Role of Oropharyngeal Decontamination Reducing SARS-COV2 and COVID-19 Infection

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Resumen

La alta morbilidad, mortalidad y contagio del coronavirus en el mundo ha creado la necesidad de desarrollar modos adicionales seguros y efectivos para prevenir COVID-19 más allá de aislamiento, higiene, vacunación, y mascarillas. **Propósito:** En este artículo presentamos y discutimos la evidencia apoyando el rol de la descontaminación orofaríngea. Discutimos las propiedades antivirales de los enjuagues bucales basados en aceites esenciales, peróxido, iodo y chlorhexidine y su uso en orofaríngeo y/e intranasal.

Se ha demostrado que la descontaminación oro-nasofaríngea posee actividad antimicrobiana contra el SARS-CoV-2 que reduce la infección clínica y síntomas asociados. **Resultados**: Algunos de estos antisépticos han demostrado la capacidad de disminuir la carga viral del SARS-CoV-2 en las primeras etapas de la infección. En un estudio clínico aleatorizado de 68 pacientes que utilizaron peróxido de hidrógeno al 3% para hacer gárgaras, ninguno desarrolló pulmonía asociada al ventilador. En otro ensayo, rociar clorhexidina en la orofaringe tiene una eficacia del 86,0% para eliminar el virus. en comparación con el 62,1% de efectividad

cuando se usa como enjuague bucal. El uso de aceites esenciales (eucaliptol, mentol, salicilato de metilo y timol) mostró acción antiviral. **Conclusión:** Se encontró que los antisépticos discutidos muestran varios niveles de efectividad en diferentes ensayos de estudio. El uso de los métodos descritos para la descontaminación nasal y orofaríngea, incluida la selección adecuada del antiséptico, la concentración adecuada y la frecuencia de uso adecuada, puede reducir la carga viral del SARS-CoV-2 y, en consecuencia, disminuir la tasa de infecciones por COVID y posiblemente las complicaciones de la COVID.

Palabras clave: coronavirus, COVID-19, SARS-COV-2, peróxido de hidrógeno, hydrogen peroxide, clorhexidina, povidona yodada, cetilpirina, aceites esenciales.

Abstract

The high morbidity, mortality, and contagiousness of the coronavirus worldwide has created the need for additional safe and effective ways of preventing COVID-19 infection other than isolation, hygiene, vaccination, and masks. **Purpose:** In this article, we present and discuss the evidence supporting the role of oropharyngeal decontamination. We discuss the antiviral properties using essential oils-based mouthwash, hydrogen peroxide, iodine-Povidone, and chlorhexidine and their use intranasally and in the oropharynx. The oro-nasopharyngeal decontamination has been shown to display antimicrobial activity against SARS-CoV-2 that reduces clinical infection and morbidity. **Results:** Some of these antiseptics have demonstrated the ability to decrease SARS-CoV-2 viral load in the early stages of the infection. In a randomized clinical trial of 68 patients using 3% hydrogen peroxide in gargles, none developed ventilator-associated pneumonia. In another trial, spraying chlorhexidine the oropharynx is 86.0% effective eliminating the virus. compared to 62.1% effectiveness when used as an oral rinse. The use of essential oils (eucalyptol, menthol, methyl salicylate, and thymol) and showed antiviral action. **Conclusion:** The antiseptics discussed were found to display various levels of effectiveness in different study trials. Using the described methods for nasal and oropharyngeal decontamination, including the proper selection of the antiseptic, the proper concentration, and the proper frequency of use may reduce SARS-CoV-2 viral load and consequently decrease the rate of COVID infections and possibly COVID complications.

Keywords: coronavirus, COVID-19, SARS-COV-2, hydrogen peroxide, chlorhexidine, Iodine-Povidone, cetylpyrine, essential oils.

Introduction

Since late 2019 infection with the SARS-Cov2 virus disseminated throughout the world and still, to this day continues infecting people. As of March 2023, over 6.8 million deaths from covid-19 have been reported worldwide (Johns Hopkins University 2023, WHO 2023). The spread continues due to the emergence to new variants, which is common with RNA viruses that are more prone to mutations than DNA viruses. SARS-COV-2 is a coronavirus that causes infectious respiratory syndrome and can lead to severe pneumonia.

Coughs and sneezes produce respiratory droplets of varying sizes that propagate respiratory viral infections. Because these droplets (aerosols) are vigorously ejected, they are dispersed in the environment and can be inhaled by a susceptible host and people some distance away could inhale them. The particles inhaled can be deposited in the nasal cavity and travel and reproduce through the pharynx. Some people do not wear face masks, and others use inadequate protection or wear them in inadequate conditions, allowing for viral particles entering through the nasal cavity. Therefore, the concept of using nasal and oral antiseptics is adding another layer of protection (Dhand & Li. 2020; Jarvis 2020; Setti et al. 2020, Bakhit et al. 2021).

This virus spreads by having contact from person to person mainly through the aerosolization of respiratory droplets. Transmission may also arise through contact with contaminated surfaces. This virus can be transmitted by talking, sneezing, coughing, or touching the nose, mouth, and eyes. Some preventive strategies that have been implemented by the government to reduce COVID-19 morbidity and mortality include, wearing personal protective equipment, physical distance, hand washing, sanitizing, and getting vaccinated (CDC, 2020). The availability of rapid antigen tests to the communities allowed early detection and gave the opportunity of isolation to stop spreading and early treatment. Although these strategies were somehow helpful, the virus continued spreading causing a significant number of cases associated with substantial morbidity and mortality. Reducing the viral load early is important because it has been shown that a high proportion of SARS-CoV-2 RNAemia and an association between RNAemia and clinical severity (Hogan et al. 2021) in addition it was also correlated with mortality (Kawasuji et al. 2022). Multiple disinfectant agents are available that may inactivate viruses, but their effectiveness is dependent upon a variety of factors such as the amount and strength of the agent, contact time, temperature, and organic load (Lin et al. 2020). Some of these antiseptics are safe for humans, but other have potential toxicities and are suitable for other surfaces.

The government should add other strategies that may help reduce the spread of COVID-19 like the practice of oropharyngeal decontamination. Oropharyngeal decontamination consists in helping reduce viral load and therefore ventilator-associated pneumonia (VAP) (Derde, L, 2009). Having daily oral care regimens using chlorhexidine and other antiseptics as an oral rinse can reduce complications and the need for ventilators by up to 40% (Dale C, 2021). Ventilator-associated pneumonia occurs in ICUs frequently, ranging from 9% to 27% leading to morbidity and possible mortality (Kalanuria, 2014).

Viral infection dynamics in oropharyngeal tissue

Nasopharyngeal and saliva samples displayed different SARS-CoV-2 viral shedding dynamics, and salivary viral burden correlated with COVID-19 symptoms, including cough, runny nose, and taste loss among others. SARS-CoV-2 can directly colonize, replicate, and infect oral tissues like the salivary glands or mucosa. High viral loads have been found in the nasal cavity, the oropharyngeal, and the nasopharyngeal mucosa (Zou et al. 2020). It has been suggested that preventive or early decontamination of nasopharyngeal decontamination can decrease viral replication, infectivity, and possible complications (Citation et al. 2020). In addition, studies support a positive correlation between SARS-CoV-2 viral load and its transmissibility (Dadras et al. 2022).

COVID-19 is a systemic disease that affects the entire body creating tissue damage in several parts of the body, affecting the lungs, heart, brain, kidneys, and as well as in tissues of the respiratory and gastrointestinal tract. The cardiovascular system delivers the necessary oxygen and nutrients from the lungs and gut to the cells, so if there is damage to these tissues other organs in the body will be affected. Based on biological principles and clinical observation, it is known that high viral loads will increase the risk of infection, severe illness, and mortality (Hogan et al. 2021; Kawasuji et al. 2022). Therefore, we will focus on measures applied to the nasal cavity, the nasopharynx, and the oropharynx as a means to decrease viral load and the chance of clinical infection.

Oral antiseptics decontamination and nasal mucosal decontamination

Since the COVID-19 pandemic is a highly transmissible disease with high morbidity and mortality, in addition to effective treatment, reducing contagion is important to achieve control. Even though physical distancing, face masks, and aseptic measures have had some results in reducing the spread of the virus and reducing viral load exposure, the use of nasal and oropharyngeal decontamination has been explored to further reduce the risks of transmission (Elsersy et al. 2022). The nose is a source of pathogens and a critical path of entry for infectious agents to the nasopharyngeal mucosa.

A global review of nasal sprays and gargles with antiviral properties suggests that several commonly used antiseptics including Chlorhexidine, povidone-iodine, Listerine, could be an option for reducing SARS-CoV-2 and possibly for COVID-19. It has been proposed that these reagents target the outer lipid membrane or can also act on the capsid by denaturing proteins (Carrouel et at. 2021). Some of these antiseptics have been shown decreasing SARS-CoV-2 viral load in the oral cavity and therefore reducing the risk or severity of the infection (Carrouel et a. 2021). Having proper hand hygiene is essential for the prevention and control of infectious diseases. Hands, nose cavity, and throat are critical infectious portals. Antiseptics such as hydroalcoholic solutions with essential oils, chlorhexidine, and povidone-iodine, are very safe for applications to the epithelium that can be used for the prevention of respiratory infections. Dental practices recommend people rinse their mouths with 1% hydrogen peroxide or 0.2% Povidone-iodine for 20 seconds prior to starting to reduce salivary oral microbes including SARS-CoV-2 and COVID-19 (Guerrero Bernal et al. 2022). A systematic review based on eleven studies found that mouthwashes including chlorhexidine, povidone-iodine, cetylpyridinium chloride, hydrogen peroxide (HP) can be effective at reducing the SARS-

CoV-2 viral load in human saliva (Ziaeefar et al. 2022).

Hydrogen peroxide

Virus-induced oxidative stress plays an important role in the control of the host immune system and the specific oxidant-sensitive pathway is one of the host's strategies against viral infections. For this reason, the implementation of nose, mouth, and throat rinsing with hydrogen peroxide may improve those local innate responses to viral infections and help shield against the current coronavirus pandemic (Caruso et al. 2020). A small, controlled study with 40 patients found that H2O2 is safe to use as a mouthwash and nasal spray. However, there was insufficient evidence to support the effectiveness of H2O2 as an auxiliary treatment for hospitalized COVID-19 patients (Di Domênico et al. 2021). However, the use of hydrogen peroxide mouthwash was tested for reducing the viral load of SARS-CoV-2 in dental clinics. It was found that a 1-minute gargle reduced virus particles in the HEPA filters in the treatment rooms, but not in the waiting room (Burgos-Ramos et.al. 2022).

A randomized trial of 68 patients in the intensive care unit reported the use of 3% hydrogen peroxide wash in the oral mucosa reduced significantly ventilator-associated pneumonia when compared to normal saline (14.7% vs 38.2%, (p=0.0279) (Nobahar et al. 2016). The use of hydrogen peroxide antisepsis was investigated in two hospitals in Ghana and found that the regular daily use of peroxide antisepsis protects healthcare workers from COVID-19 and reduces the nosocomial spread of SARS-CoV-2 (Amoah et al. 2022).

A randomized, double-blind, placebo-controlled clinical trial investigated the effect of four mouth rinses (1% povidone-iodine, 1.5% hydrogen peroxide, 0.075% cetylpyridinium chloride, and 80 ppm hypochlorous acid) on salivary SARS-CoV-2 viral load. The control groups used were distilled water and no rinse. The viral load pattern for every oral rinse group revealed a gradual reduction, but it achieved statistical significance only in the hydrogen peroxide group (Alzahrani et al. 2023).

Chlorhexidine

Chlorhexidine is a synthetic cationic surfactant with broad-spectrum antimicrobial that works by disrupting microbial cell membranes and coagulating cytoplasmic proteins (Lim and Kam 2008). The viral dynamics of two COVID-19 patients admitted to the hospital were studied for 9 days (Yoon et al. 2020). SARS-CoV-2 viral load was constantly high in the saliva; it was comparatively higher than that in the oropharynx during the early stage of COVID-19. Chlorhexidine mouthwash was effective in reducing the SARS-CoV-2 viral load in the saliva for a short-term period of approximately 2 hours (Yoon et al. 2020).

A randomized prospective study used chlorhexidine as an oral rinse and subsequent oropharyngeal spray in hospitalized COVID-19 patients. In the patients using chlorhexidine as an oral rinse only, 62.1% SARS-CoV-2 was eliminated from the oropharynx, versus 5.5% of the control group (Huang, Huang, 2021). In patients using the combination of oral rinse and oropharyngeal spray, 86.0% eliminated oropharyngeal SARS-CoV-2, versus 6.3% of control patients. It was concluded that the use of chlorhexidine is simple, safe, and may play a significant role in improving COVID-19 outcomes (Huang et al. 2021).

Iodine-Povidone

Iodine-Povidone is a water-soluble iodine-releasing agent. Iodine is a small molecule that penetrates rapidly and causes oxidation and denaturation of protein and precipitation of protein that inactivates bacteria and viruses (Lepelletier et al. 2020). The use of PVP-I gargle/mouthwash as a simple, inexpensive, and safe adjunct prophylactic measure has been advocated across the globe to reduce disease transmission (Chopra et al. 2021).

The in vitro evaluation of the inactivation of SARS-CoV-2 with hydrogen peroxide (H2O2) and povidone-iodine (PVP-I) oral antiseptic rinses at clinically recommended concentrations and contact times showed that PVP-I was able to completely inactivate the virus in vitro, at the lowest concentration of 0.5 % and at the lowest contact time of 15 seconds, while H2O2 caused minimal inactivation (Bidra et al 2020).

Iodine-Povidone is safe to use on the mucosal epithelium and nasal spray at appropriate concentrations and its use as nasal spray are well tolerated (Zarabanda et al. 2022). PVP-I (concentrations of 1-0.5%) via intranasal is an easy and well-tolerated virucide used against SARS-CoV-2 (Khan et al. 2020; Khan et al. 2021; Shankar et al. 2022; Stathis et al. 2021). In a clinical setting, gargling with PVP-I solution resulted in a 50% drop in respiratory infections (Stathis et al. 2021).

In a randomized, placebo-controlled study with 200 patients, the treatment accelerated the recovery of PCR on days 4, 7, and 10, as evidenced by PCR-positive patients (70, vs. 99%, 20 vs. 65%, 1 vs. 10%). The treatment group showed faster recovery of anosmia and ageusia when compared to the control groups ($P < 0.0001$) (Elsersy et al. 2022).

The efficacy of nasal and oropharyngeal decontamination may depend on several variables. However, in a large-scale clinical trial, a reduction in the incidence of SARS-CoV-2 infection was observed among participants who were administered povidone-iodine 3 times daily during an active outbreak (Seet et al. 2021).

Essential oils

Essential oils are plant extracts composed of volatile compounds called terpenes. It has been proposed that terpenes may interfere with membrane transport mechanisms and the inhibition of tiral proteases (Diniz et al 2021). Essential oils have been known for centuries to have immunomodulatory, bronchodilatory, and antiviral properties (Asif et al. 2020).

A variety of terpenes have been found to inhibit the SARS-CoV-2 replication in the infected cells. Other essential oils such as geranium and lemon essential oils have been studied and show potential against the SARS-Cov-2 virus (Senthil Kumar et al 2020).

In a study involving garlic, the essential oil was shown to have prevention on the spread of the virus of SARS-Cov-2, (Thuy et al. 2020). The GC-MS analysis identified that 17 out of 18 compounds were organosulfur compounds and these comprise 99.4% of the garlic essential oil. These compounds can inhibit the ACE2 protein which attaches to the Spike protein is the key step for the invasion of coronavirus into the human body. Therefore, garlic essential oil may represent another alternative against the virus SARS-COV-2.

These have also been known to have activity against SARS-COV-2 virus. Essential oils contain multiple active phytochemicals that can act synergistically on multiple stages of viral replication and induce positive

effects on the host respiratory system including bronchodilation and mucus lysis. Inhalation of steam with essential oil has previously shown a positive impact on the treatment of respiratory difficulties and is suggested for managing bronchiolitis, communicable cold and disease, rhinosinusitis, allergies, and flu asthma (Meghana et al. 2020). Essential oils from the tree called Eucalyptus Globulus are used to treat respiratory illnesses such as sinusitis, pharyngitis, and bronchitis. In a clinical study, it has been indicated that inhalation of an extract from eucalyptus called cineole which is shown to exert anti-inflammation and analgesic effects it can be effectively used in COPD (Chronic obstructive pulmonary disease) and asthmatic patients. (Juergens, 2020). The activity of using 1,8-cineole which is eucalyptol is used to fight against influenza A H1N1 virus in-vitro which can be used as well to fight other viruses. On the other hand, the bioactive compounds that being present in oils of *Eucalyptus and Corymbia* (Eucalyptus calophylla / Corymbia calophylla) are important therapeutic targets of SARS-CoV-2 with the help of molecular docking and analysis by that means it could lead to a possible novel drug that could be used for therapies to fight off SARS-COV-2 or COVID-19. The use of Eucalyptus and Corymbia species essential oils using eucalyptus and citronellol as main compounds it was shown a positive antiviral action in various research studies, (Asif et al. 2020).

Cetylpyridinium

Cetylpyridinium chloride is a cationic quaternary ammonium compound used in certain types of mouthwashes, lozenges, throat sprays, and nasal sprays. It is an antiseptic with antiviral properties that are thought to be due to viral lipid membrane disruption (Baker et al. 2020). The specific antiviral activity of cetylpyridinium on SARS-CoV-2 was studied in vitro and it was found that within the contact times (20 and 60 s) the virus was inactivated in al concentrations (0.05%, 0.1%, and 0.3%). In addition, it was found that the binding ability of both the S protein and ACE2 were reduced by cetylpyridinium (Okamoto et al. 2022).

In a randomized controlled study with 36 patients, 3 commercial oral disinfectants (povidone-iodine, chlorhexidine gluconate, and cetylpyridium chloride) were compared to water to determine the effect on the viral load of SARS-COV-2. It was found that cetylpyridium and povidone-iodine significantly decreased salivary viral load with mouth-rinsing for a period of 6 hours compared to water (Seneviratne et al. 2021).

Oral antiseptics comparisons

A systematic review of 27 studies, 16 in vitro studies, and 11 clinical trials evaluated the antiviral effect against SARS-COV-2. Povidone-iodine, cetylpyridinium chloride, and essential oils were effective in vitro, while hydrogen peroxide, chlorhexidine digluconate, povidone-iodine, and cetylpyridinium chloride were effective in vivo (Mezarina Mendoza et al. 2022)

Conclusion

Oropharyngeal decontamination has the potential to reduce the spread of SARS-CoV-2 infection. Several studies were analyzed and reviewed related to the use of oral and nasopharyngeal decontamination (antiseptics) to reduce the risks of infection, morbidity, and mortality of COVID-19. The evidence reviewed on nasal sprays and gargles with antiviral properties support that several commonly used antiseptics including Chlorhexidine, povidone-iodine, and

essential oils-based antiseptic, can reduce SARS-CoV-2 viral load, and in some cases reduced the severity of the disease. Hydrogen peroxide mouthwash reduced viral titers in three separate strains of SARS-CoV-2 and reduced the development of ventilator-associated pneumonia. Chlorhexidine appeared to be very effective when utilized as an oral rinse. Gargling with Iodine-Povidone solution resulted in a significant drop in respiratory infections. Iodine-Povidone can reduce the amount of virus particle aerosolization before it reaches barriers and surfaces. PVP-I gargle/mouthwash is a simple, inexpensive, and safe way to reduce the risk of cross-transmission of SARS-CoV-2. Essential oils like eucalyptol have positive effects on the host respiratory system not only that it was found to be efficient in reducing and resisting the virus SARS-COV-2 and COVID-19. All these antiseptics were found effective in different study trials. Using these methods can help decrease the spread of COVID-19 and SARS-CoV-2. Oropharyngeal decontamination has shown to be a successful intervention in reducing viral load.

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