A Single-Center Clinical Study to Evaluate the Efficacy and Safety of a Suture-Free Ophthalmic Hydrogel for Ocular Surface Tissue Adhesion

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A Single-Center Clinical Study to Evaluate the Efficacy and Safety of a Suture-Free Ophthalmic Hydrogel for Ocular Surface Tissue Adhesion

Research Unit: Eye Hospital of Shandong First Medical University (Shandong Eye Hospital)

Principal Investigators: Shi Weiyun, Wang Ting, Li Suxia

Protocol Summary

Study Title: A Single-Center Clinical Study to Evaluate the Efficacy and Safety of a Suture-Free Ophthalmic Hydrogel for Ocular Surface Tissue Adhesion.

Study Objective: To investigate the safety and efficacy of the suture-free ophthalmic hydrogel in achieving ocular surface tissue adhesion.

Study Subjects: Patients with ocular surface diseases (e.g., pterygium, corneal ulcer, ocular surface burn, etc.) who need to undergo conjunctival flap coverage surgery, amniotic membrane transplantation, or keratoplasty.

Study Design: Investigator-initiated, single-center, single-arm, open-label trial.

Planned Number of Subjects:

A total of 20 cases

Study Period and Expected Participant Involvement Duration:

Study Period: January 2026 – January 2027

Expected Participant Involvement Duration:

From the informed consent to use the suture-free ophthalmic hydrogel until the end of the observation period.

Contact Information:

Phone Number: 17686842936

Responsible Person: Shi Weiyun

1. Background Information

When severe ocular surface lesions occur (e.g., pterygium, corneal ulcer, ocular surface burn, etc.), the currently clinically commonly used surgical procedures such as conjunctival flap coverage, amniotic membrane transplantation, and keratoplasty are mainly fixed by suturing. However, suturing has numerous drawbacks. On the one hand, the suturing process causes additional mechanical damage to ocular surface tissues, triggers local inflammatory responses, and increases postoperative discomfort such as pain and foreign body sensation. Moreover, uneven suture tension is prone to cause conjunctival flap shrinkage or displacement, affecting the repair effect [1]. On the other hand, postoperative suture irritation continuously activates fibroblast

proliferation, leading to excessive deposition of subconjunctival collagen and the formation of dense scar tissue, which in turn impairs the stability of the ocular surface tear film and visual quality [2,3]. In addition, suturing surgery takes a long time (45-60 minutes on average) and has high requirements for the surgeon's microsurgical skills, limiting its popularization in primary medical institutions.

Therefore, a stable sutureless conjunctival flap coverage surgery is necessary to simplify the surgical process and prevent potential tissue damage and ocular surface scarring [4-6]. Tissue-adhesive hydrogels are developing rapidly as a non-invasive technology, featuring adaptability to wound morphology, strong adhesive effect, and rapid postoperative recovery. Bioadhesive hydrogels have been proven feasible for the treatment of cardiac trauma, hepatic hemorrhage, and corneal trauma, as they provide physical support while utilizing a regenerative microenvironment [7-10]. Although biological glues are commonly used in clinical ophthalmic practice, their poor mechanical properties, low adhesive strength, and insufficient biocompatibility cannot be ignored. Fibrin glue has weak adhesive properties, leading to frequent complications, mainly graft dehiscence [11]. Cyanoacrylate adhesives are toxic and form a glassy state, and are used off-label without approval from the U.S. Food and Drug Administration (FDA). ReSure (Ocular Therapeutix, Bedford, Massachusetts, USA) is an FDA-approved

polyethylene glycol (PEG)-based ophthalmic adhesive for sealing corneal incisions in cataract surgery, but it detaches within 1 to 4 days. Protein adhesives are prone to trigger immune responses, while synthetic polymer adhesives are often difficult to degrade [12,13].

Double-bond photopolymerization is a typical strategy for preparing adhesive hydrogels for the ocular surface. Under precise spatiotemporal control, gelatin methacryloyl (GelMA) hydrogels can form a robust network structure with tough mechanical strength [14-16]. However, these biological glues often have a single component and simple structure, resulting in mediocre adhesive performance. Introducing a second component is a promising improvement method that can bring new properties and synergistic effects to enhance adhesiveness. Tavafoghi et al. prepared a photocrosslinked tissue sealant with enhanced toughness by hybridizing GelMA with alginate methacryloyl (AlgMA) [10]. Zhao et al. developed a photocurable bioadhesive hydrogel composed of GelMA and oxidized dextran for keratoplasty [17]. Li et al. used an injectable photocurable gelatin system (consisting of GelMA and thiolated gelatin) to repair focal corneal wounds [18]. However, the synthesis of these composite hydrogels is often complex, and their high solid content makes them cumbersome to use. This results in the hydrogel curing before uniform application to the wound in practical use. In addition, high solid content also causes storage problems.

Based on the successful clinical translation experience of decellularized porcine cornea in the early stage, this project innovatively proposes a new concept of "in-situ repair and functional regeneration" and intends to develop an injectable ophthalmic adhesive. This technology creatively combines natural decellularized corneal matrix with low-energy photocrosslinking technology to achieve a functional breakthrough of the material by constructing a double network crosslinking system. First, transglutaminase (TGase)-mediated biological crosslinking forms an interpenetrating network between decellularized porcine corneal matrix (CECM) and GelMA, which not only retains the pro-regenerative activity of natural extracellular matrix (ECM) but also has controllable curing performance. Second, an innovative low-energy curing mode is adopted: compared with traditional ultraviolet (UV) curing, this technology uses low-energy visible light combined with bioenzymatic crosslinking, significantly improving safety. Third, relying on the signal advantages of natural ECM, the material can directly guide the rapid formation of a stratified structure of corneal and conjunctival epithelial cells, completing regeneration within 1 week. In contrast, most international similar studies require additional loading of growth factors to achieve similar effects, giving this technology dual advantages in regeneration efficiency and safety.

Based on the above research foundation, this study intends to

develop a suture-free ophthalmic hydrogel for ocular surface tissue adhesion. By combining the natural biological activity of decellularized porcine corneal matrix with the photocrosslinking properties of GelMA, and integrating low-energy visible light (465nm) curing technology, the hydrogel enables rapid, firm, and suture-free adhesion of conjunctival flaps. This design not only draws on the efficient fixation experience of photocurable adhesives in amniotic membrane transplantation but also absorbs the biocompatibility advantages of corneal repair hydrogels. At the same time, the material's degradation rate and inflammation regulation ability are optimized for the characteristics of conjunctival tissue. It is expected to reduce surgical damage and complications, improve the effect of ocular surface repair, and provide a new therapeutic option for clinical ocular surface adhesion surgery.

2. Objectives

2.1 Primary Objective

The primary objective of this clinical study is to evaluate the safety of the suture-free ophthalmic hydrogel for ocular surface tissue adhesion. Safety will be assessed based on the occurrence, severity, and frequency of all adverse events (including systemic symptoms) using the results of clinical examinations and diagnostic tests as the basis.

2.2 Secondary Objective

The secondary objective is to evaluate the efficacy (therapeutic effect) of the suture-free ophthalmic hydrogel for ocular surface tissue adhesion, with the detachment rate and conjunctival epithelial healing as the key indicators.

3. Study Design

3.1 Study Type

Investigator-initiated exploratory clinical study

3.2 Study Design

Single-center, single-arm, open-label trial.

3.3 Evaluation Items

3.3.1 Primary Evaluation Items: Safety Evaluation Items

Ocular safety: Observation of ocular surface irritation symptoms (foreign body sensation, pain, photophobia, lacrimation, etc.), immunogenicity, sensitization, elevated intraocular pressure (IOP), ocular infection, conjunctival hyperemia, and other conditions.

3.3.2 Secondary Evaluation Items: Efficacy Evaluation Items

① Conjunctival flap adhesion effect: On the 1st day, 1st week, and 1st month after surgery, the fitting status of the conjunctival flap was observed under a slit-lamp microscope to assess the presence of displacement or detachment, and the time of complete conjunctival flap adhesion was recorded.

② Ocular surface repair status: At 1 week and 1 month after surgery, the

changes in conjunctival flap thickness were examined by anterior segment optical coherence tomography (OCT), and the conjunctival epithelial healing was observed; fluorescein staining was used to evaluate the integrity of the ocular surface epithelium, and the time of complete epithelial coverage was recorded.

③ Visual function: Uncorrected visual acuity (UCVA) and best-corrected visual acuity (BCVA) were measured at each follow-up time point after surgery to assess the recovery of visual function.

④ Surgical efficiency: The surgical operation time was recorded and compared with that of traditional suturing surgery.

3.4 Study Method Overview

This is a single-center, single-arm, open-label trial to evaluate the safety and efficacy of the suture-free ophthalmic hydrogel in patients who require ocular surface adhesion surgery.

The clinical study consists of three phases: screening period, surgical period, and observation period.

After obtaining informed consent and completing subject registration, screening examinations will be performed to confirm that the subjects meet the inclusion criteria and do not violate the exclusion criteria. The surgery will be performed under topical anesthesia or peribulbar block anesthesia. After resecting the lesion tissue according to the pathological condition, a conjunctival flap of appropriate size will be

prepared. Four sutures will be placed to appose the graft with the surrounding conjunctiva to ensure no active bleeding. Blood around and under the graft will be thoroughly cleaned, and the surface and fornix will be dried with a sponge, keeping dry and avoiding irrigation before curing.

The hydrogel will be liquefied in a 37℃ water bath in advance, injected under the graft and surrounding conjunctiva, and spread evenly. Excess hydrogel overflowing around will be aspirated, and the excess hydrogel under the graft and conjunctiva will be extruded and removed by pressing. Care should be taken to avoid residual hydrogel on the surface and under the conjunctiva. The cornea will be protected with a wet cotton pad, and the hydrogel will be irradiated with a UV lamp with a wavelength of 465nm and UV energy of 18 mW/cm^2 for 60 seconds at an irradiation distance of 15 cm. After hydrogel curing, the sutures can be removed, and avoid pulling the conjunctiva forcefully. The surgery is completed, and a bandage contact lens can be worn.

On the 1st day after surgery, slit-lamp microscope examination will be performed to confirm the position and thickness of the conjunctival flap, and the ocular surface inflammatory response. During the observation period after hydrogel injection, subjects are required to return for follow-up a total of 4 times. If there are any safety concerns about the trial results, after taking necessary additional measures to address such concerns, a report will be submitted to the specific ethics committee for

re-approval.

The safety of this clinical study will also be evaluated by the ethics committee. After the completion of the first subject's trial, the principal investigator may request a meeting of the ethics committee as needed based on the occurrence of serious adverse events after treatment, to seek opinions on whether the study can continue or whether the study protocol needs to be modified.

3.5 Expected Participant Involvement Duration

The participation period for each subject in this clinical study is from the informed consent to use the suture-free ophthalmic hydrogel until the end of the observation period (1-month postoperative follow-up).

4. Subject Inclusion/Exclusion/Discontinuation Criteria

4.1 Inclusion Criteria

Patients who meet all the following conditions are eligible for enrollment.

1. Patients with ocular surface diseases (e.g., pterygium, corneal ulcer, ocular surface burn, pseudopterygium, etc.) who need to undergo conjunctival flap adhesion, amniotic membrane transplantation, or keratoplasty.

2. Aged 18 to 85 years old at the time of informed consent (regardless of gender).

3. Able to provide written informed consent and voluntarily

participate in the study.

4. No severe systemic organic diseases, such as severe heart, liver, kidney diseases, and malignant tumors.

4.2 Exclusion Criteria

Patients who meet any of the following conditions will be excluded. Items 1 to 6 apply to the eye scheduled for transplantation.

1. A history of allergy to the components of the suture-free ophthalmic hydrogel (e.g., decellularized porcine corneal matrix, GelMA, etc.) or the drugs prescribed during the perioperative and postoperative observation periods (anesthetics, antibiotics, steroid preparations, etc.).

2. Patients with systemic infectious diseases (bacterial, fungal, positive for HBV, HCV and other viruses, etc.).

3. Diabetic patients with poor blood glucose control (HbA1C ≥ 8.0%).

4. Pregnant women, women who may be pregnant, or women planning to become pregnant during the clinical study.

5. Patients who have participated in other clinical trials or studies within 1 month before obtaining informed consent.

6. Other patients deemed unsuitable for the clinical study due to comorbidities.

4.3 Discontinuation Criteria

Subject participation will be discontinued in the following situations.

After discontinuation, scheduled examinations/observations/evaluations will be performed as much as possible, and the reasons and course for discontinuation will be recorded in the case report form.

1. When the subject wishes to discontinue cooperation.

2. When it is discovered after informed consent acquisition that the subject does not meet the inclusion criteria or violates the exclusion criteria.

3. When an adverse event occurs, making it difficult to continue the study.

4. When the principal investigator and physician determine that the subject cannot comply with the provisions of the protocol.

5. When the clinical study itself is terminated.

In addition, if a severe adverse reaction occurs, the principal investigator and attending physician shall report it to the ethics committee for regenerative medicine research.

5. Subject Informed Consent Acquisition/Registration

The principal investigator or physician provides oral and written explanation of the study's purpose, methods, etc., of the study to the subject and obtain written consent for study participation.

5.1 Informed Consent Acquisition

5.1.1 Preparation of "Informed Consent Form" and "Explanatory Document"

The "Informed Consent Form" and "Explanatory Document" are prepared by the principal investigator and approved by the ethics committee.

5.1.2 Timing and Methods of Informed Consent Acquisition

When obtaining consent from the patient, the principal investigator or attending physician will first provide the patient with the "Explanatory Document" and explain the study purpose/methods, etc., in an understandable manner. Next, they address the patient's questions about the study to confirm that they have fully understood the study content. Finally, the patient’s willingness to voluntarily participate in this clinical study based on free will will be confirmed, and this will be documented by the patient signing/sealing or initialing the dated "Informed Consent Form".

When obtaining consent from the patient, the principal investigator or attending physician will confirm the patient’s contact information and the contact information of the patient’s family members or other emergency contacts, and record this in the medical records under the management of the participating institution.

5.1.3 Acquisition, Storage of "Informed Consent Form", and Case Registration

The principal investigator or attending physician who provided the explanation and the subject will each fill in the date, sign/seal or initial

the "Informed Consent Form". The original copy will be stored by the principal investigator or the physician performing regenerative medicine, and a copy will be stored by the personal information manager after linkable anonymization. After obtaining consent, the principal investigator or attending physician will entrust the case registration center to register the case. In addition, before the subject participates in the study, a copy of the signed/sealed and dated informed consent form will be provided to the subject, and the date of delivery will be recorded.

5.1.4 Documentation of Informed Consent Acquisition Date

The principal investigator or the physician performing regenerative medicine will record the date of obtaining informed consent from the subject in the case report form.

6. Study Implementation Schedule

6.1 Screening Period: 1-7 Days Before Surgery

Ocular irritation symptom scoring, visual acuity test (UCVA, BCVA), slit-lamp microscope examination, IOP measurement, anterior segment OCT examination, Schirmer's test, routine blood test, blood biochemistry, coagulation function test, four viral markers (HBV, HCV, syphilis, HIV) will be performed to confirm that the subjects meet the inclusion criteria and do not violate the exclusion criteria.

6.1.1 Informed Consent Acquisition

The principal investigator or attending physician must obtain written

informed consent from the patient and assign a subject identification code before performing any examinations/observations related to the clinical study. Informed consent must be completed 1-7 days before surgery.

6.1.2 Eligibility Confirmation

Based on the defined examinations/observations, the principal investigator and attending physician will confirm whether the candidate subject meets the inclusion criteria and does not violate the exclusion criteria (preliminary eligibility confirmation). In addition, the final eligibility confirmation will be performed within 1 week before the transplantation date based on the screening period examination results. Both preliminary and final eligibility confirmations will use the inclusion criteria in 4.1 and exclusion criteria in 4.2.

Surgical Period: The Day of Conjunctival Flap Coverage (Day 0)

The subject's body temperature and blood pressure will be measured before surgery. If the body temperature ≥38°C, systolic blood pressure >200 mmHg, or diastolic blood pressure >120 mmHg, the surgery will be discontinued or postponed.

The surgery will be performed under topical anesthesia or peribulbar block anesthesia. After resecting the lesion tissue according to the pathological condition, a conjunctival flap of appropriate size will be prepared. Four sutures will be placed to appose the graft with the surrounding conjunctiva to ensure no active bleeding. Blood around and

under the graft will be thoroughly cleaned, and the surface and fornix will be dried with a sponge, keeping dry and avoiding irrigation before curing.

The suture-free ophthalmic hydrogel will be liquefied in a 37℃ water bath in advance, injected under the graft and surrounding conjunctiva, and spread evenly. Excess hydrogel overflowing around will be aspirated, and the excess hydrogel under the graft and conjunctiva will be extruded and removed by pressing. Care should be taken to avoid residual hydrogel on the surface and under the conjunctiva. The cornea will be protected with a wet cotton pad, and the hydrogel will be irradiated with a UV lamp with a wavelength of 465nm and UV energy of 18 mW/cm^2 for 60 seconds. After hydrogel curing, avoid pulling the conjunctiva forcefully. The surgery is completed, and a bandage contact lens can be worn.

The surgical time, anesthesia method, and intraoperative complications will be recorded.

6.2 Observation Period:

1st day after surgery: Ocular examinations will be performed, including ocular irritation symptom scoring, visual acuity test, slit-lamp microscope examination, IOP measurement, confirmation of conjunctival flap position, hydrogel retention status, and ocular surface inflammatory response.

Postoperative follow-up: Subjects are required to return for

follow-up at 1 week and 1 month after surgery. At each follow-up, ocular irritation symptom scoring, visual acuity test, slit-lamp microscope examination, IOP measurement, OCT examination, Schirmer's test will be performed; fluorescein staining will be conducted if necessary. The occurrence of adverse events and all efficacy evaluation indicators will be recorded. At 1 month after surgery, conjunctival goblet cell status will be examined by conjunctival impression cytology. Pterygium recurrence will be recorded after surgery.

If there are any safety concerns during the trial, necessary additional measures will be taken, and a report will be submitted to the ethics committee for approval in a timely manner.

6.3 Unscheduled Visits

During each study period, if the subject experiences discomfort or signs/symptoms outside the scheduled examination time, an unscheduled visit may be arranged as needed to conduct corresponding examinations and record them in a timely manner.

7. Examination/Observation Items

7.1 Subject Background

Collected items: Gender, date of birth, consent acquisition date, target disease (diagnosis, transplanted eye), corneal transplantation history (presence, time, surgical method), present illness, comorbidities, past medical history, presence of drug allergies, concomitant medications,

and presence of pregnancy.

7.2 Subjective Symptoms of the Operated Eye

Examination method: Record the following items of the operated eye through subject interview (1-10).

7.3 Basic Examinations

7.3.1 Visual Acuity Examination

Method: Measure the 5-meter visual acuity (uncorrected and corrected) of the transplanted eye.

7.3.2 Intraocular Pressure Examination

Method: Measure the IOP of the transplanted eye using a handheld tonometer or non-contact tonometer.

7.3.3 Corneal Shape Analysis

Method: Examine the conjunctival flap healing and the absorption of the suture-free ophthalmic hydrogel underneath by anterior segment OCT of the operated eye.

7.4 Ophthalmological Findings

7.4.1 Conjunctival Findings

Method: Confirm the following items of the operated eye's conjunctiva through slit-lamp microscope examination, and observe the conjunctival flap apposition status for the presence of displacement or detachment.

Item	Grading
Conjunctival hyperemi	0.None 1.Mild 2.Moderate 3.Severe 9.Uncheckable
Ciliary hyperemia	0.None 1.Mild 2.Moderate 3.Severe 9. Uncheckable
Ocular discharge	0.None 1.Scanty 2.Moderate 3.Profuse 9.Uncheckable

7.4.2 Corneal Findings

Method: Observe the following items of the operated eye's cornea through slit-lamp microscope examination.

Item	Grading
Epithelial defect	0: None; 1: <1/4 cornea; 2: 1/4-1/2 cornea; 3: >1/2 cornea; 4: Unassessable
Clinical conjunctival ingrowth	0: None; 1: <1/4 cornea; 2: 1/4-1/2 cornea; 3: >1/2 cornea; 4: Unassessable
Corneal vascular ingrowth	0: None; 1: Mild (peripheral only); 2: Involving pupillary margin; 3: Covering pupil; 4: Unassessable
Corneal transparency	0: Normal; 1: Mild (pupil and iris texture visible); 2: Moderate (pupil visible, iris texture details unclear); 3: Severe (pupil unidentifiable); 4: Unassessable
Keratic precipitates (KP)	0: None; 1: KP+; 2: KP++; 3: KP+++; 4: Unassessable

7.4.3 Other Ophthalmic Examinations

Slit-lamp microscopy examination, and perimetry and fundus examination if all possible, are to be carried out in determining the following items:

Item	Score
Iris	0. no abnormalities, 1. anterior or posterior iris adhesion (less than 50% of the total circumference), 2. anterior or posterior iris adhesion (more than half of the circumference), 3. observation not possible due to corneal opacity
Cataract	0. None or mild, or pseudophakia or aphakia, 1. moderate, 2. severe, 3. observation not possible due to corneal opacity
Glaucoma	0. none or no visual field constriction, 1. central visual field remaining but visual field is constricted, 2. central visual field defects, 3. visual field examination not possible due to corneal opacity
Vitreo-Retinal Disease	0. none or little impact on eyesight, 1. retinal disease present and there may be an impact on eyesight, 2. 50% or more of the total impact on eyesight is due to retinal disease, 3. the details of fundus are unknown due to corneal opacity
Others	Evaluate non-corneal eye diseases with an impact on eyesight using three stages: 0. none 1. present 2. unknown. If 1 is selected, find staging. The optic nerve head, retinal vessels, and the macula are to be observed in the fundus observation to determine whether there are any abnormalities.

7.5 Clinical Examination Items

7.5.1 Hematological Examinations

Laboratory examination items

Examination Item	Examination Indicators
Routine blood test	White Blood Cell count (WBC), Red Blood Cell count (RBC), Platelet count (PLT), neutrophil %, lymphocyte %, monocyte %, hemoglobin (HGB)
Urine routine	Urine occult blood, Urine pH, RBC count, WBC count, Urine glucose, Urine protein, Urine ketone bodies, Urine specific gravity
Blood biochemistry	Liver function: Total bilirubin (TBIL), Direct bilirubin (DBIL), Indirect bilirubin (IBIL), Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), Gamma-glutamyl transferase (GGT), Alkaline phosphatase (ALP), Total protein (TP), Albumin (ALB); Renal function: Blood urea nitrogen (BUN), Creatinine (Cr); Electrolytes: Calcium (Ca^{2+}), chloride (Cl^{-}), potassium (K^{+}), sodium (Na^{+}), magnesium (Mg^{2+}); Myocardial enzyme profile: Creatine kinase (CK), CK-MB, Lactate

	dehydrogenase (LDH)
Blood glucose	Fasting blood glucose, Glycated hemoglobin (HbA1c)
Coagulation function (four items)	Activated Partial Thromboplastin Time (APTT), International Normalized Ratio (INR), Prothrombin activity (PT%), Prothrombin Time Ratio (PT-R), Fibrinogen (FIB), Prothrombin Time (PT), Thrombin Time (TT)
Viral screening (four items)	Hepatitis B core antibody (HBcAb), Hepatitis B e antigen (HBeAg), Hepatitis B surface antigen (HBsAg), Hepatitis B e antibody (HBeAb), Hepatitis B surface antibody (HBsAb), HIV (1+2) antibody (HIV-Ab), Hepatitis C antibody (HCV-Ab), Treponema pallidum antibody (TP-Ab)

7.5.2 Other Preoperative Ophthalmic Examinations

Items: Electrocardiogram (ECG), Serological infection screening (Syphilis, HBV, HCV). If the subject has severe ocular surface inflammation, conjunctival sac culture will be performed simultaneously.

7.6 Adverse Events

Investigate adverse events through examinations during hospitalization and outpatient visits.

8. Preparation of the Suture-Free Ophthalmic Hydrogel

8.1 Basic Material Information

Name: Suture-free ophthalmic hydrogel

Components: Decellularized porcine corneal matrix, gelatin methacryloyl (GelMA)

8.2 Volume Specification

Container: Syringe; Filling volume: 0.5 ml

8.3 Manufacture of Specified Cell-Processed Product

8.3.1 Raw Material

Decellularized porcine corneal matrix, gelatin methacryloyl (GelMA).

8.3.2 Preparation and Management of the Suture-Free Ophthalmic Hydrogel

Preparation of decellularized porcine corneal matrix hydrogel (CECM)

(1) Fresh porcine eyeballs were washed 3 times with sterile phosphate-buffered saline (PBS) in a clean bench. After scraping off the epithelium with an epithelial spatula, the central cornea was trephined with an 11 mm trephine, the corneal endothelium was scraped off, and the cornea was soaked in PBS solution containing double antibiotics (penicillin and streptomycin) for 1 hour.

(2) The porcine cornea was soaked in a solution containing 0.5% sodium lauroyl glutamate and 500 U/mL nuclease for decellularization, and incubated in a constant temperature shaker at 37℃, 120 rpm/min for

3 hours.

(3) The cornea was washed 6 times with sterile PBS for 15 minutes each time, then washed twice with sterile normal saline, followed by freeze-drying.

(4) To prepare the decellularized corneal matrix hydrogel, the samples were chopped and soaked in 0.1 mol/L hydrochloric acid solution containing 10% pepsin for 18 hours. The final concentration of the CECM solution was adjusted to 30 mg/ml and stored at -20°C until use.

Preparation of the suture-free ophthalmic hydrogel

(1) The 3% CECM solution was neutralized with 1 mol/L NaOH and 500 mM Tris-HCl (pH=7.4) first.

(2) The neutralized CECM was thoroughly mixed with 10% GelMA and 0.2% sodium phenyl(2,4,6-trimethylbenzoyl)phosphinate (NAP), filtered through a sterile filter head, and aliquoted into 1 ml syringes, then stored at 4℃.

8.3.3 Application of the Suture-Free Ophthalmic Hydrogel for Conjunctival Flap Adhesion

On the day of surgery, the principal investigator and at least two independent attending physicians with no conflicts of interest will comprehensively judge whether the suture-free ophthalmic hydrogel can

be used for conjunctival flap adhesion based on the subject's condition and ocular surface status on that day.

Routine surgical preparation: After resecting the lesion tissue according to the pathological condition, a conjunctival flap of appropriate size will be prepared. Four sutures will be placed to appose the graft with the surrounding conjunctiva to ensure no active bleeding. Blood around and under the graft will be thoroughly cleaned, and the surface and fornix will be dried with asponge, keeping dry and avoiding irrigation before curing.

The suture-free ophthalmic hydrogel will be liquefied in a 37℃ water bath in advance, injected under the graft and surrounding conjunctiva, and spread evenly. Excess hydrogel overflowing around will be aspirated, and the excess hydrogel under the graft and conjunctiva will be extruded and removed by pressing. Care should be taken to avoid residual hydrogel on the surface and under the conjunctiva. The cornea will be protected with a wet cotton pad, and the hydrogel will be irradiated with a UV lamp with a wavelength of 465nm and UV energy of 18 mW/cm^2 for 60 seconds. After hydrogel curing, avoid pulling the conjunctiva forcefully. The surgery is completed, and a bandage contact lens can be worn.

Detailed surgical information [transplantation date, anesthesia method, concomitant surgery, concomitant treatment, surgical time,

presence of Descemet's membrane stripping, post-transplantation position restriction time] and the occurrence of intraoperative complications will be recorded in the CRF.

8.3.5 Management for Insufficient Therapeutic Effect

The ethics committee will conduct an efficacy evaluation at 1 week after surgery. If conjunctival flap detachment occurs, the subject will be asked whether he/she is willing to undergo re-adhesion through an interview after the 2nd follow-up (1 week) and before the end of the follow-up study. If the subject is willing to undergo re-adhesion and the attending physician judges that the benefits of re-adhesion outweigh the risks and harms, re-adhesion surgery or re-suturing surgery will be performed 1 week after the initial surgery with research funding.

9. Adverse Event Evaluation/Reporting

9.1 Definition of Adverse Events

An adverse event is any unfavorable or unexpected sign, symptom, or disease occurring in a subject, regardless of whether it is related to treatment such as transplantation of autologous urine-derived epithelial cells.

In addition, planned hospitalization/examinations before the start of the study and hospitalization specified in the clinical study protocol are not considered adverse events in this clinical study.

Among adverse events, those meeting the following conditions are

called serious adverse events:

Resulting in death (Fetal)

Life-threatening

Requiring therapeutic hospitalization or prolonging hospitalization

Resulting in persistent/significant disability/incapacity

Congenital anomaly/birth defect

Other serious events equivalent to the above

9.2 Adverse Events Evaluation

All adverse events observed from subject registration to the end of the study will be evaluated as follows. Clinically significant abnormal changes in clinical test values compared with pre-transplantation will be reported as adverse events.

9.2.1 Onset Date of Adverse Events

Refers to the date on which the adverse event is confirmed. However, for asymptomatic complications or incidental diseases, the date of diagnosis (date of diagnostic examination) is the onset date of the adverse event.

9.2.2 Severity Classification of Adverse Events

The principal investigator and attending physician will determine the severity of all adverse events occurring during this clinical study by replacing them with the severity of adverse events based on the following classification of side effects of drugs, etc.

Grade 1: Adverse events considered mild.

Grade 2: Non-serious adverse events but not mild.

Grade 3: Adverse events considered serious. That is, depending on the patient's constitution or condition at the time of occurrence, it may lead to death or permanent functional impairment that hinders daily life.

9.2.3 Adverse Events Outcome

The outcome of adverse events is classified as follows:

Recovery	Disappearance or resolution of symptoms/signs, normalization of test values, or recovery to pre-administration values.
Improvement	Reduction in the severity of symptoms/findings by at least 1 grade, near disappearance of mild symptoms/findings, or recovery of test values to near pre-administration values.
Unrecovered	No change in symptoms/findings or test values, worsening of the severity compared with the time of occurrence in the follow-up data on the last day of the observation period, irreversible congenital abnormalities, death in which the adverse event is not the direct cause and the adverse event remains unrecovered, recovery with sequelae, or partial recovery of symptoms/findings but partial confirmation as sequelae.
	A direct correlation is confirmed between death and the adverse event. Here, "confirmation of direct correlation" means that the adverse event is the cause of death or the

Death	adverse event significantly contributed to death. The outcome of an adverse event judged (presumed) to be an indirect cause of death in the same case is not considered "death".
Unknown	Cases where follow-up cannot be performed as described in the clinical study protocol after transplantation due to transfer, relocation, etc.

9.2.4 Outcome Date of Adverse Events

Record the date of recovery, improvement, unrecovery, or death during or after treatment. In addition, if the outcome date cannot be accurately specified, record the date of confirming the outcome content.

9.2.5 Correlation Between Adverse Events and Trial Procedures and Transplantation of Autologous Urine-Derived Epithelial Cells

The correlation with trial procedures and transplantation of autologous urine-derived epithelial cells is determined in four categories as follows:

Definitely related: Clear temporal correlation (including the course after transplantation) and evidence of confirmed correlation;

Probably related: Clear temporal correlation (including the course after transplantation), and factors other than the trial treatment, such as the primary disease, comorbidities, concomitant medications, and

concurrent treatments, can be basically excluded;

Possibly related: Clear temporal correlation (including the course after transplantation), other factors such as the primary disease, comorbidities, concomitant medications, and concurrent treatments can also be presumed, but the possibility caused by the trial treatment cannot be excluded;

Unrelated: No temporal correlation. It can be presumed to be caused by other factors such as the primary disease, comorbidities, concomitant medications, and concurrent treatments.

9.3 Management When Adverse Events Occur

During the subject's study participation, the principal investigator and attending physician will conduct necessary and appropriate examinations/observations and pay attention to the subject's safety. When an adverse event occurs, ensure that appropriate treatment is implemented, pay attention to the subject's safety, and ensure that specialist diagnosis is obtained when necessary to strive to identify the cause.

In addition, during and after the subject's study participation, adequate medical measures will be taken for clinically significant serious adverse events related to the study.

After the end of the observation period, from the perspective of ensuring safety and scientific rationality, follow-up will be performed within the scope of insurance-based medical treatment if necessary. If it is

known that a disease, disability, death, or infection suspected to be caused by the provision of this surgical trial has occurred, the principal investigator and attending physician shall promptly report the situation to the administrator of the medical institution performing regenerative medicine.

9.4 Adverse Events Recording

If a new adverse event occurs during the study period, record the following items in the adverse event column of the case report form.

Event name

Onset date

Severity

Outcome (recovery, improvement, unrecovered, death, unknown)

Outcome date

Correlation with trial procedures and transplantation of autologous urine-derived epithelial cells

Management (discontinuation/continuance of the study, and treatment content for the adverse event)

9.5 Quality Defects of the Suture-Free Ophthalmic Hydrogel

Quality defects of the suture-free ophthalmic hydrogel refer to quality deviations that may occur after the hydrogel is released from production and before delivery to the operating room or before/after administration to the subject. Specifically, if the following quality defects of the

suture-free ophthalmic hydrogel are confirmed, they will be recorded in the CRF:

- Failure of the suture-free ophthalmic hydrogel to form a gel during in vitro UV curing
- The suture-free ophthalmic hydrogel is a flowable liquid at temperatures below 20°C
- Failure of the suture-free ophthalmic hydrogel to dissolve at 37°C
- Appearance of white turbidity in the suture-free ophthalmic hydrogel
- Damage to the packaging container
- Failure to store in the dark during transportation
- Other unexpected deviations

The recording items in the CRF are as follows:

- Transplantation performed (1: No, 2: Yes)
- Transplantation date
- Defect onset date
- Defect classification (1: Contamination, 2: Defective product, 3: Performance, 4: Others)
- Defect details
- Occurrence of adverse events related to the defect (1: No, 2: Yes; record in the adverse event section if "Yes")

9.6 Reporting of Adverse Events and Defects

When the following adverse events are known to occur during the implementation of this clinical study, the principal investigator and attending physician shall promptly report them to the administrator of the implementing medical institution.

10. Evaluation Items

10.1 Safety Evaluation Items

The primary safety evaluation item: [All adverse events including systemic symptoms].

The secondary safety evaluation items: [Adverse events caused by the components of the suture-free ophthalmic hydrogel] and [Adverse events caused by surgery/procedures], which are determined according to the following items and criteria:

1. Elevated intraocular pressure: Definition: Measured IOP ≥25 mmHg during postoperative follow-up, and the elevated IOP cannot be rapidly reduced with anti-glaucoma drugs.

2. Rejection reaction: Definition: A score of 2 or 3 for "keratic precipitates" in "7.4.2 Corneal Findings" (however, if the signs improve with increased steroid eye drops, it is judged as "suspected rejection reaction").

3. Infection: Definition: ① Score of 2 or 3 for "conjunctival hyperemia" in "7.4.1 Conjunctival Findings"; ② Score of 2 or 3 for "ocular discharge" in "7.4.1 Conjunctival Findings"; ③ Score of 2 or 3 for

"anterior chamber inflammation" in "7.4.3 Anterior Chamber Findings". Occurrence of ①+② or ①+③.

4. Cataract progression: Definition: Confirmed significant cataract progression compared with preoperatively in "cataract" of "7.4.5 Other Ophthalmic Findings".

5. Expulsive hemorrhage: Definition: Occurrence of expulsive hemorrhage during surgery (recorded in the surgical record).

For the above primary and secondary safety evaluation items, the type, severity, and frequency of all adverse events are evaluated using the severity classification of drug adverse reactions.

In addition, each adverse event in the secondary safety evaluation items is roughly equivalent to the following grades in the severity classification of drug adverse reactions, but the individual status of the subject is also considered in the evaluation (e.g., infection cured at a very early stage is regarded as Grade 2):

- Suspected rejection reaction: Grade 1

- Elevated IOP, rejection reaction, cataract progression: Grade 2

- Non-target cell proliferation, infection, expulsive hemorrhage: Grade 3

In addition, considering the occurrence of adverse reactions and abnormal changes in clinical laboratory test values during the clinical study, the overall safety of each subject is determined into four grades:

① Safe: No adverse reactions, no abnormal changes in clinical laboratory test values.

② Basically safe: Occurrence of Grade 1 adverse reactions or abnormal changes in clinical laboratory test values.

③ Safety concerns: Occurrence of Grade 2 adverse reactions or abnormal changes in clinical laboratory test values.

④ Unsafe: Occurrence of Grade 3 adverse reactions or abnormal changes in clinical laboratory test values.

10.2 Efficacy Evaluation Items

1. Conjunctival flap apposition status

Judgment method: At each follow-up time point, the position of the conjunctival flap is examined under a slit-lamp microscope; the conjunctival flap in position with good apposition is judged as effective.

Evaluation criteria:

① The conjunctival flap is in position with good apposition during all follow-up periods: Effective.

② The conjunctival flap is in position at least once before the 2nd follow-up with poor apposition but with good apposition at the final judgment: Suggestive of effectiveness.

③ Other situations: Ineffective.

2. Conjunctival flap healing

Judgment method: At each follow-up time point, the blood supply of

the conjunctival flap is examined under a slit-lamp microscope; the conjunctival flap with good blood supply is judged as effective.

Evaluation criteria:

① The conjunctival flap has good blood supply during all follow-up periods: Effective.

② The conjunctival flap has edema and blanching at least once before the 2nd follow-up but with good blood supply at the final judgment: Suggestive of effectiveness.

③ Other situations: Ineffective.

11. Statistical Matters

11.1 Target Sample Size and Rationale

This clinical study is the first human application of the combination of natural decellularized corneal matrix and low-energy photocrosslinking technology to achieve rapid, firm, and suture-free adhesion of conjunctival flaps. A minimum target sample size of 20 cases is set to confirm the reproducibility trend of the safety of the suture-free hydrogel, explore its efficacy for conjunctival flap adhesion, and lay the foundation for future clinical trials.

11.2 Demographic Characteristics

For demographic characteristics, the number of cases, mean, standard deviation, maximum, minimum, and median will be calculated for continuous variables. Other parameters required for descriptive

reporting will be explored as needed.

11.3 Safety and Efficacy Analysis

For continuous evaluation items, the change from baseline and the summary statistics of the measured values will be calculated at each measurement time point. For discrete evaluation items, frequency summary at each time point or cross-tabulation between baseline and each time point will be performed. In addition, trend charts will be created if necessary.

11.4 Interim Analysis

No interim analysis will be performed.

11.5 Deviations from the Original Statistical Plan

If an analysis method different from that described in the statistical plan of this clinical study protocol is adopted, all changes will be recorded in the final report.

Regarding the handling of missing, unused, and abnormal data, the ethics monitoring committee will be consulted, and the handling method will be carefully determined on a case-by-case basis.

12. Deviations from the Study Protocol

12.1 Deviations Due to Emergency Situations

When the principal investigator and attending physician do not follow this clinical study protocol to avoid an emergency risk to the

subject or for other medically unavoidable reasons, this fact must be recorded. The principal investigator will immediately submit a document describing the situation and its reasons to the medical institution administrator.

12.2 Deviations Due to Other Circumstances

If the principal investigator needs to modify this clinical study protocol, prior approval from the ethics committee must be obtained. When deviations occur due to other circumstances, the principal investigator will immediately submit a document describing the situation and its reasons to the medical institution administrator.

12.3 Compliance with Regulations, etc.

All personnel participating in this clinical study shall carefully read and understand the content of the "World Medical Association Declaration of Helsinki", "Clinical Research Act", and laws related to the safety of "regenerative medicine", etc., which should be followed in all medical research involving humans, and comply with them.

12.4 Protection of Subject Privacy

Regarding the protection of subject privacy, the following matters will be observed:

After participating in this clinical study, the identification of subjects involved in the information obtained related to the study will be managed by linkable anonymization using the subject identification code assigned

at the time of registration.

In the processing of examination/observation/evaluation results and the preparation/storage of case report forms, every effort will be made to protect the subject's privacy.

12.5 Conflict of Interest and Research Funds

12.5.1 Conflict of Interest

The management of conflicts of interest of the principal investigator and attending physician will be based on the guidelines for conflict of interest management in regenerative medicine research followed by the principal investigator.

12.6 Periodic Reports

12.6.1 Report to the Specific Certified Regenerative Medicine Committee

The administrator of the implementing medical institution will report the following matters to the ethics committee regarding the study status.

12.7 Compliance

This clinical study will be conducted in accordance with this study protocol and separately specified operating procedures. If compliance is not achieved, the situation will be recorded in detail.

The administrator of the implementing medical institution and the principal investigator will continuously confirm whether the study is being conducted properly in accordance with applicable rules, the

regenerative medicine provision plan, and the study protocol, and at the same time take necessary measures to ensure proper implementation, such as study discontinuation, modification of the regenerative medicine provision plan or study protocol, if necessary.

If a person other than the principal investigator becomes aware of non-compliance, they shall report it to the principal investigator. If the principal investigator becomes aware of or receives a report, the process and measures will be recorded, and the administrator of the medical institution performing regenerative medicine will be reported based on the severity.

12.8 Handling and Record Storage of Data and Samples

Documents related to the implementation of this clinical study will be stored in a personal information management hard disk by the document manager after being electronicized into PDF format, etc.

13. Research Costs and Compensation

We will provide you with the hydrogel free of charge. As a subject, if you suffer damage due to receiving the study drug treatment or following the study procedures correctly and in accordance with the researcher’s guidance, the sponsor will compensate you for reasonable medical expenses incurred for the treatment of study-related injuries and reasonable compensation required by relevant Chinese laws and

regulations.

References

[1] Wang Y, et al. Complications of Traditional Sutured Conjunctival Flap Surgery: A Retrospective Clinical Analysis [J]. J Cataract Refract Surg, 2020, 46(5):721-728.

[2] G. S. Noureddin, S. N. Yeung, Clin. Ophthalmol. 2016, 10, 705.

[3] P. P. Syam,H.Eleftheriadis,C.S.Liu, Ophthalmology 2003, 110, 806.

[4] B. Yüksel, S. K. ¯Unsal, S. Onat, Int. J. Ophthalmol. 2010, 3, 316.

[5] C. Kucukerdonmez, A. Karalezli, Y. Akova, M. Borazan, Eye 2010, 24,558.

[6] A. T. Trott, JAMA, J. Am. Med. Assoc. 1997, 277, 1559.

[7] M. Tavafoghi, et al., Engineering tough, injectable, naturally derived, bioadhe- sive composite hydrogels, Adv. Healthc. Mater. 9 (10) (2020) e1901722.

[8] J. Li, et al., Tough adhesives for diverse wet surfaces, Science 357 (6349) (2017) 378–381.

[9] H. Yuk, et al., Rapid and coagulation-independent haemostatic sealing by a paste inspired by barnacle glue, Nat. Biomed. Eng. 5 (10) (2021) 1131–1142.

[10] X. Zhao, et al., Natural polymer-derived photocurable bioadhesive hydrogels for sutureless keratoplasty, Bioact. Mater. 8 (2022) 196–209.

[11] S. Bouhout, et al., Cost-effectiveness analysis : fibrin glue versus sutures for conjonctival fixation during pterygion surgery, Can. J. Ophthalmol. 57 (1)(2022) 41–46.

[12] S. Nam, D. Mooney, Polymeric Tissue Adhesives, Chem. Rev. 121 (18) (2021) 11336–11384.

[13] G. Trujillo-de Santiago, et al., Ocular adhesives: design, chemistry, crosslinking mechanisms, and applications, Biomaterials 197 (2019) 345–367.

[14] S. Sharifi, et al., Tuning gelatin-based hydrogel towards bioadhesive ocular tis- sue engineering applications, Bioact. Mater. 6 (11) (2021) 3947–3961.

[15] I.A. Barroso, et al., Photocurable GelMA Adhesives for Corneal Perforations, Bio- engineering (Basel) 9 (2) (2022) 53.

[16] K. Peng, et al., Light manipulation for fabrication of hydrogels and their bio- logical applications, Acta Biomater. 137 (2022) 20–43.

[17] M. Tavafoghi, et al., Engineering tough, injectable, naturally derived, bioadhe- sive composite hydrogels, Adv. Healthc. Mater. 9 (10) (2020) e1901722.

[18] L. Li, et al., Gelatin-Based Photocurable Hydrogels for Corneal Wound Repair, ACS Appl. Mater. Interfaces 10 (16) (2018) 13283–13292.