Original Article

Evaluating the Effect of Gargling with Hydrogen Peroxide and Povidone-Iodine on Salivary Viral Load of SARS-CoV-2: A Pilot Randomized Clinical Trial

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Abstract

Background and Aim: This study evaluates the salivary viral load of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in hospitalized patients and outpatients before and after gargling with 1% hydrogen peroxide and 0.25% povidone-iodine in comparison with normal saline. **Patients and Methods:** This clinical trial was conducted on 120 participants with laboratory-confirmed coronavirus disease 2019 (COVID-19) in two groups: outpatients (n = 60) and hospitalized patients (n = 60). In each group, the patients were randomly divided into three subgroups of 20 based on their given mouthwash for gargling (hydrogen peroxide, povidone-iodine, or normal saline). Two saliva samples were taken from each patient: the first one before gargling and the second one 10 minutes after gargling 10 ml of the respected mouthwashes for 30 seconds. The TaqMan real-time polymerase chain reaction (PCR) amplification of SARS-CoV-2 was used to measure the viral load. **Results:** Saliva samples from 46% of patients were positive for coronavirus before gargling the mouthwashes. The percentage of patients with an initial positive saliva sample was significantly higher in the outpatient group (83.3%) than in the hospitalized group (5.4%) (P = 0.01). According to the findings, gargling any mouthwash similar to saline did not reduce the viral load (P > 0.05). **Conclusion:** The saliva of COVID-19 patients in the initial stage of the disease was more likely to contain SARS-CoV-2 than the saliva of the hospitalized patients. Gargling hydrogen peroxide or povidone-iodine did not reduce the salivary SARS-CoV-2 viral load.

Keywords: *COVID-19, hydrogen peroxide, mouthwash, normal saline, povidone-iodine, SARS-CoV-2*

Introduction

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that emerged in Wuhan, China, in late 2019.[1,2] The rapid worldwide spread of the disease persuaded the World Health Organization to declare it a global pandemic on March 11, 2020.[2] One of the primary sources of transmission of SARS-CoV-2 between humans is aerosols emitted by infected people coughing, sneezing, or even talking in the vicinity of other people.[3] Previous studies have confirmed the presence of this novel virus in the saliva of infected patients.[4]

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The presence of angiotensin-converting enzyme 2 (ACE2), a critical COVID-19 receptor, in the salivary gland epithelial cells may indicate the presence of SARS-CoV-2 in the saliva.[5,6] Meanwhile, secretions coming down from the nasopharynx or coming up from the lung via the action of cilia lining the airway can add to the salivary viral load.[7] Therefore, the

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saliva can carry a risk of transmission of COVID-19, and dental professionals are at a high risk of infection, as many dental interventions, such as using air turbines or ultrasonic scalers, naturally produce aerosols.[8] In addition, if appropriate precautions are not taken, the dental office can be a potential place of cross contamination for patients.[8,9] Therefore, alongside general protection measures, reducing the salivary viral load in COVID-19 patients or potential carriers can be crucial for preventing disease transmission, especially in dental offices.[6,10]

The use of antiviral mouthwash has been recommended by some national dental/health authorities as a pre-procedural preventive measure to protect dental professionals and patients.[11] For instance, Chinese health authorities suggested the use of povidone-iodine- and hydrogen peroxide-based mouthwash.[11,12] and the American Dental Association advocated the use of hydrogen peroxide-based mouthwashes to protect against SARS-CoV-2.[12-14] Nonetheless, to date, only a few *in vitro* studies have investigated the virucidal efficacy of different mouthwashes against SARS-CoV-2 and have yielded conflicting results.[15,16] Similarly, *in vivo* studies regarding the effect of using mouthwash on the salivary viral load of SARS-CoV-2 are very limited in number and have a small sample size and controversial findings.[17-19] Therefore, there is no sufficient scientific evidence to support the recommendation to use pre-procedural mouthwash to reduce the risk of infection in dental offices and the community in general.

Considering the lack of clinical trials with a sufficient sample size on the efficacy of the recommended mouthwashes on the SARS-CoV-2 viral load in the saliva, this study evaluated the potential effect of gargling 0.25% povidone-iodine and 1% hydrogen peroxide mouthwashes in reducing the salivary viral load in two groups of SARS-CoV-2-positive patients, including outpatients with initial clinical symptoms and hospitalized patients with lower respiratory tract involvement.

Methods

Study design and participants

This was a multicenter, double-blind, randomized, controlled clinical trial conducted to assess the efficacy of povidone-iodine and hydrogen peroxide mouthwashes in comparison with normal saline solution in reducing the salivary viral load of SARS-CoV-2-positive patients.

The study design was approved by the ethics committee of Shiraz University of Medical Sciences (IR.SUMS.DENTAL.REC.1399.186), and the trial was registered at the Registry of Clinical Trials (IRCT20201212049681N1) on February 28, 2021.

The two confirmed groups of COVID-19 patients from both sexes with a positive nasal swab for SARS-CoV-2 based on the reverse transcription polymerase chain reaction (RT-PCR) assay were recruited for this study.

Group 1 includes hospitalized patients (n = 60) who had a positive COVID-19 test and had been admitted to a hospital with the diagnosis of COVID-19 pneumonia based on their clinical signs and symptoms and had chest computed tomography (CT) findings compatible with the COVID-19 pneumonia pattern.

Group 2 includes outpatients (n = 60) with a recent onset of symptoms of COVID-19 who had a positive test in the previous 24 hours. The outpatients were recruited from a clinic (Hor Riahi Clinic) and the hospitalized patients from three hospitals (Shahid Faghihi, Namazi, and Aliasghar) in Shiraz, Iran.

The patients were excluded if they were under 20 or above 60 years old, were participating in another study at the same time, or had any systemic diseases. Before beginning the intervention, the aim of this research and its risks and benefits were explained to the patients. Voluntary participation was emphasized, and all the participants signed written informed consent before participating in the study.

Randomization

In each group, the patients were divided into three experimental subgroups of equal sizes, namely, subgroups A, B, and C. For this purpose, letters A, B, and C were written on separate sheets of paper, each containing twenty. The sheets were placed in a sealed opaque envelope, and then, each participant randomly picked one envelope corresponding to either A, B, or C subgroup.

Blinding

To ensure that both the participants and the clinicians were blinded to the groups, all the participants, the clinician who collected the samples, and the author were blinded to each other.

Intervention

In each group of patients, the subjects were randomly divided into three subgroups (n = 20 per group): subgroup A: 1% hydrogen peroxide (Bismoot Co., Tehran, Iran); subgroup B: 0.25% povidone-iodine (Farmadin Co., Yazd, Iran)" should be changed to "Farmadine, NanoKimia Co., Yazd, Iran); and subgroup C: normal saline (the control group).

The two saliva samples were taken from each patient: the first one before gargling and the second one 10 minutes after gargling 10 ml of the respected mouthwashes for 30 seconds. The saliva was collected by asking the patients to spit into a sterile container. The collected samples were inserted into separate tubes containing 2 mL of the virus transport medium.

Quantitative assay for the detection of SARS-CoV-2 RNA burden

In the first step, the viral genome extraction was performed using the SinaPure Viral Kit (Sinaclon Co., Iran) using 200 µl of each sample and a water sample as the extraction control.

A duplex RT-qPCR assay kit (SD Biosensor Inc., China) targeting viral RdRp and E genes and a human RNA transcript (RNase P) as the internal sample sufficiency control were used in the study for the quantification of SARS-CoV-2 genome.

The final reaction mixture (25 µl) consisted of 4.5 µl of RNA extracted sample, 6 µl of RTase mix, 0.5 µl of Rox, and 14 µl of the reaction solution. The tests were performed using the ABI 7500 real-time PCR instrument.

The test result was considered positive if the genomic target showed positive results at less than 35 cycles, and all the positive and negative control reactions gave the expected values.

Statistical analysis

Data were analyzed using the Wilcoxon signed-rank and Kruskal–Wallis tests for intragroup and intergroup comparisons, respectively. SPSS software (version 15, SPSS Inc.; Chicago, IL, USA) was used for the statistical analysis of the data, and $P < 0.05$ was taken as the level of statistical significance.

Results

Five of the 60 samples from the hospitalized group were lost because of laboratory issues, such as errors stemming from missing or mislabeled specimens [Figure 1]. Among the remaining 115 samples, the saliva samples of 53 patients (46%) were positive for SARS-CoV-2 before gargling the mouthwashes. Fifty patients (83.3%) in the outpatient group and only three (5.4%) in the hospitalized group had positive saliva samples [Table 1]. The difference between the two groups was statistically significant ($P = 0.001$).

The viral load before and after gargling was compared among 53 patients whose saliva samples were positive for the virus before gargling [Table 1]. The viral loads of the three groups of mouthwashes were not statistically different before ($P = 0.164$) and after ($P = 0.118$) gargling.

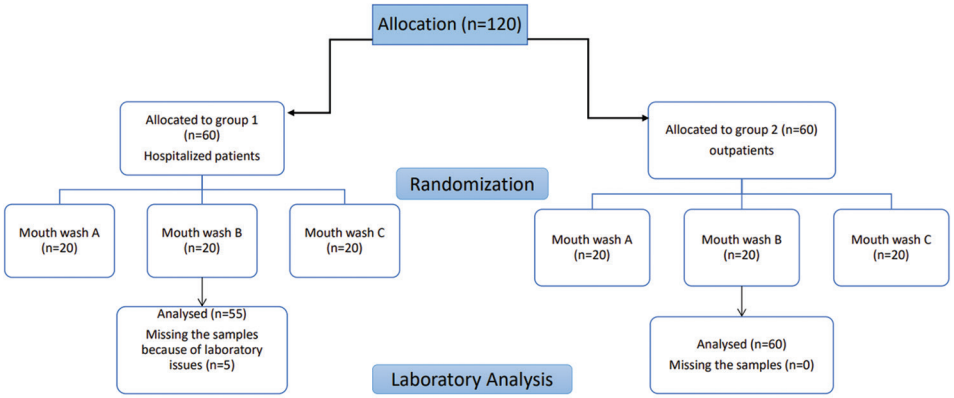

Figure 1: CONSORT chart

Table 1: Mean ± standard deviation (median) of viral load (copy/mL) before and after gargling and also viral load reduction (Δ)

Group	Number	Before	After	*P* (intragroup comparison)	Δ
Hydrogen peroxide	20	591050±2222441 (40000)	2053900±6138833 (25000)	0.962	1462850±4884893 (0)
Povidone-iodine	18	2061388±5828206 (175000)	1768694±3205600 (800000)	0.206	-292694±6728707 (70000)
Normal saline	15	2184866±4057842 (100000)	1535600±2890394 (100000)	0.463	-649266±4519460 (0)
P (intergroup comparison)		0.164	0.118		0.230

The viral loads before and after gargling did not differ significantly in any mouthwash subgroups ($P > 0.05$). When the three mouthwashes were compared regarding their resultant reduction in viral load, no significant differences were observed between them ($P = 0.23$).

Discussion

The COVID-19 pandemic has made health authorities face an exceptional situation requiring urgent prevention and treatment strategies in the absence of sufficient scientific data.[9] Given the detection of SARS-CoV-2 in the saliva of infected patients,[20] and despite the lack of any clinical data, some dental societies/authorities recommended the pre-procedural use of mouthwash for potentially reducing the intraoral viral load.[12-14] Researchers have therefore strongly recommended that clinical trials be performed on the efficacy of different pre-procedural mouthwashes.[21] This randomized clinical trial was designed to investigate and compare the effects of hydrogen peroxide and povidone-iodine mouthwashes on the salivary viral load of SARS-CoV-2-positive patients. In this study, hydrogen peroxide and povidone-iodine mouthwashes were selected mainly because of the general vulnerability of SARS-CoV-2 to oxidation[22] and also based on the findings of *in vitro* studies showing that products containing oxidizing agents, such as povidone-iodine and hydrogen peroxide, can inactivate coronaviruses.[23-26] However, chlorhexidine, a very common mouthwash, was suggested to have little or no effect against coronaviruses[27-29] and therefore was not included in this study.

In this study, the salivary viral load of each patient was measured before and after gargling 10 ml of 1% hydrogen peroxide, 0.25% povidone-iodine, or saline for 30 seconds. To reduce the risk of viral transmission, the patients performed the sampling themselves by spitting in a container without any need for invasive procedures.

Salivary tests for the detection of SARS-COV-2 have been recommended as alternative methods to nasopharyngeal and oropharyngeal swab tests. Some studies that have directly compared saliva and respiratory samples for the detection of SARS-COV-2 showed good saliva results,[3,7,30] while some others demonstrated inaccurate saliva results.[31-34]

One of the strengths of this study was that two groups of SARS-CoV-2-positive patients, including outpatients with initial clinical symptoms and hospitalized patients with lower respiratory tract involvement, were recruited.

The results of the present study showed that only 46% of the confirmed COVID-19 patients had positive saliva samples before gargling mouthwash. Nevertheless, a clear difference was found between the outpatients (83%) and the hospitalized patients (5.4%) in this regard. This difference could be attributed to the different vital shedding patterns due to the different durations of time elapsed from the onset of the disease in the two groups. In the outpatient group, the sampling was performed only one to two days after the onset of the symptoms, whereas in the hospitalized group, the sampling was performed more than seven days after the onset of the disease. Moreover, the different medications prescribed for hospitalized patients, including dexamethasone, antivirals, and immunomodulators, are likely to influence viral shedding. It is noteworthy that in hospitalized patients, a faster decrease has been reported in salivary viral load compared with that of the nasopharyngeal swabs.[30,35] Similarly, a general decline has been reported in the salivary viral load after hospitalization.[3,36,37] Contrary to the present findings, To *et al*.[3] detected SARS-COV-2 in the saliva specimens of 11 of the 12 hospitalized patients; however, in their study, the saliva samples were collected at a median of two days after hospitalization (range: 0–7 days), whereas in the current study, the median time after hospitalization was seven days (range: 4–12 days).

In the present study, SARS-CoV-2 was detected after gargling in some patients whose saliva samples were negative before gargling (who were thus excluded from the mouthwash evaluations). Although the exact reason is not clear to the authors, it can be assumed that gargling can detach some virus particles from the pharynx and make them enter the saliva.

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. This finding is in agreement with the results reported by Gottsauner *et al*.,[38] who found that the salivary viral load in SARS-CoV-2-positive patients did not reduce 30 min after the application of 1% hydrogen peroxide mouth rinse. However, the results reported by Lamas *et al*.[19] showed a decline in the salivary viral load of COVID-19 patients after the use of povidone-iodine mouthwash that lasted for three hours. However, the study had only four participants, and only two of them showed a significant drop in viral load following the use of povidone-iodine. Moreover, the participants rinsed their mouth for 1 minute, while in the current study, gargling was performed for only 30 seconds.

One of the limitations of this study was that the patients gargled the mouthwashes only for 30 seconds; this limited contact time may preclude mouthwashes to

deliver their antiviral effects. Another limitation was that the saliva samples were collected only 10 minutes after gargling, while most dental treatments usually need longer times. Longer gargling time or even repeated episodes of gargling can increase the effectiveness of mouthwashes. Moreover, the sequential use of two different mouthwashes may have additional benefits, which should be considered in future studies.

Based on the results of this clinical trial, the effectiveness of pre-procedural mouth rinsing with povidone-iodine or hydrogen peroxide before dental procedures is still controversial and should not be recommended any longer, especially since this pre-procedural mouth rinsing may cause a false sense of security among dental professionals. Therefore, for infection control during dental treatments, the authors recommend adherence to other precautionary measures, including hand hygiene, using rubber dams and powerful saliva ejectors, minimizing aerosol-generating procedures, and using extra-oral radiographs and disposable protective clothing.

Conclusion

In this clinical trial of confirmed COVID-19 patients, outpatients with recent onset of symptoms had a higher likelihood of having the virus in their saliva compared with hospitalized patients. Moreover, gargling with hydrogen peroxide or povidone-iodine was not effective in reducing the SARS-CoV-2 viral load in the saliva of the patients.

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Conflicts of interest

There are no conflicts of interest.

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