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Effectiveness of mouth antiseptics in reducing the viral load of SARS-CoV-2 load in saliva? A systematic review of clinical trials

Eficácia dos antissépticos bucais na redução da carga de SARS-CoV-2 na saliva? Uma revisão sistemática de ensaios clínicos

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ABSTRACT

This systematic review assessed the effect of mouthwashes on reducing the SARS-CoV-2 viral load in the saliva of infected patients. Fifteen electronic databases were searched using the terms "Mouthwash", "Viral Load", and "COVID-19". Only clinical trials were considered, with no language or publication year restrictions. Bias risk was assessed using the Cochrane tool (Rob 2.0) for randomized clinical trials and non-randomized trials (ROBINS-I). The quality of evidence was evaluated using the GRADE system. After the search, 1,102 references were identified and assessed for eligibility criteria. Among these, 34 were selected, and after a thorough analysis, only six were included. The mouthwashes evaluated included 1% hydrogen peroxide, iodopovidone, cetylpyridinium chloride, and chlorhexidine. The results indicated that iodopovidone, chlorhexidine, and cetylpyridinium chloride performed better compared to other options. In conclusion, the use of mouthwashes appears to be effective in reducing the SARS-CoV-2 viral load in saliva.

Keywords: COVID-19; SARS-CoV-2; Mouthwashes; In Vivo.

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RESUMO

Esta revisão sistemática avaliou o efeito dos enxaguatórios bucais na redução da carga viral SARS-CoV-2 na saliva de pacientes infectados. Foram pesquisadas 15 bases de dados eletrônicas com os termos "Mouth Wash", "Viral Load" e "COVID-19". Apenas ensaios clínicos foram considerados, sem restrições de idioma ou ano de publicação. O risco de viés foi avaliado usando a ferramenta Cochrane (Rob 2.0) para ensaios clínicos randomizados e para ensaios não randomizados. A qualidade das evidências foi avaliada pelo sistema GRADE. Após a busca, 1.102 referências foram identificadas e avaliadas de acordo com os critérios de elegibilidade. Dentre essas, 34 foram selecionadas e, após uma análise completa, apenas 6 foram incluídas. Os enxaguatórios bucais avaliados incluíram peróxido de hidrogênio a 1%, iodopovidona, cloreto de cetilpiridínio e clorexidina. Os resultados indicaram que iodopovidona, clorexidina e cloreto de cetilpiridínio tiveram um desempenho superior em comparação com outras opções. Conclui-se que o uso de enxaguatórios bucais parece ser eficaz na redução da carga viral do SARS-CoV-2 na saliva.

Palavras-chave: Covid-19; Sars-Cov-2; Enxaguatórios Bucais; In Vivo.

INTRODUÇÃO

The emergence of a new disease caused by a modification of the coronavirus strain (SARS-CoV-2) at the end of 2019 caught the world's attention. SARS-CoV-2 infection, or COVID-19, was characterized as a World Pandemic by the World Health Organization in early 2020 due to the rapid increase in cases and deaths worldwide (Wang et al., 2020; Zhou et al., 2020). Currently, the number of confirmed cases amounted to about 761 million with more than 6.8 million deaths, affecting 216 countries. People who become infected with SARS-CoV-2 may be asymptomatic or present with fever, fatigue, dry cough, myalgia and/or dyspnea, as well as headache, dizziness, abdominal pain, diarrhea, nausea and/or vomiting, to progressive, life-threatening respiratory failure (Wang et al., 2020; Li et al., 2020).

COVID-19 spreads much faster than other respiratory infections and this may be related to the long-term incubation time (Peng et al., 2020). Common routes of transmission of SARS-CoV-2 include direct transmission by coughing, sneezing and inhaling droplets, and transmission from contact with the ocular, nasal and oral membranes (Kim et al., 2020). Therefore, it is observed that the level of SARS-CoV-2 viral load in the upper respiratory tract (nasal and oral cavity, larynx, and pharynx) is higher than the lower one (trachea, lungs, bronchioles, and bronchi), regardless the presence of clinical symptoms worldwide (Wang et al., 2020; Xu et al., 2020; Zhou et

al., 2020). In addition, it was observed that cells of the oral cavity, especially the tongue, express the Angiotensin Converting Enzyme 2 (ACE2), which is a receptor for the virus, becoming target cells for SARS-CoV-2, demonstrating that the oral mucosa may be a route of transmission of COVID-19 worldwide (Zhou et al., 2020; Cavalcante-Leão et al., 2021).

In this way, reducing the viral load in nasal mucus and saliva in people with COVID-19 is a fundamental principle to decrease disease transmission, cross-infection from patients to health professionals and vice-versa, and can mitigate the overall impact on the system of health worldwide (Wang et al., 2020; Cavalcante-Leão et al., 2021).

Thus, the objective of this live systematic review was to evaluate the effects or efficacy of mouthwashes on the burden of SARS-CoV-2 in the saliva of infected patients.

MATERIALS AND METHODS

Protocol and Registration

The PRISMA recommendation (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) was followed to structure the report of this review (Moher et al, 2011). The study protocol was registered in PROSPERO (International Prospective Register of Systematic Reviews) under number CDR42021250335.

Eligibility Criteria

Clinical trials of people with COVID-19, who used mouthwashes compared to placebo and/or non-intervention, were included and measured the amount of viral load in saliva, without limits as to the language of the study or year of publication. In vitro studies, case reports or series, observational studies, or reviews of any nature and including people with other types of coronavirus were excluded.

Sources of Information and Search

The sources of information were the Academic Search Elite, CAPES FSTA Full Text Collection, Dentistry & Oral Sciences Sources, Engineering Source, Food Science Source, FSTA – Food Science and Technology Abstract, and MEDLINE Complete via EBSCO host, MEDLINE via PubMed, Embase, SciELO, LILACS, Scopus, Web of Science, CINAHL, PEDro, as well as Google Scholar. The searches were conducted without limits between November 1, 2020, and January 31, 2024. Chart 1 shows the

search strategies used in the chosen electronic databases. In addition, it was searched in the gray literature and manually in the references of the selected articles.

Chart 1 - Descriptors, synonyms, and search strategy

#4	#1 AND #2 AND #3
#3	(Viral load) OR (Viral burden) OR (Viral Titer)
#2	(Mouth wash*) OR (Mouth Rinse*) OR (Mouth Bath*)
#1	COVID-19 OR (COVID-19 Virus Disease*) OR (COVID-19 Virus Infection*) OR (2019-nCoV Disease*) OR (2019-nCoV Infection*) OR (SARS-CoV-2 Infection*)

Selection of Studies

Duplicate references were located by Mendeley and deleted after the search conclusion. The selection of studies took place in two phases. In the first phase, the titles and abstracts of the articles were independently analyzed by two researchers (MMN and LNR) and based on the review eligibility criteria. In the second phase, the same reviewers evaluated the articles selected by full-read and determined whether they were eligible or not. A third researcher resolved any discrepancies (CPSC).

Data Collection and List Process

The two researchers who selected the studies also participated in the data collection and listing process (MMN and LNR). They independently extracted data from selected articles using a form developed by the research team and a third researcher resolved any discrepancies (CPSC). The extracted data were author, year, country; objective, study design, study site, participants, intervention, control, outcome(s), sample size, main results, and conclusion.

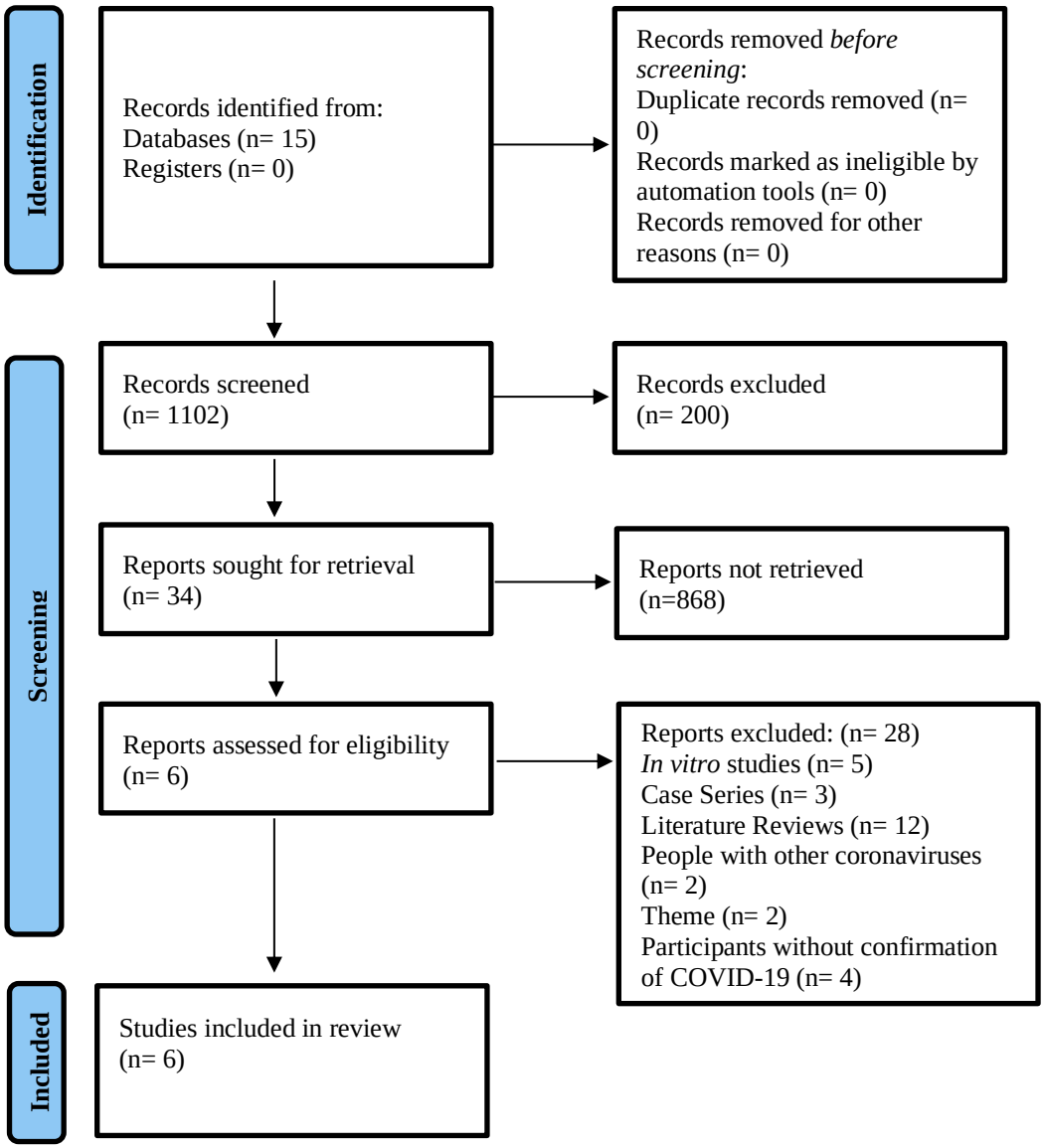
Assessment of Risk of Bias and Quality of Evidence

The included studies were assessed for risk of bias according to their design. Rob 2.0 (Cochrane risk of bias tool for randomized clinical trials) (Higgins et al., 2019) and ROBINS-I (Risk of Bias In Non-randomized Studies - of Interventions) were used for non-randomized trials. The quality of evidence for the proposed research question was evaluated by the GRADE System (Grading of Recommendations Assessment, Development and Evaluation) (Andrews et al., 2013).

RESULT

After searching the electronic databases, 1102 references were identified. No references were found by manual search and 200 duplicates were removed. After analyzing the titles and abstracts based on the eligibility criteria of this systematic review, 868 references were excluded, and 34 articles were selected. These articles were read in full and 28 were excluded. Thus, four articles were included in this systematic review (Figure 1).

Figure 1 - Flowchart of the Search and Selection of Studies.



The 28 articles were excluded because they were in vitro studies (n= 5), case series (n= 3) or literature reviews (n= 9); their participants being affected by other coronaviruses (n= 2) or COVID-19 not being confirmed (n= 3), as well as deviating

from the topic proposed by this systematic review (n= 3) (Table 1). Of the total, four studies were included. Table 2 shows the summary of included studies.

Gottsauner et al. (2020) investigated the effects of rinsing 20 ml of 1% hydrogen peroxide for 30 seconds on the intraoral amount of SARS-CoV-2 in patients with COVID-19 admitted to the isolation ward without oral changes (n= 10). There was no significant difference between baseline SARS-CoV-2 intraoral viral load and after 30 minutes the use of 1% hydrogen peroxide (p= 0.96), demonstrating that this mouthwash did not provide benefits for SARS-CoV-2 positive patients (Tables 2 and 3).

On the other hand, Seneviratner et al. (2021) evaluated the effect of three commercially available mouthwashes, Betadine Buccal (100mg/ml povidone iodine), Pearly White Chlor-Rinse (0.2% chlorhexidine gluconate) and Colgate Plax (0.075% cetylpyridinium chloride) on SARS-CoV-2 viral load in saliva. It was observed that povidone-iodine and cetylpyridinium chloride were able to reduce the salivary level of SARS-CoV-2 in COVID-19 patients for up to 6 h (p< 0.01) (Table 2). In this way, Elzein et al. (2021) evaluation of mouthwashes containing 1% povidone-iodine and 0.2% chlorhexidine gluconate showed there was a significant reduction in salivary viral load for all mouthwashes compared to distilled water (p=0.0024) (Tables 2 and 3).

Ferrer et al. (2021) evaluated the effectiveness of mouthwashes in reducing the in vivo salivary viral load of SARS-CoV-2, using mouthwashes based on 2% povidone-iodine (Betadine Oral 100mg/ml), 1% hydrogen peroxide (Oximen), 0.07% cetylpyridinium chloride (Vitis Xtra Forte) and 0.12% chlorhexidine gluconate (Chlorhexidine Dental PHB). However their effect did not differ from the control group (distilled water) (Table 2 and 3).

Azharani et al. (2022) compared the efficacy of four commercially available mouthwashes containing 1% iodopovidone (trade mark), 1.5% hydrogen peroxide (trade mark), 0.075% cetylpyridinium chloride (trade mark), and 80 ppm hypochlorous acid (trade mark) on salivary SARS-CoV-2 viral load at four-time points [baseline (T0) and 5 (T1), 30 (T2), and 60 minutes (T3) post-rinse] compared to two control groups [distilled water (group 1) and no rinse (group 2)] in a cohort of patients with COVID-19. Overall, there was a reduction in the salivary viral load of SARS-CoV-2 over time in the different mouthwash groups; however, only the H2O2 group showed a significant reduction at all three-time points (T1, T2, and T3) compared to the baseline viral load (Table 2 and 3).

Finally, Adl et al. (2023) evaluated the potential effect of gargling with 0.25% iodopovidone and 1% hydrogen peroxide in reducing salivary viral load in two groups of SARS-CoV-2 positive patients, including outpatients with early clinical symptoms and hospitalized patients with lower respiratory tract involvement. This study revealed that similar to a saline solution (used as a control), gargling with 1% hydrogen peroxide or 0.25% iodopovidone had no effect on reducing salivary viral load in SARS-CoV-2 positive patients (Table 2 and 3).

Charts 2 and 3 show the risk of bias and the quality of the studies included in this systematic literature review. The study by Gottsauner et al. (2020) presented medium risk of bias and moderate quality, Seneviratner et al. (2020), low risk of bias and low quality, whereas Elzein et al. (2021) and Ferrer et al. (2021) presented low risk of bias and high quality.

Table 1 - Reason for Exclusion of Articles (n=28)

Author, date	**Reason**
ABDULRAB et al., 2020 CASALE et al., 2020 KELLY et al., 2020 KHAN et al., 2020 IMRAM et al., 2021	*In vitro* studies
LAMAS et al., 2020 ORCINA et al., 2020 ORCINA et al., 2021	Case Series
BLASE et al., 2019 CARROUEL et al., 2020 FARZAN et al., 2020 IMRAM et al., 2020 MENDES et al., 2020 RECH et al., 2020 TELLES-ARAUJO et al., 2020 VERGARA-BUENAAVENTURA et al., 2020 STATTIS et al., 2021 FARZAN et al., 2019 BURTON et al., 2020 VERGARA-BUERNAVENTURA et al., 2019	Literature Reviews
ERGGS et al., 2015 PASSARELI et al., 2019	People with other coronaviruses
ALTURA et al., 2021 KOMINE et al., 2021	Theme
BURTOR et al., 2020 KIRKY-BAYLEY et al., 2020 MEISTER et al., 2020 BARBOUR et al., 2020	Participants without confirmation of COVID-19

Table 2 - Summary of the Study Included (n=6)

Author, year	Goals	Study design	Study Location	Eligibility Criteria	Intervention	Control	Outcomes	Sample size
Gottsauner et al., 2020	To investigate the effects of 1% hydrogen peroxide in reducing the intraoral burden of SARS-CoV-2.	Clinical trial	Germany	Patients older than 18 years, SARS-CoV-2 positive, admitted to the ward, in room air and without oral changes.	Swish 20 ml of 1% hydrogen peroxide in the mouth for 30s.	There was no control group.	Number of copies/ml of SARS-Cov-2 RNA before and 30 min after rinsing with 1% hydrogen peroxide.	1% Hydrogen Peroxide Group: n= 10
Seneviratner et al., 2020	To evaluate the effectiveness of 3 mouthwashes, Betadine (100mg/ml povidone iodine), Pearlie White Chlor-Rinse chlorhexidine (0.2% chlorhexidine gluconate) and Colgate Plax (0.075% cetylpyridinium chloride), in reducing the load salivary SARS-CoV-2.	Randomized clinical trial	China	SARS-CoV-2 positive patients without allergy to povidone-iodine, chlorhexidine and cetylpyridinium chloride; thyroid disease, being treated with radioactive iodine or lithium, pregnant and renal failure.	Swish 5 ml of 100mg/ml povidone-iodine (Betadine) in the mouth diluted with 5 ml of water or 15 ml of 0.2% chlorhexidine gluconate (Pearlie White Chlor-Rinse) or 20 ml of 0.075% cetylpyridinium chloride (Colgate Plax).	Rinse 15 ml with distilled water.	Cycle threshold (Ct) at baseline, after 5min, 3h and 6h of mouthwash use.	Povidone-iodine group; n=4; chlorhexidine group: n=6; cetylpyridinium chloride group: n=4 and control group (water): n=2; Total: n=16
Elzein et al., 2021	To evaluate *in vivo* the effectiveness of 2 mouthwashes in reducing salivary viral load of SARS-CoV-2.	Randomized controlled clinical trial	Lebanon	Patients over 16 years old, SARS-CoV-2 positive admitted to the ward in room air.	Rinse your mouth with 0.2% chlorhexidine or 1% povidone-iodine for 30s.	Rinse your mouth with distilled water for 30s.	Cycle threshold (Ct) at baseline and after 5min of mouthwash use.	Povidone-iodine group n = 27; 0.2% chlorhexidine group n = 27; 1% povidone-iodine group: n=9; control group: n=9; Total: n= 61

Ferrer et al., 2021	Test the effectiveness of mouthwash to reduce salivary viral load *in alive.*	Randomized clinical trial	Spain	Patients over 18 years old SARS-CoV-2 positive	Mouthwash with A- 2% povidone iodine (Betadine Bucal 100mg/ml), B- 1% hydrogen peroxide (Oximen), C-0.07% cetylpyridinium (Vitis Xtra Fortes), D- 0.12% chlorhexidine gluconate (Chlorhexidine Dental PHB)	Rinse your mouth with distilled water (Group E).	Number of copies/ml of SARS-Cov-2 RNA before, after 1 min, 30 min, 60 min and 120 min after using the mouthwash. baseline and 3 after a 1 min mouthwash, specifically at 30, 60 min and 120 min.	Group A: n=9; group B: n=14; Group B: n-14 (mouthwash with 1% hydrogen peroxide) group C: n=11; group D: n=12; group E: n=12 ; Total: n=58
Azharani et al., 2022	To evaluate the effectiveness of four mouthwashes on salivary SARS-CoV-2 load compared to distilled water and no-rinse.	Randomized clinical trial	Saudi Arabia	Patients over 18 years old SARS-CoV-2 positive	Rinse your mouth with 1% povidone-iodine, 1.5% hydrogen peroxide, 0.075% cetylpyridinium chloride, or 80 ppm hypochlorous acid for 30 seconds	Rinse 15 ml with distilled water (group 1) and no-rinse (group 2).	Number of copies/ml of SARS-Cov-2 RNA at baseline (T0) and 5 (T1), 30 (T2), and 60 minutes (T3) post-rinsing.	1% povidone-iodine: n=6; 1.5% hydrogen peroxide: n=11; 0.075% cetylpyridinium chloride: n=11; and 80 ppm hypochlorous acid: n=9, to distilled water; n=8 and no-rinse: n=10; Total=55
Adl et al., 2023	To evaluate the salivary SARS-CoV-2 load in hospitalized patients and outpatients before and after gargling with 1% hydrogen peroxide and 0.25% povidone-iodine in comparison with normal saline.	Multicenter randomized clinical trial	Iran	Hospitalized patients and outpatients SARS-CoV-2 positive.	Swish 10 ml of 1% hydrogen peroxide, 0.25% povidone-iodine, or saline for 30 seconds.	Rinse 10 ml with normal saline and no-rinse group.	Cycle threshold (Ct) before gargling and 10 minutes after gargling.	1% povidone-iodine: n=18; 0.25% hydrogen peroxide: n=20; normal saline: n=15; Total=53

Table 3 - Compiled from the Results and Conclusion of the Selected Articles (n=6)

	Results	**Conclusion**
Gottsauner et al., 2020	There was no significant difference between viral load at *baseline* and 30 min after 1% hydrogen peroxide mouthwash (p=0.96).	The 1% hydrogen peroxide mouthwash does not decrease the intraoral viral load of SARS-CoV-2 positive patients.
Seneviratner et al., 2020	There was no difference between the times within each group. However, Ct was higher in the 0.075% cetylpyridinium chloride group compared to the control after 5 min and 6h, as well as in the 100mg/ml povidone-iodine group compared to the control after 6h.	Commercial mouthwashes based on povidone-iodine and cetylpyridinium chloride may reduce the salivary load of SARS-CoV-2 in a patient with COVID-19.
Elzein et al., 2021	There was a significant difference between mouthwash with distilled water and 0.2% chlorhexidine (p=0.0024) and in relation to 1% povidone-iodine (p=0.012). There was no significant difference between 0.2% chlorhexidine and 1% povidone-iodine.	Mouthwashes based on 0.2% chlorhexidine and 1% povidone-iodine are effective in reducing the salivary viral load of SARS-CoV-2.
Ferrer et al., 2021	There was no significant difference in SARS-CoV-2 salivary viral load after using the different mouthwashes.	Although mouthwashes tested have shown virucidal effects *in vitro* , in the present study they did not affect the salivary viral load of SARS-CoV-2 in patients positive COVID-19.
Azharani et al., 2022	No statistically significant difference between mouthwashes groups in the efficacy of viral load reduction at the different time. The effect of 1% povidone-iodine, 1.5% hydrogen peroxide , and 0.075% cetylpyridinium chloride mouthwash on salivary viral load reduction was significant compared to the no-rinse group at 60 min.	The effect of mouthwash on viral viability needs to be further investigated by conducting viral culture experiments from saliva samples collected after the use of different mouthwash.
Adl et al., 2023	The present study revealed that similar to saline solution, gargling with 1% hydrogen peroxide or 0.25% povidone-iodine had no effect on reducing the salivary viral load in SARS-CoV-2 positive patients.	Gargling with hydrogen peroxide or povidone-iodine was not effective in reducing the SARS-CoV-2 viral load in the saliva of the patients.

Chart 2 - Risk of Bias and Quality of Randomized Studies

Study	RoB-2 Domains							GRADE System
	Randomization sequence Generation	Allocation secrecy	Masking of participants and staff	Masking in outcome assessment	Incomplete outcome data	Selective outcome reporting	Other sources of bias	
Seneviratner et al., 2020	Low	Low	Uncertain	High	Uncertain	Low	Low	⊕⊕◯◯ LOW
Elzein et al., 2021	Low	Low	Low	Low	Low	Low	Low	⊕⊕⊕⊕ HIGH
Ferrer et al., 2021	Low	Low	Low	Low	Low	Low	Low	⊕⊕⊕⊕ HIGH

RoB-2: Assessment of the study's risk of bias. GRADE system: evaluation of study quality.

Chart 3 - Risk of Bias and Quality of the Non-Randomized Study

Study	ROBINS-I Domains							GRADE System
	D1	D2	D3	D4	D5	D6	D7	
Gottsauner et al., 2020	Critical	Critical	Moderate	Critical	Moderate	Low	Low	⊕⊕⊕◯ MODERATE

ROBINS-I: Assessing the study's risk of bias. GRADE system: evaluation of study quality. D1: Bias related to confounding factors. D2: Bias related to the selection of participants. D3: Bias related to the classification of interventions. D4: Bias due to the deviation of interventions. D5: Bias due to missing data. D6: Bias I relate to the assessment of outcomes. D7: Selection bias in reporting results. Source: Authors.

DISCUSSION

The pandemic caused by the SARS-CoV-2 virus generated an unusual situation around the world, causing a sudden need for clinical protocols implementation, most of them presenting few scientifically proven data (Danion et al., 2020). In this context, the use of mouthwashes was suggested as a measurement for viral load reduction considering their ability to significantly reduce the number of microorganisms in the oral cavity. However, neither of them have bactericidal and/or virucidal efficacy (Cavalcante-Leão et al., 2021; Etievant et al., 2021), the reason why the mouthwashes

recommendation is controversial. Here we show that although most commercial formulations present no effect on SARS-CoV-2 viral load reduction, povidone-iodine or cetylpyridinium chloride has been the most effective agents, suggesting this measurement could aid in the SARS-CoV-2 management.

It is known that mouthwashes significantly reduce the number of microorganisms in the oral cavity, but not all of them have bactericidal and/or virucidal efficacy (Cavalcante-Leão et al., 2021; Etievant et al., 2021). Thus, evidence emerged from the first randomized clinical trial that examined the possible efficacy of commercial mouthwashes on SARS-CoV-2 viral load showed significant results (Seneviratne et al., 2021). The authors found mouthwashes containing cetylpyridinium chloride or povidone-iodine had a progressive effect in reducing viral load in saliva when compared to the control group exposed to water, which corroborates with the study of Azharani et al. (2022). Similar results were found in the literature, evidencing both types of mouthwashes performed 30% better than the others (Ferrer et al., 2021), as well as the superiority of 1% povidone-iodine mouthwash effectiveness when compared to the control group (Elzein et al., 2021). Furthermore, cetylpyridinium chloride demonstrated a virucidal effect when patients with influenza virus were evaluated, due to its direct attack on the viral envelope (Bhat et al., 2020). On the other hand, povidone-iodine presents virucidal efficacy due to the direct attack on the virus with and without envelope (Etievant et al., 2021). We believe the same mechanism is valid and effective for SARS-CoV-2.

The literature indicates the use of various types of mouthwash based on different active principles (Cavalcante-Leão et al., 2021; Etievant et al., 2021). Among them, the use of 1% hydrogen peroxide rinse in the oral cavity seemed to be able to reduce the viral load in patients with COVID-19 (AMIB/CFO, 2020; Institute of German Dentists, 2020). This could be translated into a reduction in the viral load found in the aerosols generated during the oral cavity manipulation, resulting in a reduction in the spread of the disease among health professionals and patients without infection (Bhat et al., 2020) Thus, the use of hydrogen peroxide was widely recommended, despite being based only on in vitro studies, where there were indications of its possible virucidal effect in the oral cavity. The available evidence, therefore, led researchers to investigate its effect in vivo to ensure its efficacy and effectiveness, as well as its safety as an antiviral agent

(Bhat et al., 2020; Meister et al., 2020; O'Donnell et al., 2020). Despite that, the use of 1% hydrogen peroxide was not able to decrease the SARS-CoV-2 viral load in saliva in vivo (Gottsauner et al. 2020; Adl et al., 2023). RT-PCR data showed no significant reduction, indicating this strategy might not be enough to assure the prevention of virus spread. Nonetheless, the available evidence is not consistent, considering that all studies included in this systematic review demonstrated hydrogen peroxide-based mouthwashes have no effect on SARS-CoV-2 viral load in the oral cavity (Gottsauner et al., 2020; Ferrer et al., 2021; Adl et al., 2023).

Another component of mouthwashes that is reliable and presents proven efficiency against oral bacteria is 0.12% chlorhexidine (Yousefimanesh et al., 2022). The literature shows that chlorhexidine is the most effective antimicrobial in vivo due to its substantively characteristic related to its ability to bind to clean oral surfaces and to be released over time (O'Donnell et al., 2020). However, its virucidal activity is still uncertain (Meister et al., 2020), since some studies have demonstrated a significant reduction in SARS-CoV-2 viral load after 0.12% chlorhexidine use compared to water rinse, but others could not find a significant effect when compared to cetylpyridinium chloride and povidone-iodine (Ferrer et al., 2021; Seneviratne et al., 2021).

Thus, this systematic literature review points out that mouthwashes based on cetylpyridinium chloride and povidone-iodine seem to be better options to control the viral load of COVID-19-positive patients (Rao et al., 2020). However, it should be considered that in one of these studies, this evidence corresponds to a study with a small sample (16 patients), with severe or critical risk of bias, mainly due to the impossibility of controlling the potential confounding effect of variables, such as the onset of COVID-19 symptoms or food consumption before the intervention. There were also differences in the concentration of mouthwashes in the study by Ferrer et al, povidone-iodine had a higher concentration (2% povidone-iodine) and a lower concentration of chlorhexidine gluconate compared to those used in other studies (0.12% chlorhexidine gluconate), which makes a precise comparison difficult. Furthermore, we emphasize that these differences in substances and concentrations of the mouthwash, as well as variations in evaluation times and how the SARS-CoV-2 viral load (number of copies or cycle threshold (Ct)), not allowed the meta-analysis conduction (Popkin et al., 2017; Bhat et al., 2020; Rao et al., 2020). Additionally, the small number of studies included

is also considered a limitation. Finally, albeit it is not the only systematic review on this subject, our study is the first to include only clinical trials which will certainly allow future updates and methodological advances in this field.

CONCLUSION

In conclusion, the use of povidone-iodine or cetylpyridinium chloride mouthwashes in patients with COVID-19 is a strategy that prevents the spread by reducing the SARS-CoV-2 viral load in the saliva of infected people. However, more in vivo research is needed to corroborate the recent findings.

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