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ORIGINAL RESEARCH

# Shelf-Stable, Cryopreserved Amniotic Membrane for the Management of Ocular Surface Disease: A Retrospective Assessment

Sean Cushman

Optometry, The Eye Institute of Utah, Salt Lake City, UT, USA

Correspondence: Sean Cushman, Optometry The Eye Institute of Utah, Salt Lake City, Utah, USA, Tel +1-801-266-2283, Email scushman@theeyeinstitute.com



**Purpose:** To assess both the short- and long-term clinical outcomes following adjunctive treatment with shelf-stable, cryopreserved amniotic membrane (CAM) in patients with ocular surface disease (OSD).

**Methods:** This was a single-center, retrospective study of consecutive patients with OSD that underwent adjunctive treatment with shelf-stable CAM with 72-hour collagen shield or bandage contact lens followed by partial tape tarsorrhaphy at a single-center between January 2024 and March 2025. Corneal staining, symptoms, visual acuity (VA), and improvements in corneal sensitivity were assessed at 1 week (± 5 days) and last follow-up (12–24 weeks). Symptomatic improvement was defined as the resolution of at least one pre-treatment symptom at follow-up.

**Results:** A total of 29 eyes of 20 patients (mean age of 66.3 ± 9.1 years) with dry eye disease (n=14), neurotrophic keratopathy (n=5), and superficial punctate keratitis (n=10) were included in this study. At 3.9±2.9 days post-CAM placement, mean corneal staining score improved from 2.26±1.07 to 1.00± 0.91 ($p<0.001$), with 84.6% of eyes demonstrating improvement (mean change: 1.59 ± 0.77). Symptomatic improvement was observed in 92.3% of eyes. At 16.0 ± 2.8 weeks post-CAM, corneal staining significantly improved to 1.55 ± 1.13 ($p=0.014$). Trace or complete resolution of corneal staining was noted in 5/20 eyes (25.0%), and 12 eyes (60.0%) had improved staining. Symptomatic improvement was noted in 65.0% of eyes. There were no complications aside from two cases that noted irritation with collagen shield use and one case of irritation on the outer lid, which was attributed to the adhesive tape.

**Conclusion:** This preliminary data suggest that shelf-stable CAM may reduce both signs and symptoms of OSD as soon as four days post-treatment, with a lasting benefit observed for up to four months on average in some patients.

**Keywords:** amniotic membrane, dry eye disease, neurotrophic keratitis, ocular surface disease, superficial punctate keratopathy

## Introduction

Ocular Surface Disease (OSD) is an umbrella term encompassing a wide range of conditions that affect the health and function of the eyes' surface, including the cornea, conjunctiva, and tear film. Relatively common subtypes of OSD included dry eye disease (DED) and neurotrophic keratopathy (NK).[1] One of the hallmark signs of DED and early-stage NK is superficial punctate keratopathy (SPK), which involves small, superficial damage to the corneal epithelium. Given the overlapping pathologies of DED and NK, patients with less progressive forms of NK (eg, Mackie grade 1) may also present with symptoms of DED such as dryness, irritation, and blurred vision.[2,3] Treatment typically includes the use of lubricating eye drops or artificial tears to alleviate symptoms, improve tear film stability, and restore the corneal epithelium.[4] However, these treatments are not effective in all patients and often require long-term therapy to manage the condition effectively.[5–7] In some cases, more advanced treatments may be necessary to address the underlying causes and improve the patient's quality of life.

Over the last decade, Amniotic Membrane (AM) has been increasingly used in order to support healing in many specialties including ophthalmology, optometry, podiatry, orthopedics, general surgery, and urology. AM is known to

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have anti-inflammatory and anti-scarring properties, which help to modulate the wound healing process and restore the damaged tissue to its original state.[8] Self-retained, cryopreserved AM in the sutureless form, known as Prokera®, has been shown to significantly reduce signs and symptoms of DED, however, it is more often used in moderate-to-severe cases.[9,10] Recently, a new shelf-stable, cryopreserved AM has been developed that retains the key structural and biological properties, including the anti-inflammatory effects of AM and has been designed to optimize comfort in patients with relatively more mild-to-moderate OSD.[11] The key differences between the new shelf-stable, cryopreserved AM and Prokera are: that it does not have a ring to hold the CAM in-place and undergoes additional terminal sterilization process, which allows it to be stored at room temperature. Potential benefits of such treatment include short-duration of treatment (eg, 2–3 days), improved patient discomfort, and both rapid and durable improvement in signs and symptoms. Herein, we assessed the short- and long-term clinical outcomes after treatment with shelf-stable, cryopreserved AM in patients with OSD.

## Materials and Methods

Following exemption and waiver of consent by the Institutional Review Board (IRB) at Sterling IRB (#13981), a retrospective chart review was conducted on consecutive patients with ocular surface disease that underwent treatment with shelf-stable, cryopreserved AM between January 2024 and March 2025 at single center (The Eye Institute of Utah). The study was found exempt from IRB review pursuant to the terms of the US Department of Health and Human Service's Policy for Protection of Human Research Subjects at 45 C.F.R. §46.104(d) applicable to Category 4 Exemption. Appropriate measures were undertaken and maintained to protect the confidentiality of study participants, and all study procedures were performed in accordance with the tenets of the Declaration of Helsinki. Patients were included for analysis if they were at least 18 years of age, had a diagnosis of dry eye disease, neurotrophic keratopathy, or superficial punctate keratopathy, and were treated with shelf-stable, cryopreserved AM (CAM360 AmnioGraft; BioTissue Holdings Inc, Miami, FL). Patients who had missing baseline and follow-up data related to corneal staining were excluded from this study. Data were collected from baseline (before treatment) and thereafter for up to six months and included patient demographics (age, gender, race), relevant ocular history, comorbidities, diagnosis, duration of diagnosis, prior treatments, concomitant procedures and treatments, duration of treatment, length of follow-up, signs (corneal staining scores), symptoms, visual acuity, corneal sensitivity, and complications.

### Treatment

Shelf-stable CAM (CAM360 Amniograft, BioTissue Holdings Inc, Miami, FL) was removed from its packaging using forceps and placed onto the concave surface of a hydrated 72-hour dissolvable collagen shield (Oasis Medical, Glendale, CA) or bandage contact lens (AIR OPTIX® NIGHT & DAY® AQUA; Alcon, Geneva, Switzerland) with the gridded backing paper face down. Sterile forceps and a sterile, polyester-tipped applicator swab were then used to peel off the backing paper and smooth out the CAM in the carrier. Prior to insertion, one drop of prophylactic antibiotic (Ofloxacin) and topical anesthetic were applied to the ocular surface. The CAM and carrier were placed over the cornea followed by two to three drops of saline to remove air bubbles and ensure hydration of the tissue. The eye was taped partially shut (Nictavi, Los Angeles, CA), and patients were instructed to continue their topical medications. The tape was removed after two to three days, the carrier (bandage contact lens or collagen shield) was removed from the eye, and the status of the CAM was noted (dissolved, fell out, present).

### Clinical Outcomes

Outcomes were assessed at 1 week (± 5 days) post-CAM treatment as well as at last follow-up visit, which ranged from 3 to 6 months post-treatment. The primary outcome measure was the change in corneal surface integrity at 1 week (± 5 days), which was assessed using fluorescein staining and was graded on a scale of 0 to 4, with 0 indicating no corneal staining and 4 indicating severe punctate keratitis.[12,13] For the purpose of this study, trace SPK was recorded as 0.5, and if corneal staining score ranged between two grades (eg, 3–4+), the average was taken. The proportion of eyes with symptomatic resolution, improved or resolved corneal staining, improved corneal sensitivity, and adverse events were also assessed at 1 week as well as last follow-up visit. Symptoms of OSD were noted at baseline and follow-up and

included dryness, ocular discomfort, burning/stinging, photophobia, itching, foreign body sensation, pain, and visual disturbances (eg, blurred vision). Symptomatic improvement was defined as the resolution of at least one pre-existing symptom at follow-up. Corneal sensitivity was assessed using cotton wisp. Snellen visual acuity (VA) was also assessed at both follow-up visits and was transformed into logMAR units for analysis.

## Statistical Analyses

All statistical analyses were conducted using IBM SPSS Statistics version 30.0 (IBM; Armonk, NY, USA). The study sample is described using summary statistics (n, mean, standard deviation, median, and maximum/minimum) for continuous data and frequency statistics (counts and percentages) for categorical data. For normally distributed data, the Independent Samples *T*-test was used to assess continuous outcome measures (ie, corneal staining score and VA logMAR) between groups, whereas a repeated measures, paired *t*-test was used to assess continuous outcomes across timepoints. For data that were not normally distributed, the respective non-parametric tests (Mann–Whitney *U*-test and Wilcoxon signed-rank test) were utilized. Bivariate and partial correlations between parameters were assessed using the Spearman's rank order correlation. A $p$ value less than .05 was considered statistically significant.

# Results

A total of 29 eyes (15 OS, 14 OD) of 20 patients met the eligibility criteria. All patients were White/Caucasian and non-Hispanic. Majority of patients were female (n=18, 90%), and the mean age at the time of treatment was 66.3 ± 9.1 years. Common comorbidities included meibomian gland dysfunction (n=24), cataract (n=12), hypertension (n=8), glaucoma (n=4), lagophthalmos (n=5), Sjogren's syndrome (n=4), diabetes (n=3), and thyroid disease (n=5).

The primary condition for the patients was recalcitrant superficial punctate keratitis, which was caused by DED (n=22), NK (n=7), ocular cicatricial pemphigoid (n=4), Sjogren's syndrome (n=2), cancer treatment (n=1), and/or blepharospasm (n=1). Median duration of diagnosis was 6.9 months (range: 0.2–63.4). Prior therapies for the condition included perfluorohexyloctane (Miebo) (n=7), cyclosporine (n=17), steroid drops (n=11), lifitegrast (n=6), ointments/gels (n=7), artificial tears (n=11), antibiotic drops (n=5), amniotic membrane (n=3), warm compresses (n=5), serum drops (n=2), and recombinant human nerve growth factors (Oxervate) (n=1). One patient was also anti-glaucoma medications (bimatoprost/dorzolamide-timolol/netarsudil). Surgical history included cataract surgery (n=12), LASIK (n=8), Pars Plana Vitrectomy (n=2), Laser Peripheral Iridotomy (n=1), superficial keratectomy (n=2), and glaucoma surgery (n=2). A total of 5 eyes were currently using contact lenses, and 9 eyes had a history of previous contact lens use.

At baseline, 7 eyes had reduced corneal sensitivity, and 22 eyes had normal sensitivity. All patients reported symptoms prior to treatment, which included dryness (n=18), discomfort (n=16), burning/stinging (n=16), itching (n=8), FBS (n=4), photophobia (n=4), pain (n=1), and visual disturbances/blurred vision (n=15). Patients reported an average of 2.8 ± 0.8 symptoms per eye. Mean corneal staining score was 2.26 ± 1.07 (median: 2, range: 1–4), and logMAR VA was 0.21 ± 0.17 (median: 0.18, range: 0.00–0.54).

All patients were treated with 1 drop of Ofloxacin and placement of CAM for two (n=16) or three days (n=13) with 72-hour collagen shield (n=27) or bandage contact lens (n=2) followed by temporary partial tape tarsorrhaphy in all cases. Concomitant medications included cyclosporine drops (n=13), preservative free artificial tears (n=17), perfluorohexyloctane (Miebo) (n=7), lifitegrast (n=2), corticosteroid drops (n=8), antibiotic drops (n=2), and serum drops (n=2).

A total of 26 of 29 eyes returned to first follow-up at a mean of 3.9 ± 2.9 days (median: 3, range: 2–12) post-CAM placement. Upon examination, the carrier was noted to be present in 17 eyes, dissolved in 5 eyes, and had fallen out (at 2 days) in 7 eyes. The instances of falling out occurred when the patients were told to remove the tape after 2 days and let it fall out when they could not come within 2–3-day follow-up. Mean corneal staining score improved to 1.00± 0.91 ($p<0.001$). Complete resolution of corneal staining was noted in 23.1% (6/26) of eyes, and an additional 6 eyes (23.1%) demonstrated only trace SPK. A total of 22/26 eyes (84.6%) had improved corneal staining (mean change: 1.59 ± 0.77), two eyes (7.7%) had no change, and two eyes (7.7%) had slight worsening by 0.5. The only factor that was correlated with corneal staining score at first follow-up visit was the use of concomitant artificial tears (r=−.57, p=0.002), with eyes that used adjunctive artificial tears having a significantly less corneal staining score (0.57 ± 0.53 vs 1.59 ± 1.00, p=0.008), nevertheless, the change from baseline was not significantly different between groups (p=0.95). LogMAR VA

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was assessed in 16 eyes and was slightly worse (0.36 ± 0.29; p=0.28). Of the seven patients with reduced corneal sensitivity, one patient demonstrated increased sensation. When assessing those eyes with pre-existing symptoms, dryness resolved in 13/18 eyes (72.2%), discomfort resolved in 8/16 eyes (50%), burning/stinging resolved in 14/16 eyes (87.5%), itching resolved in 6/8 eyes (75%), foreign body sensation resolved in 4/4 eyes (100%), photophobia resolved in 2/4 eyes (50%), pain resolved in 1/1 eyes (100%), and visual disturbances/blurred vision resolved in 11/15 eyes (73.3%). Symptomatic improvement was observed in 24 eyes (92.3%). There were no complications aside from two cases that noted irritation with treatment (both of which had co-existing thyroid disease and meibomian gland dysfunction) and one case of irritation on the outer lid due to the adhesive tape.

A total of 20 eyes returned for follow-up at a mean of 16.0 ± 2.8 weeks (median: 16.0, range: 11.9–23.1). Mean corneal staining score significantly improved to 1.55 ± 1.13 (p=0.014), and trace (n=3) or complete resolution (n=2) of corneal staining was noted in 5/20 eyes (25.0%). A total of 12 eyes (60.0%) had improved staining (mean change: 1.41 ± 0.70), 3 eyes (15.0%) had no change, and 5 eyes (25.5%) had slight worsening (mean change: −0.60 ± 0.20). When controlling for baseline corneal staining score, the only variable that was significantly correlated with corneal staining score at last follow-up was concomitant use of perfluorohexyloctane (r=0.623, p=0.004); those taking perfluorohexyloctane had significantly worse corneal staining scores at last follow-up compared to naïve eyes (2.36 ± 1.25 vs 1.12 ± 0.82, p=0.03). LogMAR VA was 0.23 ± 0.19 (p=0.84). Corneal sensitivity improved in 2 of 5 eyes (40%) with pre-existing reduced corneal sensitivity and 2 of 3 eyes (66.6%) with NK diagnosis. Symptomatic improvement was noted in 65.0% (13/20) of eyes. When assessing eyes that presented with symptoms at baseline, symptomatic resolution was noted in 3/11 eyes (27.3%) with pre-existing dryness, 3/11 eyes (27.3%) with discomfort, 7/11 eyes (63.6%) with burning/stinging, 5/7 eyes (71.4%) with itching, 3/3 eyes (100%) with foreign body sensation, 0/2 eyes (0%) with photophobia, and 5/11 eyes (45.5%) with visual disturbances/blurred vision. No complications were noted at last follow-up visit.

## Discussion

CAM has long been used in ophthalmology for the treatment of severe corneal diseases as well as ocular surface reconstruction.[14–16] Nonetheless, its regenerative properties make it a valuable treatment option for less severe OSDs, particularly those which have an underlying inflammatory component that contributes to disease progression. AM has been shown to contain potent anti-inflammatory properties that act through a multi-modal approach by promoting apoptosis of activated neutrophils and macrophages,[17–20] polarization of M1 macrophages to the M2 phenotype,[18,20] and phagocytosis of apoptotic neutrophils.[18,20] These immunomodulating properties also support epithelial adhesion and differentiation to promote corneal wound healing.[21,22] AM has also been shown to promote corneal nerve regeneration in patients with OSD,[9] which is particularly important in patients with reduced corneal sensitivity and nerve density due to NK or severe DED. This mechanism may be due in part to the abundance of nerve growth factor (NGF) within the AM, which is known to support the underlying corneal nerves[23] that ultimately elicit protective reflexes in response to corneal injury and support the corneal epithelium.[24] As a result of the aforementioned properties, CAM has been increasingly used over the last decade to treat corneal epithelial damage secondary to DED, NK, and SPK of various etiologies.[8] While self-retained CAM in the form of Prokera has been shown to significantly reduce signs and symptoms of DED,[9,10,25–27] this is the first study, to our knowledge, to assess the use of shelf-stable, ringless CAM in patients with OSD including NK, SPK, and DED.

In this study, we found that a single two-to-three-day treatment with shelf-stable CAM significantly improved signs and symptoms of OSD as early as one-week post-treatment (median: 3 days), with a lasting benefit observed up to four months (median: 16 weeks). Nearly 65% of eyes demonstrated a lasting benefit, with symptomatic improvement observed in 65% of eyes and improvement in corneal staining noted in 60% of eyes at last follow-up. Furthermore, all patients tolerated the treatment, and no premature removal was required despite two complaints of mild irritation. While no other studies have evaluated the use shelf-stable CAM for OSD, our results are similar to a previous study that assessed the clinical benefit of Prokera following two days of treatment in patients with moderate-to-severe OSD.[10] In that study, signs and symptoms improved as early as 1-week post-treatment, with a significant benefit observed up to 3 months. Specifically, corneal staining scores significantly improved from 3.1 ± 0.6 at baseline to 1.1 ± 0.3 at 1 week and 1.1 ± 0.3 at 3 months, which was accompanied by significant improvements in ocular discomfort, visual symptoms, and

DEWS severity scores. While the eyes in this study had less severe corneal staining scores at baseline indicative of mild-to-moderate OSD, corneal staining scores similarly improved to 1.00 ± 0.91 after a median of 3 days and 1.55 ± 1.13 at 16 weeks.

One clear advantage of shelf-stable CAM is its short treatment duration. In our study, we found that treatment with CAM resulted in rapid repair of ocular surface damage after 3.9 ± 2.9 days, as evidenced by corneal staining improvement in 84.6% of eyes (mean change: 1.59 ± 0.77), and absent or trace corneal staining in nearly 50% of eyes. While a number of other treatments have been shown to improve corneal surface integrity, many of these are drop therapies that require four to twelve weeks of consistent treatment to obtain a clinical benefit.[28–31] Furthermore, many of these treatments do not directly address the corneal nerves, which are often compromised in patients with OSD[32] yet play a fundamental role in the maintenance of the corneal epithelium.[33–36] For example, while lifitegrast has been shown to improve corneal staining and alleviate symptoms including ocular dryness after three months of continuous use, it does not significantly improve corneal sensitivity.[30,31] In the present study, we found that corneal sensitivity improved in 40% of eyes with pre-existing reduced corneal sensitivity, which is consistent with other randomized controlled trials that have found that treatment with CAM can significantly improve both corneal nerve density and corneal sensitivity at 3 months.[9]

Interestingly, we found that the only factor correlated with corneal staining score at first follow-up visit was the use of concomitant artificial tears (r=−.57, p=0.002), with eyes that used artificial tears demonstrating significantly lower corneal staining scores (0.57 ± 0.53 vs 1.59 ± 1.00, p=0.008). This highlights the importance of maintaining an adequate tear film to ensure the CAM tissue as well as the carrier stay hydrated while on the ocular surface to maximize the clinical benefit. Furthermore, we found that concomitant use of perfluorohexyloctane was significantly correlated with corneal staining scores at last follow-up, with eyes using perfluorohexyloctane demonstrating significantly worse corneal staining compared to naïve eyes (2.36 ± 1.25 vs 1.12 ± 0.82, p=0.03). Perfluorohexyloctane ophthalmic solution is an FDA-approved treatment that directly targets tear evaporation in patients with signs and symptoms of DED. Perfluorohexyloctane, a semifluorinated alkane, is non-aqueous and practically immiscible with water; thus, the solution forms a monolayer at the air–liquid interface of the tear film to reduce tear evaporation.[37] Based off the results of this study, it is possible that this monolayer may potentially inhibit the key components in AM (eg, growth factors and cytokines) that are water soluble from reaching the ocular surface and ultimately hinder treatment success. Further studies are warranted to confirm these findings and elucidate how perfluorohexyloctane may interfere with CAM treatment.

This retrospective study has several limitations owing to its design. There is potential bias due to reliance on pre-existing data and challenges in controlling for confounding variables. Nevertheless, a thorough examination was done through the medical records and comorbidities, surgical history, diagnosis duration, concomitant medications as well as prior therapies were assessed in this analysis. Furthermore, the time to last follow-up varied between patients making it difficult to ascertain the durability of treatment. To circumvent any potential bias, only patients that had at least 3 months of follow-up data were analyzed at last follow-up visit. Lastly, some patients had adjunctive treatment therapies during this study, which may have confounded the study results as mentioned above. Additional prospective studies are warranted to confirm duration of treatment benefit. Ultimately, this preliminary data suggests that shelf-stable, sutureless CAM in conjunction with a collagen shield or bandage contact lens may alleviate both signs and symptoms of OSD within one week, with a lasting benefit of up to four months.

## Conclusion

This preliminary retrospective data suggests that adjunctive shelf-stable CAM, corneal shield, and partial tape tarsorrhaphy was associated with improvement in corneal staining scores and symptoms in a majority of treated eyes with recalcitrant superficial punctate keratitis at both early (~4 days) and longer-term (~4 months) follow-up visits. Variability in the degree of improvement was among some patients, particularly based on concomitant therapies (eg, artificial tears and perfluorohexyloctane). Further investigation in larger studies are warranted to confirm these observations.

## Disclosure

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