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CASE REPORT

Demodex Blepharitis Treated with a Novel Dilute Povidone-Iodine and DMSO System: A Case Report

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ABSTRACT

Introduction: Povidone-iodine aqueous solution is an antiseptic commonly used in ophthalmology for treatment of the ocular surface. Dimethylsulfoxide (DMSO) is a well-known skin penetration enhancer that is scarcely utilized in ophthalmic drug formulations. We describe here a low-dose formulation of 0.25% PVP-I in a gel containing DMSO for the treatment of *Demodex* blepharitis.

Case Report: A 95-year-old female presented with chronic blepharitis involving both the anterior and posterior eyelid margins. The anterior eyelid margins demonstrated pathognomonic features consistent with *Demodex* infection, and this diagnosis was confirmed with microscopy. Previous traditional therapies had been ineffective at controlling her signs and symptoms.

Conclusion: The topical PVP-I/DMSO system was effective at treating the signs and symptoms of *Demodex* blepharitis. Further investigation of the novel agent is warranted.

Keywords: Blepharitis; *Demodex*; Infection; Inflammation; Ocular surface

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INTRODUCTION

Demodex is a well-recognized but often overlooked cause of chronic blepharitis and is implicated in ocular rosacea [1–7]. It is described as a translucent, eight-legged arachnid, and is the most common ectoparasite found on the human skin. Although prevalent in asymptomatic patients, rates of infestation with *Demodex* increase with age, nearing 100% by 70 years old [8]. Infection in humans is brought about by two distinct species, *Demodex folliculorum* and *Demodex brevis*. The former is typically found in lash follicles and manifests as anterior blepharitis, while the latter—which is smaller in size—more commonly infects the sebaceous glands, causing posterior blepharitis, meibomian gland disease, and keratoconjunctivitis. Besides the identifiable signs of

demodicosis, it has been reported that *Demodex*-infested patients may experience disturbing ocular surface symptoms which can be enumerated by ocular surface disease index scoring [9]. Both species of mite are capable of inducing inflammation in a variety of direct ways, including destruction of epithelial cells, claw-related trauma, and mechanical obstruction of glands [10]. Indirectly, *Demodex* spp. may serve as a vector transporting bacteria to deep eyelid structures and a stimulant to the host immune system. Also, reaction to the chitin exoskeleton has been implicated in granuloma and chronic chalazia formation [11, 12]. Successful treatment of *Demodex* mites has reportedly been achieved topically with tea tree oil and systemically with ivermectin or metronidazole [13–16].

Povidone-iodine (PVP-I) is a potent antiseptic that is commonly utilized in ophthalmology for ocular surface pretreatment prior to invasive surgical procedures [17–19]. It is lesser known, however, that PVP-I has historic utility in the treatment of camelid demodicosis [20]. We previously reported that a dilute PVP-I and DMSO system was useful in the treatment of rosacea blepharoconjunctivitis [21]. We report here the use of a dilute 0.25% povidone-iodine gel in a DMSO solvent gel for the treatment of a case of *Demodex* blepharitis.

CASE REPORT

Informed consent was obtained from the patient prior to the publication of this case report. A 95-year-old pseudophakic female presented to our clinic complaining of a long-standing history of ocular pruritus, dry eye, irritation, and eyelid crusting, for which she used only artificial tears and lid compresses without improvement. Treatment with tea tree oil or steroid/antibiotic combination medicines was not attempted.

Slit lamp biomicroscopic examination revealed mild bilateral anterior eyelid erythema and multiple cylindrical collarettes found at the base of the upper and lower lid eyelashes (Fig. 1a). There was no lash breakage, madarosis, poliosis, or misdirection. Inspection of the posterior eyelid margins revealed mild meibomian inspissation with capping. Secretions were slightly thickened, but not turbid. There were no mucocutaneous or marginal telangiectasias. Conjunctival examination showed mild, diffuse injection, and corneal examination was positive for scattered inferior punctate corneal erosions and a decreased tear break-up time. A diagnosis of *Demodex* blepharitis was made. To confirm the diagnosis, epilation of the affected eyelashes was performed and examined with 25× microscopy according to published protocols [22]. Visual confirmation of *Demodex* was achieved.

The patient was then prescribed a proprietary formulation of a topical gel consisting of 0.25% PVP-I in a dimethylsulfoxide (DMSO) vehicle prepared by a licensed compounding pharmacy. The treatment was administered twice daily and administered by rubbing the gel with the finger directly onto the lash line while the eye was closed. The instructions were specific: to keep the eye closed and apply the drug to the lash surface from the skin side. At the first follow-up visit, one week later, there were remarkable improvements in both patient signs and symptoms. Most prominently, the seven foci of cylindrical collarettes of the right eye and five on the left eye were no longer present (Fig. 1b). There was one remaining cylindrical dandruff focus on the left lower eyelid. A few punctate corneal erosions and a decreased TBUT remained, but the patient reported a remarkable improvement in ocular itching and irritation. At one month, the changes to the anterior eyelid were preserved, the corneal punctate erosions were no longer present, and the posterior eyelid meibum was less viscous. The patient endorsed facile utilization of the medicine with clear application instructions, and there were no reported adverse events.

DISCUSSION

It is understood that *Demodex* infestation plays an etiologic role in chronic blepharitis. Although the scope of blepharitis includes anterior, posterior, and mixed phenotypes, only the presence of cylindrical dandruff is considered pathognomonic for *Demodex* infestation

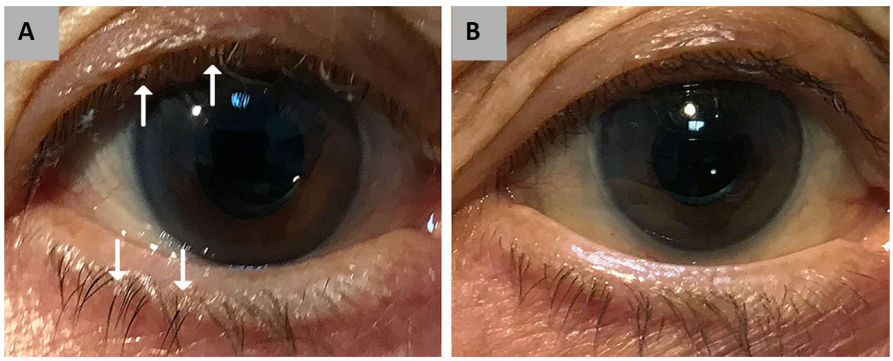

Fig. 1a–b Images of the patient with *Demodex* blepharitis treated with dilute PVP-I/DMSO. Note the cylindrical collarettes at the base of the lashes prior to treatment (**a**), and the absence of findings 1 week later (**b**)

[23]. Other ocular manifestations of *Demodex* may include keratitis, marginal infiltrates, conjunctivitis, and blepharoconjunctivitis. *Demodex* is also isolated successfully from normal human subjects, and therefore a commensal role for the mite is plausible. The evidence supporting its importance in maintaining ocular ecology revolves around the ability of *Demodex* to control bacterial populations, impose its own bacterial microflora, and outcompete other mites [24]. The current preferred treatment agent for infection is tea tree oil or its active component, terpinen-4-ol. Both have demonstrated efficacy as a demodicidal agent in vivo and in vitro [13, 14, 25]. While these agents are useful, reports of local hypersensitivity reactions and persistent mite survival do exist [14, 26]. Other traditional mite therapies designed to trap or suffocate *Demodex* have been shown to be ineffective, perhaps due to the minimal aerobic requirements of the arachnid or the robust nature of its exoskeleton. In one report, *Demodex* was found to be resistant to both 75% alcohol and 10% PVP-I [14].

Our current understanding of *Demodex* and its relation to the human skin is evolving. *Demodex* has been implicated in not only chronic blepharitis but also other dermatological inflammatory conditions, including acne and rosacea. Patients with rosacea have been shown to have a higher density of *Demodex* infestation compared to controls [7, 27, 28]. Although there is no exact relationship of symptoms or manifestations of disease with the *Demodex* population, it is thought that factors such as age, genetics, immune status, and sebum content may play a role in disease expression. For instance, in those who harbor *Demodex* but show little inflammation, the deep, ensconced location of the mite within the eyelid may create a safe harbor from host innate immunity. An eventual inciting event, activating a delayed hypersensitivity cascade, may facilitate the development of inflammatory skin conditions such as rosacea. There is also a relationship between rosacea and the presence of *Demodex* mites carrying the bacteria *Bacillus oleronius*, a Gram-negative, nonmotile endospore-forming rod [29]. Studies have found that multiple antigenic proteins produced by the bacteria are particularly immunogenic and proinflammatory [28, 30]. Finally, *Demodex* may harbor other pathogenic bacteria such as *Streptococcus* and *Staphylococcus* spp., whose superantigens have also been implicated in rosacea [31].

We have reported the first successful treatment of mixed blepharitis secondary to *Demodex* with a dilute PVP-I/DMSO gel system. Similar success with a dilute PVP-I/DMSO agent in a case of rosacea blepharoconjunctivitis has been reported [21]. This is not surprising given the potential overlap between both conditions. The result is surprising given that more concentrated 10% PVP-I solutions reportedly failed to demonstrably eradicate *Demodex* during in vitro studies. To better understand this, there are certain advantages to our treatment that must be underscored. First, dilute PVP-I concentrations have a greater capacity to deliver free molecular iodine at infection sites [32]. This increased free molecular iodine is known to be

the most antimicrobially active iodine species. We also may be seeing an anti-inflammatory effect of PVP-I, as the iodine is able to act as a reduction agent for superoxide generated in the host inflammatory cascade [33].

DMSO is a polar, aprotic solvent that has been employed as an inactive ingredient in several FDA-approved products. It has particular attributes that may enhance the efficacy of dilute PVP-I. Importantly, it is a skin penetration enhancer and exerts a concentration-dependent effect on cellular membranes. Modular dynamics simulations have shown that DMSO can partition the lipid bilayer, changing membrane fluidics, and at higher concentrations it can induce hydrophilic and hydrophobic water pores [34]. This pore formation is likely the means of enhancing the penetration of the dilute PVP-I.

In terms of potential mechanisms of action that are vital to the success of this treatment, it is likely that the PVP-I/DMSO system is able to reach the deep eyelid structures including the pilosebaceous units and the tarsal meibomian glands. As we have seen, it is in and around these structures that *Demodex* mites reside, often beyond the reach of conventional treatment agents that cannot penetrate into these locations. Once it has reached the target site, the strong solvating potential of the DMSO may have an effect on the permeability of the chitin exoskeleton, enhancing PVP-I penetration and contributing to the demodicidal effect.

The report of a single successful case is of course limited by the lack of confirmatory findings in additional cases, the lack of controls, and the lack of any study design intended to allow more rigorous evaluations of the therapy. Nonetheless, given our experience with PVP-I/DMSO systems in a variety of ocular and skin indications, we think that this promising initial report warrants additional study in expanded, controlled clinical trials.

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Disclosures. Jesse S. Pelletier is a founding member and employee of Veloce BioPharma. Jesse S. Pelletier also has a pending patent related to this work. Kara Capriotti is a founding member and employee of Veloce BioPharma. Kara Capriotti also has a pending patent related to this work. Kevin S. Stewart is a founding member and consultant to Veloce BioPharma. Kevin S. Stewart also has a pending patent related to this work. Joseph A. Capriotti is a founding member and employee of Veloce BioPharma. Joseph A. Capriotti also has a pending patent related to this work.

Compliance with Ethics Guidelines. Informed consent was obtained from the patient prior to the publication of this study.

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