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Enriqueta Pedraza Deutsch
Master's in Sciences Student, Universidad Autonoma de Nuevo Leon, Facultad de Odontologia, Monterrey, Nuevo Leon, 64460 ZIP, Mexico

Andrea Lizeth Treviño Contreras
Profesor, Universidad Autonoma de Nuevo Leon, Facultad de Odontologia, Monterrey, Nuevo Leon, 64460 ZIP, Mexico

Jesus Alejandro Torres Betancourt
Professor, Universidad Autonoma de Nuevo Leon, Facultad de Odontologia, Monterrey, Nuevo Leon, 64460 ZIP, Mexico

Julio Benitez Pascual
Professor, Universidad Autonoma de Sinaloa, Facultad de Odontologia, Culiacan, Sinaloa, Mexico

Rosa Alicia Garcia Jau
Professor, Universidad Autonoma de Sinaloa, Facultad de Odontologia, Culiacan, Sinaloa, 80013 ZIP, Mexico

Luis Martin Vargas Zuñiga
Professor, Universidad Autónoma de Guerrero, Facultad de Odontología. Acapulco de Juárez de Guerrero, México

Jose Francisco Giles Lopez
Professor, Universidad Autónoma de Guerrero, Facultad de Odontología. Acapulco de Juárez de Guerrero, México

Juan Manuel Solis Soto
Professor, Universidad Autonoma de Nuevo Leon, Facultad de Odontologia, Monterrey, Nuevo Leon, 64460 ZIP, Mexico

Corresponding Author:
Juan Manuel Solis Soto
Professor, Universidad Autonoma de Nuevo Leon, Facultad de Odontologia, Monterrey, Nuevo Leon, 64460 ZIP, Mexico

Mouth rinses against SARS-CoV-2

Enriqueta Pedraza Deutsch, Andrea Lizeth Treviño Contreras, Jesus Alejandro Torres Betancourt, Julio Benitez Pascual, Rosa Alicia Garcia Jau, Luis Martin Vargas Zuñiga, Jose Francisco Giles Lopez and Juan Manuel Solis Soto

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Abstract
Introduction: Dentists worldwide are witnessing an uncertain professional situation during times of COVID-19 pandemic, therefore the identification of specific antiviral mouth rinses to reduce salivary viral load would contribute to reducing the pandemic.
Objective: To analyze information regarding mouth rinses that help to reduce oral bacterial load of COVID-19 such as chlorhexidine, cetylpyridinium chloride, povidone iodine and hydrogen peroxide.
Methodology: Articles on mouthwashes were analyzed in the databases PubMed, SCOPUS and Google academic with emphasis on the last 5 years. This was done with the words: COVID-19 and chlorhexidine", "cetylpyridinium chloride", "povidone iodine", "hydrogen peroxide.
Results: Chlorhexidine has been shown to have a viral inactivation effect against SARS-CoV 2 and facilitates control of oral transmission. Concentrations of 0.05% cetylpyridinium chloride commonly used in mouthwashes are sufficient to promote membrane rupture of SARS-CoV-2. Povidone-iodine rapidly inactivates SARS-CoV-2 when applied for as little as 15 seconds. The indication for preoperative mouth rinsing with 1% hydrogen peroxide is recommended to reduce the SARS-CoV-2 viral load in saliva.
Conclusion: Mouth rinses can inhibit or inactivate SARS-CoV-2, some being more effective and efficient than others. Chlorhexidine and iodine were found to be the most effective mouth rinses in lowering oral viral load, while cetylpyridinium chloride and hydrogen peroxide did not perform as well in comparison.

Keywords: Chlorhexidine, cetylpyridinium chloride, povidone iodine, hydrogen peroxide and COVID-19

1. Introduction
Dentists worldwide are witnessing a completely unforeseen and uncertain situation during the COVID-19 pandemic [1]. High aerosol generation and identification of SARS-CoV-2 in saliva have suggested the oral cavity as a potential reservoir for COVID-19 transmission [2]. There is conflicting evidence regarding the effectiveness of routinely used mouth rinses, especially chlorhexidine sprays, in reducing viral load in the oral cavity during oral procedures [3]. The oral cavity, an essential part of the upper aerodigestive tract, is believed to play an important role in the pathogenicity and transmission of SARS-CoV-2 [4]. Person-to-person transmission of SARS-CoV-2 can occur directly or indirectly through saliva, and preoperative use of antimicrobial mouthrinse is thought to reduce the amount of oral microbes [5, 6, 7].
SARS-CoV-2 is characterized by an outer lipid membrane derived from the host cell from which it buds. It is highly sensitive to agents that disrupt lipid biomembranes [8].
Mouth rinses are widely used solutions due to their ability to reduce the number of microorganisms in the oral cavity [2]. The identification of specific antiviral mouthwashes to reduce the salivary viral load would contribute to reducing the COVID-19 pandemic [9]. The use of chlorhexidine, hydrogen peroxide, PVP-I and cetylpyridinium chloride is recommended to counteract the spread of COVID-19 [10].
SARS-CoV-2 is transmitted through saliva, and there is no adequate review on the effect of mouthwashes, so the objective of this work is to analyze the literature on the effect of

mouthwashes on this virus, particularly chlorhexidine, cetylpyridinium chloride, iodine and hydrogen peroxide.

2. Materials and methods

Articles on the subject published through the PubMed, SCOPUS and Google Scholar databases were analyzed, with emphasis on the last 5 years. The quality of the articles was evaluated using PRISMA guidelines, i.e., identification, review, choice and inclusion. The quality of the reviews was assessed using the measurement tool for evaluating systematic reviews. The search was performed using Boolean logical operators AND, OR and NOT. It was realized with the words "COVID-19" and "SARS-CoV-2" related with "Chlorhexidine", "Cetylpyridinium chloride", "Povidone iodine", "Hydrogen peroxide". The keywords were used individually, as well as each of them related to each other.

3. Results & Discussion

3.1 Chlorhexidine

Chlorhexidine (CHX) is used as a gold standard mouthwash worldwide [11]. CHX and flavonoid agents have been shown to have a viral inactivation effect against enveloped viruses and thus, facilitate the fight against oral transmission [12]. CHX at 0.2% concentration inactivated more than 99.9% of SARS CoV 2 virus at a minimum contact time of 30 seconds *in vitro* [3]. Chlorhexidine gluconate (0.12%) was effective at reducing the salivary load of SARS-CoV-2 for at least 60 min *in vivo* [13].

CHX is a simple and safe addition to current COVID-19 prevention guidelines and may play an important role in reducing the spread of disease [4, 14]. The overall results suggested that chlorhexidine is the most suitable active compound to reduce the salivary load of SARS-CoV-2 due to its better binding energy [15]. Most studies demonstrated that CHX has positive virucidal efficacy against HSV-1 and InfluA strains [16].

Chlorhexidine has been used for many years for oral infection control and has been shown to lower the intraoral viral load of SARS-CoV2.

3.2 Cetylpyridinium Chloride

Cetylpyridinium chloride (CPC) mouthrinses are low-cost, clinically safe and easily accessible to the general public, with an *in vitro* antiviral effect superior to chlorhexidine [17]. Concentrations of 0.05% (w/v) CPC commonly used in mouth rinses are sufficient to promote membrane rupture of SARS-CoV-2 [18]. Mouthwash solutions successfully inactivate infectious SARS-CoV-2 particles within 30 seconds *in vitro* [19]. Including CPC in mouth rinses could be a prophylactic strategy to prevent the spread of SARS-CoV-2 [20].

The effect of decreasing salivary load with CPC mouth rinse was observed to be sustained at 6 hours [2]. It has been suggested to establish a clinical protocol for dentists, in which all patients to be treated are rinsed preoperatively with a mouthrinse containing both D-limonene and CPC to reduce the likelihood of SARS-CoV-2 infection for dentists [21, 22].

CPC is used in routine oral rinses, it is recommended to include it to continuously reduce the viral load of COVID-19.

3.3 Povidone iodine

The oropharynx and nasopharynx are target sites of SARS CoV-2 [23]. Povidone iodine (PVP-I) can be safely used in the nose at concentrations up to 1.25% and in the mouth at concentrations up to 2.5% for a maximum of 5 months [24].

PVP-I is a proven antiseptic agent with excellent virucidal properties (99.99%) [25], dilute solutions of PVP-I have historically been used in Asia to treat upper respiratory tract infections [26]. Antiseptic nasal and oral PVP-I solutions are effective in inactivating SARS-CoV-2 at a variety of concentrations after exposure times of 60 seconds [27, 28]. Recent evidence has confirmed that mouthwash/gargling with 0.5% povidone-iodine (PVP-I) for 30 seconds can reduce SARS-CoV-2 virus infectivity below detectable levels [6].

In an *in vitro* study, after contact times of 15 seconds and 30 seconds, at different concentrations, it completely inactivated SARS-CoV-2 [29]. PVP-I can even disrupt SARS-CoV-2 binding to oral and nasopharyngeal tissues and reduce viral particles in saliva and respiratory droplets. Therefore, the use of PVP-I mouth rinse as a prophylactic measure has been recommended worldwide to reduce disease transmission [30, 31].

An oral prophylactic protocol with PVP-I for dental health care workers and patients as an adjunct to the current biosafety protocol could minimize the risk of transmission during the COVID-19 pandemic.

3.4 Hydrogen peroxide

Hydrogen peroxide (H_2O_2) is physiologically produced by oral bacteria and plays an important role in the balance of oral microecology as it is an important antimicrobial agent [32, 33]. Encouraging results have been demonstrated regarding the inactivation of SARS-CoV-2 on respirators and inanimate surfaces, generally due to the sensitivity of the oxidizing virus [34]. Knowledge of the antiseptic effects of H2O2 dates back to the late 19th century, and its mechanisms of action have been extensively described [35].

Saliva from patients with COVID-19 has a high SARS-CoV-2 viral load [36]. The use of H2O2 as a mouth rinse and nasal spray is safe [37]. The indication for preoperative mouth rinse with 1% H2O2 to reduce SARS-CoV-2 viral load in saliva prior to oral procedures has been significantly disseminated and influenced various dental associations in the development of dental care protocols [38]. It has been shown that *in vitro*, a 0.5% solution of hydrogen peroxide reduced human coronavirus infectivity after 60 seconds of exposure in suspension tests [39]. Another study also demonstrated that H2O2 solutions at concentrations of 1.5% and 3.0% had minimal virucidal activity after 15 seconds and 30 seconds of contact time *in vitro* [29]. However, rinses were shown to have adverse effects such as burning in the throat and nose [40].

Hydrogen peroxide was found to be effective in reducing oral viral load and inactivating COVID-19 virus, however, it is not as effective as other mouth rinses.

4. Conclusions

Preoperative mouth rinses are undoubtedly an effective option to decrease the COVID-19 viral load in saliva in order to reduce transmission in dental offices. Chlorhexidine and iodine were found to be the most effective mouth rinses for lowering oral viral load. Cetylpyridinium chloride was shown to be most effective *in vitro*. Finally, Hydrogen peroxide reduced the viral load, but was shown to have an adverse oral burning effect on patients.

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