Corneal stromal lenticule transplantation for the treatment of corneal ulcers

Yun Min Klimesova[1], Martina Nemcokova[1], Magdalena Netukova[1], Alina-Dana Baxant[1], Marcela Hlavackova[2], Jana Kacerovska[2], Pavel Studeny[1]

Purpose. To evaluate the safety and efficacy of using corneal stromal lenticules (CSLs) obtained during refractive surgery Refractive Lenticule Extraction (ReLEx) with the Small Incision Lenticule Extraction (SMILE) procedure for the treatment of corneal ulcers.

Methods. This retrospective study included 12 eyes of 12 patients, 7 men and 5 women with varying degrees of corneal ulcer. The mean age was 64 ± 18 (range 34 to 95 years). The monitoring included corrected distance visual acuity (CDVA), slit-lamp biomicroscopy examination, a Seidel test, stability of the graft and anterior segment optical coherence tomography (AS-OCT) inspection. Patients were closely monitored for possible postoperative complications for at least 6 months.

Results. In 7/12 (58%) eyes, the corneal ulcer was successfully sealed with CSL and amniotic membrane (AM) without the need for any additional surgical intervention. In 3 eyes, penetrating keratoplasty (PK) was needed in addition to CSL transplantation and in 2 eyes the scleral patch was used to fully seal after CSL transplantation. During the follow-up period no signs of rejection or infection were detected in any patient.

Conclusion. The use of CSLs from ReLEx SMILE may be considered as an alternative method for the treatment of corneal ulcers before a more extensive and definitive solution – PK – is used. Our preliminary findings suggest that properly performed CSL transplantation using cryopreserved lenticules is a safe and effective method to temporarily cover the corneal partial-thickness defect or even perforation.

Key words: corneal ulcer, corneal stromal lenticule, ReLEx SMILE, amniotic membrane, CSL transplantation

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[1]Department of Ophthalmology, University Hospital Kralovske Vinohrady and Third Faculty of Medicine Charles University, Prague, Czech Republic
[2]Eye Clinic Horni Pocernice, Czech Republic
Corresponding author: Yun Min Klimesova, e-mail: yunmini85@gmail.com

INTRODUCTION

Corneal ulcers and perforations are one of the commonest causes of significant decrease in visual acuity or even vision loss[1]. The causes may be of infectious, traumatic or autoimmune origin. In some cases, the exact cause of the disintegration of corneal tissue is unclear. The treatment of corneal ulcers is often challenging, it involves causal treatment (antibiotics, antivirals, antifungals and removing damaging noxae) along with anti-inflammatory medication (steroids, non-steroidal anti-inflammatory drugs and immunosuppressants).

However, damaged and missing corneal tissue regenerates only slightly and very slowly. Corneal ulcers start with a partial-thickness defect in the corneal epithelium layers and can progress to invade the stroma and ultimately create a full-thickness perforation. Such a condition must be urgently solved by covering the defect to restore the integrity of the eyeball and prevent intraocular tissue infection[2]. The choice of treatment depends on the size, location and degree of corneal ulcer together with the status of underlying diseases.

Current therapeutic strategies for small corneal ulcers and perforations include a variety of temporary treatment methods involving the use of amniotic membrane transplantation (AMT), tissue glue, conjunctival flaps, or a tissue "patch" prepared from a donor's cornea[3-5]. The defect is replaced with a corneal scar that often seriously affects the transparency of the cornea or the refractive state of the eye. As a permanent solution a planned penetrating keratoplasty (PK) usually follows. Large corneal ulcers and perforations always need acute PK (ref.[6]).

ReLEx SMILE is a refractive surgery method, in which a corneal stromal lenticule (CSL) is cut within the cornea by femtosecond laser and then mechanically released from the eye through a small incision using tweezers. The thickness of the CSL depends on the degree of operated refractive error. The CSL itself is essentially a waste product of the ReLEx SMILE procedure. This corneal tissue can be (cryo-)preserved as was described in the literature[7,8]. Recent studies and case reports have described autologous re-implantation and allogenic implantation in laboratory animals[8-12] and human subjects[13-17] to rectify the refractive outcome of myopic corneal refractive procedure. Cryopreserved or fresh CSLs have been also used to treat presbyopia[11], hyperopia[13-15] and keratoconus[16].

In the present study, we report the clinical results of

CSL transplantation as an alternative method for the treatment of corneal ulcers using CSLs obtained from ReLEx SMILE.

METHODS

Patients and methods

The retrospective study comprised 12 patients with corneal ulcers treated by CSL transplantation. All patients were diagnosed with a corneal ulcer with prolonged healing, mostly with very poor visual acuity and extensive findings. Four patients had corneal ulcers due to exposure keratitis, four corneal ulcers resulted from infectious keratitis, three patients had severe chemical alkali burns and one patient had severe dry eye due to rheumatoid arthritis. The procedures were conducted from April 2017 to August 2020.

The study complied with the principles of the Declaration of Helsinki and the Ethics Committee of the University Hospital Kralovske Vinohrady approved this procedure in advance. All donors were healthy individuals and provided written informed consent for CSL donation. All patients who underwent the CSL transplantation were provided written informed consent as well which included potential complications and the possible need for further intervention.

Corneal ulcers were confirmed clinically using a slit lamp biomicroscope and a Seidel test using fluorescein staining was performed to confirm eventual perforation. Corrected distance visual acuity (CDVA) was assessed preoperatively. Anterior segment optical coherence tomography (AS-OCT; Spectralis OCT, Heidelberg Engineering GmbH, Heidelberg, Germany) was performed to document the extent of corneal thinning. The representative AS-OCT image of the corneal ulcer is shown in Fig. 1. Preoperative details of all patients including demographics, visual acuity, etiology and the degree of corneal ulcers are provided in Table 1.

Tissue donors were selected from ReLEx SMILE patients with a myopic spherical refractive error greater than -3 D to ensure a central thickness of CSL of ≥ 48 µm. Serological tests of donors were performed to rule out the presence of infectious diseases (hepatitis B, hepatitis C, HIV, syphilis). None of the donors had undergone any eye surgery before.

Lenticule preparation

CSLs were obtained as a byproduct of ReLEx SMILE procedures performed by a single surgeon (JK) in the Refractive center using the VisuMax Femtosecond Laser System (Carl Zeiss Meditec, Jena, Germany). SMILE procedures were performed using a cap thickness of 135 µm, 7.5 mm flap diameter, 6.4 mm optical zone of the lenticule, 90 degree side-cute angle and a superior 4 mm incision through which CSL was extracted. Fresh CSLs were immediately transferred into a sterile vial and preserved in a preservation solution (Eusol) at 4 °C under strict aseptic conditions. The CSLs were then transported to an Eye Tissue Bank under monitored temperature and further cryopreserved at –80 °C in a balanced salt solution (BSS). After six months, the CSL grafts were serologically tested and released for transplantation. Before each surgery, a selected CSL was stored at room temperature for approximately 30 min and subsequently submerged in a 24 °C saline bath. The CSL was lightly stained with trypan blue dye 0.05% (RS-blue, Alchimia, Padova, Italy) for better visualization.

Surgical procedure

All lenticule graft surgeries were performed by a single eye surgeon (PS) with high experience in corneal surgery under topical anesthesia (oxybuprocaine hydrochloride 0.4%). The stromal bed of the recipient's eye was carefully debrided (Fig. 2) with a sponge or a crescent blade. A single CSL was placed and centered over the corneal ulcer. In three patients we used 11-0 nylon interrupted sutures to fixate the CSL to the healthy cornea rim around the

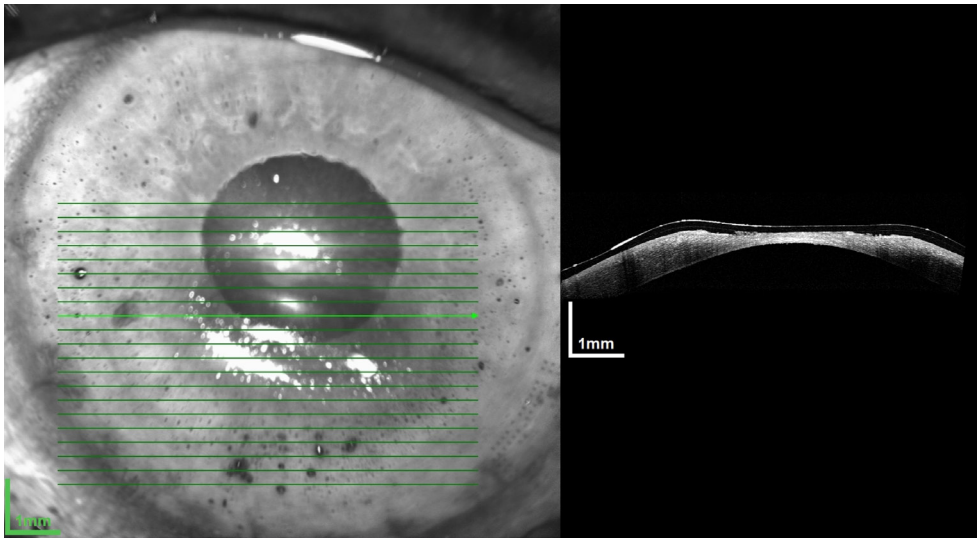

Fig. 1. AS-OCT image of the non-healing corneal ulcer with partial-thickness defect due to exposure keratitis (patient 4).

Table 1. Demographics and clinical findings.

Serial No.	Age/Sex	Eye	Initial CDVA	Diagnosis	Indication	Prior surgery
1	73/M	R	1/10	Exposure keratitis	Partial-thickness defect	Tarsorrhaphy
2	45/F	L	CF	Exposure keratitis	Descemetocele	Tarsorrhaphy, 2x AMT
3	47/M	R	HM	Alkali burn	Microperforation	2x AMT
4	63/M	L	1/10	Exposure keratitis	Partial-thickness defect	–
5$	73/F	L	HM	Fungal keratitis	Microperforation	PPV, PK, DSAEK, 1x AMT
6	36/M	R	HM	Alkali burn	Descemetocele	PK, DSAEK, LSCT, 1x AMT
7	77/M	L	1/10	Rheumatoid arthritis	Microperforation	1x AMT
8#	95/M	R	LP	HSK	Microperforation	–
9	95/F	R	1/10	Exposure keratitis	Microperforation	–
10	65/F	R	HM	Alkali burn	Descemetocele	2x PK, 4x AMT, LSCT
11	65/F	R	1/20	Infectious keratitis	Partial-thickness defect	1x AMT
12#	34/M	R	0.3	HSK	Microperforation	1x AMT

CDVA, Corrected distance visual acuity; y, Years; F, Female; M, Male; R, Right eye; L, Left eye; CF, Count fingers; HM, Hand motion; LP, Light perception; HSK, Herpes simplex keratitis; AMT, Amniotic membrane transplantation; PPV, Pars plana vitrectomy; PK, Penetrating keratoplasty; DSAEK, Descemet's stripping automated endothelial keratoplasty; LSCT, Limbal stem cells transplantation.
#eye with aciclovir treatment
$eye with topical and oral voriconazole treatment

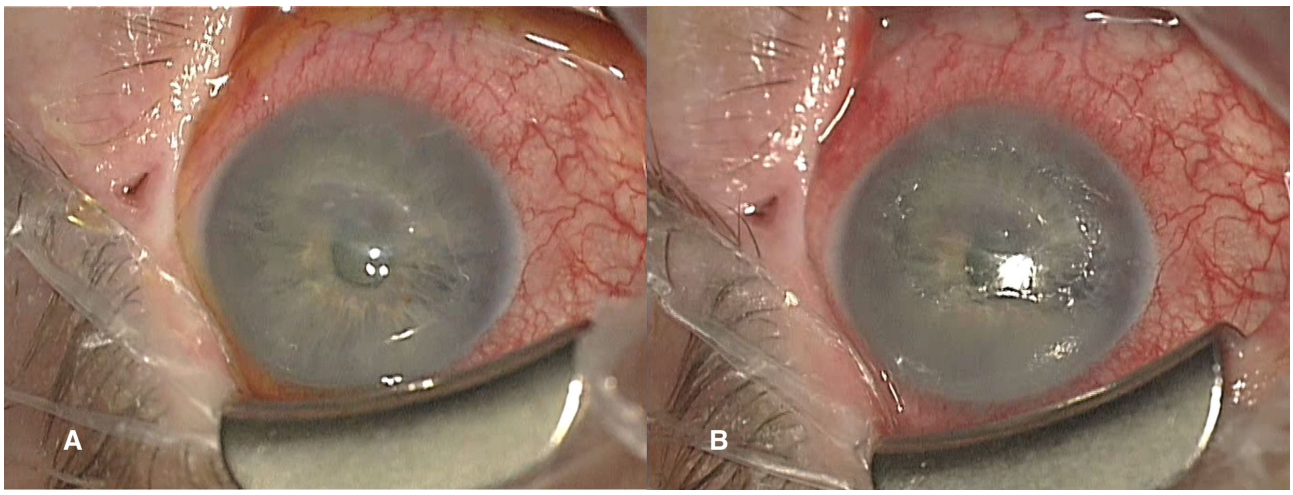

Fig. 2. A. A typical corneal ulcer before surgery. **B.** Debrided stromal bed before CSL transplantation.

wound. In the rest of the patients, the surgical procedure was modified to the no stitch method with the use of an intrastromal pocket. This was created using a crescent blade through the center of the ulcer to the approximate size of the CSL (Fig. 3). In these patients, the CSL was gently placed into the created intrastromal pocket without using any stitches. In all but one patient, an extra layer of AM with the epithelial side up was fixed by 11-0 nylon interrupted stitches to overlay the lenticule graft. A bandage contact lens was applied at the end of the procedure.

Postoperative management

All patients received routine postoperative treatment with topical tobramycin, dexamethasone (3 mg/mL + 1 mg/mL, respectively) eye drops, (Tobradex, Alcon) five times a day for two weeks after the surgery. Subsequently, topical fluorometholone (1 mg/mL) eye drops, (Flarex, Novartis) three times a day for the following month. No patients used systemic antibiotics.

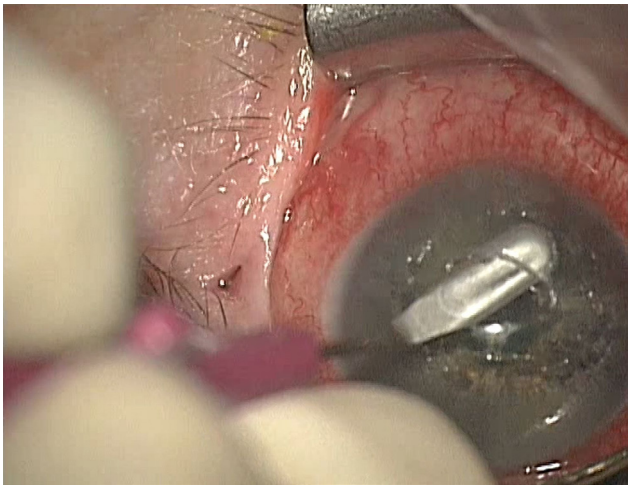

Fig. 3. Creating an intrastromal pocket with a crescent blade through the center of the corneal ulcer.

Along with the surgery and the postoperative care, four patients with infectious keratitis were also prescribed medication to treat the primal cause of their condition. In two patients, Herpes simplex keratitis was managed by oral administration of aciclovir 400 mg, five times a day for two weeks, followed by a lower dosage (twice a day) for two months. One patient was treated for fungal keratitis by direct topical administration of voriconazole 1% five times a day for two weeks followed by oral administration of voriconazole 200 mg twice a day for two months. The primal cause of the ulcers in all patients is indicated in Table 1. Mydriatic-cycloplegic eye drops were administrated as needed. Suture removal was carried out 3 months after the surgery.

Patients were monitored for at least six months. CDVA, slit-lamp microscopy examination, Seidel test and a test of the stability of the grafts were examined at predefined time intervals after the surgery – one day, one week, two weeks and after one, two, three, six and twelve months. AS-OCT was performed during the examination one month after the surgery. Additional examinations were conducted in between these follow-up periods, if necessary. Postoperative complications were closely monitored and recorded throughout the follow-up period.

RESULTS

This study treated eyes in 12 patients – 7 men and 5 women. The mean age was 64 ± 18 years (from 34 to 95 years). Three patients were diagnosed with partial-thickness defect from elongated healing of a corneal ulcer, three patients were diagnosed with descemetocele and six patients (50%) already developed corneal perforation. Prior to the CSL transplant surgery, the corneal ulcers had already been treated by AMT without success in eight patients (Table 1, 2).

CSL was successfully transplanted in all cases. There were no intraoperative complications. No signs of infection or immune rejection were observed during the follow-up period. Four CSLs were fixed by stitches and eight CSLs were implanted into a gently created intrastromal pocket. The mean CSL thickness was 87 ± 43 μm (from 48 to 152 μm).

In seven eyes (Table 2), the corneal ulcer was successfully healed using our procedure without any need for extra surgical intervention. During weeks after the CSL transplantation, the corneal grafts appeared clear with overlying AM. Approximately one month after the surgery, the grafted CSL together with the AM incorporated into the corneal stroma and reepithelization was observed (Fig. 4). Three months after the surgery, the corneal ul-

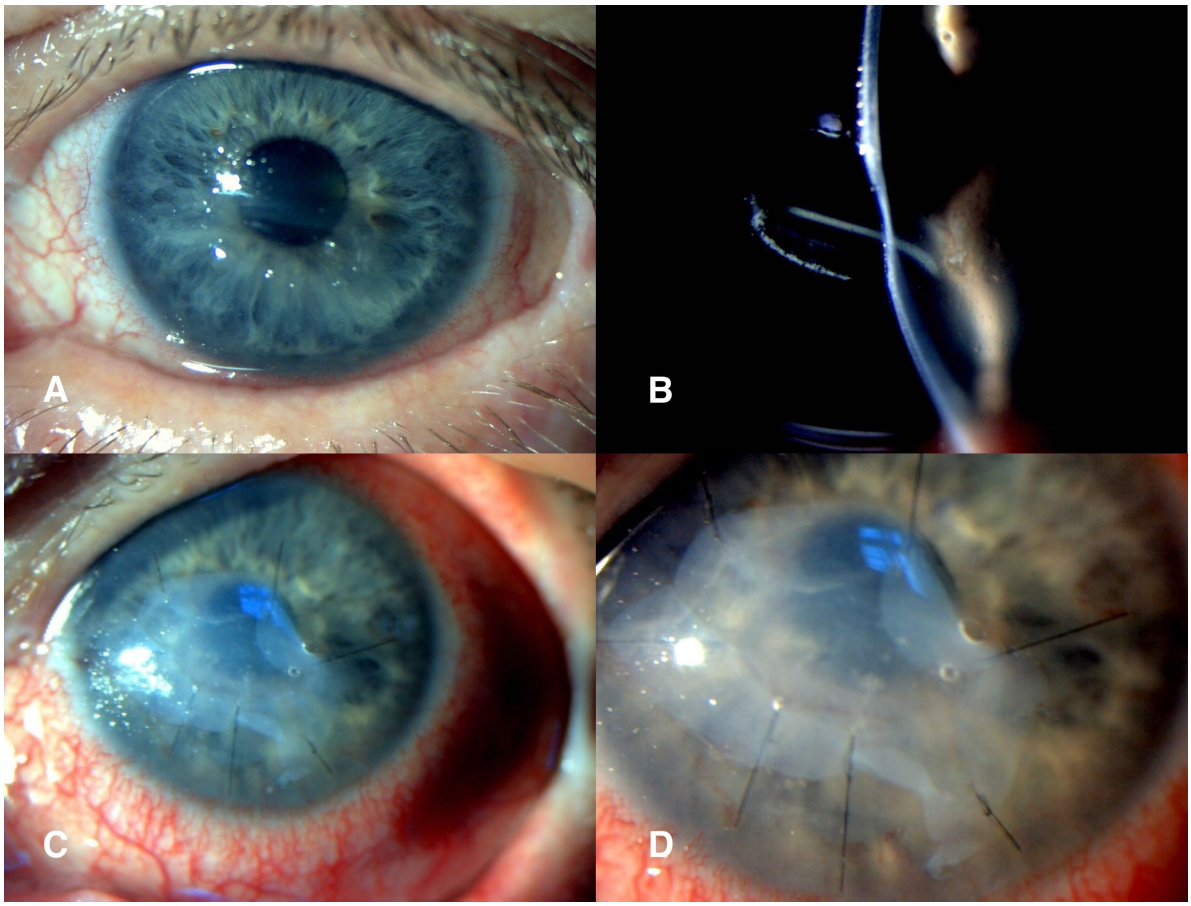

Fig. 4. Preoperative and postoperative corneal conditions in a non-healing corneal ulcer with partial-thickness defect (patient 4). **A.** Preoperative slit lamp microscope image under diffused light and **B.** slit light. **C.** Postoperative aspect of the same eye one month after the CSL and AM transplantation and **D.** in greater detail.

cers healed with minor corneal scars and the eyes with the corneal perforation showed stable closure with a negative Seidel test. In all seven patients, we observed the anterior chamber to be properly formed and good ocular tension was measured by finger measurement. CDVA generally did not worsen during the follow-up period. In two patients, a minor improvement in CDVA was achieved due to other nonrelated surgery. One patient showed better CDVA after the permanent tarsorrhaphy and the second patient after the cataract surgery.

Additional corneal ulcer treatment was necessary for five patients (Table 2). In three eyes, penetrating keratoplasty was needed despite CSL transplantation and in two eyes a scleral patch surgery was used as a palliative and alternative surgical procedure. These patients generally had very poor visual acuity prior to the surgery, extensive findings from several previous surgeries and an unclear prognosis.

In one patient (patient 10), the CSL was implanted into the intrastromal pocket without the AM covering. While covered with the bandage contact lens the corneal ulcer showed very good healing and CSL stability, but as soon as the contact lens was removed, the lenticule was dislodged. We had to reoperate on this patient and classically fix the CSL with sutures and an overlying AM.

Table 2 summarizes surgical outcomes.

DISCUSSION

Corneal ulcers with corneal thinning or even perforation can cause ocular morbidity and profound visual loss[18]. With respect to the specific cause, size, location and stage, appropriate clinical management is necessary. For small corneal ulcers, the application of a bandage contact lens may be sufficient. The application of cyanoacrylate tissue glue, conjunctival flaps or AMT can be effective in small corneal perforations. However, all these methods are limited to the size and location of the corneal lesions and mostly do not represent a convenient permanent solution. PK is widely considered the gold standard for the management of large non-healing corneal ulcers and perforations. Nevertheless, it is an extensive procedure and there is always a certain level of risk that the grafted tissue will be rejected.

The cornea is the most commonly transplanted tissue. However, the availability of cornea grafts is relatively low and it is even worse in developing countries[19]. Thus, any additional option on how to treat corneal ulcers is of great benefit. The possibility of using deep-frozen CSLs could significantly help in many cases. CSLs are obtained during the ReLEx SMILE. This surgery is quite common and theoretically produces a substantial number of usable grafts. Concurrently, the possibility of long-term storage under the ultra-low temperature makes these grafts readily available when needed.

There are only a few reports of CSLs being used for therapeutic purposes in the treatment of perforations and partial-thickness defects.

Wu et al.[20] was the first study that reported the successful usage of cryopreserved lenticules to seal corneal perforations. This preliminary experience described 6 patients treated with two overlapped lenticules using interrupted stitches. One patient had an extra AM patch overlaid on the lenticule grafts. Three patients exhibited improved postoperative CDVA. A stable closure of the corneal perforation was observed in all these cases and no evidence of infection or relapse during the 12-month follow-up period.

Jiang et al.[21] study included 20 patients (14 with corneal ulcers and 6 with corneal perforations) treated by tectonic keratoplasty with femtosecond laser intrastromal lenticule (TEKIL). They used fresh lenticules obtained from ReLEx SMILE on the same day as the TEKIL pro-

Table 2. Surgical outcomes.

Serial No.	CSL thickness (μm)	Sutures Y/N	CDVA 3 M postop.	CDVA 6 M postop.	CDVA 12 M postop.	Healed Y/N	Other surgeries after CSL transplantation
1	48	Y	1/5	1/10	0.2	Y	Permanent tarsorrhaphy after 12 M
2*	48	Y	–	–	–	N	PK after 1 M
3*	64	Y	HM	HM	–	N	Scleral patch after 7 M
4	48	N	1/50	1/10	0.3	Y	Cataract surgery after 6 M
5*	48	N	–	–	–	N	Scleral patch after 1 M
6*	128	Y	–	–	–	N	PK after 1 M
7*	128	N	1/10	1/10	–	Y	–
8	144	N	–	–	–	N	PK after 1 M
9	152	N	1/10	1/10	1/10	Y	–
10*	120	N	HM	HM	HM	Y	–
11*	48	N	1/20	1/20	1/20	Y	–
12*	64	N	0.3	0.3	–	Y	–

CSL, Corneal stromal lenticule; Y, Yes; N, No; CDVA, Corrected distance visual acuity; M, Months; HM, Hand motion; PK, Penetrating keratoplasty.
*eye already had been treated by AMT without success

cedure. Improvement was achieved in all cases and no immune rejection or perforation was detected during the 6-month follow-up period. The postoperative CDVA improved in 12 patients.

Bhandari et al.[22] published a case series of 7 patients with lamellar corneal defect or microperforation using fibrin glue to secure a fresh lenticule patch graft obtained from a ReLEx SMILE procedure on the same day. Their study revealed a clear and well-apposed lenticule graft at the last (3-month) follow-up visit in all treated eyes. In addition, the study showed significant improvement in CDVA in 5 of 7 eyes, which may be attributed to a noninfectious cause and quite good visual acuity preoperatively.

Another study published by Abd Elaziz et al.[23] used lenticules preserved at 4 °C in Optisol for approximately 7 days. Seven patients were successfully treated with a lenticule fixed by interrupted stitches over a corneal perforation. A single layer of AM was overlaid on a lenticule graft using interrupted stitches in all patients. Three patients showed better postoperative CDVA. No signs of re-perforation or infections were detected in any patient during the one-year follow-up period.

Al Saadany et al.[24] compared the use of 30 fresh lenticules with 15 AM graft in the management of corneal perforation. Corneal ulcers in all 45 patients were sealed successfully with insignificant differences between the procedures.

Many studies have proved that AMT accelerates the healing process[25]. AM contains anti-inflammatory mediators and promotes epithelialization[25-27]. In addition, there is no rejection after AMT due to its no antigenicity[28]. For this reason, we decided to use an extra amniotic membrane patch overlaid on the CSL grafts.

In contrast with most reported studies, we strictly used cryopreserved CSLs a after 6-month quarantine and a negative donor's control serological test according to Blood, tissue and cells (BTC) legislation.

In our study, seven out of twelve patients (58%) were successfully healed without any need for additional surgical intervention. While this is fewer than some other studies, this may be attributable to our relatively small and heteregenous group of patients. Another reason could be that most of our patients had very poor visual acuity before the surgery and extensive findings from several previous surgeries. We chose our patients very carefully at the beginning of this novel procedure. We included those patients who had already been indicated for PK. Futhermore, the thickness of the lenticule can also play a role as those lenticules used in the mentioned studies were generally thicker than the lenticules used in our study. However, in our limited dataset, we could not prove any correspondence between the thickness of the graft and the outcome (Table 2.)

The emergency eyeball integrity restoring surgery as an acute PK is to prevent disastrous complications such as endophthalmitis. However, it is often risky and also incurs a high risk of immune rejection. CSL transplantation could provide fine conditions to prepare for ultimate approaches such as planned PK under safer conditions to improve final visual acuity. Under certain circumstances and the correct indication, CSL transplantation can be also considered a permanent solution.

CONCLUSION

The use of CSLs from ReLEx SMILE may be considered an alternative method for the treatment of corneal ulcers under emergency conditions. These preliminary findings suggest that CSL transplantation using cryopreserved lenticules is a safe and effective method to temporarily cover the corneal partial-thickness defect or even perforation. However, a larger sample of patients and longer follow-up are required to interpret this surgical method more precisely.

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