Effect of lacrimal plugs combined with deproteinized calf blood extract eye gel for filamentary keratitis

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Abstract This study aims to investigate the efficacy of lacrimal plugs combined with deproteinized calf blood extract eye gel on the treatment of dry-eye-associated filamentary keratitis. Lacrimal plugs were inserted into both the upper and lower puncta of 15 patients (28 eyes). Deproteinized calf blood extract eye gel was applied in two patients who were not cured after this operation. All patients were asked to complete three questionnaires 1 day before the surgery and at 1 week and 1 month after the surgery. Ophthalmologic examinations were carried out and repeated at 1 day and at 1 week and 1 month after plug insertion, which include fluorescein staining, tear break-up time (BUT), Schirmer test I (STI), corneal confocal microscope (HRT-III), and impression cytology (IC). Symptoms were relieved in all patients 1 month after the application of lacrimal plugs. Deproteinized calf blood extract eye gel was applied to two patients whose symptoms remained after lacrimal plug implantation for 1 week. At 3 weeks later, the symptoms disappeared and cornea fluorescein stain was hardly identified. The lacrimal river in all patients became broader after the surgery, 11 of whom reached 0.3 mm. Cornea filamentary disappeared in all patients. The average of BUT and ST were increased to 7.50 ± 1.897 s ($p < 0.001$) and 8.12 ± 1.996 mm at 1 week after the operation and 7.94 s and 9.00 ± 1.897 mm at 1 month later, respectively. Photography from HRT-III suggested that the state of corneal epithelium was markedly improved, including the squamous metaplasia of the epithelial layer of the cornea and the bend of nerve fibers under the corneal epithelium. IC also

suggested that the squamous metaplasia of epithelial layer of conjunctiva in these patients was improved. The symptoms of patients suffering from severe filamentary keratitis were remarkably relieved by using lacrimal plugs, which could increase the tear volume of the ocular surface, improve the condition of tear film, and promote the recovery of corneal diseases. For patients with more severe symptoms, additional usage of deproteinized calf blood extract eye gel could assist the treatment. Therefore, lacrimal plugs combined with deproteinized calf blood extract eye gel are suggested to be an effective method to treat severe filamentary keratitis.

Keywords Filamentary keratitis · Lacrimal plugs · Impression cytology

Introduction

Filamentary keratitis (FK) is a chronic disorder of the cornea and, rarely, the conjunctiva, which appears as a variable-length tail extending from the ocular surface epithelium when viewed by slit lamp examination. Filamentary keratitis is of high prevalence in the elderly population which is most often a result of severe dry eye, especially aqueous tear-deficient (AQD) dry eye [1]. Since tear-film instability appears to be a component of all forms of dry eye disease, and tear hyperosmolarity is a key mechanism for ocular surface damage, the mainstay therapeutic strategy for filaments associated with dry eye is artificial tear supplementation after the mechanical removal of the corneal filaments [2]. In some occasions, however, it may require a more aggressive approach and improper treatment could result in a chronic annoying situation with recurrence.

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Filamentary keratitis can be exacerbated by preservatives in artificial tears that may increase cellular exfoliation and cytotoxic changes of the corneal epithelium, which in turn can lead to the formation of new filament receptor sites [3].

Lacrimal plug is one of the effective methods to treat dry eyes [4]. Silicone punctal occlusion can be used in addition to artificial tear supplementation. Punctal occlusion allows longer contact time of tears with ocular surfaces, resulting in symptomatic and objective improvement on conditions of aqueous deficient dry eye. Diller and Sant reported a case of FK successfully cured with plugs and contact lens [5].

This paper presented results of our research using lacrimal plugs for the treatment of FK patients by accumulating the tears and improving the microenvironment of ocular surface, which improved the life quality of the elderly.

Materials and methods

Patients

A total of 15 consecutive patients were included in the study (all female with age ranging from 41 to 83 years old, average 63.7 years), all of whom presented at Peking University Eye Center with severe FK in both eyes. All patients had been using deproteinized calf blood extract eye gel for at least 2 weeks and none had shown subjective or objective improvement in FK with the medication.

The inclusion criteria were that dry-eyed patients presented corneal filaments with positive sodium fluorescein staining [6] and with complaint of ocular irritations such as foreign body sensation, pain, and photophobia et al. All of the patients had used deproteinized calf blood extract eye gel for at least 2 weeks without relief of the symptoms. Patients with trachoma, dacryocystitis, blepharitis, anaphylactic conjunctivitis, acute viral keratoconjunctivitis, recurrent erosion, neurotrophickeratopathy, prolonged use of an eye patch, ptosis, and large-angle strabismus or having had any ophthalmologic operation in the previous 3 months were excluded.

This research was approved by the Committee for Ethical Issues on Human Research at Peking University Third Hospital.

Measurements

Before the insertion, all patients underwent a baseline examination as follows:

1. Investigation of symptoms, including eye fatigue, increase of secretion, foreign body sensation, heaviness of eyelids, dryness, pain, vision blurring, itchiness, photophobia, and red eye. Patients scored the severity of syndromes on a scale of 0–5.

2. Corneal fluorescent staining, tear film break-up time, and Schirmer test were conducted in a routine way.
3. Corneal nerves were analyzed using corneal confocal microscopy (ConfoScan 3, software version 3.4, Nidek Technologies Srl, Vigonza, Italy). A topical anesthetic was instilled in the lower conjunctival fornix of both eyes before examination. A drop of ophthalmic lubricant gel was applied on the objective tip to serve as a coupling medium. Automated mode was applied to obtain full thickness scans from the central cornea. The best-focused confocal microscopic images from the central cornea were used to observe the nerves. The field size of the photography was 422×322 mm (0.136 mm²).
4. Impression cytology samples were taken from the superior, inferior, nasal, and temporal sides of bulbar conjunctiva in all of the patients' eyes. An acetate fibrous membrane was applied to the ocular surface, after topical anesthesia, which was stained with PAS and observed under light microscopy.

All measurements were repeated at 1 week and 1 month after the insertion of punctal plugs.

Intervention

Dissolvable Visiplugins (Lacrimedics, Inc) were inserted in the upper and Smart PLUG500 (Medennium) in the lower puncta in all 28 patient eyes. Before placing each plug, one drop of anesthetic was applied to the site. Antibiotic eye drops were used after the insertion. Two patients who still had mild ocular irritations at 1 week after the insertion were given deproteinized calf blood extract eye gel for another 3 weeks.

Statistical analysis

Data were analyzed by two-way analysis of variance. $P < 0.05$ was considered statistically significant. The statistical software program was SPSS16.0.

Results

Symptoms

The most common complaints of all the 15 patients before the insertion of plugs were foreign body sensation, photophobia, and lacrimation. All of these disorders were markedly relieved after the intervention. A summary of the questionnaire is shown in Table 1.

The result of questionnaires on symptoms was analyzed by two-way analysis of variance. The diversity among

Table 1 Investigation of symptoms at 1 day before surgery and 1 week and 1 month after surgery

	Mean	Standard deviation	<i>F</i>	<i>P</i>
1 day before	50.38	4.307	29.861	.000
1 week after	29.25	2.493		
1 month after	23.88	3.482		

1 week, 1 month, and preoperative conditions was statistically significant (the variance was homogeneity, $p < 0.001$) (Table 1). At 1 week and 1 month compared with preoperative separately, the diversity was statistically significant ($p < 0.001$). The diversity between 1 week and 1 month after surgery was statistically significant ($p < 0.05$), which indicated that the symptoms became milder as time went by during 1 month after surgery.

The patients were examined 1 week after the insertion of lacrimal plugs, and the corneal irritations such as photophobia, tearing, foreign body sensation, burning sensation, tingling, and difficulty of opening the eyes were significantly reduced. A total of 13 patients had no ocular symptoms, while two patients still have mild foreign body sensation and dry eye feeling, the symptoms of which were released after usage of deproteinized calf blood extract eye gel for an additional 3 weeks. The symptoms of all the patients were relieved at 1 month after surgery. Mild epiphora developed in one patient at 1 week after surgery, but the patient did not search for further management. All of the patients had no discomfort or unbearable epiphora at 1 month after surgery.

Clinical data

Slit lamp examination revealed that corneal filaments and corneal epithelium defect could be identified in all patients before the intervention. At 1 week after operation, all corneal filaments disappeared, but there were still some small areas of corneal epithelial shedding with positive fluorescein staining in two patients who recovered at 1 month after surgery.

Before the implantation, the lacrimal river line in all patients was very narrow and even dried up. After surgery, the lacrimal river line became broader in all patients. A total of 11 patients (20 eyes) had lacrimal river line reaching 0.3 mm, while in the other four patients the lacrimal river line was less than 0.3 mm (Figs. 1, 2, and 3).

STI and tear BUT

At 1 month postoperatively, both STI and BUT improved significantly in all patients ($P < 0.001$) (Tables 2 and 3).

Fig. 1 Preoperatively, there was obviously conjunctival hyperemia, almost disappearing low lacrimal river line, visible filaments of corneal epithelium, and some corneal epithelial shedding in all patients

Corneal confocal microscope

Before the intervention, stromal cells in all patients were in activated state as suggested by the rich cytoplasm and polygonal outline of the cells. Highly reflective cell bodies were observed and the nuclei of the cells were difficult to identify (Fig. 4).

Significant squamous metaplasia could be identified before the insertions. Basal cells are active (Fig. 5), and an abnormal change of nerve fiber in subepithelium can be observed, including the disorder, asymmetrical thickness, and hyperplasia of nerve branch. It was very likely to be related to the long history of severe dry eye. There is a certain improvement discovered after surgery (Figs. 6, 7, and 8).

Fig. 2 At 1 week after surgery, corneal epithelial defects could still be identified in two patients, but the epithelial filaments disappeared, and the lacrimal river was wider, but less than 0.3 mm

Fig. 3 At 1 month after surgery, the corneal epithelial filaments disappeared, and the lacrimal river was obviously wider than before

Impression cytology

IC specimens revealed squamous metaplasia on globe conjunctiva in patients suffering FK. Conjunctival squamous metaplasia was characterized by enlarged gap among epithelial cells, increased nuclear/cytoplasmic ratio, decreased average density of goblet cells, morphologic change of epithelial cells, and altered nuclear chromatin, including atrophy nuclear cells, non-nuclear cells, and snake-like chromatin. According to Nelson grading standards (Figs. 9 and 10), all of them belong to Nelson 3. At 1 month after surgery, the squamous metaplasia of conjunctival epithelial cells in IC specimens from the patients was reduced as suggested by the decrease of the epithelial cell gap and the nuclear/cytoplasm ratio (Fig. 11). When applied to the Nelson grading standards, 18 eyes could be ranked as Nelson 2, while ten eyes remained as Nelson 3.

Discussion

Filamentary keratitis is a common chronic corneal condition characterized by filaments attached to the cornea at one or both ends. The filaments are variable in size and are comprised of degenerated epithelial cells and mucus. It is most often the result of severe dry eye, especially AQD dry eye. Both autoimmune (Sjogren's

Table 3 STI at 1 day before surgery and 1 week and 1 month after surgery

	Mean(mm)	Standard deviation	<i>F</i>	<i>P</i>
1 day before	2.31	1.195	70.368	.000
1 week after	8.12	1.996		
1 month after	9.00	1.897		

syndrome) and non-autoimmune forms can lead to filament formation [1].

It has been reported to be associated with various kinds of ocular surface diseases or conditions, such as superior limbic keratoconjunctivitis, acute viral keratoconjunctivitis, post-cataract surgery or penetrating keratoplasty, recurrent erosion, neurotrophickeratopathy, vernal keratoconjunctivitis, prolonged use of an eye patch, ptosis, and large-angle strabismus [1, 5, 7–9].

FK can result in discomforts and symptoms. Most patients have the symptoms of foreign body sensation, pain, photophobia, epiphora, and difficulty of opening the eyes. Slit-lamp examination reveals corneal filaments with one end attached to the corneal epithelium and the other dissociation. The cornea attached by the filaments can be stained with sodium fluorescein because of the corneal epithelium defect.

The major treatment of FK currently is tear substitutes and extracts of serum or autologous serum (autologous serum biomechanical and biochemical properties similar to normal tears [10]). Therapeutic effects can be achieved by

Fig. 4 In activation state, the cells are rich in cytoplasm and polygonal aspect of cell stretching and staggered contours can even be seen microscopically. The cell bodies reflected strongly, and it was more difficult to recognize the nuclei

Table 2 BUT at 1 day before surgery and 1 week and 1 month after surgery

	Mean (s)	Standard deviation	<i>F</i>	<i>P</i>
1 day before	1.50	1.095	82.488	.000
1 week after	7.50	1.897		
1 month after	7.94	1.652

Fig. 5 Corneal epithelial basal cell body increased and nuclei were prominent. The cells were activated

means of increasing tear volume to protect the corneal epithelium, reduce the mechanical friction of the eyelids, and provide basic nutrients for the ocular surface. Lacrimal plugs have been suggested to effectively increase tear volume, relieve ocular surface irritations, and improve tear film stability. Therefore, lacrimal plugs were used for the treatment of filamentous keratitis in this study to investigate their therapeutic effects.

Fig. 6 Abnormal change of nerve fiber in the subepithelium can be seen, including the disorder, asymmetrical thickness, and hyperplasia of the nerve branch

Fig. 7 Abnormal change of nerve fiber in the subepithelium can be seen, including the disorder, asymmetrical thickness, and hyperplasia of the nerve branch

In our study, the most common complaints of all of 15 patients were foreign body sensation, photophobia, and lacrimation, and two patients had difficulty in opening their eyes, which were closely related to the severity of corneal epithelium damage. The symptoms of all 15 patients were significantly improved at 1 week after surgery, but two patients still had mild foreign body sensation and dryness in their eyes. These two patients had been supplied with

Fig. 8 Postoperatively, the subepithelial corneal nerves were nearly parallel

Fig. 9 Before the implantation of the lacrimal plug, morphologic change of epithelial cells, altered nuclear chromatin including atrophy of nuclear cells, and snake-like chromatin were all observed ($\times 10$)

deproteinized calf blood extract eye gel for 3 weeks. At 1 month after surgery, all of the patients' symptoms were fully relieved, and there is no apparent tears overflow in patients, which might be because of the limited secretion of basal tear in serious dry-eyed patients. A 3-month follow-up was recommended to all patients.

Filaments disappeared soon after treatment. The tear river was obviously wider than that during the preoperative condition, which suggested that ocular surface tear increased. Corneal fluorescein staining was negative postoperatively. All of these observations indicated that the microenvironment of the ocular surface was significantly improved after the treatment [4, 11], adequate nutrition was provided for corneal healing, rupture and necrosis of corneal epithelial

Fig. 10 Before the implantation of the lacrimal plug, conjunctival squamous metaplasia was characterized by enlarged gaps between epithelial cells, increased nuclear/cytoplasmic ratio, decreased average density of goblet cells, and morphologic change of epithelial cells; non-nuclear cells can be seen ($\times 20$)

Fig. 11 At 1 month after surgery, IC specimens revealed squamous metaplasia of conjunctival epithelial cells in patients with conditions to be reduced as the epithelial cell gap decreases; the nuclear/cytoplasm ratio decreased slightly ($\times 10$)

cells was reduced, lubrication of corneal surface was increased, and shearing effects blinking on the ocular surface was reduced [12, 13], all of which are also consistent with the patients' symptoms.

Compared with the condition before treatment, at 1 month after the insertion, STI and BUT were markedly improved, although they were still lower than normal. Fluctuations of STI and BUT followed a pattern that was in accordance with the observed symptoms of dry eye in the patients. This is because aqueous tear increased significantly, but tear quality is still poor, and the tear secretion decreased in patients with chronic dry eye.

After the treatment, the ocular surface status of all patients was significantly improved. The bulbar conjunctiva hyperemia was strikingly reduced, the lacrimal river widened, and the corneal filaments disappeared. All of these illustrated that the tears increased significantly after treatment with improved ocular surface environment, which provided sufficient oxygen nutrients and a good environment for the recovery of the cornea.

The corneal stromal cells were in the activation state preoperatively. They were rich in cytoplasm and polygonal aspect of cell stretching and even staggered contours under corneal confocal microscope. Abnormal changes of nerve in subepithelium can be seen, including the disorder, asymmetrical thickness, and hyperplasia of nerve branch. The corneal nerve thickening is a typical pathological change of dry eye. On the other hand, imaging may show thickening of the illusion on a nerve because of chronic inflammation of the corneal epithelium. After surgery, there is a certain improvement of the nerve morphology.

Impression cytology method, as a simple, non-invasive, practical, and effective method for ocular surface examination [14], can be used for the pathological diagnosis of dry eye. In

this study, preoperative conjunctival impression cytology showed large conjunctival epithelial cells, intercellular boundaries that became broad and ill-defined, nuclei which were polymorphic, such as snake chromatin, nuclear condensation, fragmentation of the nucleus and nuclear cells, goblet cell density that was reduced or even not visible, and squamous metaplasia which were obvious and could be graded as Nelson 3.

Conjunctival impression cytology in patients with severe dry eye further verified that filamentary keratitis is most often the result of severe dry eye.

The abnormal morphological changes on impression cytology improved to some extent after the treatment, although the improvement was limited and remained in Nelson 2–3 grade with significantly reduced symptoms. It may be related to a long history of severe dry eye or indicate that a longer observation period was needed.

Some researchers believe that the pathogenesis of filamentary keratitis results from abnormal ocular surface mucin and other features of the ocular surface environment. Their epithelial morphology changes with the influence of ocular surface inflammation and immature epithelial shedding [13], which may be related with the environment of the ocular surface.

In this study, filamentary keratitis was caused by severe dry eye in all of the 15 patients, which was consistent with the previous reports. The implantation of lacrimal plug increased tear volume on the ocular surface, which can maintain the cornea and conjunctiva humid, increase lubricity, improve the ocular surface microenvironment, provide nutrients to the corneal epithelium, promote corneal restoration, and maintain normal metabolism of the cornea. In addition, there are tears immunoglobulin, lysozyme, complement system, and anti-inflammatory factors to avoid interference from the outside environment, which provided favorable conditions for resumption of the cornea.

Meanwhile, the recovery of corneal epithelium not only eliminated the symptoms conducive to the formation of a smooth refractive surface of the cornea but also promoted the recovery of tear film. The increase in tear volume and improvement of the quality of tear stabilized the tear film, further formed a smooth refractive surface, and significantly improved the patient's visual quality.

Therefore, lacrimal plug is one of the most effective clinical treatments of filamentary keratitis. For patients with more severe symptoms, a combined usage of deproteinized

calf blood extract eye gel could assist the treatment. The implantation of lacrimal plug mainly increased tear volume on the ocular surface, improved the ocular surface microenvironment to promote corneal restoration, and maintain normal metabolism of the cornea. Meanwhile, the recovery of corneal epithelium can enhance the stability of tear film and the absorption of nutrients within tears. The formation of the virtuous cycle of the ocular micro-environment was beneficial for the recovery of ocular refractive surface and the improvement on visual quality and the quality of life.

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