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diti Chopra, Karthik Sivaraman, Raghu Radhakrishnan, Dhanasekar Balakrishnan, Aparna Narayana

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Can Povidone Iodine gargle/mouthrinse inactivate SARS-CoV-2 and decrease the risk of nosocomial and community transmission during the COVID-19 pandemic? An evidence-based update

Running Title: Povidone-iodine, SARS-CoV-2, Coronavirus, and COVID19

Aditi Chopra[1], Karthik Sivaraman[2], Raghu Radhakrishnan[3], Dhanasekar Balakrishnan[4], Aparna Narayana[4],

[1]. Reader, Department of Periodontology, Manipal College of Dental Sciences, Manipal Academy of Higher Education, Manipal – 576104

[2]. Reader, Department of Prosthodontics and Crown and Bridge, Manipal College of Dental Sciences, Manipal Academy of Higher Education, Manipal – 576104

[3]. Professor, Department of Oral Pathology and Microbiology, Manipal College of Dental Sciences, Manipal Academy of Higher Education, Manipal – 576104

[4]. Professor, Department of Prosthodontics and Crown and Bridge, Manipal College of Dental Sciences, Manipal Academy of Higher Education, Manipal – 576104

***Corresponding Author**

Aparna Narayana *MDS PhD*

Professor and Coordinator of Centre for full mouth Implant rehabilitation Department of Prosthodontics and Crown & Bridge Manipal College of Dental Sciences, Manipal Manipal Academy of Higher Education, Manipal – 576104, India Email: aparna.narayan@manipal.edu

Abstract

The Coronavirus disease in 2019 (COVID-19), also referred to as the novel 'CoV19 (nCov19)' is caused by a new coronavirus strain similar to Severe Acute Respiratory Syndrome (SARS-CoV-2). SARS-CoV-2 spreads via respiratory droplets, saliva, or direct contact. Therefore it is important to control the viral load in the saliva and respiratory secretions. One of the most simple and cost-effective measures that can be adopted by the public and healthcare professionals to prevent cross-contamination and community transmission, is the implementation of effective oral and throat hygiene. Recent evidence has confirmed 0.5 % PVP-I mouthrinse/gargle for 30 seconds can reduce SARS-CoV-2 virus infectivity to below detectable levels. PVP-I can even interrupt SARS-CoV-2 attachment to oral and nasopharyngeal tissues and lower the viral particles in the saliva and respiratory droplets. Thus the use of PVP-I mouthrinse as prophylactic measures has been advocated across the globe to reduce disease transmission. Although the efficacy of PVP-I against SARS-CoV-2 is proven, no review articles have yet discussed the evidence and mechanisms of PVP-I against the SARS-CoV-2. Thus, this paper highlights the rationale, safety, recommendations, and dosage of PVP-I gargle/mouthrinse as an effective method to decrease the viral loads during the pressing times of COVID-19.

Keywords: COVID-19; SARS-CoV-2; Coronavirus; Povidone-iodine; Mouthwash; Global health; Viral infection; Oral health

Introduction

The Coronavirus disease in 2019 (COVID-19), also referred to as the novel 'CoV19 (nCov19)' is caused by a new coronavirus strain of SARS-CoV-2[1]. SARS-CoV-2 was confirmed as a 'Public Health Emergency of International Concern (PHEIC)', warranting a coordinated international response to fight this unprecedented public health crisis in January 2020. As of 26th September 2020, SARS-CoV-2 has affected more than 32,765,274 individuals worldwide, with nearly 993,464 deaths.

SARS-CoV-2 is a single-stranded RNA beta-coronavirus, which belongs to the 'Sarbeco virus sub-genus of the Coronaviridae family. The SARS-CoV-2 is 89% identical to batSARS-like-CoVZXC 21 and 82% equal to human SARS-CoV in its genomic sequence[2]. SARS-CoV-2 is a zoonotic disease similar to Middle East Respiratory Syndrome Coronavirus (MERS-CoV). and SARS-CoV. The SARS-CoV-2 infection may have initiated from the wet market in Wuhan, Hubei district, China[1]. The virus is believed to reside in the Chinese horseshoe bats (*Rhinolophus sinicus*)[2,3] with Malayan pangolins (*Manis javanica*) as the most likely intermediate host[4,5]. A recent paper evaluating the probable origin of SARS-CoV-2 suggested that "it could have originated either by natural selection in an animal following zoonotic transfer or by natural selection in human following zoonotic transfer"[6]. Evidence suggests that COVID-19 emerged from a single animal to human transmission, with subsequent genetic mutations resulting in rapid and continued human-to-human spread[2,7]. Human to human transmission is known to occur via respiratory droplets and contact routes primarily[3,4,8]. However, researchers have indicated that the risk of fecal to the oral transmission cannot be negated, since SARS-CoV-2 has been identified in the stools of patients[9]. With researchers intensifying their efforts to develop an effective vaccine to treat COVID-19

patients, all efforts are being made to reduce the spread of the viral particles and mitigate the spread of infection.

It is obligatory to follow effective social distancing measures and isolate both the symptomatic and asymptomatic COVID-19 patients to reduce the spread of infection. Rational use of adequate personal protective equipment (PPE) and personal hygiene in both hospitals and clinics, as well as appropriate biomedical waste management, are also essential to keep the healthcare workers from getting exposed to the viral particles of SARS-CoV-2. In addition to these non-pharmaceutical interventions, a crucial factor that could necessarily slow down the spread of the virus is scrupulous maintenance of oral hygiene using a virucidal mouth rinse/gargle. Dentists are at higher risk of acquiring SARS-CoV-2, due to proximity with the oral cavity. Therefore dentists must adopt suitable preventive measures to lower the load of SAR-CoV-2 in the oral cavity. Preoperative mouth rinsing with a suitable virucidal mouthwash is considered as the main preventive option to control the viral load in the saliva and the aerosol during and after any dental procedure.

Based on available evidence in the literature, Povidone-iodine (PVP-I), iodine with the water-soluble polymer polyvinylpyrrolidone is proven to be effective against coronavirus[10,11]. Oral and nasal decontamination by using PVP-I can reduce 'the amount of virus particle aerosolization before it reaches barriers, surfaces, and fomites[12,13]. Considering the complex dynamics involved, the paper explains the mechanisms and importance of the PVP-I gargle as a viable prophylactic measure to lower the viral loads in the oral and oropharyngeal region to interrupt the progression of the COVID-19 infection. The paper also discusses the current evidence that supports the virucidal properties of PVI-P on the novel SAR-CoV-2 and its role in preventing the spread of infection during the COVID-19 pandemic. The paper is timely and is of paramount importance to

the dentists, dental hygienists, medical healthcare workers, and also the public at large to note the importance of PVP-I in controlling SAR-CoV-2 infection.

Method

a. Search strategy, Information sources, and Keywords: The electronic databases (PubMed), ClinicalTrials.gov, EBSCO (dentistry and open science access), Scopus, Web of Sciences, Cochrane database, and ClinicalTrial.org. were searched to retrieve all data related to PVP-I and Covid19. The grey literature (Google scholar) was searched on 2nd September 2020 and updated till 22 November 2020. The following keywords were utilized for data collection: ["Povidone Iodine"[All Fields] AND "COVID19" [All Fields] AND "SARS-CoV-2" "[All Fields]. The search was complemented by hand-searching of the reference lists of included articles and performing a citation search for any additional reviews. Articles written in any language from 2000 to 2021 were included. All articles written in languages other than English were translated and reviewed. All in vitro, and in vivo studies including observational studies (cohort, case-control, cross-sectional), experimental and randomized and non-randomized analytical studies in humans or animals, letters to the editor or case series (with any patient-related information or data), case reports, literature reviews, editorials, book reviews were reviewed. The results of the searches run on the above-mentioned databases were compiled in the Mendeley reference manager (version 1.19.4) and duplicates were removed. Three members of the team (A.C, R.R, and K.S.) independently screened the articles to exclude those that do not meet the eligibility criteria. In case of any discrepancy, a mutual discussion with other members of the team (A.N and D.B) was made and all the unique citations were carefully scrutinized and selected. The total number of articles from the different databases were as follows: PubMed: 43, Scopus: 34, Web of Science: 2; EBSCO (dentistry and open science access): 9; Cochrane database and Cochrane clinical trial registry: 9; ClinicalTrial.org: 13. A thorough review of all the results was done to collect all the evidence that

confirms that PVP-I is effective against SARS-CoV-2. The results were tabulated to highlights the efficacy, rationale, and method to use PVP-I during the COVID19 pandemic.

Results

Based on the existing pieces of evidence and published literature, it was observed that currently no published randomized clinical studies are supporting the virucidal effects of any preprocedural oral rinse against SARS- CoV- 2 (Table 1 and Table 2). However, there are a lot of clinical trials and ongoing studies trying to confirm the efficacy of PVP-I against SARS-CoV2 (Supplementary Table). Based on the in-vitro studies, the ADA interim guidelines for minimizing the risk of COVID- 19 transmission suggest the preprocedural oral rinsing with 1.5% hydrogen peroxide (commercially available in the United States) or 0.2% PVP- I (not commercially available in the United States)[14-20]. The CDC recommends preprocedural rinsing with antimicrobial rinses such as chlorhexidine gluconate, essential oils, PVP- I, or cetylpyridinium chloride. PVP- I is safe for use in the oral and nasal cavities at concentrations up to 1.25%[21]. In the absence of any commercially available preparations for routine dental use during the COVID19 pandemic, it is advised to dilute 10% PVP-I by 1:20 and mix 0.5cc of the diluted PVP-I solution with 9.5cc of sterile saline or sterile water for routine clinical use[18-22]. Bidra et al. (2020) recommend the regular use of the diluted form of 0.5% PVP- I oral rinse to decrease the risk of nosocomial transmission associated with viral shedding from asymptomatic individuals.[17,18] It is also advised to frequently use PVP-I oral and nasal spray in hospital settings with inadequate PPEs (Table 1). At this concentration, iodine absorption is minimal and is below the total daily iodine intake for a healthy adult of 150 µg[22].

Discussion

The current evidence supports the virucidal properties of PVI-P against the novel SAR-CoV-2. The preoperative use of PVP-I mouthrinse/gargle is important in preventing the spread of infection during the COVID-19 pandemic. The rationale, virucidal properties, dosage, and studies proving the efficacy of PVP-I during the COVID-19 pandemic is summarized as follows:

a) The rationale for PVP-I use during SARS-CoV-2 infection

Since the oral, nasal, and respiratory tract is strongly interconnected, the importance of maintaining good oral hygiene by gargling and rinsing with an antiseptic mouth rinse during the respiratory tract infections like SARS-CoV-2 is crucial. Studies have shown various components of the oral cavity, such as gingival crevices, buccal mucosa, tongue, tonsils, palate, micro-cracks on the tooth surface, provide a perfect niche for viral particles in patients suffering from viral respiratory infections[12,13]. Moreover, the oral biofilm-induced periodontal inflammation is also linked with the development of lower respiratory tract infection that can trigger the onset of ventilator-associated pneumonia (VAP)[22-27].

Many systematic reviews and meta-analyses have confirmed the importance of good oral hygiene and the use of chemical antiseptic agents to prevent respiratory disorders and nosocomial infection[25-30]. Additionally, oral prophylaxis is also confirmed to have a critical role in regulating the SARS-CoV-2 pandemic, as intact oral mucosa circumvents the virus-invade-host theory. The receptor-binding domain of SARS-CoV-2 has an affinity for binding to human Angiotensin-Converting Enzyme 2 (ACE2) receptors[6,7,31,32]. The ACE2 receptors are prevalent in the lungs, oral tissue, and salivary glands, making them a potential site for invasion[29-32]. The oral cavity is

'identified as a high-risk infectivity site' with saliva being a primary mode of transmission of viral particles and a potential source of community-wide spread of infection[29-31].

In patients with severe COVID-19, saliva ejected from the salivary gland ducts has shown to contain 2019nCoV nucleic acid, possibly serving as an ideal candidate for non-invasive diagnostic testing[32-38]. The viral particles from the infectious respiratory fluids and salivary droplets bring about a short-distance transmission during breathing, talking, coughing, or sneezing[32,33]. Large salivary droplets, with a diameter of more than 60 μm, usually settle down quickly, limiting the transmission to only those persons who are near the source[34]. However, smaller droplets (diameter $\leq$ 60 μm), which evaporate and form droplet nuclei of diameter $<$ 10 μm, have the capacity for long-distance aerosol transmission [31]. With an estimated expulsion of 40,000 saliva droplets generated with each sneeze, it is essential to reduce the salivary viral load[34-36]. Studies have confirmed that the viral load in the saliva of an infected COVID-19 at the time of hospitalization is as high as $1{\cdot}2\times10^8$ infective copies/ml[37]. Considering the fatality rate of COVID-19 ranging between 0.39% and 4.05%, the risk of transmission from infected hospitalized individuals to healthy family members, caretakers, healthcare professionals, and other patients visiting the hospital is high[37,11]. The risk of transmission is also increased for hospitalized patients requiring procedures such as non-invasive ventilation, intubation, and suction, which generate bioaerosol and result in nosocomial transmission among healthcare workers[11]. In a retrospective study in Wuhan on hospitalized patients having novel corona virus-infected pneumonia (NCIP), approximately 40% of cases were found to have a hospital-associated transmission as the purported mechanism of acquiring infection[38]. Among the infected cases, 40 were healthcare workers and 17 patients were hospitalized for other causes. In another report, the Chinese Center for Disease Control and Prevention (Beijing, China), stated that out of 44,672 COVID-19 positive cases, 1,716

were healthcare workers[39]. Studies have confirmed that SARS-COV-2 is identified in the respiratory, nasal, and oral secretions of asymptomatic as well as mildly symptomatic COVID-19 patients[2], implying that the asymptomatic patients are potential carriers for the transmission of viral particles to healthy individuals[3,40,41]. An infected person having the SARS-CoV-2 virus in his secretions can spread the infection to nearly 406 individuals in 30 days[42]. It has been shown that a small amount of SARS-CoV-2 RNA is detected in the salivary secretion much after recovery[21]. SARS-CoV-2 infection akin to respiratory syncytial viruses (RSV) infection spreads by large infected droplets that via the air gets inoculated into the mucosa of the nose, eyes, and oral cavity[39]. It is thereby vital to lower the viral load in saliva and oropharynx to stop nosocomial transmission and reduce community-acquired infection through the judicious use of antiseptic agents, such as PVP-I, having virucidal properties, which mitigate the coronavirus threat. PVP-I mouth rinse has shown to be beneficial for healthcare professionals, mainly dentists and otolaryngologists, who are at an increased risk of exposure as they contact the oral and pharyngeal mucosa directly during diagnosis and treatment. During the procedure, viral particles get aerosolized and remain airborne for three to four hours, contaminating multiple surfaces in the surrounding area. Thus dentists need to take utmost precaution and reduce the viral load in the saliva and oropharyngeal region.

The importance of maintaining oral hygiene practices such as regular tooth brushing and denture cleaning can also reduce the number of febrile days and risk of pneumonia in frail older people. PVP-I gargle/mouth rinse/spray has been shown to reduce the incidence of nosocomial pneumonia and its attendant complications and mortality by nearly 40%[40-43]. Professional oral care, along with the diligent use of PVP-I, can reduce the levels of potential respiratory pathogens and the incidence of aspiration pneumonia[44]. Therefore, repeated use of PVP-I is indicated for symptomatic patients infected with SARS-CoV-2, particularly in the first one to two weeks after the beginning of signs

and symptoms, as the viral load in oral and oropharyngeal secretion is the highest during that time[29]. It is also essential that PVP-I is used in asymptomatic patients, as these individuals may potentially spread the infection to both healthcare professionals and the community[2,19,45].

b) Virucidal mechanism of PVP-I

PVP-I is a broad-spectrum microbicidal which inactivates bacteria, fungi, protozoans, and several viruses. The first publication about the virucidal properties of PVP-I in 1975 showed that the titers of herpesvirus type 2 were reduced by 92%[46]. PVP-I can inactivate both enveloped and non-enveloped viruses[39]. PVP-I gargle and throat spray are effective against rotavirus, adenovirus, poliovirus, mumps virus, coxsackievirus, herpes virus, rubella virus, rubella virus, human immunodeficiency virus, and influenza virus[10]. Most evidently, PVP-I gargling can decrease the occurrences of Staphylococcus aureus (including MRSA), Pseudomonas aeruginosa, and Haemophilus influenza infections by nearly 50 % in individuals diagnosed with chronic lung/respiratory infections[47-48]. PVP-I has the maximum virucidal activity among other commonly used antiseptics such as Benzethonium chloride, Benzalkonium chloride, Chlorhexidine gluconate, and alkyldiaminoethyl glycine hydrochloride[47]. With other antimicrobial agents not significantly effective against the coronaviruses, the efficacy of PVP-I to inactivate SARS-CoV-2 is critical.

The virucidal mechanism of PVP-I is due to its free or non-bound Iodine/I_2 that is released into its environment from the complex of PVP-I. In an aqueous solution, I_2 and hypoiodous acid (HOI) are the two forms of elemental iodine, which are active in terms of the antimicrobial activity of PVP-I [49]. The I_2 destabilizes the membrane envelope and causes lysis of viral proteins[40]. PVP-I targets the lipid coating of SARS-CoV-2, like all β- CoV[49-53]. PVP-I also forms various complexes with unsaturated fatty acids and amino acids within the cell, induces cytosol leakage, and impairs protein synthesis[10]. The free iodine even degenerates the nucleoproteins of the viral particles,

oxidizes the nucleic acids, alters the metabolic pathways that can cause irreversible damage to the virus. Furthermore, the free iodine scavenges the free radicals, thereby providing an anti-inflammatory property during viral infections[50-55].

c) Evidence that PVP-I can inactivate SARS-CoV-2 (Table 1 and Table 2)

The habit of gargling and rinsing with undiluted PVP-I (10-15 mL) for 30 seconds is a standard regimen to prevent sore throat[17] and for antiseptic prophylaxis before, during, or after surgery. However, extended rinsing with an appropriate dilution of PVP-I, for more than 2 minutes, up to four times a day, is advocated to reduce the incidence of airborne respiratory infections such as avian flu, SARS, swine flu[33,34]. The use of PVP-I mouthrinse has been recommended as a preventive strategy to effectively inactivate the viral load in the oral and oral pharyngeal region, infected with SARS- CoV-2[6,11]. Gargling with PVP-I has been recommended by the Respiratory Society in Japan for the prevention and treatment of hospital/ community-acquired respiratory infections.[55]

These recommendations are based on previous studies where PVP- I gargle and throat spray, revealed virucidal properties against both the low pathogenic (H5N3, H7N7, and H9N2) strains of avian influenza A and highly pathogenic (H5N1) viruses[55]. 0.23% gargle and throat spray PVP-I could reduce the viral load of avian influenza A virus to below detectable limits within 10 seconds[55-58]. Furthermore, another study confirmed the efficacy of PVP- I gargles against swine influenza viruses (H3N2, H1N1 and H1N2)[56,57]. The rapid virucidal activity of PVP-I has been proved against 'the Ebola virus (EBOV) and modified vaccinia virus Ankara (MVA), the new European test virus for enveloped viruses'[58]. Incidentally, 7% PVP-I gargle/mouthwash has demonstrated antimicrobial effects within 15 seconds of exposure against various upper respiratory tract infections based on the European standards EN14476 and EN13727[58,59]. On the other hand,

PVP-I could kill more than 99.99% of MERS-CoV and MVA within 15 seconds of its application. 0.23–1% PVP-I mouthwash for 1–2 minutes can also reduce the SARS-CoV virus infectivity to below detectable levels[56-60].

Thus, PVP-I gargling is considered beneficial in immunocompromised patients who are at risk of prolonged virus shedding. In a hospital-based clinical trial, PVP-I formulation reduced the number of episodes of respiratory infection by 58%[59]. Based on this evidence, the Ministry of Health, Labour, and Welfare in Japan has issued a guideline to use PVP-I as a preventive measure to preclude respiratory tract infection after the H1N1 swine flu outbreak in 2009. PVP-I gargle/mouthwashes are also used for the prevention of respiratory and endotracheal infections in a hospital setting. Liang et al., 2020, conducted a study to evaluate in-vivo toxicity and inactivation efficacy of PVP-I nasal spray and ophthalmic eye drop on SARS-CoV-2 and concluded that PVP-I could rapidly inactivate SARS-CoV-2[60]. In another paper published recently by Martínez et al. (2020), 1% PVP-I reduced the viral load of SARS-COV-2 load in nasal swabs and saliva to almost detectable limits, and the effects lasted for nearly 3-4 hours[61]. Chin et al. (2020) also found that 7.5% of PVP-I exposure to SARS-CoV-2 (7.8 of log10 (TCID 50/ml) caused the virus to drop below detectable levels within 5 minutes[62].

Various countries have developed their protocols regarding oral and nasal usage of PVP-I during COVID-19 (Table 1). A recent letter by Challacombe et al., 2020 recommended the use of 0.5% PVP-I solution (9 ml) as a mouthwash for 30 seconds followed by an additional 30 seconds of gargling before spitting[63]. In the United Kingdom, patients who are conscious and are infected with COVID19 or persons under examination for COVID19 were given 0.5% PVP-I rinse (0.3 mL) in both the nostril and 9 mL in the oral cavity before any procedures.[13,48,61] In unconscious patients, the application of 2 mL of PVP-I onto the mucosal surfaces of the oral cavity was advised.

0·5% (5 mg/ml) of PVP-I can be applied to oral, nasal, and oropharyngeal mucosa of patients with presumed/confirmed COVID-19 patients or healthcare personnel in close contact to prevent the risk of cross-contamination[11]. PVP-I mouth rinses, every 2-3, or about 4 times a day, is recommended for healthcare workers exposed to infected patients[11]. Another protocol in Pittsburgh recommended application of '240 ml of 0.4% PVP-I in the nasal cavity via sinus rinse delivery bottle and 10 mL of 0.5% PVP-I oral rinse every 2-3 hours, four times in a day, in patients diagnosed with COVID-19, under investigation or before high-risk procedures'[64]. The author also recommended this regime for health care workers before examining or treating suspected or diagnosed COVID-19 patients, performing high-risk procedures, and in a setting with under-resourced PPE. PVP-I is also a part of the anesthesia guideline for operative/surgical room care during the COVID-19 pandemic and recommends the use of nasal PVP-I within one hour of incision for all patients[63-65]. Most of these protocols apply to both symptomatic and asymptomatic patients.

To prevent cross-contamination among dentists, the 'American Dental Association (ADA)' has approved the use of 0.2% of PVP-I mouthwash before all dental procedures during the COVID19 pandemic. Since no commercial preparations of PVP-I for routine dental use is available, dilute the 10% PVP-I (1:20), using 0.5cc of 10% PVP-I and 9.5cc of sterile water or saline, for clinical application [11-14]. Parhar et al., (2020) stated that "until confirmatory studies are performed, it is best to dilute the PVP-I with saline (typically 7.5%) in a ratio of 1:3, to attain a concentration of less than 2%.[16] Bidra et al., (2020) tested different concentration of PVP-I (0.5%, 1% and 1.5%). against SARS-CoV-2 and concluded that all diluted concentrations inactivated the SARS-CoV-2 virus within 15 seconds[17]. The study also showed that 70% of ethanol did not inactivate SARS-CoV-2 even after 15 seconds of contact completely, but could inactivate the virus after 30

seconds[17]. Bidra et al. (2020b), in another *in-vitro* study, compared the inactivation of SARS CoV-2 by hydrogen peroxide and PVP-I and concluded that at "15-second and 30-second contact times, PVP-I oral antiseptic rinse at all the three concentrations of 0.5%, 1.25%, and 1.5% completely inactivated SARS-CoV-2[18]. The hydrogen peroxide at a concentration of 1.5% and 3.0% showed minimal virucidal activity even 30 seconds of contact time (Table 1). A recently published study tested the virucidal activity of 8 commercially available oral rinses containing different active compounds against 3 different SARS-CoV-2 isolates under conditions mimicking nasopharyngeal secretions and found that 1% PVP-I mouthwash rinse reduced the viral inactivity significantly within a short exposure time of 30secs[19,70.]

Variants of PVP-I in the form of scrubs, solutions, swab sticks, labeled for external use, should be avoided for oral and nasal applications, as they contain additional salts and co-solvents. The concentration of the PVP-I solution and the duration of exposure should be optimized to maximize the virucidal effect. The concentration and duration of PVP-I can be decided based on the mucous and salivary flow of the individual. Since the flow rate of saliva in a hospital-bound semiconscious patient is low and clearance of PVP-I is slower than usual, prolonged exposure of PVP-I is indicated[69,70]. It is recommended that, for complete viral eradication, PVP-I products should be used for two weeks at least, or until local authorities control the risk of infectivity. This intervention is not intended to cure the disease but may significantly and dramatically reduce viral spread into the community and workplaces. Thus it is recommended that individuals who are suspected to come in contact with SARS-CoV-2 infected individuals or individuals who are traveling to or coming from COVID-19 hotspots should frequently use PVP-I mouthrinse or gargle to lower the viral load of SARS-CoV-2 viral particles in the oral and oropharyngeal region.

d) Safety and tolerance of PVP-I

PVP-I gargle/mouthwash is well tolerated when compared with other antiseptic agents. Povidone-iodine can be safely administered for up to five months in the nasal cavity, and six months in the oral cavity[63]. In an in-vitro study assessing the safety of PVP-I on the oral mucosa of rats, apoptosis of cells occurred at a concentration of 1×10^2 mM for one day [64]. An in vivo study confirmed that prolonged use of 1% to 1.25% PVP-I gargle did not irritate mucosa or result in any adverse effects of up to 28 months. Povidone-iodine gargle did not stain teeth or cause a change in gustatory function[65-67]. However, there have been reports of inadvertent aspiration pneumonia in patients while gargling with PVP-I solution at 0.25% to 10%[66]. Although a small amount of iodine is systemically absorbed from the mucosa, thyroid function is not commonly affected. However, an increase in the serum thyroid-stimulating hormone concentration has been noted in individuals with prolonged PVP-I treatment (24 weeks)[41--48]. Under these circumstances, it is advisable to have a 3-week interval to allow the serum TSH levels to stabilize. PVP-I should be avoided in patients with hyperthyroidism, thyroid dysfunction states, pregnancy, and lactation[48-51]. Allergy to PVP-I is also extremely rare, with a prevalence rate of 0·4%[10].

Conclusion and summary

Oral hygiene intervention, along with the gargling/mouthwash with an antiseptic having virucidal properties is imperative during this pandemic of COVID 19. Based on the Occupational Safety and Health Administration guidelines, PVP-I is safe to use as a mouth rinse, and the existing in-vitro studies and patient-based clinical trials confirm its virucidal property against SARS-CoV-2. In vitro studies have confirmed that 0.5% PVP-I is effective in reducing SARS-CoV-2 in the nasal cavity, nasopharynx, oral cavity, and oropharynx. Since vaccines against SARS-CoV-2 are being rolled and administered globally, the use of PVP-I gargle/ mouthwash as a simple, inexpensive, and safe adjunct should be used to reduce the risk of cross-transmission of SARS-CoV-2 viral particles to the community and healthcare professionals. Routine PVP-I gargling/mouthwash/nasal spray can be implemented for all hospitalized and non-hospitalized, symptomatic, and asymptomatic patients infected with SARS-CoV-2 to reduce the viral load. It is equally essential for healthcare professionals (dentists, dental assistants, dental technicians), isolated and quarantined individuals, frequent travelers to use PVP-I mouthrinse to minimize the risk of cross-infection in both the hospital and non-hospital settings. A timely prophylactic oral hygiene regimen using appropriate gargle/mouth rinse, and promoting awareness of the harmful outcomes of poor oral health, may significantly improve the health among vulnerable patients and bridge the gap between oral and general health during the COVID19 pandemic.

Author contribution statement

Name of the authors	Contribution roles
Aditi Chopra	Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Supervision; Validation; Visualization; Roles/Writing - original draft; Writing - review & editing.
Karthik Sivaraman	Conceptualization; Data curation; Formal analysis;;; Resources; Software; Supervision; Validation; Visualization; Roles/Writing - original draft; Writing - review & editing.
Raghu Radhakrishnan	Conceptualization; Data curation; Formal analysis;; Investigation; Methodology; Project administration; Resources; Software; Supervision; Validation; Visualization; Roles/Writing - original draft; Writing - review & editing.
Dhanasekar Balakrishnan	Conceptualization; Supervision; Validation; Visualization; Roles/Writing - original draft; Writing - review & editing.
Aparna Narayana	Conceptualization; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Software; Supervision; Validation; Visualization; Roles/Writing - original draft; Writing - review & editing.

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Table 1: Recommendation for Nasal/Oral administration of PVP-I [56, 61, 61]:

Subjects	Route of administration**	Dosage
Patients who a. Have confirmed/suspected SARS-CoV-2 infection b. Are undergoing high-risk procedures (e.g. those involving nasal, oral, pharyngeal, and pulmonary secretions) c. Have resisdence in COVID-19 hotspots d. Unconscious patients^	Oral or Nasal PVP-I	Every 2–3 hours, up to 4 times/day
Healthcare providers before and after patient contact and a. Involved in care of patients with suspected/confirmed SARS-CoV-2 infection b. Involved in high-risk procedures for patients in COVID-19 hotspots c. Lack of adequate PPE (e.g. N95, PAPR)	Nasal and Oral PVP-I	Every 2–3 hours, up to 4 times/day
Patients and/or healthcare providers in COVID-19 hotspots involved in high-risk procedures involving asymptomatic patients	Optional Nasal and Oral PVP-I	Every 2–3 hours, up to 4 times/ day

**** Nasal:** 0·5% PVP-I solution can be administered in a dose of 0·3 ml into each nostril, preferably using an atomizing device (2 sprays for average device) or if not from a syringe o dropper. This will give a total dose of 0·33 mg of iodine. **** Oral:** Gargling with 10 ml of PVP-I 1% mouthwash solution (undiluted) (9 ml of the 0.5% solution) for 1-2 minutes. Hold the solution for at least 30 seconds and then gently gargled or held at the back of the throat for another 30 seconds (at least), then spit out. (2 ml of the solution will be retained and absorbed, giving an anticipated maximum total dose of 1·1 mg of iodine. ^ An oral care sponge swab or similar is soaked in 2-5 ml of 1% PVP-I and this is carefully wiped around all oral mucosal surfaces. Most of this solution will be retained in the mouth/ oropharynx (a small amount remaining in the sponge), giving a maximum total dose of 1·1 mg iodine.

Table 2: Evidence confirming the efficacy of Povidone-Iodine (PVP-I) against SARS-CoV-2

No	Study	Objective	Material and Methods	Results & Conclusion	References
1.	In-Vitro observational study	Virucidal activity of PVP-1 against SARS-CoV-2	Four products of PVP-I a. Antiseptic solution (PVP-I 10%), b. Skin cleanser (PVP-I 7.5%), c. Gargle and mouth wash (PVP-I 1%) d. Throat spray (PVP-I 0.45%) Tested for a contact time of 30 seconds for virucidal activity	All products of PVP-I inactivated the virus by ≥ 99.99% which corresponded to ≥ $4\log_{10}$ reduction of virus titre, within 30 seconds of contact.	Anderson et al. 2020 [6]
2.	In-Vitro observational study	Optimal contact time and concentration of oral PVP-I against SARS-CoV-2	a. PVP-I at a concentration of 0.5%, 1% and 1.5% compared with b. Ethanol (70%) and water for 15 and 30 seconds Tested against SARS-CoV-2-USAWA1/2020 strain	PVP-I (0.5%, 1% and 1.5%) inactivated SARS-CoV-2 completely within 15 seconds of contact. 70% ethanol group did not inactivate SARS-CoV-2 after 15 seconds of contact, but was able to inactivate the virus at 30 seconds of contact.	Bidra et al. [60]
3.	In-Vitro observational study	Compare Hydrogen peroxide (H_2O_2) and PVP- I oral antiseptic rinses against SARS-CoV- 2	a. PVP-I (0.5%, 1.25% and 1.5%) and b. H_2O_2 aqueous solutions (3% and 1.5% concentrations) at contact periods of 15 seconds and 30 seconds. Was tested against SARS- CoV- 2	PVP- I (0.5%, 1% and 1.5%) inactivated SARS- CoV- 2 completely at 15 sec. The H_2O_2 solutions (1.5% and 3.0%) showed minimal virucidal activity after 15 seconds and 30 seconds of contact time.	Bidra et al. [61]
4.	Systematic Review	To evaluate the specific efficacy of PVP-I against	All protocols for nasal and oral PVP-I against COVID-19 were	PVP-I can be safely administered for up to 5 months in the nasal cavity and 6 months in the oral cavity.	Frank et al. [62]

		SARS-CoV-2	systematically reviewed.		
5.	Short communication	The impact of PVP-I mouthwash on the salivary viral load of SARS-CoV-2.	a. Nasopharyngeal swabs and salivary samples were tested for SARS-CoV-2 in patients before and after rinsing with 15 mL of 1% PVP-I for 1 min.	PVP-I resulted in a significant drop in viral load, which remained for at least 3 hours.	Lamas et al. [53]