



Letter to the editor: Possible role of topical povidone iodine in case of accidental ocular exposure to SARS-CoV-2

Phulen Sarma¹ · Hardeep Kaur¹ · Bikash Medhi¹ · Anusuya Bhattacharyya² 

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We read the letter by Agarwal R et al. very carefully and appreciate them for nicely addressing the issues; however, we have some concerns. The authors have expressed their concern about presence of the virus in ocular secretions; however, although the prevalence is low, the presence of SARS-CoV-2 in ocular fluid is well-established. Even some patients have showed strong positivity for the virus in ocular fluid [1]. In a study, around 31.6% of the patients showed ophthalmologic manifestations similar to conjunctivitis and 16% of the patients showed SARS-CoV-2 positivity in ocular fluid [2]. A systematic review and meta-analysis have already established this issue [3]. The low prevalence of ocular fluid positivity for SARS-CoV-2 may be due to many reasons. The timing of sample collection is very important in this regard [1]. Many authors report that viral secretion can be seen only during the early phases [1, 4]. Again, sample collection may be inadequate and ocular surface swab samples collected few exfoliated cells which had a low chance of detecting the virus [1]. Again, low sensitivity of the RT-PCR-based diagnostic kits can also contribute to the low detection rate [1].

Agarwal R et al. also mentioned their concern regarding uncertainty about the ability of the virus into the systematic circulation through that through accidental hand-eye contact. Although we do not have data regarding occurrence of

COVID-19 from accidental hand eye exposure, however there is a report of occupational ocular exposure to SARS-CoV-2 (owing to dislodged eye goggles) that led to development of COVID-19 in a nurse who used a dislodged eye goggles [5]. However, we have data from rhesus macao [6], which proves that ocular inoculation may lead to establishment of an infection. In animals with conjunctival inoculation, high concentration of SARS-CoV-2 was noted in the nasolacrimal duct (NLD). Establishment of systemic infection was noted with both the route of inoculation (intra-tracheal and conjunctival inoculation) [6].

Again, the authors have expressed their concern regarding the doubtful presence of and action of ACE2 receptor in corneal and conjunctival epithelium. We all know that both ACE2 and TMPRSS2 are required for a successful establishment of a human infection [7–9]. A study by Ma et al. 2020 raised concern against the expression of TMPRSS2 in conjunctival cells and commented that conjunctiva is less likely to be infected with the virus (data generated in mouse cornea and human primary conjunctival and pterygium cell lines) [8]. Another point to be considered is that mRNA expression level differs between in vivo state and in culture [10, 11]. In human cell lines, although ACE2 was present in the conjunctival cell lines, however, they could not locate the expression of TMPRSS2 in the conjunctival cells [8]. Another study has supported these findings [12]. However, many of the other studies report in the opposite. One of the studies published from John Hopkins University School of medicine has confirmed the expression of ACE2 in cornea, limbus, and conjunctiva in surgical and postmortem specimen using immunohistochemistry (IHC). Notably, prominent staining was noted in the epithelial surface of cornea and superficial conjunctival surface. In their study, TMPRSS2 expression was noted in conjunctival specimens. These findings were further validated in western blot analysis [13]. Other studies also confirmed the presence of ACE2 receptor expression in conjunctival tissue [14, 15]. These studies summarized that COVID-19 may spread through conjunctiva [14]. Another possible route of

✉ Anusuya Bhattacharyya
anusuya.8k@gmail.com

Phulen Sarma
phulen10@gmail.com

Hardeep Kaur
Aspireachieve.shine@gmail.com

Bikash Medhi
drbikashus@yahoo.com

¹ Department of Pharmacology, PGIMER, Chandigarh, India

² Department of Ophthalmology, Government Medical College and Hospital, Sector 32, Chandigarh, India

transmission is that the pathogens in the ocular surface might get transported into the nasal and nasopharyngeal mucosa is through the nasolacrimal duct (NLD), which may be the route of entry of the disease [16]. As ACE2 and TMPRSS2 both are present in conjunctiva, the SARS-CoV-2 may take this route or the NLD route to infect the exposed person. WHO has already included the eye as a possible route of direct transmission of the disease through contact and droplet transmission and fomite transmission [17] and thus the ocular route of transmission must not be ignored [18]. Occupational ocular exposure to SARS-CoV-2 leading to COVID-19 is already reported especially in a nurse who used a dislodged eye goggles [5]. Another study supported the role of normal conjunctiva in transmission of COVID-19 [1].

Agarwal R et al. mentioned about low risk of shredding the virus in ocular secretions and commented that use of prophylactic PVP-I for accidental ocular exposure without gauging the infectivity status of the patient seems a little unrealistic and improbable. We admit that although low, but there is definite evidence of shredding of the virus in ocular secretions [3]. However, the presence or absence of the virus in ocular secretions/scrapings/conjunctival specimens do not correlate well with occurrence of ocular symptoms [3]. In our article, we are talking about accidental exposure through the ocular route e.g. spitting on face/eye of healthy doctor or police personal by COVID-19 patients. This accidental ocular exposure (to biological fluid of a COVID-19 patient) may cause establishment of a systemic infection as mentioned in earlier part of this

Table 1 Details of studies evaluating the efficacy and safety of povidone iodine in COVID-19 (at different concentrations and different target populations in different settings, e.g., in vivo, in vitro)

| Study, author | Study type | Details of study | Outcome |
|------------------------|------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Anderson DF, 2020 [11] | In vitro | Virucidal activity was evaluated by suspension assay Contact time = 30 s | PVP-I at concentrations 10%, 7.5%, 1% and 0.45% exhibited virucidal activity ($\geq 99.99\%$) against SARS-CoV-2 |
| Bidra AS, 2020 [21] | In vitro | Compared the in vitro inactivation of SARS-CoV-2 by H2O2 and PVP-I Contact time = 15 and 30 s | At both the contact times, PVP-I concentrations 0.5, 1.25, and 1.5% were successful in complete inactivation of the virus. However minimal virucidal effect was seen in case of H2O2 |
| Bidra AS, 2020 [22] | In vitro | Investigated optimal concentration and contact time of PVP-I required for SARS-CoV-2 virucidal activity | Complete inhibition was seen with 15 s contact period at concentrations 0.5, 1, and 1.5%. The results were better than 70% ethanol |
| Liang B, 2020 [23] | In vitro efficacy, in vivo toxicity | In vitro evaluation and ocular toxicity study (in rabbit) of PVP-I eye drop (gel forming) and PVP-I nasal spray (gel forming) | Dose and time dependent inactivation of SARS-CoV-2 was seen in both the cases |
| Khan MM, 2020 [24] | Clinical trial | Evaluated safety of 0.5% PVP-I solution as nasal drops | Povidone iodine 0.5% was well tolerated. |
| Lamas LM, 2020 [25] | Clinical study | Evaluations of the effect of povidone iodine mouth wash against COVID-19 | Lowering of salivary SARS-CoV-2 load was seen following PVP-I rinse |
| NCT04371965 | Clinical trials.gov | Evaluation of the effect of PVP-I nasal-spray, gargle and mouth wash on nasopharyngeal SARS-CoV-2 load | Name of study: KILLER. Status: NYR |
| NCT04410159 | Clinical trials.gov | Evaluation of comparative efficacy of tap-water gargle vs. PVP-I vs. essential oil gargle in patients with COVID-19 | Name of the study: GARGLES Status: R |
| NCT04449965 | Clinical trials.gov | Efficacy of PVP-I rinse on COVID-19 | Status: NYR |
| NCT04347954 | Clinical trials.gov | Evaluation of the efficacy of nasal spray of PVP-I on nasopharyngeal titer of SARS-CoV-2 | Status: R |
| NCT04364802 | Clinical trials.gov | Intranasal prophylaxis of PVP-I for HCWs | Name: PIIPPI Status: R |
| NCT04344236 | Clinical trials.gov | Evaluation of effect of nasal rinses and gargling of PVP-I on naso- and oropharyngeal SARS-CoV-2 load | Status: R |
| NCT04393792 | Clinical trials.gov | Sinus-wash for COVID-19 | Status: R |
| NCT04446104 | Clinical trials.gov | Evaluation of preventive effect in migrant workers (high risk group) | Status: R |
| NCT04341688 | Clinical trials.gov | Effect of gargle on intra-oral SARS-CoV-2 load | Name: GARGLES Not yet recruiting |

PVP-I povidone iodine, R recruiting, NYR not yet recruiting

letter. It is to be mentioned that in our study [19], we are not talking about use of povidone iodine for decreasing the infectivity of ocular fluid in COVID-19 patients. As COVID-19 patients are already in quarantine or isolation, this might be an unnecessary approach. Rather we are talking on accidental ocular exposure to SARS-CoV-2 in case of a healthy individual.

Regarding the virucidal and bactericidal activities of povidone iodine, it showed bactericidal activity against *S. pneumoniae* and *K. pneumoniae* and antiviral effect against H1N1, rotavirus, MERS-CoV and SARS-CoV (contact time = 15 s) at a concentration as low as 0.23% [20]. Although in our earlier letter [19], we have extrapolated data from SARS-CoV to SARS-CoV-2 (due to nonavailability of data against SARS-CoV-2); however, at the time of this current letter, we have definitive data regarding the antiviral effect of povidone iodine against SARS-CoV-2 and different effective concentrations. We searched three databases “PubMed, clinicaltrials.gov and Google scholar” using keywords “povidone iodine” and COVID-19. The details of studies evaluating the safety and efficacy of povidone iodine at different doses against SARS-CoV-2 are showed in Table 1. The findings of these studies highlight the utility of povidone iodine and may help us deciding the effective dose and tolerability of povidone iodine against SARS-CoV-2.

Many experts are now recommending PVP-I as a public-health-intervention for COVID-19 [26]. In oncology practice, especially among head and neck surgeons, there is a demand for considering it as a component of PPE (personal-protection-equipment) [27]. Some studies also recommended use of povidone iodine eye drop; however, the population group which could be beneficial was not well defined [28]. However, povidone iodine is never an alternative to the use of PPEs like protective goggles and wearing of PPF kits at this current point of time.

Agarwal R et al. have mentioned that the course of COVID-19-related conjunctivitis is self-limiting and apparently benign. We should note that the course of COVID-19-associated conjunctivitis is not a smooth road always with few of the patients requiring mild steroid [29] and even relapsing conjunctivitis is also reported [30].

Now coming to another issue of utility of povidone iodine eye drop in COVID-19-associated conjunctivitis, although covid-19-associated conjunctivitis is considered a possible benign disease, however, many have tried ribavirin eye drop [31] and ganciclovir [5, 30]. However, clinical efficacy of ganciclovir in COVID-19 is dubious [32]. In COVID-19-associated conjunctivitis, most of the bodies recommended artificial tear; however, if symptoms persisted, a mild steroid could be considered [29]. Regarding use of anti-viral agent, if at all required, povidone iodine may stand a chance; however, comparative clinical data with the standard of care (e.g., artificial tear drop) and mild steroid will be needed. The

concentration of povidone iodine to reduce infectivity of SARS-CoV is as low as 0.23% [20], and for SARS-CoV-2, it is as low as 0.45% [11]. Although irritation is a common occurrence during the use of povidone iodine eye drop, which necessitates the use of topical anesthetics a priori; however, at these low concentrations of povidone iodine, the side effect and irritability profile of povidone iodine need to be reevaluated. Again, no corneal toxicity was observed at a dose of povidone iodine 0.5% [33].

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Abbreviations 2019-nCoV, 2019 novel corona virus; SARS-CoV, Severe acute respiratory syndrome coronavirus; MERS-CoV, Middle East respiratory syndrome coronavirus; ACE2, Angiotensin converting enzyme 2; COVID-19, Coronavirus disease-2019; PVP-I, Povidone iodine; PPE, Personal protective equipment

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