Clinical study protocol

The Application of Photosensitive Hydrogel in Intranasal Endoscopic Dacryocystorhinostomy for the Anastomosis of Lacrimal Cyst Flap and Nasal Mucoperiosteal Flap

——A Prospective Randomized Controlled Single-center Clinical Study

Principal investigator: Gong Lan

Clinical Research Department: Ophthalmology

Sponsor: No

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Principal Investigator Signature:

Date：

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1、**Research background**

Chronic dacryocystitis is a common ophthalmic disease, mostly caused by nasolacrimal duct obstruction or stenosis. Tears and secretions cannot flow into the nasal cavity through the nasolacrimal duct and remain in the lacrimal sac, resulting in bacterial infection. If not treated, it can not only affect the patient's daily life, but also threaten the patient's eye health. The accumulation of pus in the lacrimal sac is a potential source of intraocular infection, which can easily lead to endophthalmitis during intraocular surgery or ocular trauma. At present, there are many measures to treat chronic dacryocystitis, the treatment principle is to dredge or re-establish the nasal drainage channel, eliminate obstruction, and inhibit infection. At present, the main treatment methods are external dacryocystorhinostomy, nasolacrimal duct intubation, lacrimal passage laser plasty and endoscopic dacryocystorhinostomy. After evolution and improvement, the operation success rate has increased to more than 90%, but there are still shortcomings such as facial skin scar, surgical trauma, damage to the "tear pump" function, and inability to treat nasal diseases at the same time. Nasolacrimal duct intubation and lacrimal passage laser plasty have the advantages of simple operation, time-saving, easy tolerance and repeatable operation. However, since they are not operated under direct vision, they are easy to form false passages, and easy to cause adhesion and scar formation between the lacrimal passage mucous membranes. The long-term efficacy is still controversial.

With the development of nasal endoscopy technology and the improvement of patients' requirements for facial aesthetics, dacryocystorhinostomy under nasal endoscopy has gradually become the main surgical method for the treatment of chronic dacryocystitis. Compared with traditional external dacryocystorhinostomy, dacryocystorhinostomy under nasal endoscope has the advantages of "tear pump" function without damage to inner canthus ligament and deep branch of orbicularis oculi muscle. It also causes no facial scar left, and can simultaneously treat the nasal complications. The operation is under high-definition magnification endoscopic vision, so that it’s also a fine, simple and minimally invasive surgery. With the widespread promotion of its clinical application, it has gradually been found that the granulation or scar formation at the anastomosis after endoscopic dacryocystorhinostomy is the main reason for the failure of the operation. **How to achieve the ideal fit between the lacrimal sac flap and the nasal mucoperiosteal flap and avoid the proliferation of granulation and cicatricial adhesion is very important for the success of**

the operation. In order to improve the success rate of operation, many explorations have been made, such as suture between lacrimal sac flap and nasal mucoperiosteal flap during operation. In order to maintain the patency of the anastomosis, artificial lacrimal duct, mitomycin C and lacrimal duct dilator stent have all been applied to the anastomosis, but they all have certain disadvantages. For example, artificial lacrimal duct and dilator stent are easy to fall off and become blocked again, and need to be removed by a second operation, which is often accompanied by bleeding and can affect wound healing. Mitomycin C has certain toxic and side effects. Though it can reduce scar hyperplasia, it can also delay anastomotic wound healing and epithelialization.

In recent years, with the wide application of new technologies and new materials, the medical community and the medical polymer material community have reached a consensus that hydrogels will become a powerful tool to solve the problem of clinical wound repair and tissue flap adhesion. Hydrogel has the most similar structure and mechanical properties of human soft tissue, which can provide a good self-healing environment. Secondly, hydrogel can form an effective physical barrier, which can quickly stop bleeding, close the wound, and effectively reduce the incidence of adhesion and infection. More importantly, hydrogel has the function of drug carrier and cell scaffold, which can carry drugs, cytokines and even stem cells. These can effectively promote wound repair and healing. Therefore, the conversion of hydrogel materials into clinical products is one of the most important goals in this field. Similar to the photosensitive dental repair technology, photosensitive hydrogels can achieve in situ modeling of irregular wounds with excellent controllability. A single component is particularly easy to clinical operation, which is an important development direction of hydrogels medical materials. However, the current technology has an important defect due to its inability to adhere firmly to and integrate with wet tissues.

Photosensitive hydrogel products will realize the innovation of hydrophilic polymer in situ crosslinking forming on the wound surface. It can be adapted to any irregular wound, and the "photocoupling reaction" technology can achieve seamless integration and strong adhesion of hydrogel material and wound. Therefore, the photosensitive hydrogel products have the following advantages: (1) Excellent adhesion ability, which can realize the close adhesion and hemostasis of irregularly shaped tissue wounds, reduce wound exposure, reduce infection risk, and take into account the analgesic function; (2) The hydrogel is used as the skeleton of biological macromolecules, and the crosslinking process is mild and controllable, with excellent biosafety and

biodegradability; (3) The hydrogel is soft and elastic, with a high degree of mechanical strength consistent with human soft tissue.

The photosensitive hydrogel uses the natural human component, hyaluronic acid, as the biological macromolecule skeleton. After packaging, it has undergone strict medical grade sterilization treatment, which meets the national GB/T 16886 standard. It is non-toxic to the human body, has no allergy and rejection reaction, and ensures the biosafety to the maximum extent (see the attachment for details). Approved by the Ethics Committee of Changhai Hospital Affiliated to Naval Medical University (see attachment for a copy of the ethics approval), clinical trials of suture-free skin trauma and chronic wound repair of more than 200 cases (including children) have been completed in its burn department since 2018, and no adverse reactions have been reported. At the same time, Yueyang Hospital of Integrated Chinese and Western Medicine affiliated to Shanghai University of Traditional Chinese Medicine, the Second Affiliated Hospital of Wenzhou Medical University and Ningbo Huami Hospital of University of Chinese Academy of Sciences respectively conducted clinical application research on postoperative wound treatment using the hydrogel, including hepatoenteropathy, prevention and treatment of pediatric prepuce adhesion, and treatment of skin donor area wounds (copy of the ethical approval letter is attached).

Therefore, based on the clinical application value of photosensitive hydrogel, this study applied it to the suture-free adhesion of lacrimal cyst mucosal flap and nasal mucosal flap in endoscopic dacryocystorhinostomy. In order to achieve wound closure and promote wound healing, it can prevent postoperative anastomotic adhesion and granulation, replace the need for suture of mucosal flap, and greatly shorten the operation time.

2、Research purpose

To study the effect of photosensitive hydrogel used for suture-free anastomosis of lacrimal cyst and nasal mucoperiosteal flap in endoscopic nasal dacryocystorhinostomy. To evaluate its ability to promoting wound healing, forming a good anastomosis, preventing postoperative anastomosis and shortening operation time.

3、Type of study design, randomized grouping method and blind level

This study was a single-blind, prospective, parallel controlled, single-center clinical study, randomized by random number method.

4、Subject inclusion criteria, exclusion criteria, discontinuation criteria

4.1Study case inclusion criteria

1) Voluntarily participate in this clinical study and sign the informed consent;

2) Gender is not limited, age 18-75 years old;

3) The patient had symptoms and signs of chronic dacryocystitis, and the results of lacrimal passage irrigation suggested that the lower rush and return or upper rush and lower return, accompanied by mucous or purulent discharge reflux;

4) CT dacryocystography suggests nasolacrimal duct obstruction without lacrimal canaliculi and/or duct obstruction.

4.2Exclusion criteria

1) Age < 18 or > 75 years old;

2) Previous history of dacryocystorhinostomy;

3) Abnormal coagulation function;

4) Tumors of lacrimal passage, especially in patients with papilloma or malignant tumors;

5) in the acute dacryocystitis attack stage;

6) obvious scar constitution;

7) Complicated with serious nasal diseases, such as severe allergic rhinitis, chronic rhinosinusitis and nasal polyps, acute suppurative rhinosinusitis, severe atrophic rhinitis, and severe deviation of nasal septum;

8) Have serious heart, liver, kidney, lung and other basic diseases, cannot tolerate general anesthesia;

9) Distance from the hospital, postoperative review is not convenient;

10) Participated in other clinical trials within the last 3 months;

11) Any medical history that the investigator determines may interfere with the test results or increase the patient's risk.

4.3Termination and exit criteria

(1) Observation of the influence of other diseases during treatment;

(2) Poor compliance, cannot strictly implement the program, failed to treat according to regulations;

(3) Drugs that may affect the observation of the study need to be used in combination during the trial;

(4) Lost follow-up;

(5) The research object asks to quit;

(6) Serious adverse events;

(7) The researcher considers it necessary for the subjects to terminate this study.

5、Research method

5.1 Subject selection: This was a single-center, randomized, parallel controlled clinical trial to evaluate the efficacy and safety of endoscopic dacryocystorhinostomy using suture and photosensitive hydrogel. The study plan included 20 subjects, all of whom were randomly assigned 1:1 to either the suture group or the photosensitive hydrogel group.

5.2 Preoperative evaluation

All patients underwent slit lamp, fundus and other ophthalmic examinations to exclude ophthalmic diseases, especially ocular surface diseases. The lacrimal duct was syringed to remove the stenosis or obstruction of lacrimal canaliculi or common duct. Endoscopic examination was performed to understand the nasal condition and observe whether there was obvious middle nasal passage stenosis, nasal septum deviation and nasal mucosal lesions. CT dacryocystography was performed to observe and measure the size of lacrimal sac, to understand the obstruction of nasolacrimal duct, and to determine the incision location. General examination such as chest film, electrocardiogram, biochemistry and coagulation were performed to rule out systemic lesions

5.3 Endoscopic dacryocystorhinostomy

The patient was placed in supine position under general anesthesia, and was routinely disinfected and laid down. Epinephrine injection 1ml was mixed with 2% lidocaine injection 20ml. The nasal mucosa was contracted with cotton pads impregnated with the mixture, and the nasal submucosal infiltration was performed on the anterior uncinate process in the anterior axillary of the middle turbinate. Under the direct vision of 0-degree ultra-wide angle endoscope, a nasal mucosa incision of about 1.0cm×0.8cm was made in the anterior axillary part of the middle turbinate parallel to the uncinate process to form a nasal mucosa flap, which separated the nasal mucosa and pushed it to the rear, covered with cotton sheets for protection, exposed the bone, and visible lacrimal-maxillary suture. The bone was thined by dynamic system, and the bone was removed by bone biting forceps. A bone window about 1.0cm×1.2cm in size was formed to expose the lacrimal sac and trim the edge of the bone window to make it smooth. The probe was introduced into the lacrimal

sac through the upper lacrimal dot and lacrimal canaliculi and lifted up the inner wall of the lacrimal sac. The puncture bayonet was gently bent about 30 degrees to cut the lacrimal sac, and the lacrimal passage was rinsed to observe whether liquid flowed from the lacrimal sac incision, so as to confirm whether the lacrimal sac wall was cut. The pedicled nasal mucoperiosteal flap was pruned and covered in the surrounding bone window, respectively. The lacrimal sac mucoperiosteal flap was anastomosed with the nasal mucoperiosteal flap. The experimental group and the control group were divided into two groups for mucoperiosteal anastomosis intervention.

5.4 Research groups:

A、Trial group: 10 patients were expected to be included. The lacrimal cyst mucosal flap and nasal mucoperiosteum flap were anastomosed with photosensitive hydrogel. Appropriate amount of photosensitive hydrogel was applied on the surface of the trimmed and flat mucosal valve, which was irradiated by a light source of 395 nm for about 15 s to solidify and bond.

B、Control group: 10 patients are expected to be included. The lacrimal membrane flap and nasal mucoperiosteal flap were anastomosed by suture method, and the 6-0 absorbable thread was used to suture 2 stitches.

5.5 Postoperative follow-up: All subjects were required to have four outpatient follow-up visits (2 weeks, 6 weeks, and 12 weeks). The following indicators should be observed at each follow-up visit:

1) Whether the postoperative symptoms of tears and pus disappeared;

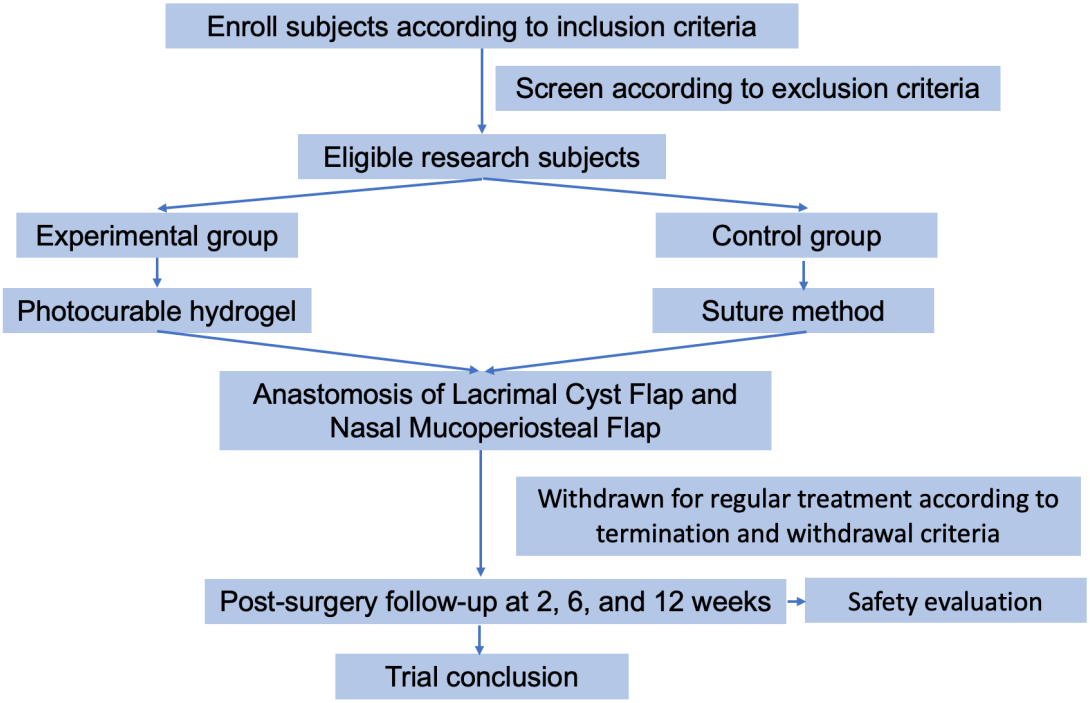
2) Whether the tear duct is unobstructed;

3) The anastomosis was well opened and there was no granulation or scar formation under endoscope.

The main evaluation index of this study was that the opening of the anastomosis was observed by nasal endoscopy at 6 weeks. The secondary outcome measures were the remission of tearing symptoms assessed by VAS scale at 2, 6, and 12 weeks.

Safety evaluation indicators: anastomotic scar, granulation, wound infection, allergic reaction, eye slit-lamp examination and vision examination.

6、Implementation steps and test flow chart



The following table is the test flow table:

Item	pre-operation	postoperation		
		2 weeks	6 weeks	12 weeks
Cases were identified for inclusion/exclusion	√			
Sign informed consent	√			
General information	√			
Medical history and treatment history	√			
Concomitant disease	√			
Signs and symptoms	√	√	√	√
Vision	√	√	√	√
Slit-lamp examination	√	√	√	√
Lacrimal duct irrigation	√		√	√
CT Dacryocystography	√			
Nasal endoscopy	√	√	√	√
Anastomotic opening state		√	√	√

Scar condition of anastomosis		√	√	√
Granulation condition of anastomosis		√	√	√
Adverse reaction evaluation		√	√	√

7、Research risk

The photosensitive wound sealing hydrogel uses hyaluronic acid, a natural component of human body, as the biological macromolecule skeleton. It is strictly sterilized after packaging, which has excellent biosafety. At present, the safety evaluation has been completed by a third party institution, and it is non-toxic to the human body, no allergy and rejection reaction, and the maximum degree of biosafety is guaranteed. As an exogenous implant, the risk of adverse reactions cannot be ruled out, including various unforeseen infections and related complications such as allergies that may occur after use. The study will focus on monitoring and follow-up observation. Any unexpected adverse event occurring during the clinical trial will be reported to the principal investigator of the clinical research unit and the ethics committee within 24 hours, and the adverse event record form (see attached case report form) will be filled in to record the occurrence time, severity, duration, measures taken and outcome of the adverse event. All adverse events will be treated as usual immediately after occurrence and followed up until symptoms or signs and corresponding physical and chemical examination return to normal or stable disease.

8、Adverse event determination

An adverse event (AE) is any adverse medical condition that occurs after a clinical trial subject receives treatment that is not necessarily causally related to the treatment. Dry eye symptoms are generally not recorded as AE, and are considered adverse events unless the severity of dry eye symptoms exceeds that prior to trial participation. This situation needs to be judged by both the subject and the researcher.

Adverse events include symptoms or signs observed by the investigator or voluntarily reported by the subject. The record of adverse events should include: event nature, start time, end time, event intensity, relationship with the investigational drug, expectation, action taken, severity, and outcome. Adverse events (both investigator-asked and observed and subject actively reported) will be

monitored throughout the trial. All adverse events will be reviewed for accuracy and completeness by the investigator in a timely manner. Severity and evaluation criteria of adverse events

Mild: The event is noticeable to the subject, but easily tolerated and does not interfere with the subject's daily activities.

Moderate: The event caused some distress to the subject, may require other treatment, and may affect the subject's daily activities.

Severe: The event is intolerable, requires additional treatment or changes in previous treatment, and significantly affects the subject's daily activities.

AE Outcome: The outcome of any adverse event will be determined and recorded using the following categories:

Recovered/relieved.

Recovering/in remission.

No recovery/no remission.

Recovered/in remission but with sequelae.

Loss of follow-up.

A threat to life or death.

Unknown.

Serious adverse events (SAEs) must be handled in a timely manner in accordance with relevant regulations, and any of the following cases are considered SAE.

Cause death.

Is dangerous to life and capable of causing permanent or significant disability.

Permanent damage to organ function.

Resulting in hospitalization or prolonged hospital stay.

Carcinogenic, teratogenic and birth defect.

9、Data management, data preservation

The case report form and research data are uniformly managed by the full-time data manager, and the database is established. At the same time, keep all research data, including original hospital records, informed consent forms, case reports, research records, etc. The retention period is 5 years.

10、Researcher Statement and ethical requirements

The principal investigator has received the national GCP training and obtained the certificate.

This clinical study was conducted in accordance with the Declaration of Helsinki and in accordance with national GCP and device regulations. Before each patient is enrolled in this study, the research physician will give a complete and comprehensive introduction to the purpose, procedure and possible risks of this study, and the subjects will give their consent after full understanding and sign the "informed consent" before starting the clinical trial. At the same time, if there are problems in the actual implementation of the clinical trial, this plan needs to be revised. The revised test plan is again submitted to the Ethics Committee for approval before implementation.

Case Report Form

Participant name: _____

Number: _____

Study start date: 20|__|__|/|__|__|/|__|__|

Study end date: 20|__|__|/|__|__|/|__|__|

Signature: _____

Instructions for filling out the case report form

1. All subjects who signed the informed consent are required to fill in the case report form.
2. The case report form must be filled in accurately and clearly, and shall not be altered at will. The error should be corrected with a horizontal line in the center, and sign the name of the modifier and the time of modification. Do not cover up the original data filled in, do not use erasers, correction fluid to cover or draw many lines. Example:~~58.6~~ 58.4 LXD 2011/10/29
3. All items on each page of CRF should be filled in. For all selected items, enter“×”in“□”to indicate this item, for example: ☒. If this item is "not done", enter "ND". For "Don't know", enter "UK". For "not available" or "not applicable", fill in "NA".
4. The dates on all forms are in the "Year/month/day" format, including the subject's date of birth. If you do not know the specific date, please use "UK" and enter the date in the form of "year/month /UK", please fill in as complete a date as possible. The clock is 24 hours.
5. Reporting of serious adverse events: If any serious adverse events occur during treatment, regardless of whether they are related to this study, the investigator shall immediately report them to the head of the study, who shall immediately report them to the research unit.

Emergency contact:

Research unit: Eye, Ear, Nose and Throat Hospital of Fudan University

Contact person：Lin Tong Contact number：13585764906

Clinical trial process：

Item	pre-operation	postoperation		
		2 weeks	6 weeks	12 weeks
Cases were identified for inclusion/exclusion	√			
Sign informed consent	√			
General information	√			
Medical history and treatment history	√			
Concomitant disease	√			
Signs and symptoms	√	√	√	√
Vision	√	√	√	√
Slit-lamp examination	√	√	√	√
Lacrimal duct irrigation	√		√	√
CT Dacryocystography	√			
Nasal endoscopy	√	√	√	√
Anastomotic opening state		√	√	√
Scar condition of anastomosis		√	√	√
Granulation condition of anastomosis		√	√	√
Adverse reaction evaluation		√	√	√

Inclusion criteria:

	Content	Yes	No
1	Volunteer to participate in this clinical study and sign informed consent		
2	No gender limitation, age 18-75 years old		
3	The patient had symptoms and signs of chronic dacryocystitis, and the results of lacrimal passage irrigation suggested that the lower rush and return or upper rush and lower return, accompanied by mucous or purulent discharge reflux		
4	Dacryocystography suggests nasolacrimal duct obstruction without lacrimal canaliculi and/or duct obstruction		

Exclusion criteria:

ID	Content	Yes	No
1	Age < 18 or > 75 years old		
2	Previous history of dacryocystorhinostomy		
3	Abnormal coagulation function		
4	Tumors of lacrimal passage, especially papilloma or malignancy		
5	Acute dacryocystitis		
6	Obvious cicatricial constitution		
7	Complicated with severe nasal diseases, such as severe allergic rhinitis, chronic rhinosinusitis and nasal polyps, acute suppurative rhinosinusitis, etc.		
8	Have serious heart, liver, kidney, lung dysfunction and other basic diseases, cannot tolerate general anesthesia;		
9	Those who are not willing to review regularly after surgery;		
10	Participated in other clinical trials within the last 3 months		
11	Any medical history that the investigator determines may interfere with the test results or increase the patient's risk		

Note: If any of the inclusion criteria is "No" and any of the exclusion criteria is "Yes", the case cannot be included in the group.

Basic patient information:

Date of birth：_____ Gender：□ female / □ male Race:_____
Vital sign：Blood pressure：____ / ____mmHg Heart rate：____times/min

History of present illness：

Symptom: _____Sign：_____

Drug allergy history：

Drug allergy： □No □Yes，please describe：_____

Past medical history：

Whether you have a past medical history：□ Yes □ No			
Name of disease	Existence or not	Name of disease	Existence or not
	□ Yes □ No		□ Yes □ No
	□ Yes □ No		□ Yes □ No
	□ Yes □ No		□ Yes □ No

Join a group

Does the subject meet all the above criteria and be formally enrolled?	□ No→Exit test→Keep research records
	□Yes→The patients were enrolled into observational clinical study

Confirm the enrollment time 20|_|_|Year|_|_|Month|_|_|Day。

Objective examination record form before operation after enrollment: |_|_|_|_|Year|_|_|Month|_|_|Day

Check item	Result
sight	
Slit-lamp examination	
Lacrimal duct irrigation	
CT Dacryocystography	
Nasal endoscopy	

Surgical record

Preoperative diagnosis： _____

Intraoperative diagnosis： _____

Name of operation： _____

Process record：

_____

_____

_____

_____

_____

Surgeon's signature：

|_|_|_|_|Year|_|_|Month|_|_|Day

Postoperative follow-up：

Name		Date of visit □□□□/□□/□□	interview1 Week □

Vision： OD_____ OS_____

Slit-lamp microscopy：

Check item	Right eye Inspection result	Left eye Inspection result
Eyelids	□Normal □Abnormal：	□Normal □Abnormal：
conjunctiva	□Normal □Abnormal：	□Normal □Abnormal：
cornea	□Normal □Abnormal：	□Normal □Abnormal：
iris	□Normal □Abnormal：	□Normal □Abnormal：
Anterior chamber	□Normal □Abnormal：	□Normal □Abnormal：
lens	□Normal □Abnormal：	□Normal □Abnormal：

Degree of symptom improvement： _____

Lacrimal duct irrigation： OD_____ OS_____

Nasal endoscopy：

Whether the anastomosis is open □Yes □No

Whether there is scar with adhesion □Yes □No

Whether there is granulation □Yes □No

Postoperative follow-up：

Name		Date of visit □□□□/□□/□□	Interview2 Week □

Vision： OD_____ OS_____

Slit-lamp microscopy：

Check item	Right eye Inspection result	Left eye Inspection result
Eyelids	□Normal □Abnormal：	□Normal □Abnormal：
conjunctiva	□Normal □Abnormal：	□Normal □Abnormal：
cornea	□Normal □Abnormal：	□Normal □Abnormal：
iris	□Normal □Abnormal：	□Normal □Abnormal：
Anterior chamber	□Normal □Abnormal：	□Normal □Abnormal：
lens	□Normal □Abnormal：	□Normal □Abnormal：

Degree of symptom improvement： _____

Lacrimal duct irrigation： OD_____ OS_____

Nasal endoscopy：

Whether the anastomosis is open □Yes □No

Whether there is scar with adhesion □Yes □No

Whether there is granulation □Yes □No

Postoperative follow-up：

Name		Date of visit □□□□/□□/□□	Interview3 Week □

Vision： OD_____ OS_____

Slit-lamp microscopy：

Check item	Right eye Inspection result	Left eye Inspection result
Eyelids	□Normal □Abnormal：	□Normal □Abnormal：
conjunctiva	□Normal □Abnormal：	□Normal □Abnormal：
cornea	□Normal □Abnormal：	□Normal □Abnormal：
iris	□Normal □Abnormal：	□Normal □Abnormal：
Anterior chamber	□Normal □Abnormal：	□Normal □Abnormal：
lens	□Normal □Abnormal：	□Normal □Abnormal：

Degree of symptom improvement： _____

Lacrimal duct irrigation： OD_____ OS_____

Nasal endoscopy：

Whether the anastomosis is open □Yes □No

Whether there is scar with adhesion □Yes □No

Whether there is granulation □Yes □No

Adverse event report form

Are adverse events occurring? □ No □ Yes, if yes, please fill in the following form:

Name of adverse event		
Clinical diagnosis		
Date and time of occurrence	|_|_|_|_|Year|_|_|month|_|_|day |_|_|hour|_|_|minute（24-hour system）	|_|_|_|_|Year|_|_|month|_|_|day |_|_|hour|_|_|minute（24-hour system）
Severity	□1Light □2Medium □3Heavy	□1Light □2Medium □3Heavy
Adverse event characteristics	□paroxysmal（Number of attacks：|_|_|） □persistence □other	□paroxysmal（Number of attacks：|_|_|） □persistence □other
Course of adverse events (including symptoms and signs)		
Adverse event processing (including the generic name, dosage, usage and other therapeutic measures of the drug used)	□No □Yes, if yes, record it _____ _____ _____ _____ _____ _____	□No □Yes, if yes, record it _____ _____ _____ _____ _____ _____
Fill in the following sections at the end of the adverse event or follow-up		
Follow-up time	Time：|_|_|_|_|Year|_|_|month|_|_|day |_|_|hour|_|_|minute（24-hour system）	Time：|_|_|_|_|Year|_|_|month|_|_|day |_|_|hour|_|_|minute（24-hour system）
Outcome of adverse events	□1Disappear/return to normal □2 Turn for the better □3 No better □4 There are sequelae, manifestations：__	□1Disappear/return to normal □2 Turn for the better □3 No better □4 There are sequelae, manifestations：
Whether to quit the trial	□ No □ Yes	□ No □ Yes

Note: * : Severity rating:

1. Light: the subject can tolerate, does not require special treatment, and has no impact on the health of the subject.
2. Medium: unbearable for subjects, which has a direct impact on subjects' health.
3. Heavy: endangering the life of the subject, causing death or disability, requiring urgent treatment.

Summary of the completion of the test

Have you completed this clinical trial?

□Yes □No, if no, please fill in the following items:

Trial exit date : |_|_|_|_|Year|_|_|Month|_|_|Day

The main reasons for quitting the trial were:

□1 Loss to follow-up

□2 Adverse event

□3 Subject automatically withdrew from the test for:_____

□4 The investigator decided to withdraw the subjects from the trial for the following reasons:

□5 Other _____

Did the patient experience any adverse events during the trial?

□Yes □No

If there were adverse events, have they all been resolved?

□Yes □No

If no, follow up to normal or pre-medication levels.

Is this a qualified case? □ Yes □ no. If no, please fill in the following items:

□1 Violation of inclusion criteria

□2 Drop-out test

□3 Poor compliance

□4 Other_____

Case Report Form (CRF) review statement

As the person in charge of the test center, I hereby declare: After review, the records of all items in this case report form are true, complete and accurate.

Principal investigator signature：_____

Date：_____Year___Month____Day