

# A Novel Tectonic Keratoplasty with Femtosecond Laser Intrastromal Lenticule for Corneal Ulcer and Perforation

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## Abstract

**Background:** Small incision refractive lenticule extraction (SMILE) is an effective laser procedure that treats myopia. This research was to describe a novel approach to treat corneal ulcer or perforation using the corneal lenticules obtained from SMILE and to evaluate the safety and effectiveness of tectonic keratoplasty with femtosecond laser intrastromal lenticule (TEKIL).

**Methods:** A total of twenty patients (22 eyes) were monitored for at least 6 months and were assessed using slit lamp microscopy, optical coherence tomography, and best-corrected visual acuity (BCVA). Postoperative complications throughout the study period were recorded.

**Results:** Corneal ulcer in 14 patients (16 eyes) and corneal perforation in six patients (6 eyes) were treated with TEKIL. The patients were ten females and ten males, with a mean age of  $58.5 \pm 16.3$  years (range: 16–81 years). In this study, the most causes of corneal ulcer or perforation were immunologic causes (54.5%). After TEKIL procedure, global integrity was achieved in all cases. No immune rejection or perforation was detected. The mean BCVA improved from  $0.17 \pm 0.20$  preoperatively to  $0.27 \pm 0.25$  postoperatively at the final follow-up ( $t = 2.095$ ,  $P = 0.052$ ). The postoperative BCVA improved in 12 eyes (54.5%) and maintained in nine eyes (40.9%). Vision function successfully maintained in all eyes (100%). In three cases, corneal ulcers were treated by reoperation of TEKIL at 3 months after the initial surgery for the reason that the residual corneal thickness was  $<250 \mu\text{m}$ .

**Conclusions:** TEKIL seems to be an effective treatment for corneal ulcer and perforation in the condition of emergency and donor shortage.

**Key words:** Corneal Perforation; Corneal Ulcer; Tectonic Keratoplasty; The Small Incision Refractive Lenticule Extraction

## INTRODUCTION

In the cases of refractory corneal ulcer and melting, subsequent corneal perforation usually happens despite intensive nonsurgical treatments. Urgent surgical intervention would be necessary in order to preserve the anatomic integrity of the eyeball to prevent the disastrous complications such as secondary glaucoma or endophthalmitis.<sup>[1]</sup> Although corneal gluing or amniotic membrane transplantation (AMT) could be used as a temporary measure for corneal perforation. In 45% of the cases, corneal transplantation would be needed eventually.<sup>[2]</sup> The long-term results of the application of AMT, conjunctival flaps, or bandage contact lens could not be satisfactory either.<sup>[3-5]</sup> However, corneal grafts are in great demand worldwide, especially in the developing countries. Small incision refractive lenticule extraction (SMILE) is a femtosecond laser refractive procedure that can correct myopia using the extraction of a refractive intrastromal corneal lenticule created by

the VisuMax FS laser system (Carl Zeiss Meditec, Jena, Germany). Angunawela *et al.*<sup>[6]</sup> reported six successful reimplantation of rabbit corneal intrastromal lenticule from SMILE into another rabbit's cornea without complications, which for the first time implied the intrastromal lenticule extracted from SMILE procedure can be used as a potential material for corneal surgery. The first implantation of the intrastromal lenticule practiced in human was reported by Pradhan *et al.*<sup>[7]</sup> who described one successful correction of high hyperopia in a young individual by the implantation of an allogeneic lenticule obtained by SMILE from a myopic donor. No adverse side effect was observed, which

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for the first time indicates the safety of the application of allogeneic corneal intrastromal lenticule in human.

Although, in the past 10 years, the number of keratoplasty in China has increased from about 5000 to more than 8000 per year, the supply of cornea donor still cannot meet the demand. A survey conducted in 2014 has demonstrated that a shortage of donor supply had been considered as the first difficulty in the treatment of corneal disease in China.<sup>[8]</sup> In this study, we applied the intrastromal lenticule extracted from SMILE procedure as corneal patch graft in the tectonic keratoplasty. We report our experience about this novel approach in a series of cases.

## METHODS

### Patients

The study was approved by the Institutional Ethics Committee of Chinese Academy of Medical Sciences Peking Union Medical College Hospital and was conducted in accordance with the principles of the *Declaration of Helsinki*. Possible benefits and risks were explained to all patients. All participants provided their written informed consent to participate in this study. The medical records of twenty patients (22 eyes) with corneal ulcer or perforation treated with tectonic keratoplasty with femtosecond laser intrastromal lenticule (TEKIL) were retrospectively reviewed. The size and the localization of corneal ulcer or perforation were measured by slit lamp microscopy or optical coherence tomography (OCT) (Visante OCT, Carl Zeiss Meditec, Dublin, USA). Best-corrected visual acuity (BCVA) before surgery was recorded. All donors provided written informed consent for lenticule donation. All donors were healthy individuals between 18 and 40 years old. The donors were selected based on the following inclusion criteria: myopic spherical refractive error ranging from -6 D to -10 D with astigmatism  $<-0.5$  D; healthy people free from systemic or ocular diseases.

### Surgical technique

Eligible candidates underwent SMILE with the standard technique by the same surgeon using the VisuMax FS laser (Carl Zeiss Meditec, Jena, Germany). The cap thickness was 120  $\mu\text{m}$  and the optical zone varied from 6.0 to 6.5 mm. After dissection of both anterior and posterior planes, the lenticule was extracted through a superior 4 mm incision. The lenticule was immediately transferred into sterile 0.9% sodium chloride solution (CR Double-Crane, Beijing, China) and prepared to be used. All the TEKIL procedures were performed immediately after the corneal lenticules were obtained. All surgeries were performed under peribulbar anesthesia (0.5% lidocaine). First, the region of ulcer or perforation was marked with a 45° microknife (Alcon Laboratories, Fort Worth, Texas, USA) and all the necrotic tissue on the surface of the cornea lesion was scraped off. One or multiple pieces of lenticules would be used in one TEKIL procedure, depending on the residual corneal thickness in each case.

The corneal intrastromal lenticule was trimmed to match the corneal lesion area and sutured to the recipient with 12 interrupted 10/0 nylon sutures (Alcon Laboratories, Fort Worth, Texas, USA). Finally, 0.3% ofloxacin topical eye ointments (Santen, Osaka, Japan) were used in the conjunctival sac.

### Perioperative treatment

Preoperative management included topical 0.5% levofloxacin eye drops (four times a day; Santen, Japan). Postoperatively, topical steroid (1% prednisolone acetate; Allergan, Irvine, CA, USA) was prescribed for 6 months four times a day. In addition, antibiotic eye drops (0.3% Ofloxacin Eye Ointment; Sinqi; Shenyang, China) was administered four times daily for the 1<sup>st</sup> month. In addition, 0.1% tacrolimus eye drops (twice 1 day; Senju, Japan) was prescribed particularly for patients who suffered immune-associated corneal ulcer or perforation.

### Perioperative evaluation

Patients were examined postoperatively on day 1, 7, and at 1, 3, and 6 months. A slit lamp microscopy was performed to check the healing of the cornea on day 1 postoperation. The following assessments were performed on day 7 and afterward: BCVA, slit lamp microscopy, and anterior segment OCT (AS-OCT). Any complications would be recorded. Surgical success was defined as the healing of corneal ulcer or perforation and the survival of the corneal grafts.

### Statistical analysis

Numerical data were expressed as a mean  $\pm$  standard deviation (SD) and statistical analyses were performed using SPSS software (version 12.0; IBM Inc., USA). The improvement of BCVA was assessed by paired-samples *t*-test. The difference between the rates of reoperation in the immune-associated corneal ulcer group and the nonimmune-associated corneal ulcer group was assessed by Chi-square test. A value of  $P < 0.05$  was considered statistically significant.

## RESULTS

### Patient information

Corneal ulcer in 14 patients (16 eyes) and corneal perforation in six patients (6 eyes) were treated with the TEKIL. The patients were ten females and ten males, with an average age of  $58.5 \pm 16.3$  years (range: 16–81 years). Nine patients suffered corneal ulcer or perforation in the right eye, with nine patients suffered in the left eye, while other two patients had involvement of both eyes. In this study, the most common cause of corneal ulcer or perforation was immunologic causes (54.5%, four Mooren's ulcer, three blepharitis keratitis conjunctivitis, two Wegener granulomatosis, one benign mucosal pemphigoid, one rheumatoid arthritis, and one Stevens-Johnson syndrome). In three cases, corneal perforation was secondary to infectious keratitis (two due to herpes simplex keratitis and one due to bacterial keratitis). In one case, the corneal

ulcer was secondary to trauma. Meanwhile, the cause of the other five corneal ulcer or perforation was unknown. The most common site of ulcer or perforation was central (eight eyes), followed by inferior (six eyes), nasal (five eyes), and temporal (three eyes). The diameter of corneal ulcer or perforation ranged from 2 to 5 mm. AMT had been performed previously in five cases (22.7%), which all had failed. The clinical characteristics of the patients are summarized in Table 1.

### Graft evaluation

The mean recipient corneal thickness was  $358.6 \pm 186.7 \mu\text{m}$  preoperatively measured by AS-OCT or A-type ultrasonography and the mean total corneal thickness 10 days, 1 month, 3 months, and 6 months after the operation was  $664.09 \pm 201.30 \mu\text{m}$ ,  $562.27 \pm 239.12 \mu\text{m}$ ,  $487.27 \pm 150.47 \mu\text{m}$ , and  $440.00 \pm 189.23 \mu\text{m}$ , respectively. The grafts and recipients matched well in all cases.

### Perioperative complications

The mean follow-up period was  $12.65 \pm 3.30$  months (range from 6 to 18 months). No immune rejection or corneal perforation occurred in any of the patients. The integrity of the globes was restored in all patients. No complication was detected and the anatomic success had been achieved in all the cases. However, in three cases, corneal ulcers were treated by reoperation of the TEKIL at 3 months after the initial surgery, for the reason that the residual corneal

thickness was  $<250 \mu\text{m}$ . The corneal graft maintained well in the follow-ups for at least 6 months after the reoperation. There was no statistical difference between the reoperation rates of the immune-associated corneal ulcer group and the nonimmune-associated corneal ulcer group ( $\chi^2 = 0.21$ ,  $P = 0.32$ ).

### Visual acuity and recovery

There was an improving tendency of the postoperative BCVA compared with the preoperative BCVA at the final follow-up ( $0.27 \pm 0.25$  vs.  $0.17 \pm 0.20$ ,  $t = 2.095$ ,  $P = 0.052$ ). Representative images of preoperative and postoperative corneal conditions in patients with a corneal ulcer or corneal perforation are shown in Figures 1 and 2, respectively, and representative OCT images of the eyes of a patient with corneal ulcer are shown in Figure 3.

### DISCUSSION

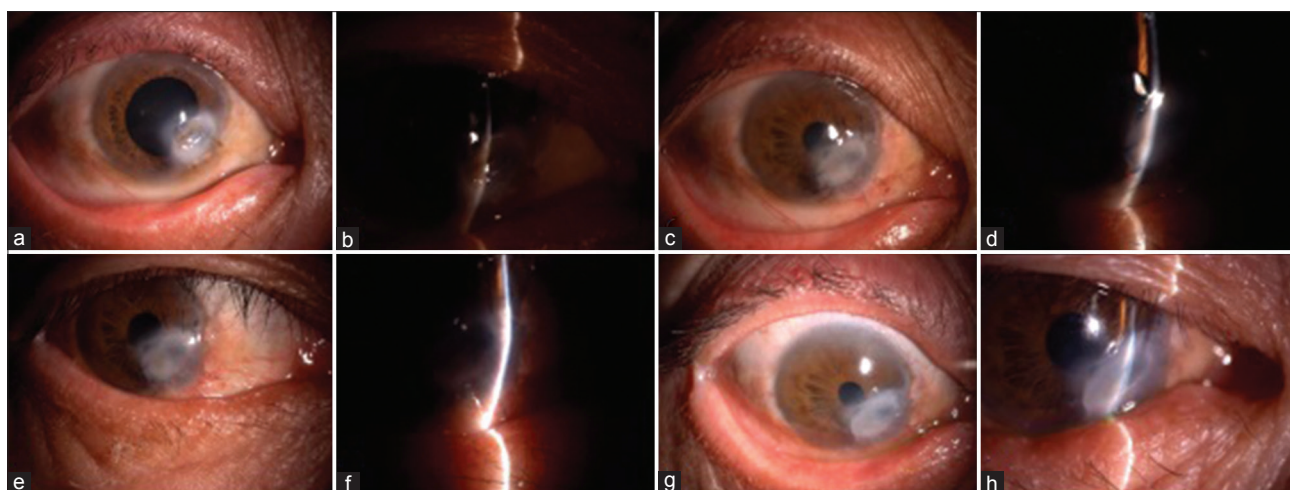
Corneal ulcer and perforation are usually with poor prognosis, including profound visual loss and various severe secondary intraocular diseases.<sup>[1]</sup> Management of corneal ulcer and perforation include the application of bandage contact lens, gluing, conjunctival flaps, AMT, and corneal transplantation. Application of cyanoacrylate glue can be the effective management of small corneal perforations. However, it is limited to size and location of the corneal lesions. AMT, conjunctival flaps, or bandage

**Table 1: Demographics and clinical findings of corneal ulcer or perforation patient underwent tectonic keratoplasty with femtosecond laser intrastromal lenticule ( $n = 20$ )**

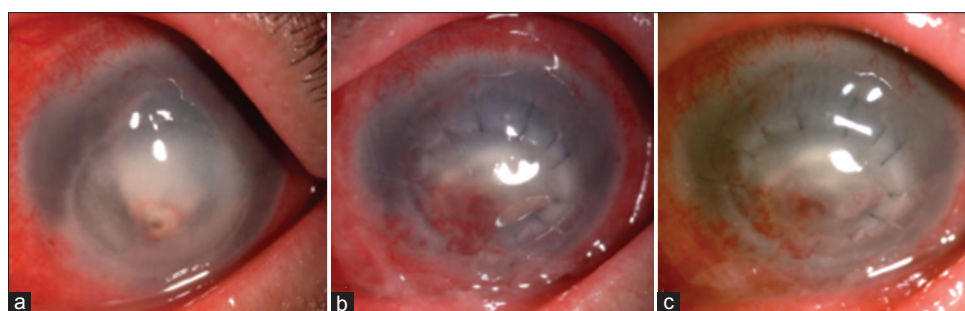
No. of patients	Gender/age (years)	Eye	Diagnosis	Prior surgery	Localization of corneal lesion	Size of corneal lesion (mm)	Initial BCVA	Perforation	Final BCVA
1	Male/62	LE	HSK	–	CT	4×3	HM	Yes	FC
2	Female/76	LE	BMP	AMT	CT	2×2	FC	No	FC
3	Male/56	RE*	MU	–	NS	4×3	0.08	No	0.15
4	Female/60	RE	UN	–	CT	3×2	0.10	No	0.10
5	Male/56	RE	UN	AMT	NS	4×4	0.01	Yes	0.01
6	Male/63	RE	UN	–	CT	3×3	FC	No	0.10
7	Male/25	RE	WG	–	IF	4×4	0.04	No	0.10
8	Male/66	LE	S-J	AMT	CT	3×3	0.02	No	0.04
9	Male/65	LE	BK	AMT	CT	4×4	LP	Yes	FC
10	Male/42	LE	MU	–	TP	5×5	0.04	No	0.50
		RE	MU	–	NS	4×3	0.08	No	0.80
11	Male/43	LE*	TM	AMT	IF	4×3	LP	No	LP
12	Female/81	LE*	PUK	–	TP	4×3	0.05	No	0.10
		RE	PUK	–	NS	4×4	0.25	No	0.40
13	Female/59	LE	UN	–	NS	3×2	0.10	Yes	0.15
14	Female/63	LE	UN	–	IF	2×2	0.40	Yes	0.40
15	Female/61	LE	UN	–	IF	3×2	0.40	Yes	0.40
16	Male/16	RE	HSK	–	CT	3×3	0.02	No	0.02
17	Female/57	RE	MU	–	TP	2×4	0.80	No	0.80
18	Female/75	RE	WG	–	IF	4×2	0.20	No	0.25
19	Female/68	LE	RA	–	CT	2×3	0.10	No	0.15
20	Female/75	RE	BKC	–	IF	3×2	0.25	No	0.25

\*Eye with reoperation. –: No amniotic membrane transplantation; LE: Left eye; RE: Right eye; HSK: Herpes simplex keratitis; BMP: Benign mucosal pemphigoid; MU: Mooren's ulceration; TM: Trauma; PUK: Peripheral ulcerative keratitis; UN: Unknown; WG: Wegener granulomatosis; S-J: Stevens-Johnson syndrome; BK: Bacterial keratitis; AMT: Amniotic membrane transplantation; CT: Central; IF: Inferior; NS: Nasal; TP: Temporal; BCVA: Best corrected vision acuity; HM: Hand moving; FC: Finger counting; LP: Light perception.





**Figure 1:** Preoperative and postoperative corneal conditions in corneal ulcer patient (patient 5). Corneas were examined by slit lamp microscope under diffused light (a, c, e, g) and slit light (b, d, f, h), respectively. (a and b) Preoperatively, the corneal ulcer was deep. (c and d) The corneal ulcer was healed 1 week after the surgery. (e and f) Postoperative aspect of the same eye at 1 month after the surgery. (g and h) The corneal graft was still semitransparent at 3 months after the surgery; however, the corneal ulcer was completely cured (original magnification,  $\times 10$ ).



**Figure 2:** Preoperative and postoperative corneal conditions in corneal perforation patient (patient 9). Corneas were examined by slit lamp microscope under diffused light. (a) Preoperatively, the corneal perforation was clear and bulbar conjunctival congestion was severe. (b) 1 week after the TEKIL, bulbar conjunctival congestion had relieved compared to the preoperative condition. (c) Bulbar conjunctival congestion had significantly relieved at 1 month after the operation (original magnification,  $\times 16$ ). TEKIL: Tectonic keratoplasty with femtosecond laser intrastromal lenticule.

contact lens cannot be satisfactory permanent treatment either.<sup>[3-5]</sup> In most of the cases, corneal transplantation would be needed eventually. The cornea is the most commonly transplanted organ worldwide.<sup>[8]</sup> In the USA, 42,642 corneal transplantations were done in 2010, compared with 12,623 solid organ transplantations in 2008, including kidney, liver, lung, pancreas, heart, and intestine.<sup>[9]</sup> In the past 10 years, the number of keratoplasty in China has been about 8000 per year.<sup>[8]</sup> However, cornea donors cannot match the demand worldwide, especially in the developing countries.

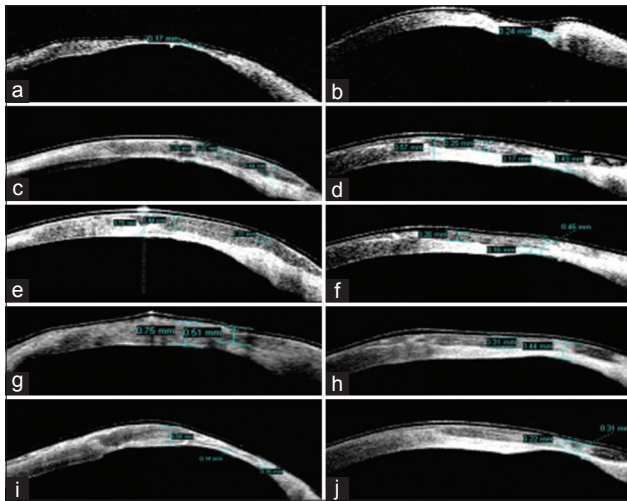
TEKIL is a novel type of tectonic keratoplasty. Tectonic keratoplasty, also known as corneal grafting, is a surgical procedure where a damaged or diseased cornea is replaced by donated corneal tissue. The corneal intrastromal lenticules extracted from the SMILE procedure are clear and high-qualified corneal tissue. People who take the refractive surgery are relatively younger than the traditional cornea donors. Pradhan *et al.* and Ganesh *et al.* have separately reported their successful implantation of the lenticules extracted from the SMILE procedure to correct high hyperopia patients.<sup>[7,10]</sup> No adverse side effects were observed in the follow-ups. They also implied that the implantation

of the extracted lenticules is potential clinical approaches of various ocular diseases, such as aphakia, hypermetropia, keratoconus, and presbyopia.

In concern of the integrity of the eyeballs, we observed that the integrity of the globes was restored in all patients. No adverse side effects were observed in the follow-ups of at least 6 months. No immune rejection or corneal perforation occurred in any patient. We found TEKIL was safe and effective clinical approaches to corneal ulcer and perforation.

In the matter of the vision acuity, we observed that the mean BCVA improved from  $0.17 \pm 0.20$  preoperatively to  $0.27 \pm 0.25$  postoperatively at the final follow-up. We found that the TEKIL procedure is an urgent surgical intervention to protect the integrity of the globes.

Wu *et al.*<sup>[11]</sup> first reported the success by using the SMILE-generated lenticules as corneal patch graft in corneal perforation cases. Their study has described their preliminary experience of the procedure. As the second study of this novel procedure, our study included twenty cases of the follow-ups of at least 6 months. Rather than general descriptions, our study provided more detailed and quantitative changes of



**Figure 3:** Optical coherence tomography images of the both eyes of corneal ulcer patient (patient 10). (a and b) Preoperatively, the residual corneal thickness of the left eye and the right eye was only 170  $\mu\text{m}$  and 240  $\mu\text{m}$ , respectively. (c and d) The total corneal thickness of the left eye and the right eye 1 week after the surgery was 780  $\mu\text{m}$  and 430  $\mu\text{m}$ , respectively. (e and f) The total corneal thickness of the left eye and the right eye at 1 month after the surgery was 700  $\mu\text{m}$  and 450  $\mu\text{m}$ , respectively. (g and h) The total corneal thickness of the left eye and the right eye at 3 months after the surgery was 750  $\mu\text{m}$  and 440  $\mu\text{m}$ , respectively. (i and j) The total corneal thickness of the left eye and the right eye at 6 months after the surgery was 350  $\mu\text{m}$  and 310  $\mu\text{m}$ , respectively.

the corneal grafts and vision acuities preoperatively and postoperatively, which might help specialists to get a better understanding of this novel procedure. Although, in three cases, corneal ulcers were treated by reoperation of the TEKIL at 3 months after the initial surgery, for the reason that the residual corneal thickness was  $<250 \mu\text{m}$  then, the corneal graft maintained well in the follow-ups for at least 6 months after the reoperation. This novel approach can be an alternative treatment for urgent corneal perforation or deep corneal ulcer, which can be performed repeatedly to keep the integrity of eyeballs, providing fine conditions for ultimate approaches, such as penetrating keratoplasty to improve final visual acuity. The rate of reoperation between the immune-associated corneal ulcer group and the nonimmune-associated corneal ulcer group showed no statistical difference, which implied that the melting of the corneal lenticule might be irrelevant to the primary immunological pathogenesis.

Some key points of the TEKIL procedure are worth mentioning. We suggest that OCT should be used preoperatively to evaluate the depth and width of the corneal lesion. Multiple pieces of lenticules are suggested being used in cases of deep corneal ulcers or perforations. Because necrotic corneal tissue and corneal pannus can bring and attract inflammatory cells, which generate and release enzymes degrading corneal collagen and proteoglycans, we suggest that it is important to remove the necrotic corneal

tissue and pannus before the suture of the corneal graft. In our research, we observed that the severity of conjunctival congestion was significantly relieved postoperatively in both infectious and immune-associated cases. Apart from the repair of the corneal lesion by the corneal patch graft, TEKIL is also an effective approach to cure corneal ulcer and perforation for halting the progression of the primary disease. We suggest that the stitches should be sutured avoiding the visual axis, preventing secondary corneal scar, and reducing postoperative astigmatism.

In summary, TEKIL, as a novel surgical approach, could successfully cure corneal perforations and corneal ulcer in urgent conditions. It could effectively preserve the global integrity and alleviate inflammatory reaction, providing fine conditions prepared to ultimate approaches, such as penetrating keratoplasty to improve final visual acuity. Above all, it helps to solve the problem of donor shortage and can be used in an emergency.

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Nil.

### Conflicts of interest

There are no conflicts of interest.

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