

# Small-diameter acellular porcine corneal stroma for peripheral corneal ulceration treatment

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## Abstract

• **AIM:** To evaluate the clinical efficacy of small-diameter acellular porcine corneal stroma (SAPS) for the treatment of peripheral corneal ulceration (PCU).

• **METHODS:** This retrospective clinical study included 18 patients (18 eyes) with PCU between April 2018 and December 2020. All patients had PCU and underwent lamellar keratoplasty with SAPS. Observation indicators included preoperative and postoperative best-corrected visual acuity (BCVA) and transparency of SAPS. The infection control rate in the surgical eye-lesion area was also calculated.

• **RESULTS:** Eighteen patients underwent lamellar keratoplasty with SAPS to treat PCU. None of the patients experienced rejection after 6mo (18/18) and 12mo (16/16) of follow-up. The BCVA ( $0.47 \pm 0.30$ ) at the 6mo follow-up after operation was significantly improved compared with the baseline ( $0.99 \pm 0.80$ ), and the difference was statistically significant ( $Z = -3.415$ ,  $P < 0.05$ ). The BCVA at the 12mo follow-up after operation was not statistically significant compared to the 6mo ( $Z = 0$ ,  $P = 1$ ). With time, the SAPS graft gradually became transparent. At the 6mo (18/18) and 12mo (16/16) follow-up, none of the patients had recurrent corneal infection.

• **CONCLUSION:** SAPS is clinically effective in the treatment of PCU, improving the patient's BCVA and reducing the incidence of rejection after keratoplasty.

• **KEYWORDS:** acellular porcine corneal stroma; lamellar keratoplasty; infectious corneal ulcer

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## INTRODUCTION

Infectious corneal ulcer is the most common blinding eye disease worldwide<sup>[1]</sup>. Bacteria, fungi, viruses, and *Acanthamoeba spp.* are the most common causes of infectious keratitis<sup>[2]</sup>. Northwestern China is dominated by resource-based industries and traditional agricultural practices. Corneal trauma is the most common type of ocular trauma caused by the activities of daily living. In addition, patients neglect the disease and abuse of antibiotics are often accompanied by fungal and bacterial infections upon visiting a doctor. Patients with infectious corneal ulcers caused by the above pathogens who do not respond well to pharmacological treatment require corneal transplantation at a later stage. However, there is a serious shortage of corneal donor materials in our country, and the patient's treatment cannot be delayed<sup>[3-4]</sup>. The emergence of acellular porcine corneal stroma has partially resolved this problem<sup>[5-6]</sup>. According to our study, as the diameter of the acellular porcine corneal stroma increases, the incidence of complications such as rejection after keratoplasty will also increase<sup>[7]</sup>. Therefore, for peripheral corneal ulcerations, we used small-diameter acellular porcine corneal stroma as a donor for transplantation to avoid the interference of the patient's postoperative optical zone and effectively improve their vision.

## SUBJECTS AND METHODS

**Ethical Approval** This study was approved by Xi'an No.1 Hospital Ethics Committee (Approval No.2023-11) and followed up the tenets of the Declaration of Helsinki. Eighteen patients (18 eyes) with peripheral corneal ulceration treated at the Xi'an No.1 Hospital from April 2018 to December 2020 were selected. Among them, 8 were males and 10 were females, aged 22-70y (mean:  $53.50 \pm 12.26$ y). After the patient was admitted to hospital, broad-spectrum antibiotic eye drops were administered. After the results of the corneal microbial culture and drug sensitivity test were reported, the relevant drugs were adjusted, and sensitive antibiotics were used for treatment. After one week of medication, none of the patients showed any significant improvement or underwent surgical treatment.

**Inclusion criteria:** 1) patients with fungal and bacterial corneal ulcers; 2) infectious corneal ulcers that are peripheral and do

**Table 1 Preoperative data of peripheral corneal ulceration**

Patient No.	Sex	Age of surgery, y	Surgical eye	Inducement	Pathogen type	Visual acuity (logMAR)	Depth of lesion (μm)	Total corneal thickness of the lesion area (μm)	Proportion of the thickness of the lesion area (%)	Hypopyon
1	M	64	Left	Branch scratches	<i>Alternaria</i>	1.5	269	522	0.51	None
2	M	70	Left	None	<i>Pseudomonas aeruginosa</i>	2.3	391	607	0.64	Yes
3	F	37	Right	None	<i>Staphylococcus epidermidis</i>	0.6	408	829	0.49	None
4	F	49	Right	Corn leaves scratches	<i>Fusarium</i>	1	165	485	0.34	None
5	M	56	Right	None	<i>Fusarium solani</i>	0.4	573	758	0.76	None
6	M	58	Right	Branch scratches	<i>Aspergillus</i>	0.3	544	729	0.75	None
7	F	62	Left	None	<i>Staphylococcus epidermidis</i>	2.2	207	413	0.5	None
8	M	58	Right	None	<i>Staphylococcus aureus</i>	0.7	253	680	0.37	None
9	F	69	Right	Foreign body (inaccurate nature)	<i>Actinomyces</i>	0.5	457	509	0.9	None
10	F	48	Right	None	<i>Fusarium</i>	0.4	341	642	0.53	None
11	M	55	Left	None	<i>Staphylococcus aureus</i>	0.1	311	655	0.47	None
12	F	64	Right	None	<i>Staphylococcus aureus</i>	2.3	623	953	0.65	None
13	F	54	Left	Branch scratches	<i>Fusarium</i>	0.4	162	654	0.25	None
14	F	48	Right	Branch scratches	<i>Staphylococcus aureus</i>	0.8	491	916	0.54	None
15	M	37	Right	None	<i>Fusarium</i>	0.1	416	702	0.59	None
16	M	22	Right	Spikes into the cornea when drilling wood	<i>Aspergillus</i>	0.5	804	1146	0.70	None
17	F	62	Right	Corn leaves scratches	<i>Fusarium</i>	2.2	324	729	0.44	None
18	F	50	Left	Branch scratches	<i>Fusarium</i>	1.6	457	743	0.61	None

not invade the pupil area at the center of 3 mm; 3) corneal ulcer reaches the stromal layer but does not penetrate the Descemet’s membrane; 4) the diameters of the acellular porcine corneal stroma are <5 mm; 5) conventional medications are ineffective.

Exclusion criteria: 1) Other eye diseases (such as glaucoma and uveitis) for which other eye operations have been received; 2) patients with hypophasia, corneal neurotrophic disorder, severe dry eye, and fundus diseases; 3) a medical history of ocular surface burns caused by acids, alkalis, heat, etc.; 4) viral keratitis.

The final follow-up for all patients was >6mo postoperatively.

**Preoperative Situation** Corneal confocal microscopy, corneal scraping, and pathogen culture in the lesion area were grouped according to the infectious pathogen. Nine patients had fungal keratitis and nine patients had bacterial keratitis. The depth of the lesion accounted for 30%-70% of the total corneal thickness in the lesion area in 14 cases and more than 70% in four cases. Among them, one patient had a hypopyon, which was infected with *Pseudomonas aeruginosa*. The hypopyon disappeared after the patient received antibiotics before surgery (Table 1).

**Observation Indicators** A slit-lamp microscope was used to check the postoperative anterior chamber, corneal transparency, and whether was rejection after keratoplasty or other complications. A standard logarithmic visual acuity chart was used to measure best-corrected visual acuity (BCVA) preoperatively and postoperatively. logMAR visual acuity was used for statistical analysis. logMAR visual acuity 2.2 is count fingers; 2.3 is hand movement; 2.5 is light perception; and 3.0 is no light perception<sup>[8]</sup>.

Corneal graft transparency was scored according to the following criteria: 0, the graft is completely transparent; 1, a slight clouding is visible, and the texture of the iris can be seen through the corneal graft; 2, the pannus can be seen, the iris tissue can be seen through the corneal graft, and the texture cannot be seen clearly; 3, corneal leukoplakia and the iris tissue cannot be seen through the corneal graft.

**Corneal Donor Materials** Acellular porcine corneal stroma (produced by SHENZHEN AINEAR CORNEA ENGINEERING Co., Ltd., China) is a porcine derived decellularized corneal stroma that can be used for the lamellar keratoplasty of infectious corneal ulcers<sup>[9]</sup>. During the operation, the thickness was selected according to the depth of the corneal lesions. Specifications (300, 400, and 450 μm).

**Surgical Methods** Lamellar keratoplasty was performed by an experienced surgeon (Cheng Y). After retrobulbar anesthesia with equal volumes of 2% lidocaine and 0.75% bupivacaine, open eyelid surgery was performed. The recipient bed was prepared by trephination using a trephine (all <5 mm in diameter) of appropriate diameter, according to the location and size of the corneal lesion. A scalpel was used to cut the ulcerated tissue layer-by-layer along the trephine scratch until the lesion was completely removed. Acellular porcine corneal stromal grafts were rehydrated in 0.9% sterile saline for 1min until they were soft. The acellular porcine corneal stroma was then treated at the same size. The graft was fixed to the recipient bed using interrupted 10-0 nylon sutures. No gas, effusion, or blood was observed between the layers. Tobramycin and dexamethasone ointments were applied to the conjunctival sac of the surgical eye, and pressure bandages were applied.

**Table 2 Comparison of BCVA before and after surgery of small diameter peripheral acellular porcine corneal stroma transplantation**

BCVA	<0.02	0.02-0.1	0.12-0.25	0.3-0.5	>0.5	Total
Preoperative	4	3	3	6	2	18
Postoperative 6mo	0	2	3	8	5	18
Postoperative 12mo	0	2	3	7	4	16

BCVA: Best corrected visual acuity.

**Table 3 Corneal transparency score after small diameter decent acellular porcine corneal stroma transplantation** n (%)

Transparency score	3d	10d	1mo	3mo	6mo	12mo
0	0	0	0	0	0	5 (27.78)
1	5 (27.78)	11 (61.11)	12 (66.67)	15 (83.33)	15 (83.33)	9 (50)
2	13 (72.22)	7 (38.89)	6 (33.33)	3 (16.67)	3 (16.67)	2 (11.11)
3	0	0	0	0	0	0
Total	18 (100)	18 (100)	18 (100)	18 (100)	18 (100)	16 (89)

**Statistical Methods** The relevant data are described by mean±standard deviation, and the infection control rate of the lesion area are counted. The BCVA was recorded using the logMAR visual acuity, which was also used for statistical analysis. The comparison of BCVA before and after surgery was performed using a non-parametric test of paired samples, and statistical analysis was performed using SPSS25.0 statistical software.  $P<0.05$  indicated a statistically significant difference. The BCVA was divided into groups according to <0.02, 0.02-0.1, 0.12-0.25, 0.3-0.5, >0.5, and Graph Pad Prism 8 was used to compare the preoperative and postoperative visual acuity.

## RESULTS

**Anterior Segment Performance** Eighteen patients underwent small-diameter acellular porcine corneal stromal transplantation for the treatment of infectious corneal ulcers. Postoperative drug therapy included topical medication for preoperative infection with microorganisms, including antibiotics or antifungal therapy, combined with 0.5% tacrolimus anti-rejection therapy and artificial tears to improve the ocular surface environment. Patients were instructed to avoid using glucocorticoid eye drops within 3wk after surgery and use low-concentration glucocorticoids locally if there was no recurrent fungal or bacterial infection after 3wk of reexamination. We observed that the corneal epithelium healed after surgery, and all the patients' symptoms improved significantly through fluorescein staining of the cornea under a slit-lamp microscope. During follow-up for more than 6mo, no cases of corneal graft rejection, corneal graft dissolution, corneal opacity, edema, or ingrowth of new blood vessels occurred. At the 12-month of follow-up, two patients were lost to follow-up, and the others had no rejection reaction.

**BCVA Before and After Surgery** The preoperative and 6-month follow-up logMAR BCVA of 18 patients who

underwent small-diameter acellular porcine corneal stroma transplantation for the treatment of infectious corneal ulcers were subjected to a paired sample non-parametric test, and the difference was statistically significant ( $Z=-3.415, P<0.05$ ). The BCVA ( $0.47\pm 0.30$ ) at the 6-month postoperative follow-up was significantly improved compared with the preoperative ( $0.99\pm 0.80$ ). The BCVA at the 12-month follow-up after operation was not statistically significant compared to the 6-month ( $Z=0, P=1$ ; Table 2).

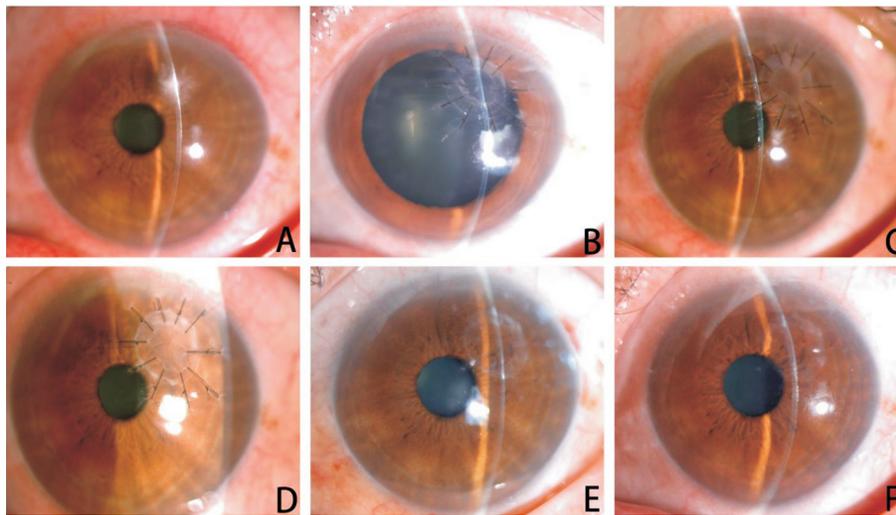
## Transparency After Acellular Porcine Corneal Stroma Transplantation

As shown in Table 3, 18 patients underwent small-diameter acellular porcine corneal stroma transplantation for the treatment of infectious corneal ulcers, and 72.22% of the patients had a corneal transparency score of 2 at 3d after surgery. The corneal grafts gradually became transparent, and 83.33% of the patients scored 1 at the 6mo after surgery. And 27.78% of patients scored 0 and 50% scored 1 at the 12mo follow-up. Therefore, with a longer follow-up time, the small-diameter acellular porcine corneal grafts gradually became increasingly transparent. Anterior segment photographs of the patients before and after surgery are shown in Figures 1 and 2.

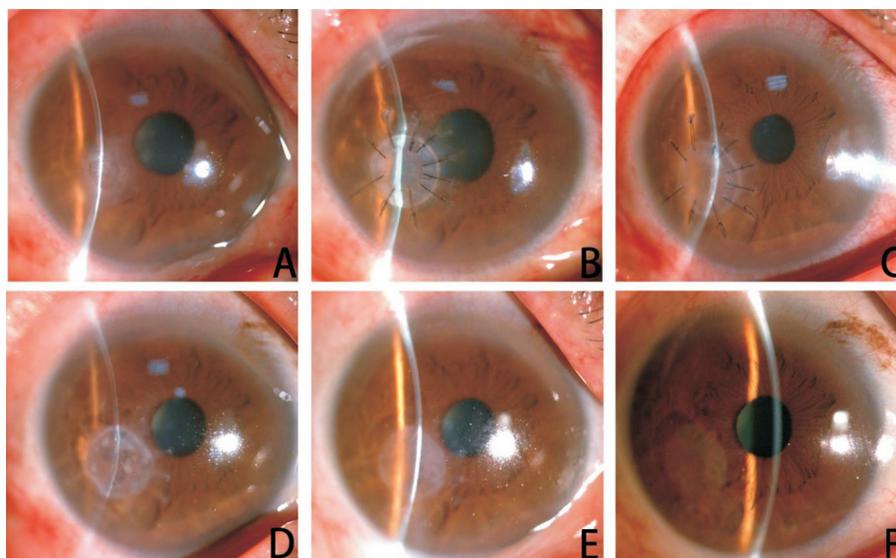
**Infection Control Rate of the Lesion Area** At the 6-month follow-up, the corneal infection in all patients was effectively controlled without recurrence, and the infection control rate was 100% (18/18). The results of corneal confocal microscope and anterior segment optical coherence tomography (OCT) before and after surgery in one patient showed that the control of postoperative infection and the growth of corneal graft in this type of patient are shown in Figure 3.

## DISCUSSION

Corneal diseases are one of the main causes of vision loss, damage due to corneal infection, or changes in appearance, and the best surgical treatment to restore vision is full-thickness or



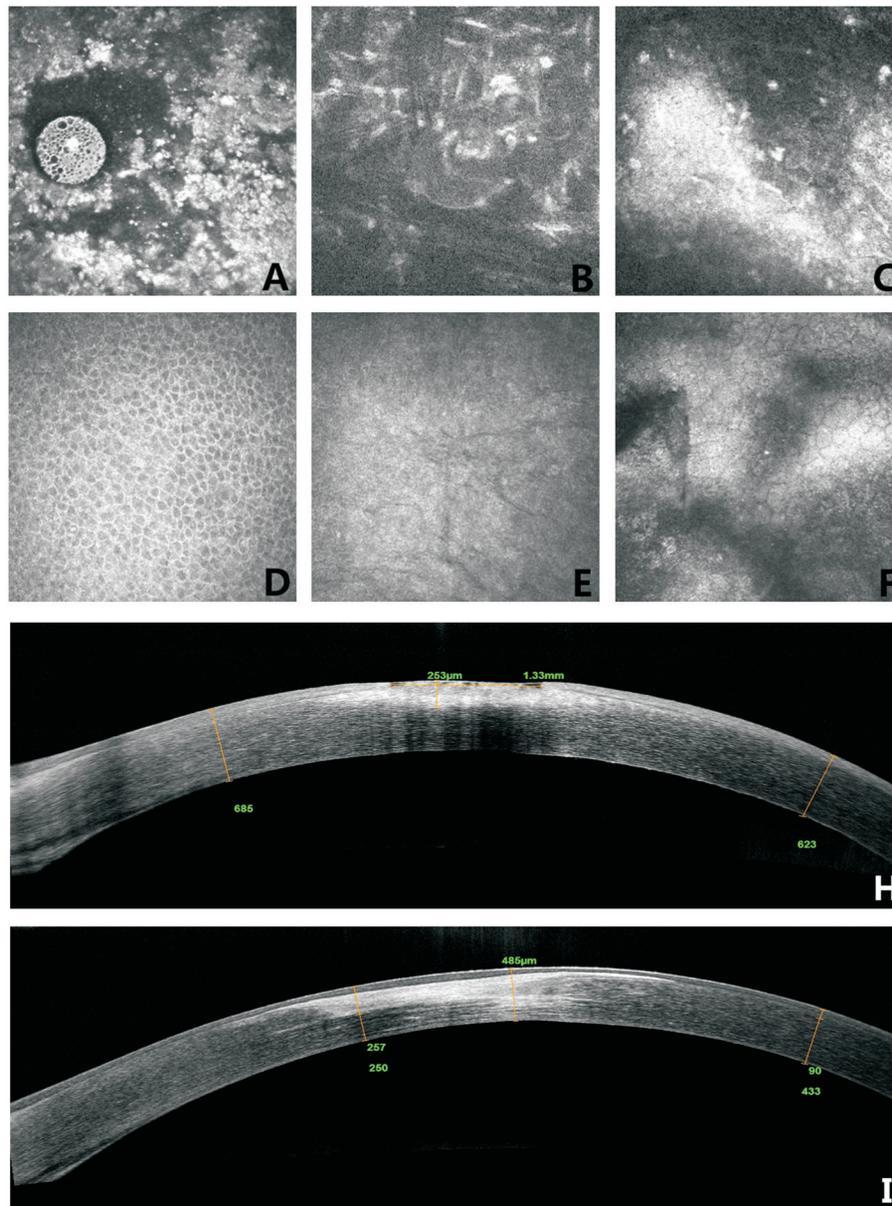
**Figure 1** Preoperative and postoperative photographs of small-diameter acellular porcine corneal stroma for peripheral corneal ulceration in a left eye A: An infection focus of about 2 mm on the cornea at 1:00-2:00 before surgery diagnosed fungal corneal ulcer of the left eye, and drug treatment was ineffective; B: Mild edema of corneal graft 3d after surgery; C: One month after surgery, edema of corneal graft gradually diminished, and the sutures were tightened without loosening; D: The corneal graft is translucent 3mo after the operation; E: All sutures have been removed 6mo after operation, and the corneal graft is transparent; F: The corneal graft was transparent 12mo after surgery.



**Figure 2** Preoperative and postoperative photographs of small-diameter acellular porcine corneal stroma for peripheral corneal ulceration in a right eye A: The corneal infection lesions at 7:00-8:00 before the operation diagnosed bacterial corneal ulcer of the right eye, and drug treatment was ineffective; B: Mild edema of corneal graft 3d after surgery; C: One month after surgery, the corneal graft edema was diminished, and the sutures were tightened without loosening; D: The corneal sutures have been removed 3mo after the surgery, and the graft is slightly edematous; E: All sutures have been removed 6mo after surgery, and the corneal graft is transparent; F: The corneal graft was transparent 12mo after surgery.

lamellar allogeneic corneal transplantation<sup>[10]</sup>. However, there is a severe shortage of corneal donors worldwide, resulting in an increasing number of patients with untreated curable corneal blindness<sup>[3-4]</sup>. The emergence of acellular porcine corneal stroma as an alternative material to allogeneic corneas has alleviated this situation<sup>[11-12]</sup>. This phenomenon can be traced back to 2003. Using *in vitro* corneal tissue engineering, Amano *et al*<sup>[13]</sup> confirmed that porcine-derived corneal stroma had low immunogenicity. Animal experiments have proven

that this material can be used as a graft to transparently heal the cornea. Therefore, it is an ideal replacement for an allogeneic cornea. The decellularized cornea completely replicates the complex structure and composition of the cornea, and produces an acellular scaffold composed of stroma<sup>[14]</sup>. The corneal stroma, as a mesh material, is beneficial for the growth of mesenchymal cells in the cornea and provides a relatively healthy microenvironment of the corneal stroma, which is beneficial for the growth of corneal epithelial cells<sup>[15-16]</sup>.



**Figure 3** Corneal confocal microscope and anterior segment OCT before and after surgery of a small-diameter acellular porcine corneal stroma for peripheral corneal ulceration A, B, and C: The preoperative corneal confocal microscope of the case in Figure 2, showed the infiltration of inflammatory cells in the corneal epithelial layer, stromal layer and endothelium; D, E and F: Photos of 12mo after surgery, all layers of inflammation were controlled; H: Preoperative anterior segment OCT showed corneal ulcers infiltrating into the corneal stroma layer; I: Twelve months after surgery, the anterior section OCT showed the position of the corneal graft and the recipient bed, and the corneal surface was smooth. OCT: Optical coherence tomography.

The acellular porcine corneal stroma lamellar transplantation can not only maintain the integrity of the eyeball, but also retain the original light transmittance of the cornea<sup>[17]</sup>. Wang *et al*<sup>[18]</sup> analyzed the immunogenicity of the three-layer porcine cornea and found that the stromal layer of the cornea was the lowest in both cellular immunity and humoral immunity, followed by the epithelial layer and the highest in the endothelial layer. However, lamellar keratoplasty has the following advantages: because the Descemet's membrane is not breached during surgery, the risk of postoperative intraocular infection is low<sup>[19-20]</sup>, and uveitis is also mild; in

lamellar keratoplasty, only the stromal layer of the cornea is sutured and fixed, and only the stromal layer is retained after decellularization of the acellular porcine corneal stroma. Therefore, endothelial cell transplantation was not performed, and corneal graft rejection was significantly reduced after surgery. Zhang *et al*<sup>[21]</sup> observed 47 patients with fungal corneal ulcers who underwent lamellar keratoplasty with porcine-derived acellular matrix material. After six months of observation, the infection was controlled in all patients, and no patients had serious adverse reactions or transplant rejection. Only four patients had different degrees of graft

dissolution during follow-up, and 34 eyes showed more than two lines of improvement in postoperative visual acuity.

The acellular porcine corneal stroma is less immunogenic than the decellularized stromal components. However, postoperative corneal transplant rejection occurs frequently in clinical practice. According to our previous clinical studies, this may be related to T cell-mediated cellular immunity and hypersensitivity to xenogeneic antigens<sup>[22]</sup>. For the surgical design of peripheral corneal ulcers, we chose small-diameter grafts and used fewer grafts compared to transpupillary grafts, which further reduced rejection after transplantation<sup>[23-25]</sup>. In this study, the trephine diameter was  $\leq 5$  mm. According to our follow-up of 18 patients with peripheral corneal ulceration treated with small-diameter acellular porcine corneal stroma, the corneal epithelium was completely covered on the graft after surgery. The graft gradually became transparent 3mo after surgery. The patient's vision significantly improved. During the 6-month follow-up, corneal infection was effectively controlled without recurrence, and the infection control rate was 100% (18/18). No postoperative rejection was observed. At the 12-month of follow-up, two patients were lost to follow-up, and the others had no rejection reaction and no keratitis recurrence.

For patients with corneal ulcers infected by fungi, bacteria, and amoebae, if the treatment is not performed timely or the effect of drug treatment is invalid, the lesions will further expand both in scope and depth, causing endophthalmitis and corneal perforation. Once the lesion expands or deepens, the graft diameter during surgery increases accordingly, which significantly increases the possibility of postoperative graft rejection and recurrence. Therefore, the timing of surgery in such patients is crucial. We believe that surgery should be actively considered if the lesion accumulates the deep stromal layer of the cornea and does not improve significantly after sensitive anti-infective therapy<sup>[26]</sup>. The purpose of early intervention is to remove the source of infection and inflammatory tissue to accelerate healing through complete debridement when the corneal ulcer is small. In addition, it can prevent the further expansion of the infection. If conservative treatment fails to cause severe ulcers and surgery is performed, the possibility of postoperative recurrence and rejection increases simultaneously. In contrast, for infectious corneal ulcers with a small peripheral diameter, early intervention can effectively prevent the disease from extending to the visual axis of the cornea, and the prognosis of vision is more secure.

It is reported that corneal nerve fibers grow into the graft after 6mo of bioengineered keratoplasty<sup>[27-30]</sup>. Before this process, graft rejection may still occur, even if the corneal epithelium is completely healed. We observed no postoperative rejection or recurrence of keratitis in 16 patients 12mo after surgery.

Therefore, the transplantation of small-diameter acellular porcine corneal stroma is safe and effective for treating corneal ulcers. Faced with a shortage of human corneal donors, acellular porcine corneal stroma is an ideal alternative for treating an increasing number of patients with corneal blindness. We will continue to observe corneal changes in these patients in the future.

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