

Self-retained Amniotic Membrane for Recurrent Corneal Erosion

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Abstract

Purpose: To evaluate the efficacy of placement of sutureless self-retained cryopreserved amniotic membrane in treating recurrent corneal erosion (RCE).

Methods: Eleven eyes of 9 consecutive patients with RCE received epithelial debridement and placement of ProKera[®] (Bio-Tissue, Inc, Miami, Florida, USA). Their clinical outcomes were retrospectively reviewed.

Results: Although corneal signs suggestive of RCE were found in 7 of 11 eyes, diagnosis of the remaining 4 eyes, including two eyes with predominant lid discomfort, was not made until the use of the cellulose sponge test to elicit a wrinkled epithelium. After debridement and placement of ProKera[®], complete epithelialization was noted in all eyes in 4 to 7 days. During the follow up of 13.7 ± 2.2 months, one eye recurred and required repeated treatment. Afterwards, all eyes were asymptomatic and regained a smooth and stable corneal epithelium. Best-corrected visual acuity was improved to at least 20/30 in all 6 eyes complaining of blurry vision and involving the visual axis.

Conclusions: Debridement followed by placement of self-retained cryopreserved amniotic membrane via ProKera[®] can be performed in the office for treating RCE. Further studies to validate its efficacy in comparison to other surgeries are warranted.

Keywords: Amniotic membrane; Recurrent corneal erosion; Sutureless; Debridement

Introduction

Recurrent corneal erosion (RCE) is a common ocular disorder resulting in repeated episodes of pain, tearing, redness, and photophobia, especially in the morning. It is frequently associated with anterior stromal dystrophies, epithelial basement membrane dystrophy, or trauma to the corneal surface, but RCE may also spontaneously occur without any predisposing factor [1,2]. The conservative treatment using lubricants [3], autologous serum [4], and bandage contact lens [5] still has 59%, 27%, and 25% recurrence, respectively. For those who are refractory to these conservative treatments, surgical intervention via debridement, anterior stromal puncture with needles or neodymium:yttrium-aluminum-garnet laser, and superficial keratectomy by excimer laser phototherapeutic keratectomy becomes necessary [1,2]. Nonetheless, these surgical interventions pose potential risks of postoperative refractive change and visual loss due to scar tissue involving the visual axis [1,2].

The main pathologic finding of RCE is poor adhesion of the corneal epithelium to the Bowman's membrane due to abnormal deposition of basement membrane under the corneal epithelium [6]. Infiltration of polymorphonuclear leucocytes is found between corneal epithelial cells and the anchoring layer in surgical specimens from RCE patients, suggesting that inflammatory cells are involved [7]. Overexpression of matrix metalloproteinases (MMPs) such as MMP-2 and MMP-9 by epithelial cells [8] and tear fluids [9] has been reported in patients with RCE. Because transplantation of cryopreserved amniotic membrane (AM) exerts anti-inflammatory, anti-scarring, and anti-angiogenic actions [10,11] and because AM contains tissue inhibitors of MMPs [12,13], we speculate that transplantation of cryopreserved AM as a biologic bandage may help treat RCE after debridement.

ProKera[®] (Bio-Tissue, Inc., Miami, FL) has been approved by the FDA as a self-retained sutureless medical device to promote corneal wound healing caused by acute chemical burns [14], acute Steven-

Johnson syndrome/toxic epidermal necrolysis [15,16], persistent corneal epithelial defect and ulcers [17], and severe bacterial keratitis [18], as well as for surgical wounds caused by excision of recurrent pterygium [17], repair of necrotizing scleritis [19], and partial [20] and total [21] limbal stem cell deficiency. Here in, we retrospectively reviewed our early clinical experiences of placing ProKera[®] in 11 eyes of 9 consecutive patients with RCE to manage wounds created by debridement.

Materials and Methods

Patients and diagnosis

This study was approved by the ethics committee of the Ocular Surface Research and Education Foundation (Miami, FL) according to the Tenets of the Declaration of Helsinki. We retrospectively reviewed 11 eyes of 9 consecutive patients who received debridement and placement of ProKera[®] (Bio-Tissue, Miami, FL) by a single surgeon (SCGT) at the Ocular Surface Center (Miami, FL) between August 2011 and February 2012 after an informed written consent was obtained from each patient. Before treatments, all patients received history-taking and complete eye examination with and without fluorescein staining to detect the suggestive signs of RCE, e.g., ragged, greyish-stained

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epithelium (Figure 1A), aggregated intra-epithelial whitish dots (Figure 1B), epithelial breakdown with surrounding loosely epithelium (Figure 1C), and persistent tear break up pattern (Figure 1D). For those eyes that appeared to be free of any of the above characteristic signs (Figure 2A), we used the test reported by Cavanaugh and Graham [22] with minor modification to detect a loosely adherent corneal epithelium. In short, after topical anesthesia with 0.5% proparacaine hydrochloride (Falcon Pharmaceuticals, Ltd), the corneal epithelium was approached vertically with the tip of a dry cellulose sponge (Weckcel, Alcon Inc. Fort Worth, TX). Upon contact, the sponge was twisted at a 90° turn like a screw driver (Figure 2B). If this maneuver yielded a wrinkled epithelium (Figure 2C), we interpreted it as a “positive cellulose sponge test” indicative of RCE. Patients without manifesting the above finding was interpreted excluded by a negative finding by the cellulose sponge test (Figure 2D).

Debridement and placement of ProKera®

Under topical anesthesia, all eyes received debridement in the office by removing all loose epithelial cells by a dry cellulose sponge (Figure 2E). Then the corneal surface was covered by placing a ProKera® (Figure 2F). For those eyes with lid-globe disparity (Figure 2F), centration of ProKera® to cover the corneal surface was assured by narrowing the lid fissure with a surgical tape placed on the skin of the upper eye lid (Figure 2G) or by a Tegaderm film (3M Health Care St, Paul, MN) (Figure 2H) especially if the lower eyelid was too lax. Afterwards, all eyes received 0.3% ofloxacin drops (Allergan Inc. Irvine, CA) 3 times daily for 4 to 7 days when ProKera® was removed. For those eyes, which showed any recurrence defined by the same clinical symptoms and signs after ProKera® insertion, the same treatment was repeated.

Results

The demographic characteristics and relevant information of these 11 eyes of 9 patients are summarized in Table 1. Of these 9 patients, 2 were male and 7 were female, and the average age was 55.4 ± 10.8 (range, 42-78 years). The most common complaint was pain, which occurred in 9 (81.8%) eyes. The other symptoms included blurry vision (6 eyes), photophobia (5 eyes), foreign body sensation (4 eyes), burning (3 eyes), and lid discomfort (2 eyes). Beforehand, 8 eyes had failed to respond to conservative treatments, including lubricating drops or ointments

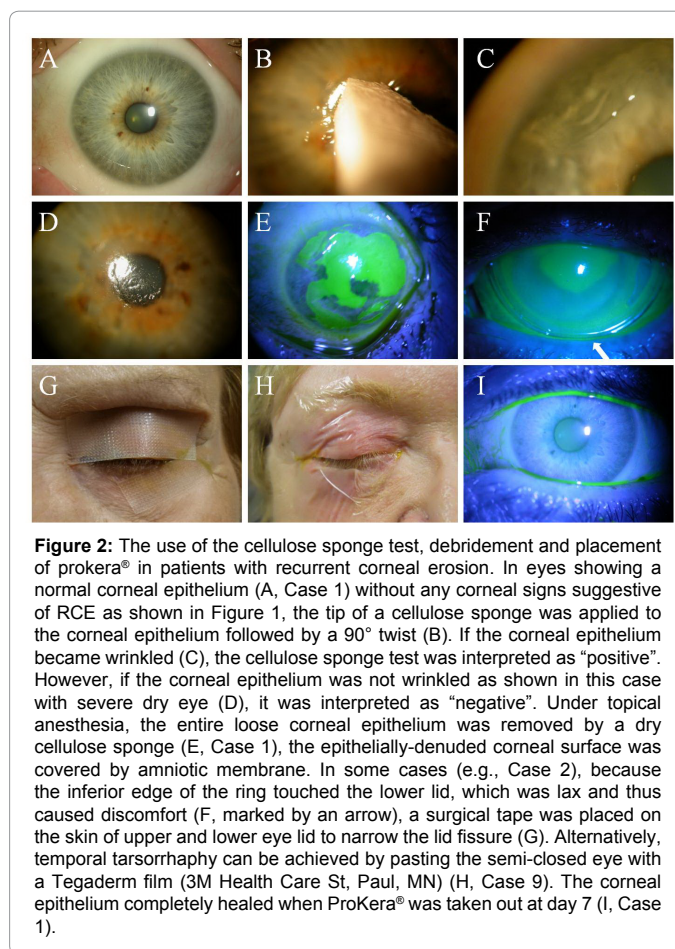


Figure 2: The use of the cellulose sponge test, debridement and placement of prokera® in patients with recurrent corneal erosion. In eyes showing a normal corneal epithelium (A, Case 1) without any corneal signs suggestive of RCE as shown in Figure 1, the tip of a cellulose sponge was applied to the corneal epithelium followed by a 90° twist (B). If the corneal epithelium became wrinkled (C), the cellulose sponge test was interpreted as “positive”. However, if the corneal epithelium was not wrinkled as shown in this case with severe dry eye (D), it was interpreted as “negative”. Under topical anesthesia, the entire loose corneal epithelium was removed by a dry cellulose sponge (E, Case 1), the epithelially-denuded corneal surface was covered by amniotic membrane. In some cases (e.g., Case 2), because the inferior edge of the ring touched the lower lid, which was lax and thus caused discomfort (F, marked by an arrow), a surgical tape was placed on the skin of upper and lower eye lid to narrow the lid fissure (G). Alternatively, temporal tarsorrhaphy can be achieved by pasting the semi-closed eye with a Tegaderm film (3M Health Care St, Paul, MN) (H, Case 9). The corneal epithelium completely healed when ProKera® was taken out at day 7 (I, Case 1).

(6 eyes), autologous serum (2 eyes), steroids (2 eyes), bandage contact lenses (1 eye), and oral doxycycline (1 case) (Table 1). All except one patient (Case 6, see Case Example below) did not receive any surgical intervention.

Slit-lamp biomicroscopy revealed a ragged, elevated, and greyish area of the corneal epithelium (Figure 1A, Case 2) in 6 eyes and intra-epithelial whitish dots (Figure 1B, Case 3) in 1 eye. Fluorescein staining revealed epithelial breakdown with surrounding loose epithelium (Figure 1C, Case 7) in 2 eyes and a persistent tear break up pattern in 5 eyes (Figure 1D, Case 5), which were all located in the area of ragged and elevated epithelia. The cellulose sponge test elicited a wrinkled epithelium (Figure 2C) in 10 eyes including the 4 eyes which did not exhibit any of the above characteristic corneal signs (Table 1).

After debridement and placement of ProKera®, 10 eyes became symptom-free during the follow up period of 13.7 ± 2.2 months (range 10–16 months). One eye (Case 2, OS) recurred with foreign body sensation and presented with the original corneal sign of epithelial staining in the area of debridement 2 months afterwards. After a repeated treatment, all symptoms resolved without recurrence in the remaining 10 months of follow up. For these 11 eyes, best corrected visual acuity (BCVA) improved in 10 eyes from 20/60 to 20/20 and 1 eye remained 20/20 as before the treatment (Table 1). In all eyes, epithelial defects created by debridement rapidly healed when the ProKera® was removed on the postoperative day 4 to 7. The resultant epithelium in all eyes was smooth, and clear and did not show fluorescein staining or a persistent tear break up pattern (Figure 2I).

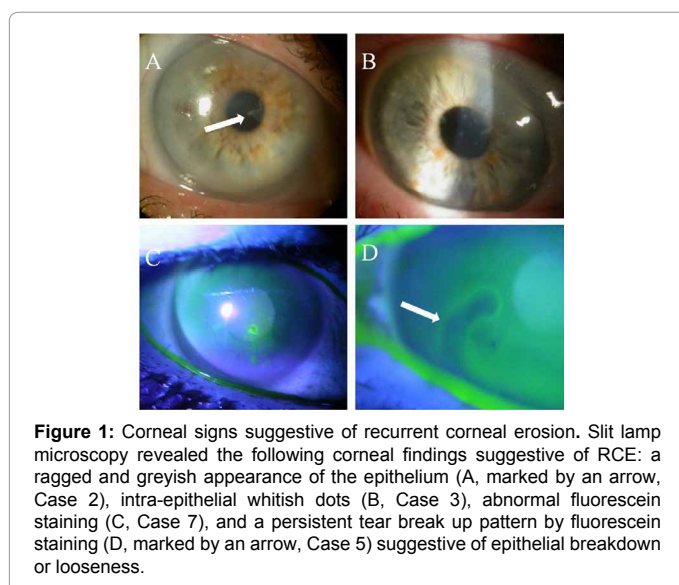


Figure 1: Corneal signs suggestive of recurrent corneal erosion. Slit lamp microscopy revealed the following corneal findings suggestive of RCE: a ragged and greyish appearance of the epithelium (A, marked by an arrow, Case 2), intra-epithelial whitish dots (B, Case 3), abnormal fluorescein staining (C, Case 7), and a persistent tear break up pattern by fluorescein staining (D, marked by an arrow, Case 5) suggestive of epithelial breakdown or looseness.

Case	Sex/ Age (y)/Eye	Previous Treatment	Signs	Fluorescein Staining	Cellulose Sponge Test	Symptoms		BCVA		Follow-up (Mo)
						Before	After	Before	After	
1	F/42/L	None	None	Negative	Positive	Pain, burning, blurry vision	Absent	20/40	20/20	16
2	F/78/R	Lubricant	Ragged epithelium	Persistent tear break up pattern	Positive	Pain, blurry vision, photophobia	Absent	20/50	20/20	15
	F/78/L	Lubricant	Ragged epithelium	Persistent tear break up pattern	Positive	Pain, blurry vision, photophobia	FBS	20/50	20/25	15
3	F/51/R	Contact lens	Intra-epithelial dots	Positive	Positive	Pain, blurry vision, FBS	Absent	20/25	20/20	13
4	M/62/L	Lubricant	None	Negative	Positive	Pain, FBS, lid discomfort	Absent	20/20	20/20	15
5	F/45/R	Doxycycline, 1% prednisolone	Ragged epithelium	Persistent tear break up pattern	Not done	Pain, FBS,	Absent	20/25	20/20	15
6	F/55/L	Lubricant, serum, Debridement	None	Negative	Positive	Pain, burning	Absent	20/25	20/20	16
	F/55/R	Lubricant, serum	None	Negative	Positive	Pain, burning, lid discomfort	Absent	20/25	20/20	16
7	F/51/R	None	Ragged epithelium	Positive	Positive	Pain, FBS, photophobia	Absent	20/40	20/30	12
8	M/52/L	Lubricant, 0.1% Dexamethasone	Ragged epithelium	Persistent tear break up pattern	Positive	Photophobia, blurry vision, tearing	Absent	20/40	20/25	11
9	F/63/R	None	Ragged, greyish	Persistent tear break up pattern	Positive	Photophobia, blurry vision	Absent	20/60	20/30	10

BCVA: Best Corrected Visual Acuity; F: Female; FBS: Foreign Body Sensation; L: Left Eye; M: Male; Mo: Month; R: Right Eye

Table 1: Clinical characteristics and outcomes.

Case Example

A 55 year-old woman (Case 6) had been suffering from repeated episodes of eye pain and burning in both eyes, which awoke her at night usually five hours into sleep for about 5 years. The left eye was much worse than the right eye and was successfully managed by the treatment described herein. Interestingly, her right eye presented with prominent eyelid discomfort upon blinking (Figure 3A, the location was pointed by her finger). She had tried topical 0.3% Propylene Glycol drops (Systane®, Alcon Inc. Fort Worth, TX) and autologous serum drops with a minimal relief. Upon examination, her symptoms including eyelid discomfort were rapidly relieved after a drop of 0.5% proparacaine hydrochloride. Although no characteristic corneal finding was noted by slit-lamp biomicroscopy with and without fluorescein staining, the cellulose sponge test elicited positive results of a loose epithelium in the corneal area where the lower lid was in contact (Figures 3B and 3C). After removal of the entire loose epithelium in this area by debridement with a cellulose sponge (Figure 3D), ProKera® was placed with tape tarsorrhaphy to ensure centration (Figure 3E). Her ocular symptoms rapidly subsided. At day 7, the ProKera® was removed and the BCVA was improved to 20/20. The resultant corneal surface was smooth and stable without any fluorescein staining (Figure 3F) during 16 months of follow up.

Discussion

The primary dysfunction of RCE lies in the adhesion of basal corneal epithelial cells to the underlying basement membrane [12]. Consequently, tearing or separation of an already loose corneal epithelium might elicit ocular discomfort. That was why eye pain was noted in 9 of 11 eyes. Such pain elicited by friction between the eyelid and the globe could occur during eyelid blinking in the daytime as well as during rapid eye movement in sleep. Depending on the severity of RCE and patient's ocular sensitivity, friction-elicited ocular discomfort might also be interpreted as photophobia (5 eyes), foreign body sensation (4 eyes), and burning (3 eyes). However, it could also

be interpreted as lid discomfort (2 eyes) (Figure 3). To clarify the issue, a drop of topical anesthetics largely eliminates these complaints. To confirm the diagnosis, slit-lamp examination to detect characteristic corneal signs suggestive of RCE was helpful in 7 eyes (Table 1, Figure 1). However, the diagnosis of the remaining 4 eyes, including the two eyes with the mere complaint of lid discomfort, was not made until the use of the cellulose sponge test (Table 1, Figures 2 and 3). Taken together, the cellulose sponge test is clinically useful to confirm the diagnosis of RCE in eyes with or without characteristic clinical history, symptoms, and signs.

The underlying dysfunction of RCE is usually refractory to conventional medical treatments as high recurrence rate has been reported with the treatment of lubricant [3], autologous serum [4], and topical corticosteroid and oral doxycycline [23]. Although surgical interventions were more effective in refractory cases, they are usually limited by potential risk of developing refractive change or scarring over the visual axis [1,2]. Six of 11 eyes experienced blurry vision because RCE involved the visual axis. Debridement of a loosely adherent corneal epithelium is necessary to promote the healing from the healthy periphery but still results in 18% recurrence if used alone [24]. Presumably because of the therapeutic action of cryopreserved AM to promote wound healing by reducing inflammation, scarring, and angiogenesis [10,11], and its efficacy in promoting epithelial growth from limbal epithelial stem cells [25,26], complete epithelialization following debridement was noted in all 11 eyes when ProKera® was removed at 4 to 7 days after placement. During the follow up period of 7 to 13 months, the resultant corneas in 10 eyes were devoid of any abnormal signs suggestive of RCE. Consequently, BCVA improved in these 10 eyes including those who did not complain of blurry vision. There was one recurrence (Case 2, OS), which was successfully retreated. Compared to conventional AM transplantation, placement of ProKera® facilitates the patient care as it can be inserted and changed in the office at ease. During the follow up, the extent of epithelialization can be monitored by fluorescein staining without having to remove the device. Future prospective studies to compare to other conventional

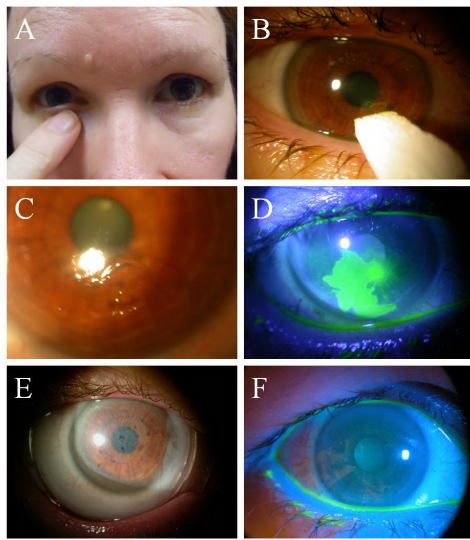


Figure 3: A case with unusual presentation of recurrent corneal erosion. The patient (Case 6) pointed at the location of lid discomfort (A). Her right cornea did not exhibit any suggestive signs of RCE, and hence the cellulose sponge test applied to the corneal surface that was in contact with the lower lid (B). This resulted in a wrinkle epithelium with epithelial breakdown (D). The entire loosely adherent epithelium in this area was then removed by debridement (D) and ProKera® was placed (E). At day 7 after treatment, the cornea was completely epithelialized without any fluorescein staining (F) for the next 16 months of follow up.

measures are needed to determine whether cryopreserved AM can be a better alternative to treat RCE involving the visual axis and to reduce recurrences.

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