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Accelerated Restoration of Ocular Surface Health in Dry Eye Disease by Self-Retained Cryopreserved Amniotic Membrane

Anny M.S. Cheng, MD¹, Dandan Zhao, MD², Rendian Chen, MD³, Han Y. Yin, MD⁴, Sean Tighe, MS¹, Hosam Sheha, MD, PhD¹, Victoria Casas, MD¹, and Scheffer C.G. Tseng, MD, PhD¹

¹Ocular Surface Center and Tissuetech Inc., Miami FL, USA

²Department of Ophthalmology, Yan'An Hospital of Kunming City, Kunming, Yunnan, China

³Department of Ophthalmology, Shenzhen Children's Hospital, Shenzhen, Guangzhou, China

⁴Florida International University Herbert Wertheim College of Medicine, Miami, FL, USA

Abstract

Purpose—To evaluate the clinical efficacy of self-retained cryopreserved amniotic membrane in treating dry eye disease.

Methods—Retrospective review of 10 patients treated with self-retained cryopreserved amniotic membrane (PROKERA® Slim [PKS], Bio-Tissue, Miami, FL) for moderate-to-severe dry eye refractory to conventional maximal medical treatments. Patients' symptoms, use of medications, conjunctival inflammation, corneal staining, and visual acuity were compared before and after treatment.

Results—PKS was placed in 15 eyes of the 10 patients for 4.9 ± 1.5 days. All patients experienced symptomatic relief for a period of 4.2 ± 4.7 months ($p < .001$). Such improvement was accompanied by reduction of OSDI scores ($p < .001$), use of topical medications ($p < .001$), conjunctival hyperemia ($p < .001$), corneal staining ($p < .001$), and improvement of the visual acuity ($p = .06$). Linear regression analysis estimated that the optimal duration of PKS placement was 5 days to achieve an average symptom-free duration of 4 months in patients with dry eye. Surprisingly, PKS placement also generated improvement in the contralateral eyes.

Conclusion—This pilot study suggests that self-retained cryopreserved amniotic membrane via PKS can be used to treat moderate dry eye diseases and warrants further prospective controlled studies.

Corresponding author: Scheffer C. G. Tseng, MD, PhD, Ocular Surface Center, 7000 SW 97th Avenue, Suite 213, Miami, FL 33173, USA. TEL: (305) 274-1299, FAX: (305) 274-1297, stseng@ocularsurface.com.

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Single-copy reprint requests to: Scheffer C. G. Tseng, MD, PhD (address below).

Keywords

amniotic membrane; dry eye; keratitis; ocular surface; PROKERA®

I. INTRODUCTION

Dry eye disease (**DED**) is a multifactorial disease of the tears and the ocular surface that results in discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface.¹ Progress has been made in the understanding of the etiology and pathogenesis of DED as well as other ocular surface diseases that mimic or aggravate DED. These advances have led us to adopt a practical algorithm for clinicians to restore the integrity of the ocular surface with an attempt to maintain a stable tear film.²

Despite different underlying pathogenic processes, DED is characterized by a common denominator of ocular surface inflammation. This, in turn, causes cell damage and a self-perpetuating cycle of deterioration. Therefore, interruption of this inflammatory cascade is a key tactic in preventing potential corneal surface damage and scarring.²⁻⁴ Different treatment modalities have been tried to suppress inflammation, prevent further damage, and restore ocular surface integrity. These treatments include medications such as steroids and cyclosporine; however, results can be variable and refractory in some cases.

Cryopreserved amniotic membrane (**CAM**) has anti-inflammatory, anti-scarring, and anti-angiogenic effects when transplanted to the ocular surface to treat different diseases.⁵⁻⁷ CAM has been used as a temporary biological bandage by sutures or through a self-retaining device, (PROKERA® Slim [PKS], Bio-Tissue, Miami, FL, USA) to restore a healthy and smooth corneal epithelium in a variety of ocular surface diseases.⁸ In this study, we retrospectively reviewed 10 consecutive cases of moderate-to-severe dry eye that had been treated by self-retaining CAM. Our preliminary results demonstrated its effectiveness in controlling inflammation, restoring ocular surface integrity, and reducing the frequency of concomitant topical medications.

II. METHODS

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 to retrospectively review 10 patients (15 eyes) with moderate-to-severe DED that were consecutively seen at Ocular Surface Center (Miami, FL) between August 2013 and January 2015. Table 1 summarizes the patients' demographics, ocular comorbidity, previous therapies, clinical presentations, and concomitant medications at presentation. Patients completed an evaluation of the symptoms and signs of dry eye disease to be classified into the dry eye severity grade from 1 to 4, as published in the Report of the International Dry Eye Work Shop (**DEWS**) 2007.¹ The severity of symptoms was graded according to the Ocular Surface Disease Index (**OSDI**) score,⁹ ranging from 0-12 (no disability), 13-22 (mild), 23-32 (moderate), and 33-100 (severe). Conjunctival inflammation was graded according to the conjunctival injection as none (0), mild (1), moderate (2), and severe (3). The corneal surface integrity was scored as clear (0), scattered superficial punctate keratitis

(**SPK [1]**), moderate SPK (2), and diffuse SPK with or without corneal epithelial defects (3). Schirmer strip wetting by the fluorescein clearance test and tear film breakup time (**TFBUT**) were carried out as outlined in the DEWS report.¹ Concomitant medications and Snellen visual acuity were recorded.

Because of persistent symptoms and/or epithelial breakdown of the ocular surface despite maximal medical treatments, PKS was inserted in one eye at a given time with an attempt to alleviate the symptoms and restore the ocular surface health. After the patient's written consent was obtained, PKS was thawed at room temperature for a few minutes, rinsed with saline, and inserted in the office under topical anesthesia with 0.5% proparacaine hydrochloride eye drops. It was first placed into the superior fornix while the patient looked down and was then slid under the lower eyelid. After placement, the patients were asked to use or reduce the numbers of concomitant topical medications at will. Patients returned to the office for removal of the PKS and were followed up as needed thereafter. The followup visits were documented, and the patients were evaluated in the same manner as before the placement of PKS. These findings are also summarized in Table 1.

Descriptive statistics for continuous variables are reported as the mean $\pm$ SD and analyzed using SPSS software, version 19.0 (SPSS Inc, Chicago, IL, USA). Differences and correlation between parameters were analyzed by the student's t-test, the Wilcoxon signed ranks test, or the Spearman's rank order correlation. A *p* value less than .05 was considered statistically significant. A simple linear regression was calculated predicting PKS placement duration and symptom-free duration based on the symptoms severity and variables under investigation.

III. RESULTS

This study included 15 eyes of 10 patients (2 males and 8 females) with a mean age of 68.7 ± 16.2 years (range, 39 to 87 years). Relevant clinical data of each patient are summarized in Table 1. No associated systemic disease such as Sjögren disease, rheumatoid arthritis, systemic lupus erythematosus, progressive systemic sclerosis, polymyositis, or dermatomyositis that contributed to DED symptoms were reported among all patients. The 15 eyes had previously received 2.5 ± 0.9 (range, 1 to 5) topical concomitant medications, including autologous serum (10.8%, 4/37), artificial tears (48.6%, 18/37), steroid (21.6%, 8/37), cyclosporine (10.8%, 4/37), and antibiotics (8.1%, 3/37). Eleven out of 15 eyes (73%) received optimal conventional therapy, including bandage contact lens in 7 eyes (46.7%), punctal occlusion in 11 eyes (73%), and/or cauterization in 2 eyes (13%). Six out of 15 eyes (40%) underwent conjunctivochalasis (**CCh**) surgery (n=4), pterygium surgery (n=1), laser in situ keratomileusis (**LASIK**) (n=1), and blepharoplasty (n=1) with an average of 6 ± 3 (range, 1 to 10) years prior to PKS placement, whereas the mean duration of dry eye symptoms in the 15 eyes was 13.6 ± 11.8 (range, 1 to 37) years.

Despite the aforementioned medical treatments, the patients remained symptomatic and cited various complaints, including dryness (12/15 [80%]), irritation (12/15 [80%]), burning (5/15 [33.3%]), gritty sensation (9/15 [60%]), photophobia (8/15 [53.3%]), redness (7/15 [46.7%]), sharp pain (5/15 [33.3%]), soreness (5/15 [33.3%]), blurred vision (5/15 [33.3%]),

itching (4/15 [26.7%]), sticky sensation (2/15 [13.3%]), and mucus formation (2/15 [13.3%]). The severity of symptoms was graded by the OSDI score as mild in 2 eyes (13.3%), moderate in 5 eyes (33.3%), and severe in 8 eyes (53.3%), with a mean score of 33.5 ± 10.8 (range, 18.8 to 54.2), indicating that our overall study population had moderate-to-severe dry eye symptoms. All eyes had corneal SPK with scoring as 1+ (mild) in 11 eyes (73.3%), 2+ (moderate) in 3 eyes (20%), and 3+ (severe) in 1 eye (6.7%). The mean TFBUT and Schirmer wetting length was 4.7 ± 1.6 (range, 3 to 8) sec and 2.5 ± 1.8 (range, 0 to 5) mm, respectively. All eyes were classified by the DEWS grading as 1+ (very mild) in 0 eyes, 2+ (mild) in 4 eyes, 3+ (moderate) in 11 eyes, 4+ (severe) in 0 eyes. The grading of symptoms by the OSDI score was significantly correlated with the DEWS grading score ($r = 0.74$, $p = .001$). The number of medications increased in eyes with higher OSDI scores, for example, autologous serum (75%, 3/4, $p = 0.4$), artificial tears (60%, 11/18, $p = 0.3$), cyclosporine (75%, 3/4, $p = 0.4$), and punctal cauterization (100%, 2/2, $p = 0.4$).

Fifteen eyes of 10 patients received PKS, and of those, 5 patients had PKS placed in both eyes and 5 had it only in one eye. Placement and removal of PKS were uneventful in all cases. The average PKS placement duration ranged from 2 to 8 days, with a mean of 4.9 ± 1.5 days, at which time the CAM was either dissolved or cloudy; the latter was due to accumulation of inflammatory debris as shown in Figure 1.

Immediately after removal of PKS, all patients reported a significant relief of symptoms as evidenced by a significant reduction of the OSDI, which decreased from 33.5 ± 10.8 to 18.3 ± 6.2 ($p < .001$). Furthermore, there was a significant reduction from 1.6 ± 0.7 to 0.5 ± 0.5 of conjunctival inflammation ($p < .001$) and complete resolution of pre-existing superficial punctate keratitis in all 15 eyes ($p < .001$). Interestingly, we also noted a significant reduction in the number of concomitant topical medications from 2.5 ± 0.9 to 0.7 ± 0.7 after PKS placement ($p < 0.001$; Figure 2). This was illustrated by complete withdrawal of all topical medications ($n = 6$), discontinuation of autologous serum ($n = 4$), cyclosporine ($n = 4$), and/or antibiotics ($n = 3$), a decrease in use of artificial tears ($n = 11$), and a decrease in use of topical steroid drops ($n = 2$). Furthermore, 7 of 15 eyes (46.7%) exhibited an improved distance visual acuity from 1 to 3 Snellen lines; however, such an improvement did not reach statistical significance ($p = .06$).

Interestingly, the 5 fellow eyes that had inadequate and incomplete blinking but did not receive PKS (Cases # 3, 4, 5, 6 and 7) also showed a complete relief of symptoms such as dryness ($n = 3$), irritation ($n = 4$), burning ($n = 1$), gritty sensation ($n = 1$), redness ($n = 3$), and blurred vision ($n = 1$). Consequently, the OSDI score was significantly reduced from 32.9 ± 6.6 to 22.1 ± 6.4 ($p = .006$) in the fellow eye upon the immediate removal of PKS. This unexpected outcome might be explained by the finding that blinking became complete and frequent when PKS was inserted to the fellow eye (see video 1, available online).

Accompanied by the symptom relief was the significant reduction of the number of concomitant topical medications from 2.8 ± 1.3 to 0.8 ± 0.8 immediately after PKS removal in these 5 fellow eyes ($p = .003$). There were no marked differences between pre- and immediate post-PKS removal in conjunctival inflammation grading ($p = .1$) or corneal SPK grading ($p = .2$). Three (60%) out of 5 eyes had improved Snellen acuity of 1 line and the

other 2 eyes (40%) remained unchanged immediately after PKS removal of the fellow eyes ($p=.5$).

The patients remained symptom-free during the follow-up period of 4.2 ± 4.7 months (range, 0.3-6.8 months); some representative cases are illustrated in Figure 3. We used a linear regression model to determine the relationship between the OSDI severity and the duration of PKS placement, as well as between the OSDI severity and the symptom-free duration in order to evaluate the efficacy of PKS placement. The result showed that the OSDI severity was inversely proportional to the PKS placement duration (Figure 4, $r = -0.66$, $p=.24$) but was directly proportional to the symptom-free duration ($r = 0.1$, $p=.9$). The intersection between these two linear regression lines estimated that the optimal time of placing PKS was 5 days to achieve an average symptom-free duration of 4 months in moderate DED.

After 4.2 ± 4.7 months, we noted recurrence of all symptoms except sticky sensation in all cases, although to a lesser extent. There was a tendency for the reduction of the OSDI scores, i.e., from 33.5 ± 10.8 (before PKS placement) to 31.3 ± 10.9 (final follow up [$p=.2$]), and of the number of topical medications, i.e., from 2.5 ± 0.9 (before PKS placement) to 2.4 ± 0.9 (final follow up [$p=.8$]). This trend was also observed in the 5 fellow eyes, i.e., the OSDI scores from 32.9 ± 6.6 to 27.1 ± 10.3 ($p=.5$) and the number of topical medications from 2.8 ± 1.3 to 2.0 ± 1.4 ($p=.8$).

IV. DISCUSSION

Self-retained CAM has been successfully used in refractory ulcerative keratitis,¹⁰ neurotrophic keratitis,^{11,12} recurrent epithelial erosion,^{11,12} high-risk corneal grafts,¹³ acute chemical and thermal burns,^{12,14} acute Stevens-Johnson syndrome/toxic epidermal necrolysis,¹⁵ necrotizing scleritis,¹⁶ and partial or total limbal stem cell deficiency.¹⁷⁻¹⁹ Herein, we provide the first evidence that self-retained CAM via PKS may be considered as a new strategy to achieve rapid resolution of symptoms and restoration of ocular surface health in patients with refractory DED.

DED is a multifactorial and complex disorder in which ocular surface inflammation plays a central role. We believe one rationale for the ability of PKS to generate a positive outcome in treating DED is because CAM contains anti-inflammatory mediators in its stromal matrix.²⁰⁻²⁴ This is suggested by CAM's use as a temporary patch, which has been reported to entrap polymorphonuclear cells in rabbit excimer laser ablation^{25,26} and human patients with chemical burns.^{14,27} Notably these adherent cells underwent rapid apoptosis^{25,27} to abort the inflammatory process. Similarly, adhered mononuclear cells, including lymphocytes and macrophages, also underwent rapid apoptosis when adhered to the AM stroma in a murine model of herpes simplex virus-induced necrotizing keratitis.²⁸⁻³¹ Such a unique anti-inflammatory action of CAM has been recapitulated in an in vitro culturing system using murine macrophages.³² This action has also been seen with the use of the water-soluble AM extract (AME),³³ and recently with HC-HA/PTX3 purified from AME.³⁴ Herein, we also noted that CAM of PKS turned cloudy with accumulation of inflammatory debris (Figure 1), consistent with what has been reported based on the histopathologic

study.¹⁴ Because the inflammatory coagulum progressively accumulates to increase the cloudiness of the CAM and potentially hinder its effectiveness, a change to a new CAM may be necessary. In fact, the use of PKS has facilitated such a change based on other studies in managing chemical burns,¹⁴ severe bacterial keratitis,¹⁰ and limbal stem cell transplantation,¹⁸ where PKS was changed 7, 9, and 10 days, respectively. Moreover, the anti-inflammatory effect of the HC-HA/PTX3 complex purified from CAM also extends from innate to adaptive immune responses by facilitating apoptosis of stimulated neutrophils, polarizing M2 macrophages and suppressing activation of Th1 and Th17 lymphocytes and expansion of Tregs.^{34,35} Hence, although no patient had an immune etiology underlying their tear-deficient DED in the present study, we speculate that PKS can also be used to treat autoimmune DED.

In addition to chronic inflammation, we cannot ignore the pathogenic role of hydrodynamic aspects mediated by the neurotrophic state³⁶ and infrequent/incomplete eyelid blinking in DED.² Intriguingly, recent studies have suggested that quantitation of subbasal corneal nerves can be used to gauge the severity and the improvement following treatment,³⁷⁻³⁹ because the loss of subbasal corneal nerves correlates with an increase of the dendritic cell density in DED patients.^{40,41} Because CAM is rich in nerve growth factor, which helps corneal nerve regeneration,^{42,43} we speculate that CAM of PKS may also help restore corneal sensitivity not only by reducing inflammation mediated by dendritic cells but also by facilitating the return of subbasal corneal nerves. This speculation is supported by Suri et al,¹² who have reported favorable outcomes of PKS in treating corneas with different causes of neurotrophic keratopathy.

Future prospective controlled studies are needed to corroborate whether PKS helps treat DED by reducing inflammation and restoring corneal innervation and to explain why 5 days of PKS placement was effective in treating moderate DED and achieving a symptom-free period of 4 months. Given that eyelid blinking plays an important role in achieving balanced and consistent tear distribution, PKS might also facilitate adequate blinking because of the polycarbonate ring that may stimulate more blinking. (available online at <http://>) This likelihood explains why placement of PKS facilitated the ocular surface recovery not only in the eye with PKS placement but also in the fellow eye.

Because CAM is not transparent, it is known to decrease the distance visual acuity from -0.22 ± 0.06 logMAR to 0.92 ± 0.45 logMAR within 30 minutes, and then to 1.04 ± 0.35 logMAR within 60 to 90 minutes as reported.⁴⁴ Even though CAM can accumulate inflammatory debris (Figure 1), which presumably potentially further reduces the visual acuity, the patients did not experience activity limitation because only one eye received PKS at a given time and the wear time was limited to an average of 5 days. Upon the removal of PKS, the visual acuity was improved, although not statistically significantly.

It has been reported that PROSE (prosthetic replacement of the ocular surface ecosystem) has been used for treating severe DED by maintaining a stable tear film, protecting from exposure, and preventing friction-induced microtrauma.⁴⁵ There has not been any report describing the combined use of PROSE and topical steroids. Setting aside the potential known side effects of steroid, it should be noted that the HC-HA/PTX3 complex purified

from CAM uniquely exerts its anti-inflammatory effect extending from innate to adaptive immune responses, an action that cannot be replicated by steroids. Future prospective clinical trials are needed to determine whether PKS is superior to PROSE and steroids in treating severe DED.

Recent studies indicate that DED comprises a public health problem^{46,47} with substantial economic implications,⁴⁸ including increased prescription medication usage and expenditures for DED.⁴⁹ Herein, we reported a significant reduction of topical medications in patients with refractory DED, presumably due to rapid resolution of symptoms and restoration of ocular surface health. Future studies are needed to determine whether this new treatment modality could help reduce the overall health care cost.

Recurrences have been reported in 25% following placement of PKS in such neurotrophic conditions as herpes zoster keratitis, poor systemic health, and chemical burn.¹² Hence, we also believe that a single use of PKS more likely does not correct the underlying pathogenesis of DED. It remains to be determined whether repetitive use of PKS generates a more lasting effect. Future studies are necessary to resolve this issue.

V. Conclusion

This pilot study is limited by being retrospective in nature and lacking a control group and randomization. Nonetheless, the data suggest that self-retained cryopreserved amniotic membrane via PKS can be used for treating moderate dry eye diseases and warrants further prospective randomized controlled studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Self-retained CAM before and after treatment. The CAM looked clear before PKS placement in a patient with moderate dry eye (A), and then became cloudy 5 days later due to accumulation of inflammatory debris (B). This demonstrates that PKS works as a magnet to attract the inflammatory cells out of the ocular surface.

Figure 2.

Changes in concomitant topical medications after PKS placement. All patients demonstrated a significant reduction in the number of concomitant topical medications ($P<.001$). In six eyes, all topical medications, including artificial tears, were completely withdrawn. Three out of those six eyes had mild DED, whereas the other three had moderate-to-severe DED.

Figure 3.

Representative case: Self-retained CAM for mild, moderate, and severe DED. Cases of mild DED with 1+ OSDI (top row), moderate DED with 2+ OSDI (second row), and severe DED with 3+ OSDI (third row). They were treated with PKS for an average of 5 days. After PKS removal, the symptoms were completely resolved, the eye was quiet, the cornea was clear, and the ocular surface remained stable for 4 months. (Left column is before PKS cornea SPK, middle column is after PKS placement, and right column is immediately after PKS removal.)

Figure 4.

Relationship between PKS placement duration and the therapeutic lasting effect. OSDI severity was inversely proportional to the PKS placement duration ($r = -0.66$, $p = .24$) but was directly proportional to the symptom-free duration ($r = 0.1$, $p = .9$). The intersection between these two linear regression lines estimated that the optimal time of placing PKS was 5 days to achieve an average symptom-free duration of 4 months in moderate DED.

Summary of Relevant Clinical Data.

TABLE 1

Patients	Age (Y)	Gender	Eye	Prior ocular surgery	Comorbidity	Prior therapies	FU(mo)	PKS placement (Days)	Symptoms		OSDI severity			Conjunctival Grading			Corneal Grading			DEWS score			Topical concomitant medications			Visual Acuity		
									Pre	I	Pre	I	Post	Pre	I	Post	Pre	I	Post	Pre	I	Post	Pre	I	Post	Pre	I	Post
1	82	F	R	CCh	A	AT,Plug,CL	0.3	6	dr.ir	0	dr.ir,pho	1	0	1	1	0	1	1	0	1	2	1	0	2	20/25	20/20	20/25	
2	82	F	L	-	A	ST,Plug,CL	3.3	4	dr.ir	0	dr.ir,pho	1	0	1	0	0	1	1	0	1	2	1	0	2	20/25	20/25	20/25	
	80	F	L	-	A	AT,ST,Plug,CL	13.6	2	dr.ir,bur,sti,mu	0	dr.ir,bur,ity,pho	2	0	1	2	0	1	1	0	1	2	2	1	3	20/30	20/20	20/25	
3	80	F	R	CCh	A,B	AT,ST,Abx,Plug,CL	16.8	8	dr.ir,bur	0	dr.ir,bur,ity	2	1	1	2	0	1	1	0	1	2	3	2	3	20/25	20/20	20/25	
	63	F	R	-	A,CCh,D	SE,AT,ST,Abx,CYC,Plug,CL	4.7	4	red,pa,gri,pho	0	ity,pa,gri	2	1	2	2	1	1	2	0	1	3	5	2	4	20/25	20/20	20/20	
4	63	F	L*	-	A,CCh,D	SE,AT,ST,CYC,Abx,Plug,CL	4.7	0	red,mu	0	red,ity,pa,gri	2	1	2	1	0	1	0	0	1	2	5	2	4	20/20	20/20	20/20	
	67	F	R	Pterygium	A,CCh	AT,ST,Plug	2.5	6	dr.ir,red,pa,gri,pho,so	0	red	2	1	0	2	1	2	2	0	0	3	2	0	0	20/25	20/25	20/20	
5	67	F	L*	-	A,CCh	AT,ST,Plug	2.5	0	ir,red,gri	0	red	2	1	0	2	1	2	2	0	0	3	2	0	0	20/25	20/20	20/20	
	83	F	L	-	A,CCh,D	AT,Plug	1.9	6	dr.ir,pa,gri,pho,bv	0	dr.ir,mu,bv	2	0	2	2	1	2	1	0	1	3	2	1	2	20/40	20/30	20/30	
6	83	F	R*	-	A,CCh,D	AT,Plug	1.9	0	dr.ir,bv	0	dr.ir,mu,gri,bv	2	1	2	2	2	2	1	0	1	2	2	1	2	20/30	20/25	20/30	
	43	M	R	LASIK	FL,D	SE,ST,CYC,Plug,Caut	6.3	3	dr.ir,bur,gri,pho,so	0	dr,pa,gri,pho,so	3	2	2	2	1	2	1	0	1	3	3	1	2	20/20	20/20	20/20	
7	43	M	L*	-	-	SE,ST,CYC,Plug,Caut	6.3	0	dr.ir,bur,pa,pho,so	0	dr,gri,pho,so	3	2	2	2	1	2	0	0	1	2	3	1	2	20/20	20/20	20/20	
	87	F	R	Blp, CCh	FL,D	AT,Abx,Plug,Caut	1.5	4	dr.ir,red,gri	0	dr,ir,gri	3	1	3	3	1	3	1	0	1	3	2	0	2	20/40	20/40	20/30	
8	87	F	L*	Blp, CCh	FL,D	AT,Plug	1.5	0	dr,ir,red	0	dr,ir	3	2	3	1	1	2	1	0	1	2	2	0	2	20/30	20/30	20/30	
	69	F	R	-	B	AT	2.2	4	dr,ir,ity,gri,pho,so,bv	0	dr,ir,ity,gri,so,bv	3	1	3	2	1	2	2	0	2	3	2	0	2	20/25	20/20	20/20	
9	69	F	L	-	-	AT	2.1	5	dr,ir,ity,gri,pho,so,bv	0	dr,ir,ity,gri,so,bv	3	1	3	2	0	2	3	0	2	3	2	0	2	20/40	20/25	20/20	
	74	M	R	-	D	AT,CYC	1.6	6	dr,ir,red	0	dr,ir,red,	3	1	3	1	1	1	1	0	1	3	3	1	3	20/20	20/25	20/25	
10	74	M	L	CCh	A,D,B	AT,CYC	1.5	4	dr,ir,red	0	dr,ir,red,	3	1	3	1	0	1	1	0	1	3	3	1	3	20/25	20/20	20/25	
	39	F	R	-	A	SE,AT,ST,Plug,CL	2.6	5	bur,red,ity,pa,gri,pho,bv	0	bur,red,mu,gri,pho,bv	3	2	3	1	0	1	1	0	1	3	3	1	3	20/20	20/20	20/20	
39	F	L	-	A	SE,AT,ST,Plug,CL	2.8	6	bur,red,sti,mu,ity,pa,gri,pho,bv	0	bur,red,mu,pa,gri,pho,bv	3	2	3	1	0	1	1	0	1	3	3	1	3	20/20	20/20	20/25		

Abbreviations: A,blepharitis; Abx,antibiotics; AT,artificial tears; B, lagophthalmos; Blp,blepharoplasty; bur,burning; bv,blurred vision; Cau,punctal cauterization; CCh,conjunctivochalasis; CL,bandage contact lens; CYC,cyclosporine; D,sunken globe; dr, dryness; F,female; FL,floppy eyelid; FU, follow up; gri; gritty sensation; Immediately after PKS removal; ir,irritation; ity,itchy; L,left; M,male; mo,months; mu,mucous formation; pa,pain; pho,photophobia; Plug,punctal plug; Post, final follow-up after removal of PKS ; Pre,before placement of; R,right; red:redness; SE,autologous serum; so,ocular soreness; ST, steroid; sti,sticky; Y,years; -, absent

The definition of grading or severity is detailed in the text.

* Fellow eye without placing PKS