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Povidone Iodine (PVP-I) Nasal Spray: A Potential Agent Against SARS-CoV-2

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ABSTRACT

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), which is also recognized as COVID-19 virus, is a type of coronavirus that is enveloped with lipid bilayer surrounding the inner viral core. The nasopharynx is one of the known principal reservoirs of the COVID-19 virus. High loads of SARS-CoV-2 virus were identified within the nasopharynx in both symptomatic and asymptomatic patients. Povidone Iodine (PVP-I) nasal spray, a powerful antiseptic that is scientifically proven to eliminate numerous types of harmful microorganisms like bacteria and viruses and was also proved to provide protection or coat barriers over the nasal mucosa. When utilized intranasally, it prevents SARS-CoV-2 from binding to the ACE-2 receptor and penetrating into the body. It was observed that SARS-CoV-2 can be entirely inactivated in a span of 15 seconds within contact using PVP-I nasal antiseptic sprays at doses of 0.5%, 1.25%, and 2.5%. Povidone-iodine (PVP-I) shows a profile for mucosal tolerance and significant deactivation of the COVID-19 virus at the lowest concentrations in both time-dependent and dose-dependent manner, giving it the potential to be an effective agent against the said virus. The aforementioned assessment seeks to unravel the therapeutic potential of PVP-I nasal spray against COVID-19 virus based on scientific evidence from various studies. This review will significantly benefit those individuals who seek to understand further about PVP-I nasal spray which will provide them with approaches to verify facts about it.

Keywords: Povidone Iodine; PVP-I; Nasal Spray; SARS-CoV-2; COVID-19 virus; Antiviral

Introduction

SARS-CoV-2 is a coronavirus that is genetically related to SARS-1. It is a member of the Coronaviridae family, which is a subfamily of the Nidovirales order. It is primarily spread through the air and is highly infectious, but it has a low morbidity rate compared to other airborne organisms. [1]. Human coronavirus was first linked to adult upper respiratory infections and children's respiratory illnesses. They were first linked to living beings in 1960 after isolating them from a sick individual. The Coronaviridae are RNA viruses with a single-stranded positive (+) sense. The human coronavirus have enveloped viruses with a lipid bilayer surrounding the inner viral core and 20nm-diameter surface projections [2]. They are spherical and pleomorphic, with a wavelength range of 80-220 nm. Droplet nuclei, which require contact points with the nasal track or an oral route, appear to be the most common way for the virus to spread. There is also evidence of fecal-oral transmission [1].

The ACE2 is the fundamental receptor of SARS-CoV-2 and the nasal cavity has the most elevated articulation of it [3]. The nasopharynx, nasal cavity, and oral cavity serve as reservoirs for SARS-CoV-2 shedding; virucidal treatments applied to these surfaces may lower virus load. As indicated by various examinations, povidone-iodine is a rapid virucidal agent that could inactivate SARS-CoV. [4]. Povidone-iodine exhibited prevention of SARS-CoV-2 from attaching to oronasopharyngeal tissues, resulting in a reduction in virus particles in saliva and respiratory droplets [5]. The povidone-iodine complex generates free iodine, which oxidizes unsaturated fats in the viral cell divider, then disables the chain cytosolic enzymes of the respiratory tract, and the host tissue inflammation decreases [3].

Within 15 seconds of contact with the utilization of povidone-iodine nasal antiseptics at 0.5%, 1.25%, and 2.5% doses, SARS-CoV-2 was entirely inactivated. Upon testing, no cytotoxic consequences for cells were recognized [6]. Moreover, its in vitro efficacy was proven to be effective against SARS-CoV for as much as 0.23% concentration [7]. Povidone-iodine intranasal usage may have an ancillary role in alleviating viral transmission along with personal protective equipment and was proven to safely administer at concentrations of 1.25% and below [8].

Povidone-iodine has a favorable mucosal tolerance profile [4].In in vitro experiments, fixations of less than 2.5 percent had no effect on the relapse of ciliary rhythms or the production of neurotic changes in respiratory tracts, mucosal cells, and ciliated nasal epithelium.[9].In one study, povidone-iodine was discovered to be ciliotoxic at only 5% and 10% concentration levels, but not at 8% density. Moreover, low levels of povidone-iodine have never

been shown to discolor teeth or cause considerable severe reactions. Patients who have iodine allergies, are enduring radioiodine therapy, or have thyroid issues should avoid using povidone-iodine oronasal spray [10].

Based on scientific evidence from various studies, this review seeks to elucidate the therapeutic potential of PVP-I nasal spray on COVID-19 virus. This review will greatly benefit those who want to learn more about PVP-I nasal spray and will provide them with methods to verify facts about it.

2. Methods

This article reviewed researched and collected data related to COVID-19 and Povidone-iodine (PVP-I) using various studies and peer-reviewed articles from journal databases such as Google Scholar, PubMed, BioMed Central, SpringerLink, and ResearchGate.

2.1 Sinonasal pathophysiology of SARS-CoV-2

COVID-19, a new coronavirus disease in 2019, is caused by SARS-CoV-2, a highly infectious and lethal virus. The nasopharyngeal and paranasal sinus cavities are the locations of its manifestations and transmission. The nasopharyngeal cavity, where genetic predisposition genes are expressed at high levels and may be influenced by host and environmental factors, may be a primary site of COVID-19 infection. The nose has been identified as the source of the majority of viremia, indicating that it is a major route of contamination. Numerous reports of healthcare-associated infection (HAI) throughout the rhinologic processes have highlighted this, and health-care workers are now considered to be at high risk of SARS-CoV-2 transmission. While sinonasal symptoms such as rhinorrhea and congestion appear to be a less common COVID-19 symptom, anosmia without nasal obstruction has been identified as a highly specialized determinant of COVID-19 positive patient populations. SARS-CoV-2 transmission might happen through air borne particles as tiny as 5 m in size, which can stay aloft for a prolonged period of time. It is then quickly breathed and has the potential to permeate the proximal alveoli and lungs. These respiratory tract particles could be thrown to the ground by gravity and snorted into the nasal cavity, or they could be inoculated to the respiratory epithelium by touching surfaces with live viruses. The nasopharyngeal cavities are thought to be a primary site for SARS-CoV-2 infectious disease. [11-15]

The nose is a vital component for mucosal immunity. It works in the upper airways and plays a key role in both immune homeostasis and host protection against invading pathogens. COVID-19 virus infiltrates the human body primarily by TMPRSS2 +ACE2 + nasal epithelial cells. The primary host would respond to the virus in a resistant microenvironment which will be procured from the Nasopharynx-Associated Lymphoid Tissue (NALT) system. This primarily recognizes those exogenous airborne agents. SARS-CoV-2 interacts with the S protein on the ACE2 receptor upon entering the respiratory tract. The Proteolytic cleavage of S promotes SARS-CoV-2 infection alongside a cellular protease TMPRSS2 mediates, then followed by viral nucleic acid release, protein synthesis, and aggregation of new viral particles. SARS-CoV-2 can be passed on through the respiratory droplets emancipated by COVID-19 positive patients. The droplets, which are large particles, can be deposited within a few meters of the emitting object and infect people near it, whereas aerosols, which are smaller in diameter (<5 µm), can infect subjects from a distance. In addition, contaminated things could also be a cause of infection, particularly in the absence of regular hand hygiene [16-21].

2.2 Povidone Iodine (PVP-I) Chemical Properties and Its Potential Antiviral Effects

PVP-I is an iodine-producing agent, composed of a mixture amidst polyvinylpyrrolidone and iodine. There is a dynamic equilibrium existing in an aqueous solution between the active bactericidal agent, the PVP-I-complex and the free iodine (I2). When diluting a 10% solution of PVP-I, the levels of iodine increase with the dilution and then follow a bell-shaped curve, hitting the highest level of about 0.1% strength of solution, subsequently decreasing with succeeding dilutions. The antimicrobial action of PVP-I is highly correlated with free iodine content. [22-24] PVP-I works as an antiseptic in a variety of ways and has been deemed to possess the greatest spectrum of activity compared to other antiseptics like chlorhexidine. Molecular I2 and hypoiodous acid, which supply free iodine, are the two most effective antiseptic metabolites of PVP-I. Amino acids, nucleic acids, and cell membranes are all oxidized by free iodine molecules. PVP-I stops viruses from attaching to cellular receptors by oxidizing cell surface receptors [25].

The World Health Organization included the PVP-I in its list of essential medicines. WHO also emphasized its high potency in killing viruses of significant concern like influenza and Hepatitis A, including Middle East Respiratory Syndrome. The mechanism of action of PVP-I's virucidal activity is inhibiting neuraminidase, which is a viral enzyme. The inhibition of the enzyme prevents the virus from spreading to healthy cells by blocking its viral release. Furthermore, PVP-I also inhibits a homotrimeric glycoprotein called haemagglutinin which results in the blockage of host cell receptor attachment. Because PVP-I targets both critical parts of the virus, it reduces the possibility of the virus developing resistance. Research shows that PVP-I preparations are effective against these diseases but not limited to them, these diseases are HIV, influenza, rota-viruses, herpes, measles, and mumps [26-27].

2.3 Povidone Iodine (PVP-I) Nasal spray as a potential agent against SARS-CoV-2

One of the principal reservoirs of the COVID-19 virus is the nasopharynx. Peak SARS-CoV-2 heaps were found in the nasopharynx of symptomatic and asymptomatic carriers. Hence, nasal decontaminants have been strongly recommended besides personal protective equipment to curb the transmission of the virus [6]. PVP-I utilized intranasally, was proved to provide a protective barrier or coating over the nasal mucosa, preventing SARS-CoV-2 from binding to the ACE-2 receptor and entering into the body. The free iodine is discharged by the PVP-I complex after dilution. Afterwards, fatty acids in the viral cell wall become oxidized. Subsequently, the respiratory chain cytosolic enzymes become inactivated. Finally, it reduces swelling in the host tissue [10].

In consonance to Kirk-Bayley, J., et al., journal article by Khalil, I., et al., stated that PVP-I outperforms other antiseptics like chlorhexidine and benzalkonium chloride in terms of virucidal action. It was distinguished to be dynamic in in vitro versus coronaviruses, SARS-CoV and MERS-CoV that have induced pandemics over the most recent twenty years. SARS-CoV-2 is in direct relation to SARS-CoV since it is substantially homologous with SARS-CoV. Eggers' gathering explored the virucidal action of povidone-iodine to MERS-CoV and found that the most reduced powerful centralization of povidone-iodine was 1% when utilized for 30 seconds under squalid conditions culminating in a ≥99.99% drop in viral activity, but this was ineffective at 0.1%. Eggers conducted an additional investigation and discovered that the concentration remained high at 0.23%. SARS-CoV activity was suppressed to undetectable levels after 2 minutes of in vitro treatment with several PVP-I formulations. According to recent comparisons, SARS-CoV-2 should behave similarly [28].

Conforming to the journal article of Khalil, I. and Barma, P., it stated that povidone-iodine is a more potent virucidal than other antiseptics that have been established to fight against SARS-CoV and MERS-CoV. After diluting povidone-iodine in an aqueous solution, The PVP-I complex generates free iodine that could oxidize those fatty acids found in the viral cell wall, then deactivates the respiratory chain cytosolic enzymes, and reduces host tissue inflammation. The principal receptor of SARS-CoV-2, ACE2, is highly exhibited in the lymphocytes of oral tissues, nasal cavity, goblet and ciliated cells, nasopharynx and oropharynx within the nose's respiratory epithelium. PVP-virucidal I's efficiency against the SARSCoV-2 virus was determined in a clinical trial after 60 seconds of incubation at 22±2oC in 5.0%, 2.5%, 0.5% nasal antiseptic concentrations. Some authors proposed that in hospital settings where COVID-19 is detected or diagnosed, a solution of 5% PVP-I (0.55 mg/mL accessible iodine) has been administered to nasopharyngeal, oropharyngeal, and oral mucosa of patients in close contact with workers in the medical field to prevent cross-contamination. During inadvertent ocular exposure or contact, lubricating drops that contain 1 mL of 5% PVP-I mixed with 4 mL of Benzalkonium chloride (BAK) in stat dosage significantly reduces the risk of contamination. The use of 0.2% povidone-iodine may help to prevent ventilator pneumonia.
[3]

In the study of Frank, S. et. al., within 15 seconds, PVP-I nasal antiseptics at 0.5%, 1.25%, and 2.5% concentrations successfully deactivated SARS-CoV-2. The positive control, ethanol 70%, following 15 seconds of exposure to SARS-CoV-2, failed to completely deactivate the virus. Thus, Povidone-iodine nasal antiseptics demonstrated superior in vivo efficacy against the standard positive control at 15 seconds of exposure time. In another study by Anderson, D. et al., PVP-I within 30 seconds of contact with SARS-CoV-2 virus demonstrated a ≥ 4 log10 reduction of the COVID-19 virus titers, complementary to a ≥ 99.99% kill, indicating a rapid virucidal activity in accordance to the European Chemicals Agency time-points for disinfectant efficacy. [29]

The intranasal use of PVP-I was proven to be safe at concentrations of 1.25% and below as an agent to mitigate viral transmission [6]. Povidone-iodine was tested for 5 months in the nasal cavity and showed no reduction of ciliary beat frequency nor exhibited pathological changes in mucosal cells, upper respiratory, or ciliated nasal epithelium. Chronic mucosal utilization for up to 5% did not exhibit any clinical thyroid disease. Moreover, contact sensitivity was rarely observed, and no adverse events were reported in conscious children or adults. [6, 30, 31].

Given that Povidone-iodine (PVP-I) has a good profile for mucosal tolerance and significant inactivation of the SARS-CoV-2 at the lowest concentrations in both time-dependent and dose-dependent manner, it can be concluded that Povidone-iodine (PVP-I) nasal spray has the potential to be a virucidal agent contra to the COVID-19 virus that is shedding in the nasal cavities nasopharynx..

Povidone Iodine is a well-known antiviral, antibacterial, and antifungal chemical that helps defend against viruses and other microorganisms that cause common upper respiratory tract infections.[32] Since povidone-iodine, often known as Betadine, has been used as an antibiotic for more than 20 years, it has shown to function against a variety of coronaviruses, including increasing experimental data against COVID-19.[33] According to a study conducted, employing an iodine solution can efficiently inactivate the virus that causes COVID-19. Even the smallest dose of iodine, 0.5 percent, was sufficient to totally deactivate the virus in 15 seconds. [34]

Conclusion

As stated in the aforementioned studies, Povidone-iodine (PVP-I) administered intranasally can potentially be used as a virucidal agent to SARS-CoV-2. The PVP-I nasal spray could have an adjunctive role to mitigate transmission aside from the utilization of personal protective equipment and practice of physical distancing, therefore, it could be an additional defense against the risks of COVID-19.

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