

**Title:**

Early clinical outcomes after small incision lenticule extraction surgery (SMILE)

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**Conflicts of interest:**

None

## **Abstract**

**Purpose:** Dry eye is known to impact on clinical outcomes after laser vision correction and the use of a newer 'all femtosecond laser' surgical approach may be associated with less impact on the ocular surface post-operatively. The purpose of this study was to evaluate the early clinical outcomes and tear instability after the first small incision lenticule extraction (SMILE) cases undertaken by three surgeons at a single site in the UK.

**Methods:** Retrospective audit. Seventy-one eyes of 37 patients underwent SMILE surgery using the Zeiss VisuMax laser system (Carl Zeiss Meditec, Germany). Uncorrected and corrected distance visual acuity, spherical equivalent refraction, fluorescein enhanced tear break up time, simulated keratometry and complications were evaluated pre- and post-operatively where applicable.

**Results:** The study population consisted of 21 males and 16 females. The mean  $\pm$  standard deviation age was  $33 \pm 8$  years. The results showed that 100% of eyes achieved 20/40 or better and 88% achieved 20/20 or better uncorrected distance visual acuity. The spherical

equivalent refraction after surgery was within  $\pm 0.50D$  in 82% of eyes at three months. There was no significant difference in tear break up time from pre-operative levels at three months. Complications were infrequent.

**Conclusions:** This early data from surgeons' first SMILE procedures suggest SMILE provides good outcomes in terms of refractive predictability and visual acuity with minimal impact on the tear film. Longitudinal research will further improve our understanding of the longer-term impact of SMILE on clinical outcomes, ocular surface metrics and patient reported outcomes.

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**Keywords:** Small incision lenticule extraction, SMILE, learning curve, ocular surface, dry eye, outcomes

### **Highlights**

- Ophthalmic surgery can lead to or exacerbate dry eye signs and symptoms
- SMILE appears to be a safe and efficacious option for the correction of myopia and myopia with astigmatism
- Early clinical outcomes data from surgeons' first procedures compare favourably to excimer based LASIK and surface ablation techniques
- Small incision lenticule extraction (SMILE) may have less impact on the ocular surface compared to other forms of laser vision correction

## **Introduction**

The application of femtosecond lasers has revolutionised corneal refractive surgery and has led to further improvements in safety, visual outcomes as well as the development of newer surgical approaches [1]. Small-incision lenticule extraction (SMILE) is a technique that uses a single (femtosecond) laser platform to create an intrastromal lenticule using photo pulses at high frequency ( $10^{-15}$  seconds) [2-5]. A small superior incision is created to allow removal of the lenticule using forceps, thus avoiding the need for a formal flap. Previous research has described the impact of corneal refractive surgery on the nerve plexus, corneal sensitivity and dry eye [5, 6]. Theoretically, intrastromal techniques such as SMILE should reduce the effects on corneal denervation and dry eye and preserve biomechanical stability when compared to flap-related procedures [7]. The purpose of this study was to evaluate the clinical outcomes and tear film stability before and after the first cases of SMILE undertaken by surgeons in the early learning curve at a specialist eye hospital.

## **Patients and Methods**

This study was a retrospective analysis performed at a private eye hospital in London, UK to evaluate the early clinical outcomes of the first SMILE procedures undertaken by three surgeons with the VisuMax laser platform (Carl Zeiss Meditec, Jena, Germany). The study population comprised 71 eyes from 37 patients (21 males and 16 females) with myopia, with or without astigmatism, (mean spherical equivalent refraction (SEQ)  $-5.61 \pm 2.25$  Dioptres (D), ranging from  $-10.88$  D to  $-1.25$  D). The surgeries were bilateral in 34 patients, and three patients had unilateral surgery.

All surgeries were non-monovision treatments where the target refraction was plano (0 D) to achieve emmetropia. No attempt was made to correct presbyopia in the study population.

Inclusion criteria for the study were myopia treatment up to  $-10.00$  D with ocular astigmatism up to  $-5.00$  D, patients seeking to become more spectacle independent and seeking an advanced corneal refractive laser approach. Exclusion criteria were unstable refractive error, previous ocular surgery or trauma, ocular abnormalities or disease, progressive myopia or astigmatism and any systemic disease which could affect wound healing (e.g. diabetes). Informed consent was obtained and the study was performed in accordance with tenets of the Declaration of Helsinki.

## **Pre- and post-operative examinations**

A standard protocol of testing was carried out for all patients pre-operatively. This included recording of ocular and medical history, measurement of uncorrected and corrected distance visual acuity, subjective manifest and cycloplegic refraction using an automatic phoropter head, scotopic pupil size measurement with a handheld pupilometer, ocular motor balance and dominance testing, anterior segment assessment and fluorescein tear break-up time (TBUT) assessed with a slit lamp and dilated posterior segment assessment. Diagnostic testing included objective refraction and simulated keratometry (SimK) using an Oculus Pentacam (OCULUS, Germany). The anterior simulated keratometer readings were taken before and 3 months after surgery considering the “25-picture scan” mode and only the scans graded with acceptable quality by the instrument were referenced. All the keratometer readings considered were based on a  $15^\circ$  ring around the anterior corneal apex.

Spherical equivalent refraction, uncorrected distance visual acuity (UDVA) and TBUT were measured before and 3 months after surgery. Corrected distance visual acuity (CDVA) was compared with post-operative uncorrected vision. Operative complications were recorded. Visual acuity data were measured with a computerized test chart (Topcon, Tokyo, Japan) and recorded in Snellen/logMAR. TBUT was performed by instilling 1 drop of preservative-free 1% sodium fluorescein (from a 0.5ml minim) onto the bulbar conjunctiva. This avoided reflex tearing which can occur through the use of a vital dye impregnated strip. The patients were instructed to blink naturally, without squeezing, several times to distribute the fluorescein. Within 10-30 seconds of the fluorescein instillation, patients were asked to undertake one complete blink and then stare straight ahead without blinking until the TBUT measurement was completed. Background illumination intensity was kept constant and a cobalt blue light with a Kodak Wratten #12 yellow filter was used to enhance observation of the tear film. The examiner recorded the time with a stopwatch between the last complete blink and the first appearance of black spots (tear disruption). The measurements were repeated 3 times and then averaged.

### **Surgical technique**

The Zeiss VisuMax femtosecond laser platform was used for all surgeries: the frequency was set to 500 kHz with a spot energy of 140 nJ. The spot distance was 4.3  $\mu\text{m}$  and the tracking distance was 1.8  $\mu\text{m}$ . The lenticule diameter was between 6.5 and 7 mm, depending on the degree of astigmatism with a small incision position at 50/130 degrees and a tunnel size from 2 to 4 mm. The standard depth of anterior lenticule was 135-140  $\mu\text{m}$ , except in patients with thin corneas where it was reduced to 100-140  $\mu\text{m}$ . The same approach was used in all patients.

### **Statistical analysis**

Statistical analysis was performed using SPSS 23.0 (IBM Corp, Armonk, NY, USA).

The main outcome measures were: SEQ, UDVA, CDVA, TBUT and SimK. The Shapiro-Wilk test was used for testing normality of the data, the Student's t-test was used to compare pre- vs post-operative SEQ, while non-normally distributed data such as UDVA, CDVA, TBUT and SimK were analysed using Wilcoxon signed ranks tests. Pearson's correlation coefficient was used to assess the association between the individual clinical signs of TBUT and SimK after surgery. A p-value of less than 0.05 was considered to be statistically significant.

### **Results**

Mean patient age was  $33 \pm 8$  years. Pre- and post-operative summary data are shown in **Table 1**.

The mean SEQ refractive error 3 months after surgery (SEQ\_3M) was found to be statistically significantly reduced compared to pre-operatively (SEQ\_PRE) ( $p < 0.01$ ). The residual post-operative refractive error was within  $\pm 0.50$  D of target in 82% and within  $\pm 1.00$  D in 94% of eyes (**Figure 1**).

After surgery, UDVA improved significantly ( $p < 0.01$ ) (**Table 1**). There was no significant difference between pre-operative CDVA and post-operative UDVA at 3 months ( $p = 0.15$ ) (**Figure 2**).

Three months after surgery TBUT was not significantly different from that measured pre-operatively (**Figure 3**).

A moderate but positive trend ( $r = 0.44$ ) was found between the changes in TBUT and SimK after surgery without significance ( $p > 0.05$ ) (**Figure 4**).

Complications were recorded in 3 eyes, which included a minor epithelial abrasion in two eyes and some difficulty removing the lenticule in one eye. None of the complications were visually significant and the results highlighted the safety profile of SMILE by way of mitigating the flap complications that sometimes occur with LASIK [8].

## Discussion

This retrospective study reports on the early clinical outcomes of three surgeon's first SMILE procedures carried out at a single centre, private eye hospital in the UK. SMILE is a relatively new approach to corneal laser vision correction and offers possible advantages over other laser vision correction procedures for certain patient groups. The results show good refractive predictability with 82% of eyes achieving a residual post-operative refractive error within  $\pm 0.50$  D of target by 3 months after surgery. Three out of the 71 eyes received an enhancement which was undertaken successfully using LASEK resulting in 0.00 logMAR CDVA in one eye and 0.10 logMAR in two eyes, one month after the LASEK enhancement, respectively. This represents an overall enhancement rate of 2.8% which compares favourably with previous studies reporting enhancement rates post-LASIK [9]. Comparing SMILE with photorefractive keratectomy at 6 months, the refractive outcomes showed positive results, especially in low to moderate astigmatic correction with a faster visual rehabilitation [10].

The mean 3 month UDVA approximated the pre-operative CDVA. Overall the 3 month UDVA exceeded the pre-operative CDVA value in 8 eyes (11.3%) and in eyes where the UDVA was lower than pre-operative CDVA, the mean difference was 0.02 logMAR (range 0.1 to 0.4 logMAR). 88 % of eyes achieved a UDVA 0.00 logMAR or better at 3 months and this compares favourably to reported data for myopic and astigmatic patients in both LASIK and LASEK [11, 12]. Ganesh et al. [13] observed better results in terms of UDVA and CDVA with SMILE compared to PRK surgery after 3 months: UDVA logMAR  $-0.013 \pm 0.034$  vs  $-0.061 \pm 0.066$  and CDVA logMAR  $-0.046 \pm 0.062$  vs  $-0.091 \pm 0.064$ , with PRK and SMILE respectively. All SMILE patients achieved 20/20 UDVA whereas only 97% achieved 20/20 after PRK. Additionally, Blum et al. [5] reported positive results in terms of refractive predictability and UDVA in a 5-year follow-up study after SMILE where more than 57% of the study population gained 1 to 2 Snellen lines compared to the previous follow-up. Additional data with a greater number of patients and expanded refractive parameters will enable the assessment of the consistency of the present study results [13-15]. Longer-term follow-up data are used to optimise the laser settings and to refine the clinical outcomes.

The presence of dry eye post-laser refractive surgery is well documented and a multitude of causes have been proposed previously [6, 16]. These include an increased presence of inflammatory mediators in the tear film causing irritation of the ocular surface [17] or damage to conjunctival goblet cells through flap creation with a microkeratome or a femtosecond laser, resulting in disruption of the mucin layer of the tear film [18, 19]. However perhaps the most significant reason is believed to be neurotrophic dry eye due to disruption of the anterior corneal nerve plexus upon stromal ablation and flap creation or epithelial scraping [20, 21]. As these nerves form part of the neural loop connecting the cornea and lacrimal gland, the outcome

is a reduction in lacrimal gland secretion, corneal sensitivity and reflex tearing, which results in aqueous deficient dry eye. One of the highlighted benefits of SMILE is the minimal disruption to the anterior corneal nerve plexus, through the use of a side cut tunnel (rather than a flap) and removal of mid-posterior stromal tissue (rather than anterior) [14, 22]. The intended result should, therefore, be a preservation of the TBUT which is used to assess tear film stability. In a previous article by Demirok et al. [23], the researchers found no reduction in different dry eye metrics such as TBUT, Schirmer test and tear film osmolarity before and after SMILE up to 6 months. However, central corneal sensitivity was found to be reduced at 1 week, 1 month and 3 months after surgery. Other authors [24] found TBUT was reduced at 6 months with a statistically significant reduction in TBUT after 1 week ( $4.32 \pm 3.57$  s), 1 month ( $5.68 \pm 4.84$  s) and 3 months ( $5.03 \pm 3.83$  s) compared to before SMILE ( $8.58 \pm 4.42$  s). Qiu et al. [25] found significant TBUT changes after SMILE:  $13.60 \pm 1.72$  s and  $8.70 \pm 1.76$  s, before and 3 months after surgery respectively. The researchers postulated that the TBUT reduction recorded may be produced by the suction ring (e.g. reduction in goblet cell density together with increased tear film instability). Wang et al. [16] showed a return to pre-operative TBUT values 6 and 12 months after SMILE as previously observed by Li et al. after 6 months [24]. The results obtained from our study show the mean reduction in TBUT at 3 months post-operatively was 0.7 seconds with an almost identical standard deviation as other authors have reported [26, 27]. This compares favourably to previously published results comparing SMILE with LASIK which show a greater depression in TBUT with LASIK, lasting 6 months or longer due to an extended period of reduced corneal sensitivity [24]. It should be noted however that the difference in TBUT results pre and post-operatively was not statistically significant. It will be interesting to review this and other tear film metrics over longer follow-up periods with a larger cohort of patients.

SMILE surgery is arguably less invasive [5] and is designed to reduce the impact on the biomechanics of the cornea tissue compared to LASIK [15]. SMILE does not interfere with the anterior lamellae, the strongest layer of the stroma, while keeping Bowman's layer intact [28]. The Oculus Pentacam has been used to observe the changes in higher order aberrations in LASIK, wavefront-LASIK, femtosecond-LASIK and SMILE [29] although the present study appears to be the first report where changes in keratometry were considered to be correlated with TBUT before and after SMILE. Previously, Hong et al. [30] postulated that flattening of the corneal surface after PRK may be responsible for reduced TBUT (Schirmer test stable but 48% of eyes showed reduced TBUT 6 month after surgery). Our results suggest a positive but moderate correlation between TBUT and SimK.

The limitations of this study are that it is a retrospective analysis and the availability of tear film parameters was somewhat limited. As dry eye disease is multifactorial, further investigations on the additional tear film metrics after SMILE are underway and will be useful in other 'real world' settings. However, this early data of three surgeons' first procedures suggest SMILE represents a safe and effective method of correcting myopia and astigmatism, whilst offering the benefits of a "flapless" surgery.

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## Tables and Figure legends

Table 1 Clinical data: SEQ, spherical equivalent refraction; D, diopters; UDVA, uncorrected distance visual acuity; logMAR, log of the minimum angle of resolution; CDVA, corrected distance visual acuity; TBUT, tear break-up time; s, seconds; K, keratometry; D, diopters; CDVA\_PRE, corrected distance visual acuity before surgery; UDVA\_3M, uncorrected distance visual acuity 3 months after surgery. \**p*-values are calculated by a two-tailed Student's *t*-test if distributed normally (SEQ), or by non-parametric tests, for UDVA, CDVA and TBUT.

Figure 1 Post-operative Spherical Equivalent Refraction (D)

Figure 2 Pre- and post-operative Visual Acuity (decimal Snellen scale)

Figure 3 Pre- and post-operative Tear Break-Up Time (s)