Review Article

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Povidone: Iodine as Miraculous Oral Rinse Against Viruses

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ABSTRACT

Background: Various microbes like viruses, bacteria, fungi and protozoa can give rise to many common oral and oropharyngeal conditions such as dental caries, periodontal disease, gingivitis, also cause upper respiratory tract infections like sore throat, common cold and influenza. Respiratory syncytial viruses can be spread by large droplets propelled through the air and inoculated into the eyes, nose and mouth at close range. Considering these modes of transmission, oral hygiene by gargling, together with hand washing and mask use, may be beneficial to help minimise the risk of both community- and hospital acquired respiratory infections. Various in vitro studies demonstrated rapid bactericidal and virucidal activity of PVP-I gargle/mouthwash against respiratory pathogens. In the current scenario of Covid -19 pandemic, recommending PVP- I mouth rinsing as a practice along with regular handwashing with soap can be considered.

Keywords: PVP-I (Povidone iodine), mouthrinses, viruses.

INTRODUCTION

The general health and well-being of an individual is closely linked to the status of the oral and oropharyngeal cavities.[1,2] Various microbes like viruses, bacteria, fungi and protozoa can give rise to many common oral and oropharyngeal conditions such as dental caries, periodontal disease, gingivitis, also cause upper respiratory tract infections like sore throat, common cold and influenza[2]. Seasonal endemic viruses such as influenza are another significant cause of respiratory infection with worldwide, annual influenza epidemics estimated about 3–5 million cases of severe illness and 250,000–500,000 of deaths[3]. In addition to seasonal endemic viruses, emerging and re-emerging virus outbreaks such as severe acute respiratory syndrome and Middle East respiratory syndrome corona viruses (SARS-CoV and MERS-CoV) require close contact for human-to-human transmission and can spread nosocomially[4,5].Unlike the remaining four corona viruses, which are typically associated with mild, self-limiting respiratory illness, SARS-CoV and MERS-CoV cause severe respiratory symptoms and are associated with considerable mortality[6]. Outbreaks can, however, be quickly and effectively controlled with preventive strategies based upon early accurate viral diagnosis, knowledge of the current epidemiological season and effective hygiene practices to decrease the risk of transmission[7].

Effective hand hygiene minimises transmission of pathogens from contaminated hands of an infected individual through either direct person-to-person contact or indirectly via contamination of surfaces[8,9]. Respiratory syncytial viruses, SARS-CoV and MERS-CoV can be spread by large droplets propelled through the air and inoculated into the eyes, nose and mouth at close range[10]. Considering these modes of transmission, oral hygiene by gargling, together with hand washing and mask use[11], may be beneficial to help minimise the risk of both community- and hospital acquired respiratory infections. Gargling is also deemed to bring about

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favourable effects through removal of oral/pharyngeal protease that helps viral replication[12].

Povidone-iodine (PVP-I)

Povidone-iodine (PVP-I) is a broad-spectrum antimicrobial that has been used in infection control and prevention for over 60 years[13] and is available in various preparations for use as a disinfectant for the skin, hands and mucosal surfaces, as well as for wound treatment and eye applications. PVP-I has well-established general antimicrobial activity, demonstrating in vitro efficacy against gram-positive, gram-negative and some spore-forming bacteria (clostridia, Bacillus spp.) and mycobacteria[14-18] and a wide range of enveloped and non-enveloped viruses[19-21]. Recent in vitro studies have demonstrated rapid virucidal activity of PVP-I products against Ebola virus, MERS-CoV and European reference enveloped virus [modified vaccinia virus Ankara (MVA)][22,23]. The benefit of gargling with PVP-I has already been noted in Japanese clinical respiratory guidelines[24].

History

In 1955, PVP-I was discovered at the Industrial Toxicology Laboratories in Philadelphia by H. A. Shelanski and M. V. Shelanski. In vitro study by them found that the complex was less toxic in mice than tincture of iodine. In an in vivo study, the product considered to be better than other iodine formulations.[25]

Structure

Povidone-iodine is a chemical complex of the polymer povidone (polyvinylpyrrolidone) and triiodide (I_3^-) as shown in figure 1.[26]

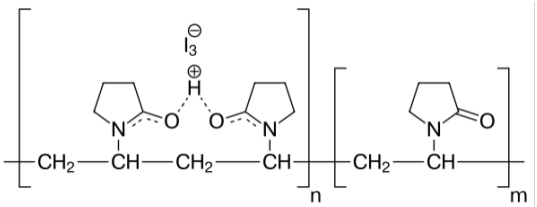

Fig 1: Structure of Povidone iodine complex.

Virucidal activity of PVP-I

Previous in vitro study demonstrated rapid bactericidal and virucidal activity of PVP-I gargle/mouthwash against all respiratory pathogens tested according to European standard requirements. The minimum 15 seconds contact time proved to be sufficient for PVP-I7% gargle/mouthwash to be effective at the recommended dilution in Japan of 1:30 (equivalent to a concentration of 0.23% of the active ingredient)[28]. In other in vitro virucidal studies, PVP-I gargle was found to inactivate a panel of viruses including adenovirus, mumps, rotavirus, poliovirus (types 1 and 3), coxsackie virus, rhinovirus, herpes simplex virus, rubella, measles, influenza and human immunodeficiency virus. In this study, chlorhexidine gluconate (CHG), benzalkonium chloride (BAC), benzethonium chloride (BEC) and alkyldiaminoethyl-glycine hydrochloride (AEG) gargles were ineffective against adenovirus, poliovirus and rhinovirus but generally showed activity against other above mentioned viuses[19]. In a study by Kariwa et al., application of PVP-I products with concentrations of 0.23–1% for 1–2 min reduced SARS-CoV virus infectivity from 1.17 ×10^6 TCID 50/ml to below detectable levels, although shorter contact times were not investigated[20]. In a study by Ito et al., PVP-I products including 0.23% gargle and 0.23% 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 10s of PVP-I incubation[29]. In another study, the results confirmed the virucidal efficacy of PVP-I products including PVP-I gargle against swine influenza viruses (H1N1, H3N2 and H1N2)[30]. A study by Harrison MA et al, all Betadine products completely inactivated the virus at povidone-iodine concentrations of greater than or equal to 0.5% (10- to 20-fold dilutions of stock) except for Betadine Lubricating Antiseptic Gel, which required 2.5% for efficacy (1:2 dilution)[31]. In 2009, following the H1N1 swine flu outbreak, Japan's Ministry of Health, Labour and Welfare recommended daily gargling as a protective hygiene measure to prevent upper respiratory tract infections (URTIs)[32], this practice supported by findings from various studies that examined the role of gargling in both healthy individuals and those with frequent or persistent URTIs[12,33,34]. General information of the included studies has been given in table 1.

Table 1: General information of the selected articles.

S. No	Reference	Studies conducted	Results
1	Martínez Lamas L et al[44], 2020	Analysis of the impact of a mouthwash with PVP-I on the salivary viral load of SARS-CoV-2 in 4 patients with COVID-19.	The SARS-CoV-2 load was reduced significantly with the use of 15 mL of 1% PVP-I mouth rinse for 1 min.
2	Pelletier JS et al[54], 2020	Efficacy of Povidone-Iodine Nasal and Oral Antiseptic Preparations Against Severe Acute Respiratory Syndrome-Coronavirus 2 (SARS-CoV-2)	Nasal and oral PVP-I antiseptic solutions are effective at inactivating the SARS-CoV-2 at a variety of concentrations after 60-second exposure times. The formulations tested may help to reduce the transmission of SARS-CoV-2 if used for nasal decontamination, oral decontamination, or surface decontamination in known or suspected cases of COVID-19.
3	Bindra AS et al[52], 2020	Investigate the optimal contact time and concentration for viricidal activity of oral preparation of povidone-iodine (PVP-I) against SARS-CoV-2 ('corona virus') to mitigate the risk and transmission of the virus in the dental practice.	PVP-I oral antiseptics at all tested concentrations of 0.5%, 1%, and 1.5%, completely inactivated SARS-CoV-2 within 15 seconds of contact.
4	Hassandarvish P et al[56], 2020	Assess the in vitrovirucidal activity of an oral povidone iodine (PVP-I) product against SARS-CoV-2.	PVP-I gargle and mouthwash product, undiluted and at 1:2 dilution, demonstrated potent and rapid virucidal activity (≥4 log10 reduction of viral titre) in 15 seconds against SARS-CoV-2 in vitro.
5	Eggers M et al, 2018[31]	In vitro bactericidal and virucidal efficacy of povidone-iodine (PVP-I) 7% gargle/mouthwash at defined dilution against oral and respiratory tract pathogens was studied	PVP-I gargle/mouthwash diluted 1:30 (equivalent to a concentration of 0.23% PVP-I) showed effective bactericidal activity against Klebsiella pneumoniae and Streptococcus pneumoniae and rapidly inactivated SARS-CoV, MERS-CoV, influenza virus A (H1N1) and rotavirus after 15 s of exposure.
6	Eggers M et al, 2015[25]	In vitro efficacy of three formulations of povidone iodine (PVP-I: 4% PVP-I skin cleanser, 7.5% PVP-I surgical scrub, and 1% PVP-I gargle/mouthwash) against a reference virus (Modified vaccinia virus Ankara, MVA) and MERS-CoV was studied	A reduction in virus titer of ≥4 log10 (corresponding to an inactivation of ≥99.99%) was achieved versus MVA and MERS-CoV, under both clean and dirty conditions, within 15 s of application of each undiluted PVP-I product.
7	Kariwa H et al, 2006[23]	The efficacy of several povidone-iodine (PVP-I) products, a number of other chemical agents, and various physical conditions were evaluated for their ability to inactivate the severe acute respiratory syndrome coronavirus (SARS-CoV).	Treatment of SARS-CoV with PVP-I products for 2 min reduced the virus infectivity from 1.17 x 10(6) TCID50/ml to below the detectable level.

8	Ito H et al, 2006[32]	Antiviral activity of PVP-I products against H5, H7 and H9 avian influenza A viruses were investigated using embryonated hen's eggs.	Viral infectious titers were reduced to levels below the detection limits by incubation for only 10 s with the PVP-I products
9	Kawana R et al, 1997[22]	Inactivation of a range of viruses, such as adeno-, mumps, rota-, polio- (types 1 and 3), coxsackie-, rhino-, herpes simplex, rubella, measles, influenza and human immunodeficiency viruses, by antiseptics such as PVP-I solution, PVP-I gargle, PVP-I cream, chlorhexidine gluconate, alkyldiaminoethyl-glycine hydrochloride, benzalkonium chloride (BAC) and benzethonium chloride (BEC) were studied in accordance with the standardized protocol in vitro.	PVP-I drug products, inactivated all the viruses within a short period of time.
10	Harrison M A et al, 1989[34]	Eleven povidone-iodine-containing products (Betadine) and chlorhexidine gluconate solution were tested for their ability to inactivate human immunodeficiency virus (HIV) in a cell culture system.	All Betadine products completely inactivated the virus at povidone-iodine concentrations of greater than or equal to 0.5% (10- to 20-fold dilutions of stock) except for Betadine Lubricating Antiseptic Gel, which required 2.5% for efficacy (1:2 dilution).

Mechanism of action of PVP-I

The non PVP-bound 'free' iodine, an active moiety, is released into solution from the PVP-I complex. PVP itself has no microbicidal activity. The free iodine penetrates the cell wall and inactivates the cells by forming complexes with amino acids and unsaturated fatty acids, resulting in impaired protein synthesis and alteration of cell membranes[35] (**Figure.1)**. This basic mechanism of action leads to strong microbicidal activity expressed by multiple modes of action that include the disruption of microbial metabolic pathways, as well as destabilisation of the structural components of cell membranes, causing irreversible damage to the pathogen[36]. The consumed free iodine is then replaced by PVP bound iodine. The determining factor of the microbicidal action of PVP-I is the concentration of free iodine[37-39]. A study by Schreier H et al., investigating the virucidal activity of different disinfectants, electron micrographs revealed how exposure to iodine led to degeneration of the nucleoproteins of viral particles, which was the main mechanism ofaction[40]. However, in a study by Sriwilaijaroen N et al., revealed that disruption of surface proteins essential for the spread of enveloped viruses[41].

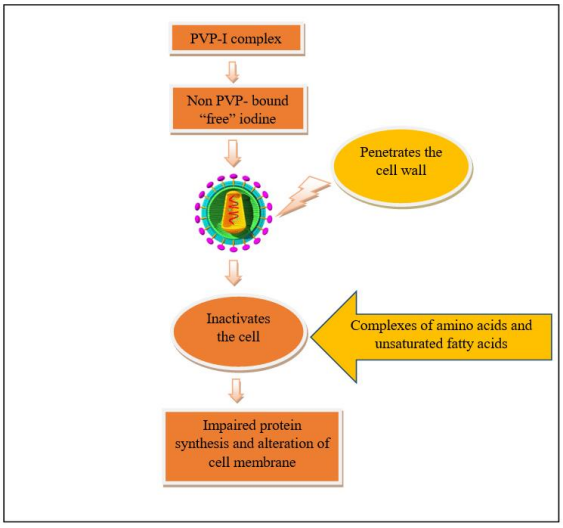

Fig 1: Mechanism of action of PVP-I.

Povidone iodine in the era of COVID-19

With the potential to reduce the incidence of airborne or droplet-transmitted respiratory infections (e.g. SARS, avian flu, swine flu)[20,30], undiluted PVP-I can be used as a protective measure by rinsing the mouth for 2 min up to four times a day. With the outbreak of nCoV-19, preprocedural mouthrinse containing oxidative agents such as 1% hydrogen peroxide or 0.2% povidone is recommended, for the purpose of reducing the salivary load of oral microbes, including the potential nCoV-19 carriage[43]. For

routine hygiene practices, gargling followed by rinsing of the mouth for 30 second using 10–15 ml of diluted or undiluted PVP-I mouthwash is suggested. Careful instructions on proper dilution of PVP-I mouthwash or gargle should be advised. In one recent in-vivo study that included 4 COVID-19 patients, the SARS-CoV-2 load was reduced significantly with the use of 15 mL of 1% PVP-I mouth rinse for 1 min and it was evaluated by real-time reverse transcriptase PCR (rRTPCR) in the saliva for 3 hours.[44] Another recent study demonstrate that the PVP-I gargle and mouthwash (1% w/v) have virucidal activity in vitro against SARS-CoV-2.[45]

Contraindications of PVP-I

Over the year, the safety profile of PVP-I is well-established. Although measurable systemic absorption may occur with the long-term use of PVP-I, its clinical manifestation as thyroid dysfunction is not very common[36]. According to some studies use of PVP-I mouthwash for four times daily for 2 weeks or once daily for 24 weeks did not affect the thyroid function[46,47]. However, long term use of PVP-I for gargling should be avoided by people with high risk of developing thyroid dysfunction due to excessive intake of iodine, pregnant women and breast feeding mothers[48]. Rare complications are also reported as allergic dermatitis after prolonged skin contact with PVP-I[49].

Role of other mouthrinses against COVID -19

Chlorhexidine (CHX) is a cationic bisbiguanide that has a broad-spectrum antiseptic property. CHX is also known to have antiviral activity. A recent study showed that there was a transient decrease in viral load after 2hour of post-gargling in the patients using CHX mouthrinse (0.12%, 15mL for 30s) on days 3 and 6, but it increased again after that.[50]

H_2O_2 is a chemical compound which is a widely used antimicrobial and has virucidal activity of which coronavirus and influenza viruses were found to be most sensitive.[51] In a recent in vitro study demonstrated that with the concentration of 0.5%, 1.25%, or 1.5% for PVP-I and 3% or 1.5% for H_2O_2, PVP-I significantly inactivated the virus after 15-30s of contact whereas H_2O_2 reported minimal inactivation.[52]

Cetylpyridinium chloride (CPC) is a quaternary ammonium compound. CPC has antiviral effect that significantly reduce the duration and severity of cough and sore throat. The mechanism of action could be lysosomotropic mechanism and its ability to destroy viral capsids. With this, it can be ruled out that CPC could be used against coronaviruses.[53]

Based on various studies, clinical status related to the use of mouthrinses shows more effective role of PVP-I than any other mouthrinses against COVID-19.

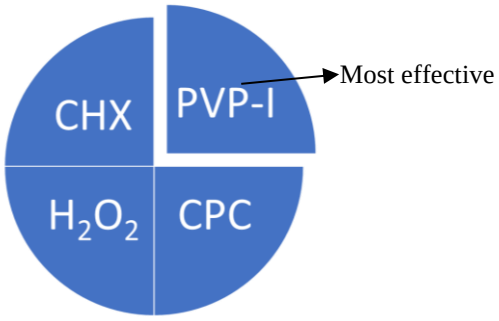

Fig 2: Clinical status of mouthrinses.

CONCLUSION

Mouthwashes or mouth rinses are used as supplemental aid in the daily oral hygiene regimen. Antiseptics, such as PVP-I, used in many clinical practices to treat or prevent many infections. Recommended gargling with antiseptic mouthwash for the control of oral and respiratory tract infections, the rapid bactericidal and virucidal efficacy of povidone iodine against pathogens causing oral and respiratory tract infections observed in other in vitro and in vivo studies and the established safety profile of PVP-I from over 60 years of use, provide a strong rationale for the use of PVP-I oral solution for protective oropharyngeal hygiene management for individuals at high risk of exposure to oral and respiratory pathogens. In the current scenario of Covid -19 pandemic, recommending PVP- I mouth rinsing as a practice along with regular handwashing with soap can be considered.

CONFLICTS OF INTEREST

The authors declare they have no potential conflict of interests regarding this article.

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