolarity measurement has higher sensitivity and stability¹⁰.

The tear osmolarity value for healthy subjects is 300 mOsm/L. Tear hyperosmolarity is one of the reasons for abnormal ocular sensation⁶. Versura et al¹¹. demonstrated that the positive predicted value of tear osmolarity in the clinical diagnosis of dry eye disease was 98.4%, with a likelihood ratio of 10.99. Benelli et al¹². found that tear osmolarity tended to decrease to 5.0-9.0 mOsm/L after topical use of lubrication. Corneal refractive surgery is likely to lead to tear osmolarity changes. Vestergaard et al¹. reported that tear osmolarity did not significantly differ before and at 6 months after FLEX and SMILE.

Corneal reinnervation and sensitivity after SMILE

The human cornea contains an abundant quantity of nerve fiber plexuses that originate from the nasociliary nerve branch of the trigeminal nerve. The corneal nerve of human eyes is mainly located at the anterior 1/3 of the corneal stroma, penetrates the Bowman's layer, and forms a shallow stromal nerve plexus in a radiating pattern¹³. Corneal nerve integrity is an essential condition for maintaining corneal sensitivity. The corneal nerve fibers and related nerve factors and neuropeptides play a vital role in maintaining the physiological stability of the cornea. Corneal flap creation and stromal ablation can interfere with the sensory transduction of the corneal nerve, decrease corneal perception, reduce the reflex

arc impulsion, and decrease tear fluid secretion. The expression levels of neuropeptide and corneal nerve trophic factors, such as neuropeptide P and calcitonin gene-related peptide are down-regulated after refraction surgery¹⁴, which tends to reduce corneal sensation¹⁵. These stable behaviors are driven by the neural reflex mediated by corneal sensitivity¹⁶. Therefore, regeneration of the corneal nerve plays a pivotal role in restoring corneal physiological characteristics, tear secretion, and wound healing.

SMILE is a novel type of refractive surgery that does not require the assistance of a mechanical microkeratome and extra laser. It is a surgical procedure without flap creation—SMILE replaces the corneal flap with a corneal cap, which enormously decreases the severity of corneal trauma, reduces the ablation area of corneal surface nerve fiber, and maintains the integrity of the anterior stromal nerve of the corneal cap as much as possible. SMILE is performed with the assistance of femtosecond laser photodisruption, which causes almost no heat transfer and exerts only a slight effect on the corneal nerve.

Regeneration of the corneal nerve appears to occur after refraction surgery. Vestergaard et al¹. observed that the density of the stromal nerve, viewed under a confocal microscope, was reduced by (9.21 ± 7.80) mm/mm² on average at 6 months after SMILE, hinting that SMILE was better than FLE_x at protecting the corneal central nerve. Li et al⁸. measured the reduction in the density of the stromal nerve at 1 week and 1 and 3 months and found a significantly smaller reduction in density after SMILE than after femtosecond laser LASIK, whereas no statistically significant difference was noted 6 months after surgery. They also demonstrated that the density of the stromal nerve is positively correlated with central corneal sensitivity.

The human corneal nerve is mainly located in the anterior 1/3 part of the cornea. Hence, the deeper corneal stromal ablation during SMILE yields less nerve injury¹⁷. Reduction in corneal sensation tends to cause a decreased blink reflex and promotes tear evaporation, thereby leading to a reduction in tear secretion. Demirok et al¹⁸. assessed the corneal sensation using a Cochet-Bonnet esthesiometer and found that the corneal sensation at 1 week, 1, and 3

months after SMILE and femtosecond laser LASIK was significantly decreased compared with preoperative level and was restored to the level prior to surgery. The corneal sensation at different time points was considerably higher after SMILE than after femtosecond laser LASIK. Li et al⁸ found that the corneal sensation at 1 week, 1, and 3 months was higher following SMILE than after femtosecond laser LASIK, but with no statistical significance. The postoperative corneal sensation remains to be further investigated.

Goblet cells after SMILE

Suction pressure and time are vital factors that can activate the mechanism giving rise to dry eye after LASIK¹⁹. A suction ring creates a vacuum that holds the eye in place until the corneal flap is successfully created. The application of the suction ring tends to cause mechanical trauma, such as conjunctival nerve injury, goblet cell degranulation, and reduction in goblet cell density. The size of the suction ring applied during femtosecond laser and mechanical microkeratome LASIK varies and produces different pressure on the ocular surface. The peak intraocular pressure has been reported as 160.52 ± 22.73 mmHg during corneal ablation with a Moria2 mechanical microkeratome, which is significantly higher than the 119.33 ± 15.88 mmHg obtained with the IntraLase procedure in porcine eyes²⁰. The low incidence of dry eye syndrome after femtosecond laser LASIK has been assumed to be associated with suction ring pressure²¹ as lower suction pressure seems to induce less goblet cell injury.

Rodriguez et al¹⁹. found that the goblet cell density at 1 week, 1, and 3 months after femtosecond laser LASIK was significantly lower than that following conventional mechanical microkeratome LASIK, probably resulting from the longer suction time of the femtosecond LASIK. The goblet cell density was restored to the normal range at 6 months postoperatively for both treatments. Sun et al²². observed that the conjunctival staining score at 6 months after femtosecond laser LASIK was still significantly lower compared with preoperative score, whereas the conjunctival staining score did not significantly differ before or after mechanical microkeratome LASIK.

The suction time during femtosecond laser LASIK was 33 s and 8.3 s for mechanical microkeratome LASIK. Although the suction ring pressure in the femtosecond laser group was smaller, the suction time was longer, suggesting the importance of suction time. The influence of alternative factors, such as suction ring material, *etc.* should be verified in future work. At present, the transmitting frequency of the femtosecond laser is 60 kHz. The corneal cutting during SMILE could be completed within 20–30 s via a femtosecond laser pulse, which significantly alleviates the conjunctival injury induced by long time suction. However, the effects of SMILE on conjunctival goblet cells have yet to be reported.

Ocular surface inflammation after SMILE

Corneal wound healing after refractive surgery occurs by an extremely complicated cascade²³. After keratocyte apoptosis within the injured zone, adjacent corneal cells are activated to transform into corneal fibroblasts or myofibroblasts and these cells migrate to the stromal ablation zone. Pro-inflammatory chemokines from the epithelium or from keratocytes responding to IL-1 and TNF- α trigger stromal infiltration by inflammatory cells, such as monocytes, granular cells and lymphocytes, which play a role in the phagocytosis of apoptotic and necrotic debris. Myofibroblasts are involved in collagen and extracellular matrix remodeling through production of collagen, glycosaminoglycans, collagenases, gelatinases, and MMPs.

The persistent vibration of the mechanical microkeratome may cause corneal epithelial injury during mechanical microkeratome LASIK²², whereas a smooth and static suction ring is applied to flatten the cornea during femtosecond laser LASIK and dramatically alleviates the corneal epithelial damage. Netto et al²⁴. compared keratocyte apoptosis after flap creation by femtosecond laser and mechanical microkeratome at a frequency of 15, 30 and 60 kHz, and found that the level of keratocyte apoptosis was the highest using 15 kHz femtosecond laser and elevated along with the increasing frequency. The level of keratocyte apoptosis was almost equivalent between the femtosecond laser and mechanical microkeratome

groups. The energy level of femtosecond laser seems to exacerbate corneal cell death and the severity of the inflammatory response²⁵.

Dong et al. utilized TUNEL assay to detect corneal cell apoptosis in rabbit models and found significantly fewer TUNEL-positive corneal stromal cells after the SMILE procedure at 4 and 24 h postoperatively than after the LASIK procedure. In addition, immunocytochemistry showed that the CD11b-positive cells were significantly fewer in the SMILE group at week 1 postoperatively than after femtosecond laser LASIK. SMILE induced less epithelial trauma due to its small incision and less contact with cytokines for free of lifting the cap. Nevertheless, femtosecond laser may cause corneal epithelial injury and release a great quantity of chemokines during flap creation, which facilitates the dispersion of cytokines at the interface via tears and epithelial debris. Necrotic debris among corneal layers is also a vital factor leading to corneal inflammatory response.

Femtosecond laser is a type of near-infrared ray with short pulse duration, high instant power, and mild thermal effect. As a type of ultraviolet radiation, excimer laser could cut the corneal tissue through the breakdown of molecular bonds, which yields more severe corneal trauma and more necrotic cell debris among the corneal stromal layers. Therefore, compared with femtosecond laser LASIK, SMILE could induce less corneal stromal apoptosis and inflammatory response.

Outlook

SMILE is an innovative refractive correction approach that uses the femtosecond laser. SMILE alters the approach of stromal ablation, which has mainly relied on the excimer laser in the past, and eliminates the need for simultaneous use of two instruments during femtosecond laser LASIK. SMILE is a safe, feasible, and predictable surgical procedure that has advantages in reducing the incidence of dry eye, nerve injury, and ocular surface inflammation. Taken together, the results that have led to a deeper understanding of the ocular surface situation after SMILE now facilitate the mastery and utilization of the femtosecond refractive correction technique.

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