THE USE OF POVIDONE-IODINE FOR PREVENTION OF COVID-19 INFECTION.

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Abstract

In late 2019 a novel coronavirus, SARS-CoV-2 causing Coronavirus disease 2019 (COVID-19) appeared in Wuhan China, and on 30 January 2020, World Health Organization (WHO), declared the current outbreak of COVID-19 a public health emergency of international concern. There is no treatment for the COVID-19 infection besides preventive measures recommended by WHO. Povidone iodine is an antiseptic has been used mainly for the prevention or management of wound infections for over 150 years. Its antibacterial, antiviral and antifungal properties as well as its safety is well documented. This article reviews the studies that have assessed the antiviral efficacy of povidone-iodine and its potential use as prophylactic to avoid the COVID-19 infection and its infectivity in the community. The evidence suggests its use on oropharyngeal and nasopharyngeal mucosa of in the health-care workers, COVID-19 patients and community as additional measure helping to abate the pandemic.

Introduction

Povidone-iodine (PVP-I) is an old antiseptic used in practice of medicine as a surgical scrub; for pre- and post-operative skin cleansing; for the treatment and prevention of infections in wounds, decubitus ulcers, cuts, and burns; in gynecology for vaginitis associated with candidal, trichomonal or mixed infections (1,2, 3). For these purposes, PVP-I has been formulated at concentrations of PVP-I is available in different strengths and formulations: as a 10%, 7.5% and 1% PVP-I gargle and mouthwash across Asia; it is also available as a throat spray (0.45% w/v formulation), thereby allowing flexibility in dosing regimens to suit individual patient's needs. The safety profile of PVP-I at such concentrations is well established and many available products in the market are over the counter. PVP-I in solution, nasal and throat spray, surgical scrub, ointment, swab dosage forms, eye drop, and vaginal suppositories. It contains from 9.0% to 12.0% available iodine, calculated on a dry basis (4). The most well-known brand for PVP-I is BETADINE.

Virudical activity of PVP-I

PVP-I has been reported as a broad-spectrum microbicide with potency to inactivate bacteria, fungi, protozoans, and several viruses. The first publication about the virucidal efficacy of PVP-I was reported in 1975 where the PVP-I can reduce the titers of herpesvirus type 2 by 92% (5). Povidone-iodine has been reported as having the highest virucidal activity profile

among several antiseptics such as chlorhexidine gluconate CHG, benzalkonium chloride (BAC), benzethonium chloride (BEC) and alkyldiaminoethyl-glycine hydrochloride (6). Using a standardized *in vitro* approach, PVP-I gargle was found to inactivate a panel of viruses that included adenovirus, mumps, rotavirus, poliovirus (types 1 and 3), coxsackie virus, rhinovirus, herpes simplex virus, rubella, measles, influenza and human immunodeficiency virus. PVP-I had a wider virucidal spectrum, covering both enveloped and nonenveloped viruses, than the other commercially available antiseptics. (6)

In a more recent study, PVP-I products, that included gargle and throat spray, demonstrated rapid virucidal activity against both a highly pathogenic (H5N1) and low pathogenic (H5N3, H7N7 and H9N2) strains of avian influenza A viruses, with viral titres falling below the detection limits of the assay with only 10 s of PVP-I incubation (7). Furthermore, the results of a study confirmed the virucidal efficacy of PVP-I products including PVP-I gargle against swine influenza viruses (H1N1, H3N2 and H1N2) (7).

Recent study *in vitro* demonstrated the virucidal activity of PVP-I against a wide range of viruses and rapid virucidal activity against the Ebola virus, MERS-CoV, and European modified vaccinia virus Ankara (MVA) (8,9). The first evidence of the virucidal activity of PVP-I against SARS coronavirus was published in 2006 (10). German researchers demonstrated the virucidal activity of PVP-I as skin cleanser against the Ebola virus and as gargle/mouthwash against MERS-CoV and MVA (8). Thanks to the funding from Mundipharma Research GmbH & Co, German researchers published the of SARS-CoV, MERS-CoV, influenza virus A (H1N1), and rotavirus is done rapidly after 15 seconds of exposure (9). Mundipharma Research have developed several PVP-I based products and a gargle/mouthwash.

It has also noted that respiratory Syndrome (MERS) coronavirus or endemic human coronaviruses, which is killing thousands of human beings currently, can persist on inanimate surfaces like metal, glass, or plastic for up to 9 days where the PVP-I (0.23–7.5%) readily inactivated coronavirus infectivity by approximately 4 log₁₀ or more (11).

Over a decade ago randomized controlled clinical trials found evidence for the effectiveness of gargling with PVP-I and chlorinated tap water in preventing general upper respiratory tract infectious (12) and influenza-like illness (13). An analysis of credibility confirmed these findings are consistent with substantial efficacy (14).

Dynamic in viral shedding and transmissibility of SARS-COV-2

In a recent paper released on 27 March 2020 in the journal *Lancet Infectious Disease*, the French researchers confirmed the high viral loads in upper respiratory tract samples are suggestive of the potentially high risk of transmissibility during the very first days of symptoms (15). This finding is in line with data reported by Zou and colleagues beginning of this year, who analyzed viral load in the upper respiratory tract in relation to day of onset of symptoms in 17 symptomatic patients in whom higher viral loads were detected soon after symptom onset (16). This observation suggests that the virus shedding pattern of patients infected with COVID-19 have a high viral load in the upper respiratory tract at the disease onset.

Supported the above findings, a recent paper showed the viral shedding of patients with laboratory-confirmed COVID-19 peaked on or before symptom onset, and a substantial proportion of transmission probably occurred 2 to 3 days before symptom onset.

Approximately, 44% of secondary cases were infected during the index cases were in asymptomatic (17). Here, it can hypothesize that the asepsis of the coronavirus viral load generated at the upper of the respiratory tract in the individuals is of substantial importance for the control of COVID-pandemic.

Recommendations about the PVP-I products in the COVID-19 outbreak.

None of the above constitute a compelling evidence for the use of PVP -I against COVID-19 infection. However, considering the proven *in vitro* efficacy of PVP-I, it is regrettable that the regulatory bodies have not recommended its use since the extensive preclinical evidence and use in medicine for non-COVID-19 indications is comparable to the chloroquine (CQ) and hydroxychloroquine (HCQ). In that scenario, on March 28, 2020 the FDA authorized the use antimalaria medications of them under an Emergency Use Authorization (EUA) (18) and the European Medicines Agency (EMA) on 1 April 2020 issued a guidance of CQ/HCQ only for clinical trials or emergency use programs (19). Therefore, these 2 medications are being using nowadays in COVID-19 patients by clinicians without conclusive evidence about their efficacy.

Per concept the use of PVP-I it would be an effective method of preventing the growth and spread out of the viruses-containing airborne/droplet from the nose and mouth of an infected individual. It is also possible that a reduction of COVID-19 viral load at nose, nasopharynx and oropharynx may help to the individual to present less severe infection. The destruction of the COVID-19 viral load at the upper respiratory tract will reduce of infectivity of infected individual and use as prophylactic for negative patients and consequently help to eradicate the COVID-19 pandemic and all terrible consequences. Therefore, the regulatory authorities should be urgently considered the use of PVP-I to support the control of the outbreak along the suggestion for the initiation of randomized controlled clinical trials.

From the clinical trial point of view, the protocol for healthcare workers and patients should expedite drafted taking in consideration several PVP-I formulations and presentations are available in the market that differ in their composition and indications. It is unknowns the exact effective concentration of PVP-I in the presence of mucins and saliva, but there is an assumption that the use of a concentration twice as strong as that found to be virucidal *in vitro* would be enough. British researchers have suggested the in the hospital setting a 0.5% PVP-I solution be applied to the oral, oropharyngeal and nasopharyngeal mucosa of patients with presumed/confirmed COVID-19 and the healthcare personnel in close contact with the virus. (20). The frequency of the PIP-I should be also determined.

Meanwhile, it can be recommended to the population at risk of infection or COVID-19 positive patients the empiric use of the PVP- based mouthwash for gargles and mouth rinse together with PVP-I-containing nasal rinse or spray or swabs or solution drops 4 times a day at least. The frequency 2 times a day for prophylaxis with PVP-I for mouth and nose based products to the people who is not exposure or has not get in contact with COVID-19 positive patients might be enough.

The use of PVP-I products for a complete viral eradication should be at least 2 weeks or till the risk of infectivity was controlled by local authorities. This intervention is not provided with curative intent for the disease but may provide a significant to dramatically reduce viral spread into the communicate and workplaces.

Every country has different PVP-I products in the market which are no expensive. However, local physicians should look at of the available products in the market a recommended the use for the viral cleaning and protection. The mouthwash shouldn't be swollen. The PVP-I used in humans is innocuous, but the physician should be aware some allergic (hypersensitivity) cases have been reported, the cautious use when the skin is broken or burn these circumstances may cause toxic levels of iodine to be absorbed into your blood. The thyroid function should be monitored in case the patient has a thyroid problem, however It has been estimated that 6 months of use of daily 5% PVP-I mouthwashes, equivalent to 5.5mg per day, 1 mL cause no change in serum T3, T4 or free T4 (20).

I must also highlight here that besides the use of the PVP-I products, it is imperative to continue following the recommendations about the necessary protective measures advised to the public by WHO.

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