

Review article

Efficacy of intraoral antiseptics in SARS-CoV-2 infection control in dental clinics

Eficácia de antissépticos intraorais no controle da infecção por SARS-CoV-2 na clínica odontológica

Eficacia de los antisépticos intraorales en el control de la infección por SARS-CoV-2 en la clínica dental

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RESUMO

Justificativa e Objetivos: No contexto da pandemia de COVID-19, em que a principal rota de transmissão da doença se dá pelo contato com saliva contaminada, procedimentos odontológicos de rotina representam um risco potencial de contágio para profissionais e pacientes. Para diminuir a ocorrência de infecção cruzada, são necessárias formas de controle da carga microbiana oral, como o uso de enxaguantes bucais pré-operatórios. Dessa forma, o objetivo desta revisão de literatura foi avaliar a potencial eficácia de diferentes antissépticos intraorais no controle de infecção por SARS-CoV-2 na clínica odontológica. **Conteúdo:** Trata-se de uma revisão da literatura, realizada nas bases de dados LILACS, Biblioteca Cochrane, CAPES e MEDLINE, através dos termos de busca “mouth rinse”, “dental care”, “COVID-19”, “cetylpyridinium chloride”, “povidone-iodine”, “chlorhexidine” e “hydrogen peroxide”. Entre os 46 artigos potencialmente relevantes, foram selecionados 14 artigos, com textos completos publicados, nos últimos 5 anos. Esses foram analisados e categorizados conforme o tipo de estudo (revisão de literatura, estudos *in vitro* e estudos *in vivo*). Os antissépticos destacados como mais relevantes em termos de eficácia antiviral foram iodopovidona, cloreto de cetilpiridínio, peróxido de hidrogênio e clorexidina. **Conclusão:** Poucas evidências foram encontradas em relação à eficácia de antissépticos orais contra o SARS-CoV-2. Vale ressaltar que alguns estudos realizados com iodopovidona e clorexidina demonstram resultados promissores no combate à infecção pelo SARS-CoV-2. Contudo, a realização de estudos clínicos randomizados é de extrema importância para determinar a eficácia desses compostos no controle da COVID-19 na prática odontológica.

Descritores: Assistência Odontológica. Controle de Infecção. SARS-CoV-2. COVID-19. Antissépticos Buciais.

ABSTRACT

Background and Objectives: In the context of the COVID-19 pandemic, in which the main route of transmission is through contact with contaminated saliva, routine dental

procedures represent a potential risk of contagion for professionals and patients. To reduce the occurrence of cross-infection, ways of controlling oral microbial load are necessary, such as the use of preoperative mouthwashes. Thus, the aim of this literature review was to assess the potential efficacy of different intra-oral antiseptics in SARS-CoV-2 infection control in dental clinics. **Content:** This is a literature review, carried out in the LILACS, Cochrane Library, CAPES and MEDLINE databases, using the search terms “mouth rinse”, “dental care”, “COVID-19”, “cetylpyridinium chloride”, “povidone-iodine”, “chlorhexidine”, and “hydrogen peroxide”. Among the 46 potentially relevant articles, fourteen articles were selected, with full texts published in the last 5 years. These were analyzed and categorized according to the type of study (literature review, *in vitro* and *in vivo* studies). The antiseptics highlighted as most relevant in terms of antiviral efficacy were povidone-iodine, cetylpyridinium chloride, hydrogen peroxide and chlorhexidine. **Conclusion:** Little evidence has been found regarding the effectiveness of oral antiseptics against SARS-CoV-2. It is worth mentioning that some studies conducted with povidone-iodine and chlorhexidine show promising results in combating SARS-CoV-2 infection. However, conducting randomized clinical studies is extremely important to determine the effectiveness of these compounds in controlling COVID-19 in dental practice.

Keywords: Dental Assistance. Infection Control. SARS-CoV-2. COVID-19. Mouthwashes.

RESUMEN

Justificación y objetivos: En el contexto de la pandemia de COVID-19, en la que la principal vía de transmisión de la enfermedad es a través del contacto con saliva contaminada, los procedimientos dentales representan un riesgo de contagio para profesionales y pacientes. Para reducir la infección cruzada, son necesarias formas de controlar la carga microbiana oral, como el uso de enjuagues bucales preoperatorios. Por lo tanto, el propósito de esta revisión de la literatura fue evaluar la efectividad de diferentes antisépticos intraorales para controlar la infección por SARS-CoV-2 en la clínica dental. **Contenido:** Esta es una revisión de la literatura, realizada en las bases de datos LILACS, Cochrane Library, CAPES y MEDLINE, utilizando los términos de búsqueda “*mouth rinse*”, “*dental care*”, “COVID-19”, “*cetylpyridinium chloride*”, “*povidone-iodine*”, “*chlorhexidine*” y “*hydrogen peroxide*”. Entre los 46 artículos potencialmente relevantes, se seleccionaron 14 artículos, con textos completos publicados en los últimos 5 años. Estos fueron analizados y categorizados según el tipo de estudio (revisión de la literatura, estudios *in vitro* y *in vivo*). Los antisépticos destacados como más relevantes en términos de eficacia antiviral fueron povidona yodada, cetilpiridinio cloruro, peróxido de hidrógeno y clorhexidina. **Conclusión:** Se encontró poca evidencia con respecto a la efectividad de los antisépticos orales contra el SARS-CoV-2. Vale la pena mencionar que algunos estudios realizados con povidona yodada y clorhexidina muestran resultados prometedores contra el SARS-CoV-2. Sin embargo, realizar estudios clínicos aleatorios es importante para determinar la efectividad de estos compuestos en el control de COVID-19 en la práctica dental.

Palabras clave: Cuidado Dental. Control de Infecciones. SARS-CoV-2. COVID-19. Antisépticos Orales.

INTRODUCTION

The first cases of infection by the new human coronavirus (SARS-CoV-2) were registered in December 2019 in the city of Wuhan, China.¹ The virus belongs to the family *Coronaviridae*, the same as the etiological agents of Severe Acute Respiratory Syndrome (SARS-CoV) and the Middle East Respiratory Syndrome (MERS-CoV). COVID-19, a frequently asymptomatic but potentially lethal disease, has spread throughout the world.^{2,3} Given its vertiginous spread, the World Organization of Health (WHO) declared COVID-19 a global pandemic on March 11, 2020.

SARS-CoV-2 has a positive and unique RNA strand as its genome.⁴ It is a virus whose lipid envelope composition has not yet been determined experimentally, but it is known to be similar to influenza and herpes simplex viruses, containing phosphorylcholine, cholesterol, sphingolipids and “spike” glycoproteins.⁵ The latter are essential for the binding of the micro-organism with the host cells, contributing to its high degree of infectivity.⁵

Although its incubation period is estimated to be long, between 2 to 14 days, any infected individual can transmit the disease, even before the onset of symptoms.⁶⁻⁸ This is because, in the first 10 days after infection, it still in the asymptomatic phase, the virus accumulates in the nasal and oropharyngeal mucosa, in addition to the salivary glands, in whose cells there is a high expression of the transmembrane protein angiotensin-converting enzyme 2 (ACE2), the main receptor of SARS-CoV-2 in the cells.⁹ It is inferred, furthermore, that its expression in the salivary glands is greater than in the lungs, which suggests that these sites are reservoirs for the virus before they infect other organs such as lungs, kidneys, and heart.¹⁰

This factor gives saliva a high viral load, which can reach 1.2×10^8 /ml of infectious copies, which makes it play a crucial role in the disease transmission route.¹¹ In this regard, the current pandemic resulted in many implications for dental practice, since professionals need to be in constant contact with patients' oral fluids, including saliva and even blood. Moreover, some dental procedures that require the use of water jets, ultrasonic scrapings and low and high-speed handpieces release small saliva particles ($\leq 5 \mu\text{m}$), also known as aerosols, into the medium, which can transport SARS-CoV-2 as well as other pathogens.^{12,13} In general, aerosols have delayed stabilization, which causes them to remain suspended in the air for a period of up to 4 hours after the procedures, in

addition to possibility of being transported over distances greater than one meter and eighty.^{14,15}

In fact, to mitigate cross-infection resulting from contact with contaminated aerosols, it is possible to reduce their production, with the replacement of motorized instruments by manuals or reducing the salivary microbial load through the use of preoperative oral antiseptics.⁴ However, in certain cases, high-speed engines and water jets are essential for carrying out the procedures. Therefore, the use of antiseptics is essential to reduce the risk of disease transmission in dental clinics.¹²

One of the most used oral antiseptics in dentistry is chlorhexidine gluconate (0.12%), due to its low toxicity and inhibition of oral biofilm development.¹⁶ However, the National Health Commission of China, through the Diagnosis Directive and Treatment of new Coronavirus Pneumonia, recommended the replacement of the compound by other antiseptics, as previous studies in the United States and England showed that its virucidal potential is limited and little known.^{4,17} Thus, many researchers have sought to assess the effectiveness and mechanism of action of other antiseptics that can help control the disease, such as povidone iodine (PVP-I), cetylpyridinium chloride (CPC) and hydrogen peroxide (H₂O₂), compounds that are already present in the chemical composition of many commercially available mouthwashes.^{2,18}

The Brazilian National Health Regulatory Agency (Anvisa - *Agência Nacional de Vigilância Sanitária*), as well as the Federal Council of Dentistry (CFO – *Conselho Federal de Odontologia*), have recommended mouthwashes with PVP-I (0.2%) or H₂O₂ (0.5% to 1.5%) before the procedures as a complement to the traditional protocol of oral rinses with chlorhexidine (CHX).^{19,20} On the other hand, the Brazilian Association of Dental Education (ABENO - *Associação Brasileira Ensino Odontológico*) maintains the use of CHX as the main antiseptic and only indicates PVP- I (0.2%) and CPC in a titration of 1:4.000 in cases of allergic sensitivity.²¹ It is noteworthy that such recommendations are made based on the mechanism of action of these antiseptics, since their effectiveness against the new coronavirus is still has not been clinically proven.³

Therefore, the present literature review aimed to assess the potential efficacy of different intraoral antiseptics in SARS-CoV-2 infection control in dental clinics.

METHODS

This study is a descriptive and qualitative literature review. The literature review text was structured according to the PRISMA items ³⁵ (Main Items for Reporting Systematic Reviews and Meta-analyses), checklist and flowchart for systematic reviews.

Eligibility criteria

Articles with publication date referring to the last five years, which had their full texts published in English and which addressed the efficacy of intraoral antiseptics in SARS-CoV-2 infection control in dental clinics were considered for this review.

Exclusion criteria

Editorials and studies that were based on the authors' perspectives and that did not address the scientific knowledge regarding the efficacy of intraoral antiseptics in SARS-CoV-2 infection control in dental clinics were excluded.

Information source and search strategy

The databases used in this review included the Latin American and Caribbean Literature on Health Sciences (LILACS), the Cochrane Library, the CAPES Journal Portal, in addition to the Online System for Search and Analysis of Medical Literature (MEDLINE). The following search terms were used "mouth rinse", "dental care", "COVID-19", associated by the Boolean operator AND, and "cetylpyridinium chloride", "povidone-iodine", "chlorhexidine" and "hydrogen peroxide", these, in turn, are associated by the OR operator. A bibliographic search was carried out from June 30 to July 7, 2020.

Selection of studies

In phase 1, three reviewers (F.A.S.M., G.O.J. and A.V.R.F.) selected the articles independently. Disagreements were discussed and sorted out with a fourth reviewer (E.A.A.). Duplicate articles, which were in different databases, were excluded from the review. Articles that appeared to meet the inclusion criteria, as well as articles that lacked information in their abstracts, were selected for full reading in phase 2, in order to determine the work eligibility. A supplementary article was included after checking the reference lists. Data extraction and assessment of the quality of evidence were performed

using the GRADE method³⁶ (Grading of Recommendations Assessment, Developing and Evaluation) in studies that met the inclusion criteria.

Data collection

Three reviewers (F.A.S.M., G.O.J. and A.V.R.F.) independently collected all data. The differences were discussed with a fourth reviewer (E.A.A.). Data were extracted and organized into tables. The following variables were verified: country and place of study, n sample, study design, antiseptic used (including concentration and duration of treatment), antiviral potential against SARS-CoV-2, and authors' conclusions.

Data were expressed as antimicrobial potential of the antiseptic (family *Coronaviridae* and other viruses) for the literature reviews included in the study. For *in vitro* and *in vivo* studies, the antiviral potential of the antiseptic against SARS-CoV-2 was analyzed.

Risk of bias in individual studies

The reviewers (F.A.S.M., G.O.J. and A.V.R.F.) performed an analysis of the articles independently and any disagreement was sorted out by consulting a fourth reviewer (E.A.A.). The GRADE method (Grading of Recommendations Assessment, Developing and Evaluation) was used to assess the quality of evidence in literature reviews and *in vitro* and *in vivo* studies regarding the antiviral activity of antiseptics against SARS-CoV-2. The quality of evidence was checked based on risk of bias, inconsistency, indirect evidence, and inaccuracy.

RESULTS AND DISCUSSION

Selection of studies

In the first stage of the article selection process, 46 potentially relevant articles were selected from the Latin American and Caribbean Literature in Health Sciences (LILACS) electronic, Cochrane Library, CAPES Journal Portal, in addition to the System Online Search and Analysis of Medical Literature (MEDLINE) databases. After reviewing titles and abstracts, 19 articles were excluded as they were in different databases. The abstracts of the remaining 27 articles were read; however, 7 articles were excluded because they were not related to the review topic. Among the 20 selected articles, 7 did not meet the inclusion criteria of this review and were excluded. Thirteen

articles were included and 1 complementary article selected after checking the reference lists, totaling 14 articles (Figure 1).

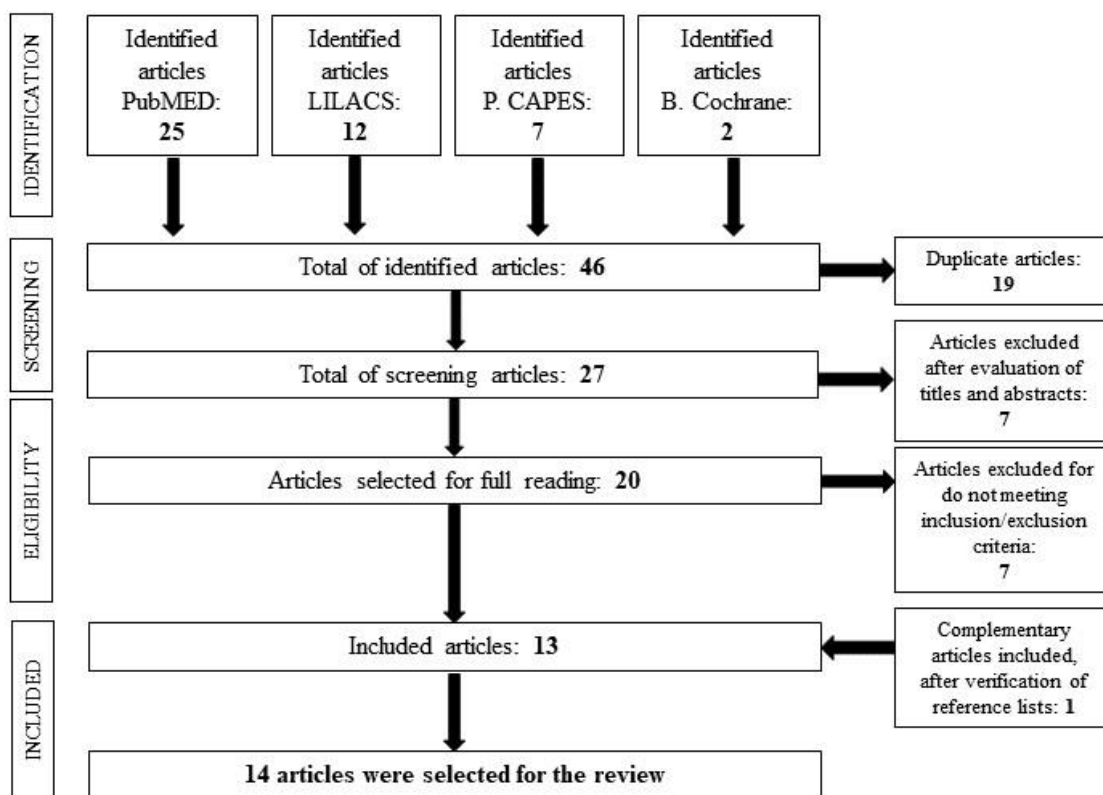


Figure 1. Flowchart of included studies according to search strategy

Studies included

The characteristics of studies included in this review are shown in Tables 1, 2 and 3. These were subdivided into three categories: literature reviews (Table 1), *in vitro* experimental studies (Table 2), and *in vivo* experimental studies (Table 3).

Table 1. Selected literature reviews according to authorship, analyzed antiseptics and antimicrobial potential, n=9

Authors	Country	Analyzed antiseptics	Results: Antimicrobial Potential
Herrera et al.; 2020 ²	Germany	CHX, PVP-I, CPC, and H ₂ O ₂ .	CHX: Rapid inactivation of lipophilic viruses. PVP-I: Effective against enveloped and non-enveloped viruses. CPC: Effective against enveloped influenza viruses such as H1N1 and MERS-CoV. H ₂ O ₂ : Recommended use for its oxidizing activity, no evidence against SARS-CoV-2.
O'Donnel et al.; 2020 ⁵	United Kingdom	CHX, PVP-I, and H ₂ O ₂ .	CHX: Effective against enveloped viruses. A combination of CHX and ethanol is recommended to reduce the viral load of coronavirus species.

			0.23% PVP-I showed similar efficacy against SARS-CoV to that of ethanol (70%). H ₂ O ₂ : Disruption of lipid membranes by the release of oxygen free radicals. Little damage is reported within the range of 1 to 3%, concentrations used for tooth whitening.
Marui et al.; 2019¹²	Brazil	CHX and CPC.	CHX and CPC: No significant differences between them in the elimination of microorganisms from saliva aerosols.
Ge et al.; 2020¹³	China	CHX and CPC.	CHX 0.12%, which has already been shown to be effective against several infectious enveloped viruses. Use of 0.05% CPC for patients with CHX allergy.
Parhar et al.; 2020¹⁷	USA	CHX and PVP-I.	CHX: <i>In vitro</i> studies on inanimate surfaces showed that coronavirus species were sensitive to CHX in combination with ethanol or cetrimide. Povidone iodine (0.23%): 99.99% reduction of influenza A viruses, SARS-CoV-1 and MERS-CoV.
Kanagalingam et al.; 2015²³	Singapore	PVP-I.	Virucidal activity greater than CHX. Potential antiseptic for SARS-CoV control.
Frank et al.; 2020³	USA	PVP-I.	Virucidal antiseptic fast-acting, effective against SARS-CoV and MERS-CoV.
Baker et al.; 2020²⁴	USA	CPC.	CPC has a similar mechanism of action to some drugs that are effective against SARS-CoV-2.
Caruso et al.; 2020²⁵	Italy	H ₂ O ₂ .	H ₂ O ₂ nose/mouth/throat rinsing can improve local innate responses to viral infections and help protect against the new coronavirus (SARS-CoV-2).

Source: The authors (2021).

Table 2. *In vitro* studies selected according to authorship, analyzed antiseptics, characterization of samples and antiviral potential against SARS-CoV-2, n=2

Articles	Country	Analyzed antiseptics	Methodology	Results: Antiviral potential
Bidra et al 2020²⁶	USA	PVP-I (0.5%, 1.25%, 1.5%) and H ₂ O ₂ (1.5%, 3.0%).	Antiseptic and virus solutions were incubated at room temperature (22°C) for 15 and 30s. Negative control (water).	PVP-I at the 3 concentrations completely inactivated the SARS-CoV-2 present in the samples in the time periods of 15s and 30s. H ₂ O ₂ , at concentrations of 1.5% and 3.0%, showed minimal antiviral activity after 30s.
Bidra et al 2020²⁷	USA	PVP-I (0.5%, 1%, 1.5%) and ethanol (70%).	Antiseptic and virus solutions were incubated at room temperature (22°C) for 15 and 30s. Negative control (water).	PVP-I at the 3 concentrations showed similar virucidal potential over the same period of time (15s), with complete virus inactivation. Cytotoxicity was not observed. Ethanol (70%) took twice as long as PVP-I to completely inactivate the virus (30s).

Source: The authors (2021).

Table 3. *In vivo* studies selected according to authorship, analyzed antiseptics, sample characterization and antiviral potential against SARS-CoV-2, n=3

Articles	Country	N sample	Antiseptics	Methodology	Results: Antiviral potential
Yoon et al.; 2020 ¹⁶	South Korea	2 hospital patients with COVID-19	CHX (0.12%), 15mL, 30s	Saliva samples were collected 1h, 2h and 4h after rinsing with CHX.	The viral load in saliva decreased significantly and remained stable for 2 hours.
Lamas et al.; 2020 ²⁸	Spain	4 hospital patients with COVID-19	PVP-I (1%), 15mL, 1min	Saliva samples were collected 5min, 1h, 2h and 4h after PVP-I mouthwash.	In all samples, SARS-CoV-2 was present. Most showed a decrease only after 1 hour of application.
Khan et al.; 2020 ²⁹	India	315 patients with COVID-19; 17 hospital professionals.	PVP-I (0.5%), 30s	Patients gargled with PVP-I for 30s before the test.	Antiviral potential has not been analyzed.

Source: The authors (2021).

After analyzing the articles, it was possible to identify four most relevant antiseptics in oral viral load control: CHX, PVP-I, CPC, and H₂O₂.

Chlorhexidine (CHX)

One of the most common antiseptics in dental clinics, CHX has been recommended for medicinal use since the 1950s, being frequently used to control dental biofilm and treat gingivitis.^{17,30} In low concentrations (0.12%), it has bacteriostatic effect; in higher concentrations (2%), it has bactericidal effect.³⁰ Its mechanism of action involves the lysis of the bacterial cell wall, which usually occurs after thirty seconds of application.^{4,17} It has its proven efficacy against gram-positive and gram-negative bacteria, aerobics and anaerobics.²

However, its virucidal effects are controversial according to the analysis of the results obtained (Tables 1 and 3). Among the nine literature reviews selected, five addressed CHX characteristics.^{2,5,12,13,17} In general, all articles reported its efficacy against lipophilic or enveloped viruses, but not against non-enveloped ones. Experimental studies proving the inactivation of coronavirus species are still scarce.² However, two more recent articles reported that coronavirus species showed sensitivity when subjected to the application of CHX solution combined with other compounds, such as ethanol (70%) and cetrimide on inanimate surfaces (Table 1).^{5,10}

Regarding the elimination of microorganisms present in aerosols, CHX was potentially less effective than PVP-I, having similar efficacy to CPC.^{12,17} However, an *in*

in vivo study carried out with two patients affected by COVID-19, who were given mouthwash for 30s with 15 mL of 0.12% CHX gluconate, showed that the viral load of SARS-CoV-2 in saliva significantly decreased and maintained is stable for 2 hours after application (Table 3).

Povidone iodine (PVP-I)

PVP-I is used in dentistry for oral decontamination, periodontal and peri-implant treatment, in addition to post-tooth extraction therapy.²⁷ However, its use is restricted, being contraindicated for individuals with iodine allergy, pregnant women, with thyroid disease active and patients on radioactive iodine therapy, as allergic reactions and thyroid dysfunctions have already been reported.^{27,31}

Its mechanism of action occurs through the release of free iodine, which interrupts microbial metabolic pathways, destabilizes the structural components of cell membranes and leads to irreversible damage to pathogens, as it oxidizes nucleic acid molecules.^{3,18} It has proven efficacy against species of influenza, such as H1N1, since it acts to block viral activity by inhibiting hemagglutinin and neuraminidases proteins, thus preventing the binding of the virus to cell receptors as well as the release of the viral particle and consequent infection of new cells.³

The results showed that five review articles indicated the potential efficacy of PVP-I against coronavirus species (Table 1), given that it is characterized by having a larger viral spectrum than CHX, acting against enveloped or non-enveloped viruses.^{2,3,5,17,23} Furthermore, three *in vitro* studies demonstrated the inactivation of SARS-CoV and MERS-CoV by the antiseptic.^{2,17,18} Although allergic reactions have been pointed out by some studies, other studies did not find them in the literature evidence of mucosal toxicity or irritation, even with prolonged use (Table 1).^{2,3,5,17,31}

Regarding SARS-CoV-2, the two *in vitro* studies already carried out applied different concentrations of PVP-I to virus samples grown in cell media (Table 2). Antiseptic and virus solutions were incubated at room temperature (22°C) for 15 and 30s. Thus, it was observed that PVP-I was able to completely inactivate the virus after 15 seconds of application, at concentrations of 0.5%, 1%, 1.25% and 1.5%, with no cytotoxicity being observed.^{26,27}

On the other hand, only one of the two selected *in vivo* studies assessed the virucidal potential of PVP-I (1%) (Table 3). This did not demonstrate a significant antiseptic efficacy against the new coronavirus, since a considerable reduction in viral

activity in saliva only occurred in 75% of patients assessed and only 1 h after its application (Table 3).²⁹ There were no reports of allergic reactions after rinsing with PVP-I in 0.5% and 1% titrations.^{29,30}

Cetylpyridinium chloride (CPC)

CPC is a quaternary ammonium cation, soluble in water and highly cationic at neutral pH.² It belongs to the group of surface-active agents and is often found in oral antiseptics and disinfectants.^{2,24} Furthermore, it is important in dentistry for its antibacterial, antiplaque and antigenivitis properties.²⁴

The virucidal effect of CPC occurs mainly against enveloped viruses by releasing cations that act by breaking the lipid envelope, thus preventing cell infection.³² Its spectrum of action includes influenza virus strains (H1N1, AH3N2, A, B and A resistant to oseltamivir), respiratory syncytial virus, parainfluenza and HIV (Table 2).^{3,12,13,22,24} The action of CPC against coronaviruses was recently demonstrated.³⁴ Of the 36 antiseptics tested by Shen et al. (2019), CPC was ranked the ninth most relevant against four species of coronaviruses, including the virus that causes MERS.^{33,34}

There are no records of *in vitro* or *in vivo* experiments verifying the effectiveness of CPC against SARS-CoV-2. However, due to its mechanism of action, which is similar to that of some drugs used against the new coronavirus, the use of CPC-based mouthwashes is recommended in case of any need to change the traditional preoperative protocol (CHX 0.12%), as in patients allergic to CHX.^{13,24} The occurrence of allergic reactions to CPC is rare, although there are reports of pigmentation of the tongue and teeth.²³

Hydrogen peroxide (H₂O₂)

Widely used in concentrations at 1 to 3% as a tooth whitening agent, H₂O₂ causes disruption of lipid membranes by releasing oxygen free radicals, making it very effective against enveloped viruses.^{2,5}

Although higher concentrations (> 5%) can induce damage to soft and hard tissues of the body, little damage is reported within the concentration range used in dental clinics.⁵ In addition to this, its inactivation in the oral mucosa is rapid due to the presence of catalase enzyme, physiologically produced by the body and by bacteria of the oral microbiota, which reduces its possibility of causing allergic reactions.⁵

Some studies discussed the virucidal potential of H₂O₂, including three literature reviews and one *in vitro* study (Tables 1 and 2). Some authors recommended its use due to antioxidant properties.^{2,5,25} Caruso et al. (2020) highlighted that mouth and nasal rinses with antiseptic can improve the local innate response to viral infections due to oxidative stress caused by it (Table 1).²⁵

Regarding efficacy against SARS-CoV-2, Bidra et al. 2020 assessed the virucidal effect of H₂O₂ at two concentrations (1.5% and 3%), verifying a minimal reduction in viral titer after 30s of interaction of H₂O₂ with the virus (Table 2).²⁶ Thus, H₂O₂ was less effective than PVP-I used in the study, since PVP-I at concentrations of 0.5%, 1.25% and 1.5% completely inactivated SARS-CoV-2 after 15s of interaction.

Assessment of the quality of evidence (GRADE)

Table 4 shows the assessment of the quality of evidence performed by the GRADE method.³⁶ Literature reviews showed moderate quality of evidence due to the risk of bias in some selected articles. Although many articles discuss the relevance of antiseptic activity against viruses related to SARS-CoV-2 such as SARS-CoV and MERS-CoV, some studies do not present results in randomized clinical trials, with a significant number of patients.^{2,5,12,17,25} The absence of these data compromises the quality of evidence and can hinder decision-making related to the use of these antiseptics in dentists' practice.

Furthermore, the *in vivo* studies analyzed showed very low quality of evidence, presenting methodological limitations and inconsistency of results (Table 4). The very low quality of evidence is associated with a reduced number of subjects in the studies^{16,28}, differences in the results presented by patients²⁸ and the lack of testing to confirm the suggested results.²⁹ Although the pandemic was a major factor for the development of research around the world, it is extremely important that other studies with a lower risk of bias are carried out to determine the real effectiveness of these intraoral antiseptics in COVID-19 control in dental clinics.

On the other hand, *in vitro* studies showed high quality of evidence, demonstrating the antiviral activity of PVP-I against SARS-CoV-2.^{26,27} These data are promising and may contribute to future randomized clinical trials capable of investigating the action of PVP-I in preventing SARS-CoV-2 contamination.

Table 4. Assessment of the quality of evidence of the results found for efficacy of intraoral antiseptics in SARS-CoV-2 infection control in dental clinics

No. of studies	Design	Methodological limitations (Risk of bias)	Quality assessment				Effect Relative Risk (95%CI*)	Quality (GRADE)	Importance
			Inconsistency	Indirect evidence	Inaccuracy	Other considerations			
9	Literature review	Serious	No serious inconsistency	No important indirect evidence	No serious inaccuracy	None	-	Moderate	Important
2	<i>In vitro</i> studies	No serious limitations	No serious inconsistency	No important indirect evidence	No serious inaccuracy	None	< 0.67 log ₁₀ IDCC5 0/0.1 mL	High	Important
3	<i>In vivo</i> studies	Serious	Serious	No important indirect evidence	Serious	None	VL < after 2 h, VL < in two patients	Very low	Important

CI: confidence interval; GRADE: Grading of Recommendations Assessment, Developing and Evaluation; IDCC: Infecting dose of 50% of cell culture; VL: viral load.

Source: The authors (2021).

CONCLUSION

Routine dental procedures constantly release saliva aerosols containing pathogens into the medium, potentially increasing the risk of cross-infection. Therefore, considering that the main route of transmission of SARS-CoV-2 through contact with contaminated saliva, the use of preoperative oral antiseptics in dental clinics is essential to control transmission, as they can considerably decrease the salivary viral load.

Little conclusive evidence has been found regarding the efficacy of different oral antiseptics against SARS-CoV-2. However, PVP-I and CHX showed promising results in SARS-CoV-2 infection control in some studies. However, it is necessary to carry out randomized clinical studies to prove the real effectiveness of these antiseptics in combating SARS-CoV-2 infections.

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REFERENCES

1. Zhu N, Zhang D, Wang W, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. *N Engl J Med.* 2020;382(8):727-733. <https://doi.org/10.1056/NEJMoa2001017>
2. Herrera D, Serrano J, Roldán S et al. Is the oral cavity relevant in SARS-CoV-2 pandemic?. *Clin Oral Invest* (2020). <https://doi.org/10.1007/s00784-020-03413-2>
3. Frank S, Capriotti J, Brown SM, et al. Povidone-Iodine Use in Sinonasal and Oral Cavities: A Review of Safety in the COVID-19 Era [published online ahead of print, 2020 Jun 10]. *Ear Nose Throat J.* 2020;145561320932318. <https://doi.org/10.1177/0145561320932318>
4. Peng X, Xu X, Li Y, et al. Transmission routes of 2019-nCoV and controls in dental practice. *Int. J. Oral Sci.* 2020, 12, 9. <https://doi.org/10.1038/s41368-020-0075-9>
5. O'Donnell V, Thomas D, Stanton R, et al. Potential Role of Oral Rinses Targeting the Viral Lipid Envelope in SARS-CoV-2 Infection, *Function*, 2020, 1(1), zqaa002. <https://doi.org/10.1093/function/zqaa002>
6. Chang D, Xu H, Rebaza A, et al. Protecting healthcare workers from subclinical coronavirus infection. *Lancet Respir Med.* 2020;8(3):e13. [https://doi.org/10.1016/S2213-2600\(20\)30066-7](https://doi.org/10.1016/S2213-2600(20)30066-7)
7. Backer JA, Klinkenberg D, Wallinga J. Incubation period of 2019 novel coronavirus (2019-nCoV) infections among travellers from Wuhan, China, 20-28 January 2020. *Euro Surveill.* 2020;25(5):2000062. <https://doi.org/10.2807/1560-7917.ES.2020.25.5.2000062>
8. Zou L, Ruan F, Huang M, et al. SARS-CoV-2 viral load in upper respiratory specimens of infected patients. *N Engl J Med.* 2020;382(12):1177-1179. <https://doi.org/10.1056/NEJMc2001737>
9. Wölfel R, Corman VM, Guggemos W, et al. Virological assessment of hospitalized patients with COVID-2019. *Nature.* 2020;581(7809):465-469. <https://doi.org/10.1038/s41586-020-2196-x>
10. Xu J, Li Y, Gan F, et al. Salivary Glands: Potential Reservoirs for COVID-19 Asymptomatic Infection. *J Dent Res.* 2020;99(8):989. <https://doi.org/10.1177/0022034520918518>
11. To KK, Tsang OT, Chik-Yan Yip C, et al. Consistent detection of 2019 novel coronavirus in saliva [published online ahead of print, 2020 Feb 12]. *Clin Infect Dis.* 2020;ciaa149. <https://doi.org/10.1093/cid/ciaa149>
12. Marui VC, Souto MLS, Rovai ES, et al. Efficacy of preprocedural mouthrinses in the reduction of microorganisms in aerosol: A systematic review. *J Am Dent Assoc.* 2019;150(12):1015-1026.e1. <https://doi.org/10.1016/j.adaj.2019.06.024>

13. Ge Z, Yang L, Xia J, et al. Possible aerosol transmission of COVID-19 and special precautions in dentistry. *J. Zhejiang Univ. Sci. B* 21, 361–368 (2020). <https://doi.org/10.1631/jzus.B2010010>
14. Veena HR, Mahantesha S, Joseph PA, et al. Dissemination of aerosol and splatter during ultrasonic scaling: a pilot study. *J Infect Public Health*. 2015;8(3):260-265. <https://doi:10.1016/j.jiph.2014.11.004>
15. Kutter JS, Spronken MI, Fraaij PL, Fouchier RA, Herfst S. Transmission routes of respiratory viruses among humans. *Curr Opin Virol*. 2018;28:142-151. <https://doi:10.1016/j.coviro.2018.01.001>
16. Yoon JG, Yoon J, Song JY, et al. Clinical Significance of a High SARS-CoV-2 Viral Load in the Saliva. *J Korean Med Sci*. 2020;35(20):e195. Published 2020 May 25. <https://doi:10.3346/jkms.2020.35.e195>
17. Parhar HS, Tasche K, Brody RM, et al. Topical preparations to reduce SARS-CoV-2 aerosolization in head and neck mucosal surgery. *Head Neck*. 2020. Epub ahead of print. <https://doi.org/10.1002/hed.26200>
18. Kirk-Bayley J, Combes J, Sunkaraneni V, et al. The use of povidone iodine nasal spray and mouthwash during the current COVID-19 pandemic may reduce cross infection and protect healthcare workers. *Papers SSRN.com*. 2020. <http://dx.doi.org/10.2139/ssrn.3563092>
19. Agência Nacional De Vigilância Sanitária (Anvisa). Nota Técnica GVIMS/GGTES/ANVISA Nº 04/2020, de 8 de Maio de 2020. Disponível em: <<http://portal.anvisa.gov.br/documents/33852/271858/Nota+T%C3%A9cnica+n+04-2020+GVIMS-GGTES-ANVISA/ab598660-3de4-4f14-8e6f-b9341c196b28>>. Acesso: 9 de julho de 2020.
20. Conselho Federal de Odontologia (CFO). Comissão Especial de Acompanhamento do Coronavírus na Odontologia. Recomendações Para Atendimentos Odontológicos Em Tempos De Covid-19. Brasília: Conselho Federal de Odontologia, 2020. 11p. Disponível em: <<http://website.cfo.org.br/wp-content/uploads/2020/05/Cartilha-cfocovid19.pdf>>. Acesso em 9 de julho de 2020.
21. Associação Brasileira de Ensino Odontológico (ABENO). Consenso Abeno: biossegurança no ensino odontológico pós-pandemia da Covid-19. Porto Alegre: ABENO, 2020. 69p.
22. Souza MT, Silva MD, Carvalho R. Revisão integrativa: o que é e como fazer. *Einstein (São Paulo)*. 2010;8(1):102-6. <https://doi.org/10.1590/s1679-45082010rw1134>
23. Kanagalingam J, Feliciano R, Hah JH, et al. Practical use of povidone-iodine antiseptic in the maintenance of oral health and in the prevention and treatment of common oropharyngeal infections. *Int J Clin Pract*. 2015;69(11):1247-1256. <https://doi:10.1111/ijcp.12707>

24. Baker N, Williams AJ, Tropsha A, et al. Repurposing Quaternary Ammonium Compounds as Potential Treatments for COVID-19. *Pharm Res* 37, 104 (2020). <https://doi.org/10.1007/s11095-020-02842-8>
25. Caruso AA, Del Prete A, Lazzarino AI. Hydrogen peroxide and viral infections: A literature review with research hypothesis definition in relation to the current covid-19 pandemic [published online ahead of print, 2020 Jun 1]. *Med Hypotheses*. 2020;144:109910. <https://doi:10.1016/j.mehy.2020.109910>
26. Bidra AS, Pelletier JS, Westover JB, et al. Comparison of In Vitro Inactivation of SARS CoV-2 with Hydrogen Peroxide and Povidone-Iodine Oral Antiseptic Rinses [published online ahead of print, 2020 Jun 30]. *J Prosthodont*. 2020;10.1111/jopr.13220. <https://doi:10.1111/jopr.13220>
27. Bidra AS, Pelletier JS, Westover JB, et al. Rapid In-Vitro Inactivation of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Using Povidone-Iodine Oral Antiseptic Rinse [published online ahead of print, 2020 Jun 8]. *J Prosthodont*. 2020;10.1111/jopr.13209. <https://doi:10.1111/jopr.13209>
28. Lamas LM, Dios PD, Rodríguez MT, et al. Is povidone-iodine mouthwash effective against SARS-CoV-2? First in vivo tests [published online ahead of print, 2020 Jul 2]. *Oral Dis*. 2020;10.1111/odi.13526. <https://doi:10.1111/odi.13526>
29. Khan MM, Parab SR, Paranjape M. Repurposing 0.5% povidone iodine solution in otorhinolaryngology practice in Covid 19 pandemic [published online ahead of print, 2020 Jun 18]. *Am J Otolaryngol*. 2020;41(5):102618. <https://doi:10.1016/j.amjoto.2020.102618>
30. Karpiński TM, Szkaradkiewicz AK. Chlorhexidine--pharmaco-biological activity and application. *Eur Rev Med Pharmacol Sci*. 2015;19(7):1321-1326.
31. Eggers M, Koburger-Janssen T, Eickmann M, et al. In vitro bactericidal and virucidal efficacy of povidone-iodine gargle/ mouthwash against respiratory and oral tract pathogens. *Infect Dis Ther*. 2018;7(2):249-259. <https://doi.org/10.1007/s40121-018-0200-7>
32. Popkin DL, Zilka S, Dimaano M, et al. Cetylpyridinium Chloride (CPC) Exhibits Potent, Rapid Activity Against Influenza Viruses *in vitro* and *in vivo*. *Pathog Immun*. 2017;2(2):252-269. <https://doi:10.20411/pai.v2i2.200>
33. Mukherjee PK, Esper F, Buchheit K, et al. Randomized, double-blind, placebo-controlled clinical trial to assess the safety and effectiveness of a novel dual-action oral topical formulation against upper respiratory infections. *BMC Infect Dis*. 2017;17(1):74. Published 2017 Jan 14. <https://doi:10.1186/s12879-016-2177-8>
34. Shen L, Niu J, Wang C, et al. High-Throughput Screening and Identification of Potent Broad-Spectrum Inhibitors of Coronaviruses. *J Virol*. 2019;93(12):e00023-19. Published 2019 May 29. <https://doi:10.1128/JVI.00023-19>

35. Galvão TF, Pansani TSA, Harrad, D. Principais itens para relatar Revisões Sistemáticas e Meta-análises. A recomendação PRISMA. Epidemiol. Serv. Saúde. 2015;24(2):335-342. Published 2015 abr-jun. <https://doi:10.5123/S1679-49742015000200017>
36. Galvão TF, Pereira MG. Avaliação da qualidade da evidência de revisões sistemáticas. Epidemiol. Serv. Saúde. 2015;24(1):173-175. Published 2015 jan-mar. <https://doi:10.5123/S1679-49742015000100019>

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