Topical Ocular Povidone-Iodine as an Adjunctive Preventative Practice in the Era of COVID-19

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Abstract: Ophthalmologists and patients have an inherent increased risk for transmission of SARS-CoV-2. The human ocular surface expresses receptors and enzymes facilitating transmission of SARS-CoV-2. Personal protective equipment alone provides incomplete protection. Adjunctive topical ocular, nasal, and oral antisepsis with povidone iodine bolsters personal protective equipment in prevention of provider-patient transmission of SARS-CoV-2 in ophthalmology.

Key Words: antisepsis + PPE, prevention, provider-patient transmission, SARS-CoV-2, topical ocular povidone iodine

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Submitted August 4, 2020; accepted November 8, 2020.

The authors have no funding or conflicts of interest to declare.

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 ISSN: 2162-9989
 DOI: 10.1097/APO.0000000000000353

The ongoing coronavirus disease of 2019 (COVID-19) pandemic caused by the SARS-CoV-2 virus has altered societal behaviors and fundamentally changed the delivery of healthcare. From the first cases recognized in late December 2019 by physicians in China, it has rapidly spread across the globe. Millions of people worldwide have documented infection with SARS-CoV-2; millions more are suspected as undocumented cases and globally over a million people have died. The widespread distribution of this disease, in contrast with the more limited spread of the earlier severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) outbreaks, has provided many in the West an up-close look at the clinical course, transmission dynamics, and infection control measures as they evolve in a complex public health dilemma. Steps have been taken to mitigate the spread of COVID-19 through policies directed at reducing viral transmission. Although some strategies have delayed or succeeded in preventing hospitals and clinics from being overburdened, there are still lingering health concerns.

Since the beginning of the pandemic, ophthalmologists have played a pivotal role in identifying early cases of COVID-19. In the face of lethal consequences, one ophthalmologist in China, Li Wenliang, was recognized as one of the first physicians to alert others about the outbreak and encourage colleagues to take protective measures. As the SARS-CoV-2 virus becomes endemic, ophthalmologists will remain duty-driven to develop protocols that best protect healthcare personnel (HCP) and patients. The ophthalmic manifestations of COVID-19 have been described and the causative virus has been positively identified in both tears and conjunctival secretions. Once present on the ocular surface, SARS-CoV-2 may infect the cornea, conjunctiva, or potentially the lacrimal glands. Cases of conjunctivitis, keratoconjunctivitis, anterior uveitis, retinitis, and optic neuritis have all been described in ocular infections with coronaviridae. The expression of the receptors for angiotensin-converting enzyme 2 (ACE2) and identification of the transmembrane protease serine 2 that promotes viral entry on the human ocular surface are likely contributors to this specific ocular tropism.

A key concept in the potential transmission of SARS-CoV-2 from the ocular surface during ophthalmic examinations, procedures, and surgeries requires an understanding of the eye-nasopharynx-lung axis. Tears and ocular secretions drain via the lacrimal canaliculi and nasolacrimal duct with eventual passage to the nasal cavity. Through rostral movements orchestrated by ciliated nasal epithelial cells (also with ACE2 receptors) and mucociliary clearance mechanisms in the nasal cavity, secretions eventually reach the nasopharynx. Microaspirations from the nasopharynx, mostly during sleep or during episodes of regurgitation may reach the alveolar surfaces with ACE2-positive alveolar epithelial cells, type 2 and eventually the deep lung.

Emerging data underscore the prominent role played by the upper and lower respiratory tract in SARS-CoV-2 virus replication and transmission. The oropharynx and nasopharynx are clearly targeted by the virus and subject to high numbers of infective copies. A gradient of ACE2 expression exists within the respiratory tract with the greatest density of receptors expressed in the ciliated epithelial and goblet cells of the nose and waning expression in the distal alveolar and bronchiolar regions. These upper respiratory tract cells likely serve as a nidus for viral replication and eventual dissemination. Because of preferential receptor density, it is speculated that the nasal surfaces represent a dominant initial site of infection and that seeding of the deeper lung from the nose may be responsible for the heterogeneous manifestations and severity variances of COVID-19 disease. These findings serve to illuminate both the role the eye may play as a potential portal of infection and the risks associated with viral particle translocation to the pulmonary system.

Current strategies to contain viral transmission revolve around the adoption of droplet-based transmission precautions. For the ophthalmologist, this involves the donning of personal protective equipment (PPE), including a surgical mask or respirator, goggles, gowns, and gloves. It is clear, however, that despite these measures, more protection is required as nosocomial spread...
remains a significant occupational hazard. One of the hallmarks and challenges of COVID-19 transmissivity is spread by asymptomatic, presymptomatic, or postsymptomatic individuals. Despite robust infection control protocols that include daily HCP and patient assessments, it can never be fully determined if an individual may be shedding infectious virion. Moreover, the close sustained patient contact required in an ophthalmic examination in conjunction with the inability of protective masks to fully guard against viral droplet or aerosols creates a further risk of exposure. Ophthalmic care providers are able to fully protect their own eyes from exposure to SARS CoV-2 with the donning of goggles or shields, but the same strategy cannot be applied to our patients without significant degradation in the quality of the ophthalmic examination. Given the scope of these concerns and the two-way risk between HCP and patient, other strategies to discourage viral transmission should be considered.

One such strategy may involve the use of the disinfectant povidone-iodine (PVP-I) for application on the ocular surface. A related ophthalmic protocol already exists that describes the application of PVP-I to the nose and mouth in order to reduce transmissivity of SARS-CoV-2. PVP-I is an essential antiseptic that has been successfully utilized since its inception in 1955. It comprises part of the World Health Organization’s list of essential medicines. PVP-I has traditionally been used in the wound care and in the treatment of skin infections. The focus of its deployment in ophthalmology typically pertains to prophylaxis against ocular infection in the preparation of the eye prior to invasive ophthalmic procedures. Currently, PVP-I 5% and 10% solutions are routinely employed in the setting of anterior segment ocular surgery and intravitreal injections. The broad adoption by ophthalmologists across a variety of clinical and surgical settings is a testament to the versatility, efficacy, and safety of PVP-I when applied locally to ocular tissues.

There are a number of fundamental factors that contribute to the antiseptic capacity of PVP-I. These properties include rapid, broad-spectrum, microbicidal antimicrobial activity with no known resistance, antibiotic activity, and good tolerability. PVP-I works through a variety of means at the cellular level to destroy microbes. The precise sequence of these events has yet to be fully elucidated. Denaturation of proteins, oxidation of membranes, and disruption of the respiratory chain are all mechanisms implicated in microbial killing. These reactions are propagated by the oxidative effects of a halogenated species that is electrophilic in nature. In more recent literature, attention has focused on compounds or solutions that contain dilute PVP-I. In contrast to full strength solutions, these formulations represent an interesting alternative because they may be equally or more efficacious and less toxic to delicate tissues such as the eye. In iodophor chemistry, it is well described that lower concentrations of PVP-I solution paradoxically demonstrate an increased concentration of free or molecular iodine (I2). For example, a 10% solution of PVP-I contains 5 ppm of free iodine, whereas a solution of 0.1% contains 24 ppm. It is the molecular or free iodine that is mostly responsible for germicidal effect.

As a virucidal agent, PVP-I has demonstrated efficacy against many endemic and pandemic global pathogens responsible for human infections, including HIV, HSV, polio, adenovirus, coxsackievirus, influenza virus, MERS, SARS, and SARS-CoV-2. A 1997 study compared PVP-I to other antiseptics in inactivating a broad range of both enveloped and nonenveloped viruses and demonstrated PVP-I to have the broadest spectrum of antiviral activity among agents listed. The antiviral effects of PVP-I are thought to be mechanistically similar to the antibacterial activity of iodine. One well-studied feature includes the ability of PVP-I to inhibit both viral attachment and virion release of the influenza virus through interaction with hemagglutinin and neuraminidase proteins. A variety of other nonspecific mechanisms are also likely. Recent studies reported the rapid, successful activity of PVP-I oral/nasal formulations against SARS-CoV-2 with complete virus inactivation after only 15 seconds of exposure.

The safe, efficacious use of repeated topical application of PVP-I on the human ocular surface as an antiviral agent has also been described. Perhaps no single indication has been better explored than viral conjunctivitis where dilute PVP-I has been applied both as a single agent and in combination with steroid with mixed results. A prospective study performed in the Philippines examined a dilute 1.25% PVP-I solution dosed 4 times daily for acute conjunctivitis. A diagnosis of viral conjunctivitis was made if bacterial cultures were negative and certain diagnostic criteria were met. Of the 459 children enrolled, 98 received topical PVP-I for a presumed viral etiology. The authors found that the use of PVP-I was as ineffective as topical antibiotic with respect to days to cure. In another study conducted on infants during an outbreak of viral conjunctivitis in a neonatology ward, a 2.5% PVP-I solution was used to irrigate the conjunctiva of 15 infants. The authors reported that the treatment reduced symptoms, decreased pseudomembrane formation, and shortened recovery time. Finally, in another retrospective publication, topical PVP-I 0.5% was administered 3 times daily to adults suffering from viral conjunctivitis. In this manuscript, the authors concluded that the PVP-I treated group recovered more rapidly and PVP-I was safe for human use.

The safety and tolerability of topical PVP-I formulations have also been assessed. In an in vivo rabbit study conducted with various PVP-I concentrations, corneal toxicity and epithelial healing were examined. The authors found that concentrations of 0.5% or less were nonirritating when administered 6 times per day. Wound healing was, however, delayed by 1 day in the 0.5% group and considered to be similar to gentamicin in the 0.33% group. In another rabbit study, concentrations of PVP-I instilled into the conjunctival sac induced severe corneal epithelial damage at 5.0% and 2.5%, whereas concentrations at 1.0% or less were considered safe. In a recent study, 56 patients with red eyes and a positive rapid adenoviral immunoassay test were enrolled and randomized into 1 time 5% PVP-I administration and vehicle. Safety and tolerability were assessed by corneal fluorescein staining/visual acuity and participant-rated overall ocular discomfort, respectively. The authors found that ophthalmic 5% PVP-I was safe and well tolerated in the setting of a one-time treatment. Finally, in a randomized 0.6% PVP-I/0.1% dexamethasone trial for viral conjunctivitis, 66 patients were treated 4 times daily for 5 days with the study medicine. Although the study was underpowered to report on the primary endpoint, safety and tolerability were found to be satisfactory and consistent with previous clinical trials when assessed by the reporting of adverse events. It was notable that although many patients reported at least 1 ocular treatment as emergent adverse event, none were reported as severe.

Additional considerations in the utilization of topical PVP-I as an antiviral on the human ocular surface are the concerns of...
resistance, cross-resistance, and disruption of the normal ocular flora. Antiseptic resistance and cross-resistance, although rare, has been reported with biocides, chlorhexidine, and quaternary ammonium compounds.\textsuperscript{48,49} PVP-I, in contradistinction, and due to multiple, nonspecific, and overlapping mechanisms of action, has never been reported to cause resistance or cross-resistance. With respect to the influence on bacterial flora, the ophthalmic application of PVP-I results in an eventual restoration of microbial homeostasis.\textsuperscript{50}

Given the scope of the current pandemic and new, focused initiatives with respect to infection control of SARS-CoV-2, we recommend that 1 drop of PVP-I ophthalmic solution, preferably dilute, is placed on each patient’s eye prior to and after ophthalmic clinic visits, oculair procedures, and surgeries. When HCP are unable to don eye protection, we recommend that they adopt the same strategy as well. The rationale for this therapy is logical, and similar PVP-I-based protocols have already been recommended in the ophthalmic setting to protect the nose and mouth from SARS-CoV-2 infection and decrease virally transmitted particles. We believe that these actions are crucial for 3 reasons. First, it has been shown that epithelial cellular infection with the related SARS-CoV virus may take 4-24 hours to establish.\textsuperscript{51} Given the prodigious antiviral effects of PVP-I against SARS-CoV-2, there likely exists a therapeutic window where PVP-I application may disrupt an initiating infection on the ocular surface. Second, as we have indicated, the eye acts not only as a portal to the nasopharynx but also to the deeper respiratory tract. Disruption of the virus on the ocular surface may protect those who are exposed from potentially more devastating extension into the pulmonary system. Third, it is possible that despite optimized infection control protocols involving patient screening, history, body temperature, and even laboratory testing that SARS-CoV-2 is potentially actively present on a patient’s eye in the clinic setting and being shed in tears/ocular secretions. Placing a drop of PVP-I in this setting may reduce infected secretions, which are commonly transmitted to fomites such as surfaces, doorknobs, or ophthalmic equipment.

CONCLUSIONS

The pandemic with COVID-19 continues to spread in waves across the globe with surges in new cases of SARS-CoV-2 in selected regions and the resurgence of the virus in other areas after relative abatement. Ophthalmologists and ophthalmic patients have an inherent risk of transmission of SARS-CoV-2 due to the required proximity with routine oculair examinations and the exposed ocular surface. The ocular surface of both eyes represents a remarkably large surface area for potential contact. The presence of viral receptors and host enzymes that promote viral entry into cells on the expansive ocular surface area thus make the eye an efficient portal of entry. Rigorous infection control practices, including PPE with masks, while beneficial, are incompletely effective at prevention of infection. PVP-I has been demonstrated to be actively microbicidal, including viricidal against SARS-CoV-2 within 15 seconds of contact. Topical PVP-I has a long clinical record of effective and safe use in ophthalmology with good tolerability. Topical ophthalmic PVP-I application before and after clinical eye examinations, oculair procedures, and ophthalmic surgeries is a rational, safe, potentially protective adjunct to PPE and other infection control measures in an ongoing COVID-19 era. Otorhinolaryngology, dentistry, and other specialties at unique risk have current recommendations for nasal and oral antisepsis with PVP-I as well as other agents to bolster protection against SARS-CoV-2. Ophthalmologists are well advised to consider the adoption of these adjunctive, practical, protection practices of topical ocular PVP-I along with nasal and oral PVP-I application to reduce the likelihood of transmission to both provider and patient. Prospective, randomized clinical trials among HCP to further assess and define the protective role of adjunctive PVP-I versus placebo are warranted.

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