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Editorial

Is there a Universal Drug for Keratitis?

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Keratitis represents the fifth most common cause of blindness worldwide [1] and a leading cause of irreversible visual impairment [2]. No age group is immune to it [3]. In the adult population older than 40 years 3.372 million suffered from moderate or severe deterioration of vision due to corneal opacity, as was estimated in 2020 by Wang., *et al* [4]. Early recognition and prompt treatment initiation are key to sight preserving in order to achieve the best outcomes in patients with keratitis.

Infectious keratitis is commonly caused by bacteria, viruses, fungi and parasites [1]. Bacterial keratitis, as the most common one, in majority of cases is due to *Staphylococci* spp., *Pseudomonas aeruginosa* and *Streptococcus pneumonia* [5]. Herpes simplex virus (HSV) is a widely spreaded causative agent also for viral keratitis [3]. Other important causal organisms for fungal keratitis are filamentous (*Fusarium* spp., *Aspergillus* spp.) or yeast (*Candida* spp.) fungi [3]. Besides, *Acanthamoeba* spp. could cause parasitic keratitis [3] with such devastating consequences, as a corneal perforation.

Ophthalmologists face a host of multiple challenges in the management of infectious keratitis. The first challenge is a fast proper diagnosis. Despite the culture of corneal scrapings are currently recommended, its efficacy rate is fluctuating in 38 - 66% [1,6]. Besides, delayed results of antimicrobial resistance (after 48h) kept from timely initiation of etiologically-oriented treatment instead of starting empiric antimicrobial therapy [1]. Another challenge is a proper selection of highly effective therapeutic agents for each type of keratitis previously mentioned. Despite significant advancements in antibioticotherapy, resistance issue still represents a challenge.

Aforementioned highlights the urgent need for the search of accessible, universal, highly impactful, time-efficient, cost-effective therapeutic agents. A good candidate could be the povidone- iodine (PVI), taken into account time-approved usage in ophthalmology as an antiseptic agent for preoperative preparation of the eyelids, eyelashes and conjunctiva [7] and recently as a 0.6% povidone iodine eye drops in anti-VEGF intravitreal injection [8]. Povidone-Iodine is described as “an iodophor solution containing a water-soluble complex of iodine and polyvinylpyrrolidone (PVP)with broad microbicidal activity. Free iodine, slowly liberated from the polyvinylpyrrolidone iodine (PVPI) complex in solution, kills eukaryotic or prokaryotic cells through iodination of lipids and oxidation of cytoplasmic and membrane compounds” [9]. Antibacterial properties of PVI are well studied and well confirmed, including the latest findings [10-12]. Recently a special attention is paid on it’s antiviral effect [13]. Virucidal activity of PVI was evaluated in multiple laboratory studies, specifically impact on adenovirus [14-16] and confirmed in clinical studies [17-21]. Besides adenovirus, antiviral effect of PVI has been widely studied [22-36]. Multiple *in vitro* studies have documented the broadest spectrum of PVI’s antiviral activity against herpes simplex virus, influenza, hu-man cytomegalovirus, HIV, Ebola virus, mumps, rotavirus, poliovirus, coxsackievirus, rhinovirus, rubella, measles, papillomavirus, murinenorovirus. Laboratory studies have shown efficacy also against SARS-CoV [37,38]. The above sources appear to indicate there is a biological base for the antiviral effect of PVI on outer eye structures. The latest *in vitro* study conducted by Wang and Jacobs [39] revealed cysticidal effects on *Acanthamoeba* in case of keratitis.

Povidone-iodine in keratitis

First therapeutic use of povidone-iodine for corneal ulcer was documented in 1969 [40], followed by other report [41]. A lot has changed since then, however ongoing research have shown continued interest on this topic.

Recently the efficacy of 1% povidone-iodine eye drop in keratitis caused by *Streptococcus pneumoniae* and *Escherichia coli* was evaluated in experimental study [42]. The researchers concluded that this agent was effective and comparable with topical antibiotics (Chloramphenicol 0.5% eye drop or ciprofloxacin 0.3%).

Prospective, randomized clinical trial of povidone-iodine 1.25% ophthalmic solution comparing to topical antibiotics (neomycin-polymyxin B-gramicidin or ciprofloxacin 0.3%) for treatment of bacterial keratitis [43] evidenced no significant difference in 2 approaches, indicating the efficacy of povidone-iodine. Another prospective study results showed that topical 0.66% polyvinylpyrrolidone-iodine (PVP-I) is safe and effective in patients with infectious keratitis, specifically caused by gram-positive pathogens [44]. Bordin [45] presented a case of corneal ulcer of unknown etiology treated by 0.66% PVP-I and concluded that "PVP-I 0.66%, an antiseptic with broad-spectrum activity against bacteria, fungi, viruses, and protozoa, was found to be effective in treating the signs and symptoms of the ulcer until its complete closure and resolution".

For the first time 0.66% povidone iodine was successfully used [46] in case of corneal ulcer associated with chronic immune-mediated inflammatory diseases, such as rheumatoid arthritis.

Grzybowski., *et al*. [7,47] also advocate a use of povidone iodine in keratitis. Ndoye Roth., *et al*. [48] presented positive findings on monotherapy by 2.3% povidone iodine eye drop or combination with azole for fungal keratitis treatment. Ramatchandirane., *et al*. [49] reported successful management of fungal keratitis caused by multidrug-resistant *Cladosporium* species using 5% povidone-iodine.

Povidone-iodine was also successfully used in combination with antifungal and antibiotic agents for a rare case of pigmented corneal ulcer caused by *Ochroconis* fungi [50].

Cysticidal effect with promising impact of povidone-iodine on *Acanthamoeba* related keratitis was shown in multiple studies [38,51-53].

Summarizing, careful thoughtful management of keratitis is vital to successful outcomes.

Accumulating evidence have shown promising results of povidone-iodine pharmacotherapy in keratitis. However, continued development is necessary to fully utilize it's therapeutic potential.

Ongoing efforts must address the following challenges, such as the optimal concentration and dosing of the eye drops to accelerate a tolerance and bioavailability and prevent toxicity to cornea in order to improve efficiency. Recent studies on the matter have evidenced experimentally [54] and clinically [55] that a new formulation of PVI as a 0.6% povidone-iodine nanoemulsion eyedrops have a good safety, tolerability and efficacy profile.

Currently available findings suggest that povidone-iodine represents an attractive universal viable option for treating all types of keratitis opening a new therapeutic avenue.

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