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Research Article

A Novel Transdermal Ophthalmic Preparation for Blepharitis in a Dilute Povidone-Iodine and Dimethyl Sulfoxide (DMSO) System: A Case Series

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Abstract

Introduction: Gel formulations of dilute povidone-iodine and dimethyl sulfoxide have been routinely employed in our practice for the treatment of blepharitis. A retrospective review of our clinical experience with this regimen was undertaken to evaluate the tolerability and efficacy of this therapy and to determine if further prospective study may be beneficial.

Methods: A retrospective chart review of all patients employing this therapy in our practice for at least 4 weeks was completed. Clinical examination findings, patient-reported symptoms and details of therapy were recorded.

Results: A total of seventeen patients were identified and all seventeen were included in this report. All 17/17 (100%) of patients demonstrated complete or partial resolution of blepharitis clinical signs and patient-reported symptoms after at least 4 - 6 weeks of treatment. None discontinued use due to intolerance. There were no reported adverse advents.

Conclusion: In this retrospective review, blepharitis patients topically treated with this dilute povidone-iodine gel have experienced both subjective and objective improvement in clinical signs and symptoms of disease. Further prospective, controlled studies of dilute topical povidone-iodine gel formulations for blepharitis may be warranted.

Keywords: *Blepharitis; Dimethyl Sulfoxide (DMSO); Dilute Povidone-Iodine*

Abbreviations

AAO: American Academy of Ophthalmology; DMSO: Dimethyl Sulfoxide; IOP: Intraocular Pressure; IPL: Intense Pulsed Light; IRB: Institutional Review Board; MRSA: Methicillin-Resistant *Staphylococcus aureus*; PVP-I: Povidone-Iodine; TNF: Tumor Necrosis Factor

Introduction

Chronic blepharitis is a complex multifactorial disease that affects both the anterior and posterior margin eyelid structures. Classifications for blepharitis were modernized in the 1980s by including staphylococcal infection, seborrhea and meibomitis in the pathogenesis of chronic lid disease [1]. More recent advancements have elucidated a better understanding of commensal ocular flora and biofilms, clarified the role of *Demodex* mites and refined the description of co-morbid conditions such as acne rosacea [2-6]. Despite this progress, many aspects of the disease are not fully understood. While the precise mechanisms responsible for blepharitis remain obscure, it can broadly be stated that both inflammatory and infectious mechanisms are involved. The sequelae secondary to blepharitis are numerous and may range from dry eye, foreign body sensation and recurrent chalazia to more severe sight-threatening manifestations such as

corneal infiltrates and eyelid cicatrization. The scope of the problem is significant as blepharitis may affect almost 50% of all patients presenting to eye care specialists [7]. Current treatments for blepharitis as outlined by the AAO Preferred Practice Patterns include warm compresses, eyelid cleansing, antibiotics (topical and/or systemic), and topical anti-inflammatory agents [8]. There is no cure for this disease, nor are there any FDA approved medical treatments; the potential for control of signs, symptoms, and sequelae hinges on disciplined patient compliance with a regular treatment regimen. This retrospective case series describes recent experience in our offices with a novel povidone-iodine (PVP-I) formulation in the treatment of chronic blepharitis.

Methods

In accordance with the Declaration of Helsinki, an IRB waiver from Sterling IRB, Atlanta, GA, (www.sterlingirb.com), IRB ID # 5689 was obtained prior to commencement of this study. The IRB chairman (or designee) determined that the study was 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. In all cases, patient informed consent was obtained for both treatment and publication of this material. A retrospective review of cases presenting to the authors' private ophthalmology clinics from April-August 2017 identified 17 patients seeking care for blepharitis who were subsequently treated with a low-dose PVP-I formulation. All patients had previously failed traditional therapy for blepharitis that included lid scrubs, artificial tears, topical antibiotics and steroids. There were 7 males and 10 females with an age range of 27 - 92 years and average age of 71 years. The blepharitic manifestations ranged in presentation from anterior only (11.8%), posterior only (23.5%) and mixed (64.7%). Each patient was prescribed a novel formulation of a topical gel comprised of 0.25% PVP-I in a dimethyl sulfoxide (DMSO) vehicle that was prepared via a licensed compounding pharmacy. Patients were instructed to rub the gel with a finger twice daily into the skin of the upper and lower eyelids at the lash line. Signs recorded at the time of the follow-up visit included lower eyelid erythema, eyelid crusting, conjunctival injection and meibomian gland secretions if possible. If patients failed to show up for appointments, attempts were made to contact the patient by mail or telephone. Any adverse events were recorded at each visit as per routine in our practice for all of our ocular surface disease patients. Patients were instructed to discontinue the formulation after their second visit and they were not followed for recurrence of their condition.

Results

All 17/17 (100%) of patients demonstrated complete or partial resolution of the blepharitis signs after 4-6 weeks of treatment (Table 1). The most commonly resolved signs in patients presenting with blepharitis were anterior eyelid erythema and conjunctival injection (Figures 1a/b and 2a/b). All 17/17 (100%) of patients reported subjective improvement or resolution of symptoms. 13/17 (76.5%) of patients reported complete resolution of symptoms. Mild irritation that included stinging, tingling or burning at the application site was experienced by 2/17 (11.8%) of patients. There were no serious adverse events.

Age	Gender	Symptoms		Blepharitis findings		Conjunctival inflammation	
		Pre Tx	1M Post Tx	Pre Tx	1M Post Tx	Pre Tx	1M Post Tx
27	Male	Itching/Burning	Resolved	Posterior Blepharitis	Improved meibum viscosity	None	None
88	Male	Foreign sensation	Resolved	Mixed Blepharitis	Improved lid erythema, scurf, meibum viscosity; resolved lid edema	2+	None
83	Female	Tearing/Burning	Resolved	Mixed Blepharitis	Improved lid erythema, scurf, meibum viscosity; resolved lid edema	1+	None
67	Female	Burning	Improved	Mixed Blepharitis	Improved eyelid eythema; resolved lid edema	1+	None
88	Male	Discharge/Itching	Resolved	Mixed Blepharitis	Improved lid erythema, scurf, meibum viscosity; resolved lid edema	2+	None
78	Female	Blurry vision	Improved	Mixed Blepharitis	Improved scurf, meibum viscosity; resolved lid edema and lid erythema	1+	None
76	Male	Blurry vision/Tearing	Resolved	Mixed Blepharitis	Resolved lid edema, lid erythema; scurf; improved meibum viscosity	1+	None
79	Male	Stinging/Burning	Resolved	Mixed Blepharitis	Resolved lid edema, lid erythema; scurf; improved meibum viscosity	1+	None
92	Male	Tearing/Burning	Improved	Mixed Blepharitis	Improved lid erythema, scurf, meibum viscosity; resolved lid edema	1+	1+
56	Female	Burning/Tearing	Resolved	Anterior Blepharitis	Resolved lid edema, lid erythema; scurf	None	None
69	Female	Tearing/Redness	Resolved	Posterior Blepharitis	Improved meibum viscosity	1+	None
73	Male	Blurry vision	Resolved	Posterior Blepharitis	Improved meibum viscosity	None	None
82	Female	Burning/Tearing	Resolved	Anterior Blepharitis	Resolved lid collarettes, edema, erythema	None	None
31	Female	Burning	Resolved	Posterior Blepharitis	Improved meibum viscosity	None	None
73	Female	Burning/Itching	Resolved	Mixed Blepharitis	Improved lid erythema, scurf, meibum viscosity; resolved lid edema	1+	None
73	Female	Tearing/Burning	Resolved	Mixed Blepharitis	Improved lid erythema, scurf; resolved lid edema	2+	None
72	Female	Stinging/Burning	Improved	Mixed Blepharitis	Improved lid erythema, scurf, edema	1+	1+

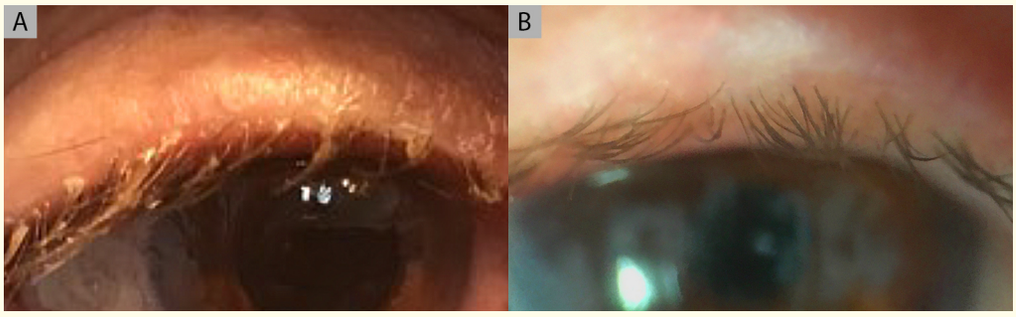

Figure 1a-b: *Images of a patient with mixed blepharitis treated with dilute PVPI/DMSO. Note the significant eyelid erythema and eyelash collarettes prior to treatment (a) and absence of these finding on upper eyelid at follow up visit (b).*

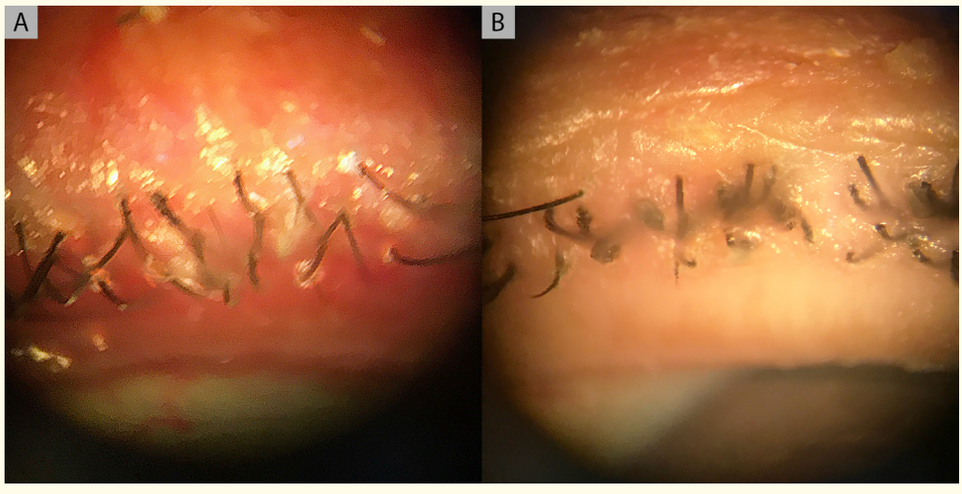

Figure 2a-b: *Images of a patient with severe mixed blepharitis anterior eyelid erythema, edema, and scurf treated with dilute PVPI/DMSO. Note the exuberant eyelid erythema, edema, scurf prior to treatment (a) and improvement of especially eyelid edema and erythema at follow up visit (b).*

Discussion

Chronic blepharitis remains a common, often recalcitrant condition for which there is currently no cure. Compounding this dilemma is the fact that traditional methods of treatment are often found to be inadequate and frustrating for patients. Much of the current research has focused on the infectious and inflammatory components of blepharitis by utilizing medicines containing an antibiotic and anti-inflammatory agent alone or in combination. Of the more recent clinical trials, there have been several involving the use of azithromycin in the form of Azasite® ophthalmic solution in a polycarbophil vehicle for the treatment of blepharitis [9-11]. The largest of these trials enrolled 122 patients and concluded that tobramycin/dexamethasone provided faster anti-inflammatory relief than azithromycin [12]. In another study published in 2012, 308 patients with blepharoconjunctivitis were randomized to receive either loteprednol/tobramycin or tobramycin/dexamethasone [13]. This study demonstrated non-inferiority of the former and illuminated the risk of IOP rise in the latter. In parallel, newer non-traditional methods of treatment have been introduced such as Intense Pulse Light Therapy (IPL), Lipiflow®, BlephEx® and various neutraceuticals. There are currently no robust clinical trials performed to date to substantiate their claims of efficacy. Despite this body of literature and a better understanding of the disease, achieving a consensus on best treatment remains challenging. Among the many reasons cited for this include the heterogeneous nature of the disease, variability of study design and disagreement among outcome measures [14].

We believe dilute PVP-I to be a potentially useful addition to the blepharitis armamentarium for a variety of reasons. PVP-I achieves anti-sepsis by interacting with target cells in a variety of ways including poisoning the electron transport system, inhibiting cellular respiration and destabilizing cell membranes [15]. In the presence of an iodophor, such as polyvinylpyrrolidone, much of the iodine is carried in a complexed or bound triiodide form. This renders the concentration of free iodine low, further serving to decrease toxicity and irritation of the preparation that are experienced at higher concentrations of PVP-I. Although there are many complex interactions of iodine in aqueous solutions, only molecular iodine (I_2), hypoiodous acid (HOI), and iodide ion (I-) are responsible for the antibacterial effect. Lower doses of PVP-I are paradoxically more effective as antiseptics, presumably due to increased liberation of free molecular iodine by lower solution concentrations of PVP-I [16]. A more dilute solution unwraps the polymeric aggregate structure that contains complexed iodine, allowing more access to the bulk solution and in turn more liberation of free molecular iodine [17].

DMSO is a polar, aprotic solvating entity that has been utilized as an inactive ingredient for a variety of topical medicines. There is abundant anecdotal literature regarding the utility and safety of DMSO in the eye, however, there has never been any systematic examination of DMSO-containing agents in the setting of ophthalmic clinical trials.

This low-dose PVP-I formulation was successful in all the patients who received it in our practice over the period of this study (April-August 2017). The study retrospectively examined data of patients who demonstrated all forms of blepharitis including anterior, posterior and mixed. We believe that part of the potency of this therapy applied to the eyelid skin is derived from the penetration enhancing qualities of the solvent increasing the ability of a normally superficial acting PVP-I to penetrate into deeper tissue structures where it is able to act in similar fashion to an ideal single agent. We believe that penetration into the deep eyelid may help alleviate chronic, ensconced bacterial populations that reside in the follicles, meibum, and sebaceous glands. Another contribution may come from the infrequently discussed anti-inflammatory action of PVP-I, which is capable of acting as a reducing agent for superoxide and inhibiting metalloproteinases along with other potent mediators of inflammation such as TNF alpha [18-20]. Finally, we maintain that addressing the role biofilms play in the genesis of blepharitis is vital to successful outcomes. Biofilms serve as a protective and nutritious extracellular matrix allowing bacterial populations to expand and even thrive. Pertinent studies have illuminated the crucial role PVP-I plays in disrupting these extracellular matrices, especially those related to MRSA and *C. albicans* [21]. It has been hypothesized that this function is critical in disrupting the downstream pathogenic bacterial cycle, which includes quorum sensing, gene activation, and eventual expression of virulence factors [22].

This series is, to our knowledge, the first published case series utilizing a transdermal approach to treat blepharitis with a PVP-I based formula. Such an approach is favorable when addressing eyelid inflammation because it avoids unwanted side effects that may be imparted by some topical drops. Moreover, this therapy avoids larger controversial issues such as the development of antimicrobial resistance and the untoward effects of steroids on the ocular surface. This retrospective case series is limited by the lack of controls and study design, which would permit further rigorous study. Moreover, ocular surface disease questionnaires, blepharitis scoring scales and high-resolution anterior segment photography were not used. Chronic blepharitis is a lid disease where the primary pathology resides in the lid but the most common clinical signs and symptoms occur on the ocular surface. We believe a single pharmaceutical agent that targets the lid pathology in order to resolve the ocular surface signs and symptoms could represent a new approach to the very common disease. Further study of this novel low-dose PVP-I agent is warranted.

Declarations

An IRB waiver was obtained prior to the commencement of this manuscript. Informed consent both to treat and publish was obtained from all the patients involved in this retrospective work. All data generated or analyzed during this study are included in this published article. All authors endorse financial competing interests. All authors except KS are employees of Veloce BioPharma and receive salary, own stock and patents related to this work. KS owns stock of Veloce BioPharma. There are no non-financial competing interests. All authors listed in this manuscript made substantial contributions that are consistent with those published by the ICJME.

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