Critical Review
Periodontology

Efficacy of mouthrinses in reducing oral SARS-COV-2 load: a review

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Abstract: Accumulated evidence has shown that the oral cavity may be an important reservoir for SARS-CoV-2. Some authors have suggested that the use of mouthrinses could reduce SARS-CoV-2 viral load in the saliva. Thus, the aim of this review was to synthesize evidence about the efficacy of mouthrinses in reducing the salivary viral load of SARS-CoV-2. 2. Nine randomized controlled trials (RCTs) have investigated the efficacy of different mouthrinses in reducing salivary SARS-CoV-2 loads. Various active ingredients have been tested in these trials: 0.5%,1% and 2% povidone-iodine, 0.2% and 0.12% chlorhexidine (CHX), 0.075% cetylpyridinium chloride (CPC), 0.075% CPC with Zinc lactate, 1% and 1.5% hydrogen peroxide (HP), 1.5% HP + 0.12% CHX and ß-cyclodextrin and citrox. The studies reported an intra-group reduction in the salivary levels of the virus, when compared with the baseline. However, the majority of these trials failed to demonstrate a significant inter-group difference between active groups and the control group relative to the decrease in salivary SARS-CoV-2 loads. Although promising, these results should be confirmed by larger trials.

Keywords: SARS-CoV-2; COVID-19; Mouthwashes; Saliva.

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Introduction

As of August 16, 2022, the pandemic caused by SARS-Cov-2 has resulted in 588.757.628 cases of COVID-19 and 6.433.794 deaths worldwide.[1] The main route of transmission of SARS-CoV-2 is from person to person through small respiratory droplets, when a contaminated person coughs, sneezes, or talks.[2] Airborne transmission through aerosols[3] can also contribute to the spread of the virus.

The oral cavity may be an important reservoir for SARS-CoV-2. The virus has been detected in the saliva[4] and on the back of the tongue.[5] Interestingly, a postmortem study in COVID-19 fatal cases detected SARS-CoV-2 in major salivary glands[6] and periodontal tissues.[7] Even asymptomatic patients present high viral loads of SARS-CoV-2 in the oropharynx, which emphasizes the importance of the oral cavity in transmission of the virus.[8]

Dental professionals present high risk of SARS-CoV-2 infection because of their proximity to the patients´ oral cavity.[9] Furthermore, dental procedures in which high-speed turbines, air-water syringes and ultrasonic instruments

are used, generate contaminated spray and aerosols,[10,11] which may allow airborne transmission of the virus in the dental setting.[12,13]

Since the onset of the pandemic, reinforcement of standard practices and additional infection control measures have been recommended as a part of routine dental healthcare.[14] The use of personal protective equipment, methods for reducing airborne contamination, limitation of aerosol-generating procedures, and methods for reducing surface contamination have been advocated to prevent transmission of SARS-CoV-2 infection in the dental setting.[15] Since transmission of the virus can occur through contaminated aerosols, some authors have suggested that the use of pre-procedural mouthrinses could reduce the risk of contamination by SARS-CoV-2 in the dental office.[16-20] The rationale is that mouthrinses with antiseptic substances could reduce the viral load in saliva and other oral tissues, thus reducing the number of active aerosolized viral particles from the oral cavity. There is good evidence that preprocedural rinses reduce bacterial load in the dental aerosol.[10] However, the evidence about the efficacy of mouthrinses in reducing the viral load in the oral cavity is still controversial. Thus, the aim of this review was to synthesize the evidence about the efficacy of mouthrinses in reducing the salivary viral load of SARS-CoV-2.

Rationale for the effect of mouthrinses against SARS-COV-2

SARS-CoV-2 is susceptible to a wide variety of antiseptics, such as ethanol (> 75%), povidone-iodine (> 0.23%), and hydrogen peroxide (> 0.5%).[20] The majority of the substances inactivate the virus by damaging its outer lipid layer.[21]

Various ingredients of mouthrinses have been tested against SARS-CoV-2 in *in vitro* studies. Povidone iodine (PVP-I) has been the substance most tested, and has demonstrated virucidal activity against this virus.[22-24] Other substances tested include chlorhexidine (CHX)[25,26] and hydrogen peroxide (HP),[24,27] with divergent results according to the study. If these active ingredients have a virucidal effect against the virus, they may be efficient in reducing the viral load of SARS-CoV-2 in the oral cavity. However, results from *in vitro* studies do not necessarily reflect the clinical efficacy of mouthwashes. Thus, this hypothesis needs to be investigated in *in vivo* studies.

In addition to the *in vitro* studies described above, some case reports[17,28] and case series[29] have assessed the effect of pre-procedural mouthwashes in reducing the salivary viral load of patients with COVID-19 Each study tested the reduction of salivary viral load of SARS-CoV-2 using different active ingredients, namely: CHX[17] PVP-I[28] and HP.[29] Two studies[17,28] detected a reduction in the salivary viral load of hospitalized patients after rinsing with 0.12% CHX and PVP-I mouthrinses, respectively. However, their results are based on the observations of two patients each, and lack a control group. Another study[29] investigated the effect of a 1% HP rinse in 12 patients, in whom HP rinsing failed to reduce salivary viral loads. All of these studies had limitations such as the small sample size, absence of a control group, and lack of randomization. Therefore, the effect of mourthrinses on the salivary load of SARS-CoV-2 needs to be verified in randomized trials.

Randomized controlled trials

When correctly designed, conducted, and reported, randomized clinical trials (RCTs) produce the strongest reliable evidence in evaluating health interventions. In this context, we searched the internet up to July 2022 for RCTs that investigated the efficacy of mourthrinses on the reduction of the salivary load of SARS-CoV-2. The following search strategy was used in MEDLINE (via Pubmed): (mouthwash* OR "mouth rinse" OR "oral rinse" OR rinse OR hydrogen peroxide OR povidone iodine OR cetylpyridinium OR essential oils OR chlorhexidine) AND (COVID-19 OR COVID19 OR SARS-CoV-2).

Nine parallel arm randomized trials that evaluated the efficacy of mouthrinsing in reducing salivary viral load were published in the period between December 2020 and July 2022. The characteristics of the studies are shown in Table.

Table. General characteristics of randomized controlled trials that verified the efficacy of mouthrinses in reducing the salivary viral load of SARS-CoV-2

Author (Country)	Test products and rinsing time	Control group	Primary outcome	Time frame	Main results
Seneviratne et al., 2020[30] (Malaysia)	Test group 1: 0.5% PVP-I diluted with 5 ml of water (0.5% w/v), 5 mL, for 30 seconds (Betadine Gargle and Mouthwash®). N = 4 Test group 2: 0.2% CHX, 15 mL, for 30 seconds (Pearlie White Chlor-Rinse®). N = 6 Test group 3: 0.075% CPC, 20 mL, for 30 seconds (Colgate Plax®). N = 4	Sterile water, 15 mL for 30 seconds. n = 2	Change in cycle threshold (Ct) values of salivary SARS-CoV-2 after mouthrinsing.	Saliva samples were collected at baseline, 5 minutes, 3 hours, and 6 hours post-rinsing.	There was a significant saliva viral load reduction for 0.5% PVP-I group at 6 hours and 0.075% CPC group at 5 minutes and 6 hours, compared to control.
Elzein et al, 2021[32] (Lebanon)	Test group 1: 1% PVP-I, 15 mL, for 30 seconds (trademark not mentioned). N = 25 Test group 2: 0.2% CHX, 15 mL, for 30 seconds (trademark not mentioned). N = 27	Distilled water, 15 mL, for 30 seconds. n = 9	Change in cycle threshold (Ct) values of salivary SARS-CoV-2 after mouthrinsing.	Saliva samples were collected at baseline and 5 minutes post-rinsing.	There was a significant saliva viral load reduction for both mouthrinses compared to control. No significant difference was found between the groups.
Chaudhary et al. 2021[37] (United States)	Test group 1: 0.5% PVP-I, 7.5 mL, for 30 seconds. Next, patients expectorated and rinsed with 7.5ml for further 30 seconds (trademark not mentioned). N = 10 Test group 2: 0.12% CHX, 7.5 mL, for 30 seconds. Next, patients expectorated and rinsed with 7.5ml for further 30 seconds (trademark not mentioned). N = 10 Test group 3: 1% HP, 7.5 mL, for 30 seconds. Next, patients expectorated and rinsed with 7.5ml for a further 30 seconds (trademark not mentioned). N = 10	Saline solution, 7.5 mL, for 30 seconds. Next, patients expectorated and rinsed with 7.5ml for further 30 seconds. n = 10	Change in cycle threshold (Ct) values of salivary SARS-CoV-2 after mouthrinsing.	Saliva samples were collected at baseline, 15- and 45-minutes post-rinsing.	There was a significant saliva viral load intragroup reduction for 0.5% PVP-I, 0.12% CHX and saline solution 15 and 45 minutes post-rinsing. However, there were no differences between the groups.
Carrouel et al, 2021[31] (France)	Test group: CDCM, 30 mL, for 1 minute. Three rinses daily (at 09:00, 14:00 and 19:00) were performed for 7 days. N = 88 (76 analyzed)	Placebo solution, 30 mL, for 1 minute. n = 88 (78 analyzed)	Viral load in saliva, calculated as the number of RNA copies per mL of saliva (log10 copies/mL).	Saliva samples were collected on day 1 at baseline and immediately post-rinsing, at 09:00, 14:00 and 19:00 hours. On the following 6 days, one sample immediately post-rinsing was taken at 15:00 hours.	There was a significant saliva viral load reduction in the test group, compared to control on day 1 (4 hours after the initial dose). For 7 days, a modest benefit was verified.

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Eduardo et al, 2021[33] (Brazil)	Test group 1: 0.12% CHX, 15 mL, for 30 seconds (PerioGard®). n = 12 (8 analyzed) Test group 2: 0.075% CPC + 0.28% Zinc lactate, 20 mL, for 30 seconds (CPC + Zn; Colgate Total 12®). n = 12 (7 analyzed) Test group 3: 1.5% HP, 10 mL, for 1 minute (Peroxyl®). Test group 3: n = 12 (7 analyzed) Test group 4: 1.5% HP + 0.12% CHX, 10 mL of HP, for 1 minute, followed by rinsing with 15 mL of CHX for 30 seconds (Peroxyl® + PerioGard®). n = 12 (12 analyzed)	Distilled water, 20 mL, for 1 minute. n = 12 (9 analyzed)	Change in cycle threshold (Ct) values of salivary SARS-CoV-2 after mouthrinsing.	Saliva samples were collected at baseline, immediately post-rinsing, 30 minutes, and 1-hour post-rinsing.	There was a significant intragroup reduction in the saliva viral load in the 4 test groups but not in the control group. However, there were no significant differences between the tests and the control group.
Costa et al, 2021[38] (Brazil)	Test group: 0.12% CHX, 15 mL, for 30 seconds (trademark not mentioned). Next, patients spat and rinsed the same product for 30 seconds. N = 55 (50 analyzed).	Placebo solution, 15 mL, 30 for seconds. Next, patients spat and rinsed the same product for 30 seconds. n = 55 (50 analyzed).	Change in cycle threshold (Ct) values of salivary SARS-CoV-2 after mouthrinsing.	Saliva samples were collected at baseline, 5 minutes, and 1-hour post-rinsing.	There was a significant saliva viral load reduction in the test group, compared to control, at 5 minutes and 1-hour post-rinsing.
Ferrer et al., 2021[34] (Spain)	Test group 1: 2% PVP-I (diluted: 3 mL of povidone-iodine 10% for oral use, with 12 mL of distilled water), for 1 minute (Betadine Gargle and Mouthwash®). The dosage was not mentioned. N = 18 (9 analyzed) Test group 2: 1% HP (diluted: 5 mL of hydrogen peroxide 3%, with 10 mL of distilled water), for 1 minute (Oximen©). The dosage was not mentioned. n = 16 (14 analyzed) Test group 3: 0.07% CPC, for 1 minute (Vitis Xtra Forte©). The dosage was not mentioned. n = 17 (11 analyzed) Test group 4: 0.12% CHX, for 1 minute (Clorhexidina Dental PHB©). The dosage was not mentioned. n = 17 (12 analyzed)	Distilled water, for 1 minute. The dosage was not mentioned. n = 16 (12 analyzed)	Viral load in saliva, calculated as the number of RNA copies per mL of saliva (log10 copies/mL).	Saliva samples were collected at baseline, 30 minutes, 1- and 2-hour post-rinsing.	There was no significant saliva viral load reduction in the 4 test groups, compared to control, at 30-, 60- and 120-minutes post-rinsing.

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Alemany et al., 2022[35] (Spain)	Test group: 0.07% CPC, 15 mL, for 1 minute (Vitis® CPC Protect, Dentaid). n = 60 (51 analyzed for viral load by RT-qPCR and 40 analyzed for nucleocapsid ELISA).	Distilled water, 15 mL, for 1 minute. n = 58 (54 analyzed for viral load by RT-qPCR and 40 analyzed for nucleocapsid ELISA).	Viral load in saliva, calculated as the number of RNA copies per mL of saliva (log10 copies/mL) and levels of SARS-CpV-2 nucleocapsid protein levels of lysed viruses.	Saliva samples were collected at baseline, 1 and 3 hours post-rinsing.	There was no significant viral load reduction in test group, compared with to control. However, the levels of SARS-CoV-2 nucleocapsid protein of lysed viruses were significantly higher in the CPC group compared with the control group at 1 and 3 hours post-rinsing.
Barrueco et al., 2022[36] (Spain)	Test group 1: 2% PVP-I, for 1 minute (Betadine © Bucal 100 mg/mL). The dosage was not mentioned. n = 9 (5 analyzed) Test group 2: 1% HP, for 1 minute (Oximen©). The dosage was not mentioned. N = 6 (5 analyzed) Test group 3: 0.07% CPC, for 1 minute (Vitis Xtra Forte©. The dosage was not mentioned. n = 9 (7 analyzed) Test group 4: 0.12% CHX, for 1 minute (Clorhexidina Dental PHB©). The dosage was not mentioned. n = 9 (6 analyzed)	Distilled water, for 1 minute. The dosage was not mentioned. n = 10 (6 analyzed).	Viral load in saliva, calculated as the number of RNA copies per mL of saliva (log10 copies/mL) and its infectious capacity (incubating saliva in cell cultures).	Saliva samples were collected at baseline, 30 minutes and 1 hour post-rinsing.	There was no significant viral load reduction in PVP-I, HP and CHX groups, compared with the control. Significant reduction in salivary viral copy numbers of 1.5 log and a 97.16% reduction in viral infectivity were obtained for CPC, 1 hour post-rinsing.

The number of participants ranged from 16[30] to 176.[31] Different types of active ingredients and combinations were tested: 0.5%,1% and 2% PVP-I, 0.2% and 0.12% CHX, 0.075% CPC, 0.075% CPC + Zinc lactate, 1% and 1.5% HP, 1.5% HP + 0.12% CHX and ß-cyclodextrin and citrox (CDCM).

Sterile water, distilled water, saline solution, and placebo were used as controls. Seven of the studies were located at hospitals,[30-36] one in a university[37] and another one in a Municipal Family Health Unit.[38]

All studies were conducted with COVID-19 positive patients. The method for COVID-19 diagnosis was positive nasopharyngeal RT-PCR in all studies The investigations included symptomatic patients,[30,34,36] asymptomatic to mildly symptomatic patients,[31,35] mildly to moderately symptomatic patients,[33,38] asymptomatic, post-symptomatic, and pre-symptomatic patients.[37] One study failed to provide information relative to patients´ symptoms.[32] The primary outcome of six studies was change in cycle threshold (Ct) values of salivary SARS-CoV-2[30,32,33,36-38] and in three studies[31,34,35] it was the number of RNA copies per mL of saliva (log10 copies/mL) after mouthrinsing. In one study,[36] in addition to the Ct values, the infectious viral load was assessed in cell cultures, and in another study,[35] apart from the RNA copies per mL of saliva, levels of SARS-CoV-2 nucleocapsid protein of lysed viruses were verified after mouthrinsing.

One investigation[30] verified that 0.075% CPC and 0.5% PI mouthrinses significantly decreased SARS-Cov-2 salivary viral load when compared

with the control. No significant difference between CHX and water was verified. Elzein et al.[32] reported that 1% PVP-I and 0.2% CHX were effective against salivary SARS-CoV-2 compared with the control group, 5 minutes after rinsing. No significant difference was verified between the test groups. Another investigation[37] demonstrated that 0.5% PI, 0.12% CHX, and 1% HP mouthrinses significantly decreased viral load by 61– 89% at 15 minutes and by 70–97% at 45 minutes. However, there were no significant differences between any of the active groups and the control group. Another group[31] reported that CDCM, three rinses daily, was significantly more effective than the placebo, 4 hours after the first dose, and the second dose maintained a significantly lower value. Furthermore, at day 7, there was still a greater median percentage decrease in salivary viral load over the time in the test group compared with the placebo. One of the trials[33] showed that rinsing with three different mouthrinses (CPC + Zn, HP and CHX) temporarily reduced the salivary load of SARS-CoV-2 after 30 and 60 minutes post-rinsing in relation to baseline and this effect was not verified in the control. Nevertheless, there were no significant differences between the tests and the control group. Although HP effectively reduced the viral load immediately after rinsing, it returned to its baseline value within 60 minutes after rinsing. The lack of substantivity of HP might explain this finding. The sequential rinse of CHX after HP did not provide any additional benefits. Another study[38] also reported significant reduction in viral load in the test groups compared with the control. The effect of CHX was observed after 5 and 60 minutes. In contrast, one of the trials[34] showed that none of the mouthrinses tested (PVP-I, HP, CPC and CHX) significantly reduced viral load at 30 minutes, 1- and 2-hour post-rinsing, compared with the control. Nevertheless, the results were highly divergent among participants. Clear decreases were verified in some participants or at some time points and increases at other times. Along the same line, another group[35] verified no differences between the test and control relative to viral load reduction. Furthermore, levels of SARS-CoV-2 nucleocapsid protein of lysed viruses were significantly higher in the CPC group compared with the control group at 1 and 3 hours post-rinsing. One of the investigations[36] showed no significant reduction in viral load in HP and CHX groups. There was a significant reduction in numbers of salivary viral copies and viral infectivity in the CPC group, 1 hour after mouthrinsing. However, there was no significant reduction in viral load in PVP-I, HP and CHX groups, compared with the control.

Critical review of the evidence

The evidence from the nine RCTs relative to reducing viral loads in saliva was controversial. Although the majority of studies verified significant reduction in intragroup viral loads, there was contrasting evidence when the active groups were compared with a control group. Some studies showed a significant reduction in viral load when using 0.5% PVP-I,[30] 1% PVP-I,[32] 0.075% CPC,[30] 0.2% CHX,[32] 0.12% CHX[38] and CDCM,[31] when compared with the control group. Others did not indicate a significant reduction when using 0.2% CHX,[30] 0.12% CHX,[33,34,37] 0.075% CPC,[33-35] 0.5% PVP-I,[37] 2% PVP-I,[34,36] 1% HP[34,36,37] compared with the control. Nevertheless, assessing the viral load might not be an adequate method for determining the efficacy of substances targeting the viral envelope but not the viral RNA. There is evidence that RNA may persist in saliva after the disruption of virus particles, probably due to protection by protein complexes.[39] RNA extraction methods can identify the RNA irrespective of its status (*i.e.*, immerse within intact viral particles or released from disrupted particles). Therefore, real-time PCR for viral detection might not indicate the presence of complete viral particles.[35] It is not known whether any residual viral genome equivalents identified are infectious.[34]

On the other hand, one study exhibited a significant increase in nucleocapsid protein levels in saliva, indicating enhanced disruption of viral particles by CPC compared with the control at 1 and 3 hours after mouthrinsing. Baseline levels were similar in the groups, and the disruption of nucleocapsid protein was increasingly higher in the test group during

the following assessments.[35] This finding showed evidence of the potential of CPC for reducing the spread of viruses.

Another study[36] for the first time evaluated the virus infectivity in saliva samples in cell cultures (infectious viral load) and indicated a significant reduction in virus infectivity in the CPC group compared with the control, 1-hour post-rinsing. The decrease in the mean quantity of infectious viruses corresponded to a reduction of 97.16% in virus infectivity. Based on this data, a significant antiviral effect was achieved. However, it was not immediate. One hour of waiting after mouthrinsing would be required for a significant antiviral effect. As it was the only study about the effects of mouthrinses in virus infectivity, the use of mouthrinses should be further explored using this methodology.

Other aspects should be investigated in future studies, such as the influence of modification in product dosages or concentration, as well as rinsing time and the time frame of saliva sampling after mouthwash. Additional baseline data such as a complete oral exam could also be considered. Furthermore, given the difficulties in culturing SARS-CoV-2 virus from clinical specimens, using viral RNA load as a surrogate continues to be a reasonable approach. Nonetheless, it is important to clarify that viral analyses performed by RT-PCR are incapable of determining the viability and transmissibility of viruses. Finally, it is important to recall that the majority of the trials presented small samples sizes, which could be associated with type II error. In other words, these studies may be underpowered to detect differences between the groups. Thus, future studies with large sample sizes and viral culture are necessary before definitive conclusions can be drawn.

Conclusions

So far, there is no robust evidence that mouthrinses are effective for reducing the salivary loads of SARS-CoV-2. More randomized trials with larger sample sizes are necessary.

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