

## MANAGEMENT OF GLAUCOMA MEDICATION INDUCED DRY EYE DISEASE WITH SELF-RETAINED CRYOPRESERVED AMNIOTIC MEMBRANE

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### ABSTRACT

#### Background

Approximately half of glaucoma patients have dry eye disease (DED) due to anti-glaucoma medication use. Herein, we evaluated the effectiveness of self-retained cryopreserved amniotic membrane (AM) in managing glaucoma-induced DED.

#### Methods

A retrospective chart review was conducted on consecutive patients treated with self-retained cryopreserved AM (Prokera Slim, BioTissue, Miami, FL) for ocular surface disease induced by chronic use of glaucoma medication. Data collected included demographics, diagnosis, associated signs and symptoms, concomitant therapies, and benefit duration.

#### Results

Eight eyes of eight female patients (aged  $80.0 \pm 3.9$  years) developed DED from chronic use ( $8.4 \pm 2.3$  years) of glaucoma medication. DED was refractory despite use of conventional therapies, including topical cyclosporine (n=7), gels (n=5), artificial tears (n=5), and lifitegrast (n=2). However, after treatment with self-retained cryopreserved AM, SPK grade significantly improved from  $3.25 \pm 0.7$  to  $0.38 \pm 0.5$  (p=0.01). Furthermore, visual acuity (VA) improved in all patients by an average of  $1.4 \pm 0.5$  lines (range: 1-2), with a significant improvement in LogMAR VA observed post-treatment (logMAR .28 to .16, p=0.01). This was accompanied by decreased pain (n=5), decreased foreign body sensation (n=5), and improved comfort (n=2) that lasted an average duration of  $5.3 \pm 1.0$  months.

#### Conclusion

This retrospective study suggests that a single placement of self-retained cryopreserved AM can restore corneal surface health with a lasting benefit in patients with glaucoma-induced DED who are refractory to conventional therapy directly or indirectly by promoting blinking and tearing reflexes.

*Keywords:* Amniotic Tissue, Dry Eye, Glaucoma, Ocular Surface

## INTRODUCTION

Ocular surface disease is prevalent among patients who are medically treated for glaucoma, with 40–60% of glaucoma patients affected by dry eye disease (DED).<sup>1</sup> While this is partly because both diseases increase in prevalence with age, the use of glaucoma medications has been shown to have deleterious effects on the ocular surface such as reducing corneal sensitivity, tear film stability, or basal secretion.<sup>2,3</sup> Unfortunately, patients who use more anti-glaucomatous medication suffer from worse DED, with severity directly related to elevated intraocular pressure.<sup>4</sup> This causes deteriorated quality of life, discomfort, and visual changes in these patients, resulting in decreased treatment adherence and, ultimately, visual impairment.<sup>5</sup>

Traditional therapies for DED secondary to glaucoma medication include artificial tears, omega 3, cyclosporine A, or lifitegrast eye drops. However, these treatment options may fail to provide proper relief for severe forms of dry eye, requiring alternative treatments. One such treatment includes sutureless (self-retained) cryopreserved amniotic membrane (AM), which has been regarded as the standard for treating ocular surface disease in the United States. When used to treat ocular surface damage, this treatment modality has provided symptomatic relief in many patients with moderate to severe dry eye that is refractory to traditional treatment.<sup>6-10</sup> Nonetheless, no reports have been published regarding its utility in managing DED caused by chronic use of glaucoma drops.

## METHODS

This is a retrospective, single-center, chart review of consecutive patients who presented with ocular surface damage induced by chronic use of anti-glaucomatous therapy and were subsequently treated with self-retained cryopreserved AM (Prokera Slim, BioTissue, Miami, FL). The study was conducted at a private practice (Westlake Eye Specialists, West Lake Hills, TX) following

the tenets of the Declaration of Helsinki and was exempted under 45 CFR §46.101(b)(4) by the Sterling Institutional Review Board. In addition, appropriate measures were undertaken to protect the confidentiality of study participants.

Patients were included in the study if they were 18 years or older, had been diagnosed with primary open-angle glaucoma, presented with ocular surface disease induced by chronic use (>3 months) of glaucoma medication, and were subsequently treated with self-retained cryopreserved AM. The diagnosis of DED was based primarily on clinical findings, including positive corneal fluorescein staining, positive Schirmer test I (< 10 mm wetting after 5 minutes), and symptoms (dryness, irritation, foreign body sensation). Data collection was limited to information existing in the electronic medical records between January 2015 and May 2019. It included patient demographics (age, gender, ethnicity), relevant medical history, prior dry eye treatments, duration and type of anti-glaucomatous therapy, visual acuity (VA), corneal staining, symptoms (discomfort, foreign body sensation, pain), concomitant therapies, and complications.

The cryopreserved AM was thawed at room temperature for several minutes and rinsed with saline before insertion with topical anesthesia (0.5% proparacaine hydrochloride eye drops). While holding the upper eyelid, the device was placed into the superior fornix while the patient looked down and slid under the lower eyelid. After ensuring proper centration, tape-tarsorrhaphy was done over the lid crease to maintain centration and minimize discomfort. Patients returned to the office after ~5 days for removal of the device, and patients resumed all anti-glaucoma and other DED therapies. Slit-lamp examination with fluorescein staining was performed at baseline and follow-up, which ranged from 4 to 6 months.

All statistical analyses were performed using SPSS Software version 20.0 (IBM; Armonk, NY, USA). Continuous outcomes were reported as mean ± standard deviation (range), and categorical data are reported as frequency and percentage. In addition,

ordinal variables, including SPK grade and VA were compared between timepoints using the Wilcoxon Signed Rank test for non-parametric data. A *P* value less than .05 was considered statistically significant. TissueTech awarded an investigator-initiated grant for this project.

## RESULTS

A total of 8 eyes (2 OD, 6 OS) of 8 patients met the eligibility criteria and were included for analysis. All patients were female, and the average age at treatment was  $80.0 \pm 3.9$  years. As summarized in Table 1, these patients developed DED after chronic use ( $8.4 \pm 2.3$  years) of glaucoma medication and remained symptomatic despite the use of conventional DED therapies for 2 to 3 years including topical cyclosporine (88%), gels (63%), artificial tears (63%), and lifitegrast ophthalmic solution (25%). The anti-glaucoma medications used by the patients at the time of treatment included prostaglandin analogues in 4 patients (50%), fixed  $\alpha$ -agonist/ $\beta$ -blocker combinations in 2 patients (25%), and  $\beta$ -blockers in 1 patient (13%). One patient (13%) took both a prostaglandin analog and a fixed  $\alpha$ -agonist/ $\beta$ -blocker combination. The average frequency of anti-glaucoma

medication use (drops per day) was  $1.9 \pm 0.8$  (range: 1-3).

At baseline visit, chief complaints included foreign body sensation (100%), ocular pain (75%), and blurred vision (25%). Slit-lamp examination revealed signs of DED in all 8 patients as demonstrated by positive fluorescein corneal staining (Figure 1); the average SPK score at baseline was  $3.25 \pm 0.7$  (range: 2-4). The average intraocular pressure (IOP) was  $14.3 \pm 3.3$  mmHg.

Treatment outcomes are presented in Table 2. Following placement of self-retained cryopreserved AM for 5 days, SPK severity significantly improved to  $0.38 \pm 0.5$  at a median of 6 months ( $p=0.01$ ). This was accompanied by marked symptomatic improvement in 88% (7/8) of patients, with complete resolution of symptoms noted in 5 patients (63%). Only one patient noted unresolved dryness following treatment. Furthermore, visual acuity (VA) improved in all patients by an average of  $1.4 \pm 0.5$  Snellen lines (range: 1-2), with a significant improvement in LogMAR VA post-treatment (logMAR .28 to .16,  $p=0.01$ ). The average benefit duration was  $5.3 \pm 1.0$  months (4-6). There were no significant changes from baseline in IOP following treatment ( $14.3 \pm 3.3$  vs.  $14.1 \pm 3.6$  mmHg, respectively;  $p=0.68$ ).

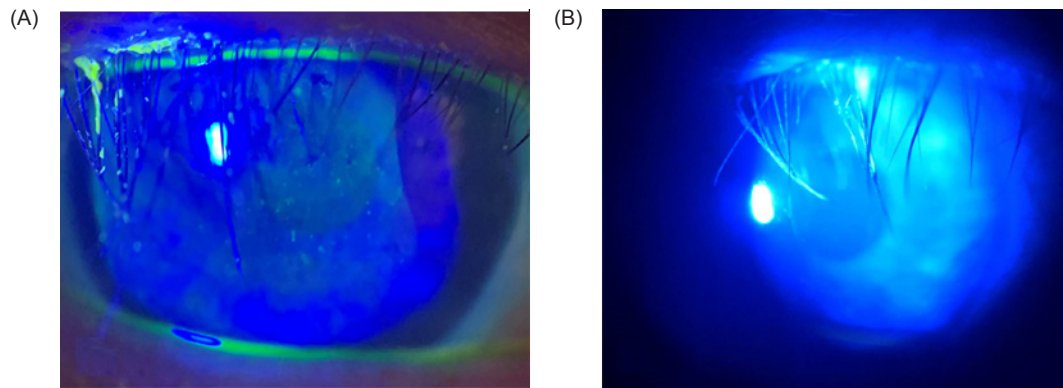
**TABLE 1.** Patient Characteristics.

Pt	Age (Years)	Sex	Eye (R/L)	Duration of POAG	Glaucoma Drops <sup>a</sup>	Number of Drops/Day	Prior DED Treatments
1	77	F	L	>10 years	prostaglandin	1	xiidra, restasis
2	81	F	L	>10 years	prostaglandin	1	tears, gel
3	82	F	L	>10 years	combigan	3	gel, restasis
4	88	F	R	>10 years	prostaglandin	1	restasis
5	76	F	L	5 years	combigan	2	tears, gel, restasis
6	77	F	L	7 years	prostaglandin	2	tears, restasis
7	79	F	L	>5 years	$\beta$ -blocker	2	tears, gel, xiidra, restasis
8	80	F	R	>10 years	Prostaglandin & combigan	3	tears, gel, restasis

<sup>a</sup>Combigan contains both a  $\beta$ -blocker and  $\alpha$ -agonist

DED = dry eye disease; POAG = primary open-angle glaucoma; Pt = patient.

**FIG. 1** Representative Case. The patient presented with moderate dry eye disease caused by chronic usage of anti-glaucoma medication demonstrated by positive fluorescein staining (A). After treatment with amniotic membrane, the ocular surface healed completely within 4 days (B) with a clear cornea that remained stable for 6 months.



**TABLE 2.** Treatment Outcomes.

Pt	Symptoms		IOP (mmHg)		VA		SPK		Duration of Effect (mos)
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	
1	FBS, Pain	None	16	17	20/80	20/60	2	0	6
2	FBS, Pain	None	19	19	20/25	20/20	3	0	6
3	FBS, Pain	dryness	9	9	20/30	20/25	3	0	4
4	FBS, BV	improved	16	14	20/60	20/40	4	1	6
5	FBS, BV	improved	15	15	20/25	20/20	4	0	6
6	FBS, Pain	None	12	10	20/40	20/25	3	1	4
7	FBS, Pain	None	11	12	20/30	20/25	4	1	4
8	FBS, Pain	None	16	17	20/40	20/30	3	0	6

*BV = blurred vision; FBS = foreign body sensation; IOP = intraocular pressure; Pt = patient; SPK = superficial punctate keratitis; VA = visual acuity.*

No complications or adverse events attributed to self-retained AM were observed.

### DISCUSSION

DED is prevalent among medically treated patients with glaucoma, primarily stemming from the cytotoxic preservatives commonly found in glaucoma medications, such as benzalkonium chloride (BAC).<sup>11</sup> Topical administration of BAC breaks down the corneal epithelium and decreases the

goblet cell density, adversely affecting the tear film stability, tear osmolarity, conjunctival hyperemia, and eyelid margins.<sup>12-14</sup> In this study, all 8 patients presented with recurrent signs and symptoms of DED despite the use of conventional therapies for 2 to 3 years. Nevertheless, using self-retained cryopreserved AM as an alternative DED treatment improved both signs and symptoms of DED with a lasting benefit of at least  $5.3 \pm 1.0$  months. Such clinical benefits are consistent with previous studies in which self-retained cryopreserved AM was

shown to improve DED with or without an immune-mediated mechanism for as long as 3 to 6 months in patients who are refractory to conventional and systemic immunotherapies.<sup>8,9,15</sup>

While conventional treatments such as artificial tears and gels tend to be palliative by providing lubrication and inhibiting tear evaporation, AM is known to exhibit anti-inflammatory and anti-scarring properties.<sup>16</sup> Even though some DED treatments target inflammation, they generally do so through a single mode of action. For example, lifitegrast, a commonly used treatment for DED, inhibits T-cell-mediated inflammation by blocking the binding of LFA-1 and ICAM-1.<sup>17</sup> AM, on the other hand, mitigates the inflammatory response through a multi-modal approach that extends to both the innate and adaptive immune responses.<sup>18-22</sup> This is achieved by promoting apoptosis of LPS/IFN- $\gamma$ -activated neutrophils and macrophages,<sup>18-21</sup> promoting polarization of M1 macrophages to the M2 phenotype,<sup>19,21</sup> promoting phagocytosis of apoptotic neutrophils,<sup>19,21</sup> and suppressing macrophage infiltration<sup>19,21</sup> as well as CD4+ T cell activation.<sup>19,22</sup>

In addition, the anti-inflammatory properties of AM support a healthy environment for the adhesion, growth, and differentiation of ocular surface cells. This is supported by studies in which AM has been shown to promote corneal epithelialization<sup>23</sup> and used as a substrate to preserve and expand limbal epithelial stem cells<sup>24,25</sup> as both conjunctival<sup>26</sup> and corneal<sup>27</sup> epithelial cells. Additionally, AM has been shown to promote corneal nerve regeneration in patients with the ocular surface disease, which plays a vital role in epithelial stem cell proliferation and corneal healing directly or indirectly by promoting blinking and tearing reflexes.<sup>28-31</sup> Collectively, these actions may explain the lasting benefit observed with complimentary alternative therapy despite failing other conservative therapies.

## CONCLUSION

This retrospective study suggests that a single placement of self-retained cryopreserved AM can

restore corneal surface health with a lasting benefit in patients with glaucoma-medication-induced DED who are refractory to conventional therapy directly or indirectly by promoting blinking and tearing reflexes.

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