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Original paper

Effect of oral antiseptics on the viral load of SARS-CoV-2: A randomized controlled trial

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation;
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Abstract

Background. In the oral cavity, which plays an important role in the transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), it is possible to reduce the viral load of SARS-CoV-2 with antiseptics, thereby minimizing the transmission of the virus during dental procedures.

Objectives. The aim of this study was to clinically evaluate the effect of the hypochlorous acid (HClO) and povidone-iodine (PVP-I) solutions on the oral viral load of SARS-CoV-2.

Material and methods. This randomized controlled trial was conducted on 75 patients hospitalized in the COVID-19 ward of a local hospital. All the patients included in the study were within the first 24 h of hospitalization and the first 5 days of coronavirus disease 2019 (COVID-19) symptoms. The viral load of mouthwash samples was measured with the cycle threshold (*Ct*) value of SARS-CoV-2 through a real-time reverse transcription polymerase chain reaction (RT-PCR). The patients were divided into 3 groups. The effect on the patient's SARS-CoV-2 viral load was investigated after gargling the mouths and throats for 30 s with HClO, PVP-I and isotonic saline. First, a sample was taken after gargling with isotonic saline, then another sample was taken after gargling for 30 s with a particular antiseptic to determine the viral load of SARS-CoV-2.

Results. Comparing the before and after mouthwash samples from all 3 groups, there were no statistically significant differences in the *Ct* values before and after gargling ($p > 0.05$). However, there were statistically significant differences in the number of negative samples after the use of HClO and PVP-I, which were positive before gargling ($p < 0.05$).

Conclusions. In the light of the data obtained in this study, there is insufficient evidence that gargling with HClO or PVP-I reduces viral load. Taken together, these findings imply no role for antiseptics in the transmission of SARS-CoV-2 by the aerosol generated during dental procedures, or more generally, SARS-CoV-2 infection control.

Keywords: viral load, COVID-19, SARS-CoV-2, hypochlorous acid, povidone-iodine

Cite as
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Introduction

On March 11, 2020, the World Health Organization (WHO) declared that the coronavirus disease 2019 (COVID-19) outbreak was a pandemic phenomenon. As of March 21, 2022, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus responsible for COVID-19, has infected more than 470 million people worldwide, with nearly 6 million deaths. COVID-19 has been reported to have potentially harmful effects on people's physical and mental health, causing economic uncertainty and social isolation as well as deaths.[1,2] The WHO classified SARS-CoV-2 as an airborne pathogen and reported that it was transmitted by close contact with the aerosols and droplets emitted by asymptomatic and pre-symptomatic individuals as well as those with symptoms.[3] Epithelial cells in the oral mucosa and salivary glands contain a large number of viral entrance factors for SARS-CoV-2, such as angiotensin-converting enzyme 2 (ACE2) and the transmembrane protease serine subfamily (TMPRSS) enzymes.[4] Mild to moderate cases of COVID-19 infection have proven to be associated with oral symptoms,[5] and therefore patients with infectious diseases may present with oral problems.[6] The contamination of aerosol from the oral cavities of patients is a potential danger to dentists, assistant staff and other patients,[7] and thus the World Economic Forum has recognized dentists as one of the professions with the highest risk for COVID-19.[8] Therefore, in addition to strict protection measures, saliva is thought to be important in preventing the transmission of COVID-19, especially during oral treatment, in terms of reducing viral load in COVID-19 patients.[9]

Antiseptics can be used effectively to reduce viral load, lowering the risk of respiratory tract infections.[10] It has been reported that oral antiseptics may be beneficial both in reducing the severity of the disease by lessening the pathogenicity of the virus, and also in preventing the virus from remaining in the mouth and being transferred from the body to the outside.[11] An important step in reducing viral load is the use of antiseptics with an ingredient that exhibits antiviral effects, such as hydrogen peroxide (H_2O_2), povidone-iodine (PVP-I), chlorhexidine (CHX), cetylpyridinium chloride (CPC), cyclodextrins, Citrox®, phthalocyanine, essential oils, or hypochlorous acid (HClO). Reviews of the available research concluded that antiseptics with antiviral effects could decrease the severity of COVID-19 by reducing the SARS-CoV-2 oral viral load, lowering the risk of transmission, and therefore might be useful in the current pandemic situation.

One of the antiseptics approved for the fight against SARS-CoV-2 is HClO.[12] It has a broad spectrum, works quickly and is considered to be very safe. Currently, it is used to control and prevent a variety of skin and mucosal infections.[13] Hypochlorous acid destroys viruses through chlorination by forming chloramines and nitrogen-centered radicals, causing single- and double-stranded DNA breaks, rendering nucleic acid inoperative, and inactivating the virus.[14] Presently, 0.01% HClO is approved by the Australian Register of Therapeutic Products (ARTG) as an effective disinfectant against COVID-19.[15]

Povidone-iodine has been shown to be an effective antiseptic against enveloped and non-enveloped viruses; its antimicrobial activity has been used for years.[16] An in-vitro study conducted in Japan found that the applied PVP-I mouthwash showed antiviral activity against several different viruses, such as adenovirus, rotavirus, poliovirus (types 1 and 3), coxsackievirus, rhinovirus, herpes simplex virus (HSV), rubella virus, measles virus, mumps virus, influenza virus, and human immunodeficiency virus (HIV).[17] In another in vitro study, it was reported that 0.23% PVP-I rapidly inactivated severe acute respiratory syndrome coronavirus (SARS-CoV), Middle East respiratory syndrome coronavirus (MERS-CoV), influenza A virus subtype H1N1, and rotaviruses with a 15-second action time.[18]

Nasopharyngeal swabs are considered the gold standard as the diagnostic biomaterials recommended for suspected cases of SARS-CoV-2 infection. However, it has been reported that the collection of such specimens is not suitable for all patient types.[19] As an alternative to nasopharyngeal swabs, saliva has been reported to be a safe and reliable tool for the diagnosis of COVID-19, offering greater safety, and logistic and economic benefits.[20]

Due to the lack of clinical data, the aim of this study was to clinically evaluate the effect of the HClO and PVP-I solutions on the viral load of SARS-CoV-2 in COVID-19 patients. The null hypothesis was that there would be no difference in reducing the SARS-CoV-2 viral load between the HClO or PVP-I solutions.

Material and methods

Study design

The present study is a randomized, blind, controlled clinical trial investigating the effect of oral antiseptics with the HClO and PVP-I solutions on the intraoral viral load of SARS-CoV-2-positive patients hospitalized in the isolation ward of Erzurum Regional Training and Research Hospital, Turkey. This study was approved by the Institutional Review and Ethics Board of Erzurum Regional Training and Research Hospital (approval No. 2021/16-237), conducted according to the 2008 Declaration of Helsinki with later amendments and registered at ClinicalTrials.gov (NCT 05214196). The written informed consent was obtained from all participants. The randomization of the groups was performed using a computer program.

Power analysis

The sample size was determined by α = 0.05 and a power (1-β) of 80%. Due to the variability value (σ), a 0.37 change in viral load was used. Relying on this data, the minimum number of patients required for this study was computed as 75, for 3 groups.

Patients and samples

A flow chart of the study is presented in Fig. 1. A total of 75 adult patients who had the presence of SARS-CoV-2 RNA confirmed by real-time reverse transcription polymerase chain reaction (RT-PCR), had COVID-19 infection and were able to follow hospital treatment guidelines were included in the study. According to the inclusion criteria, all patients had a high viral load (cycle threshold (*Ct*) value <25) in the nasopharyngeal samples on admission to hospital and were within the first 5 days of COVID-19 symptoms. Samples were collected within the first 48 h after hospital admission (2 ±1 days after the SARS-CoV-2 RT-PCR test). Individuals, irrespective of gender, were at least 20 years of age and at most 83 years of age. In addition, it was necessary to have the mental ability to understand the instructions given and not to have any physical disability to implement them. The exclusion criteria were severe acute or chronic medical or psychiatric condition, a history of significant adverse effects following the use of oral hygiene products, such as a toothpaste and antiseptics, active uncontrolled thyroid disease, developmental/cognitive disability, pregnancy, and presently undergoing the radioactive iodine therapy. Those who were intubated and supported with a mechanical respirator were excluded from the study. Before brushing their teeth and eating/drinking anything in the early morning, the participants were asked to open 5-milliliter vials of sterile 0.9% saline (Gifrer®; Haks® Group, Istanbul, Turkey) and empty the contents into their mouths. The sample was gargled,

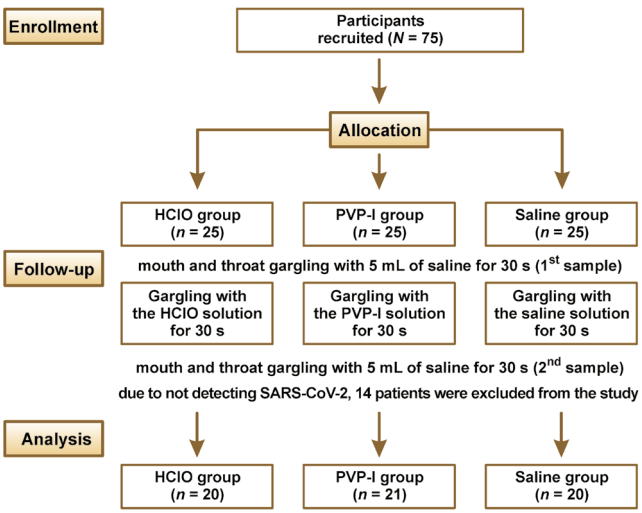


Fig. 1. Consolidated Standards of Reporting Trials (CONSORT) flow diagram
HClO – hypochlorous acid; PVP-I – povidone-iodine; SARS-CoV-2 – severe acute respiratory syndrome coronavirus 2.

and then collected into a sterile container. Next, 20 mL of 0.02% HClO solution was given to 25 patients, 20 mL of 0.5% PVP-I solution was given to 25 patients and 20 mL of 0.9% saline solution was given to 25 patients. Mouth and throat gargling was performed with the solutions for 30 s. It was insured that patients did not eat or drink anything for 30 min; then, they gargled with 5 mL of 0.9% saline for 30 s, similar to the 1st sample, and this sample was then collected into a sterile container. All samples were cryopreserved at –80°C until the time of analysis. The patients' demographic and clinical data was obtained from hospital electronic records.

Detection of viral load

The effectiveness of antiseptics of the HClO, PVP-I and isotonic saline solutions in the initial and final samples taken from each patient was investigated by means of the real-time RT-PCR method. The initial diagnosis of patients with the nasopharyngeal samples and the investigation of the presence of SARS-CoV-2 nucleic acid in the mouthwash samples were performed with the use of the Bio-Speedy® SARS-CoV-2 Double Gene RT-qPCR kit (Bioeksen R&D Technologies, Istanbul, Turkey) and the Rotor-Gene Q 5plex real-time PCR instrument (Qiagen, Hilden, Germany). This kit is a real-time, one-step RT-PCR test that targets the *ORF1ab* and *N* genes in the viral genome, including the extraction and sample quality control targeting the human RNase P gene. Both positive and negative controls were included in each run to generate a valid result. All of the analyses were carried out in the COVID-19 reference laboratory by the staff experienced in molecular methods. The Bio-Speedy SARS-CoV-2 Double Gene RT-qPCR test has been approved by the U.S. Food and Drug Administration (FDA) and added to the Emergency Use Authorization (EUA) list; it provides results with 99.6% sensitivity and 100.0% specificity according to the manufacturer's package insert. Since the RT-PCR tests used in the detection of SARS-CoV-2 are qualitatively designed, viral load was measured through the surrogate markers of the *Ct* values for SARS-CoV-2-specific gene targets, using the RT-PCR assays applied to the specimens. The RT-PCR result was considered negative when the *Ct* value could not be measured up to 40 cycles. Although the *Ct* values do not provide a complete quantitation, they are semi-quantitative in the measurement of viral load.

Statistical analysis

The results were described as mean ± standard deviation (*M* ±*SD*). The normal distribution suitability of the parameters was determined with the Kolmogorov–Smirnov and Shapiro–Wilk tests. Since the baseline and post-gargle values showed normal distribution, the paired-samples *t* test for dependent samples was used to compare the means of numerical data from 3 dependent groups. The one-way analysis of variance (ANOVA) was performed to examine differences

between the groups and the independent samples *t* test was used to examine differences between the paired groups. The Wilcoxon test was used for the analysis of the positive and negative results of the SARS-CoV-2 test, which did not show normal distribution, and the Kruskal–Wallis test was used for comparisons between the groups. A *p*-value <0.05 was considered to be statistically significant. The statistical analysis was performed with the use of the IBM SPSS Statistics for Windows software, v. 20.0 (IBM Corp., Armonk, USA).

Results

The presence of SARS-CoV-2 in the patients of the present study was confirmed through the initial gargle sample. Fourteen of 75 patients were excluded from the study, as SARS-CoV-2 could not be detected in their samples. The age and gender distribution of the 61 patients included is provided in Table 1. Table 1 also shows the distribution of the positive and negative results of the SARS-CoV-2 test. A *Ct* value ≥40 was considered negative. In the comparisons made within the groups, it was determined that the HClO and PVP-I groups showed statistically significant negative results ($p < 0.05$) (Fig. 2). However, in the comparison between the groups, it was found that there were no significant differences between the groups ($p > 0.05$).

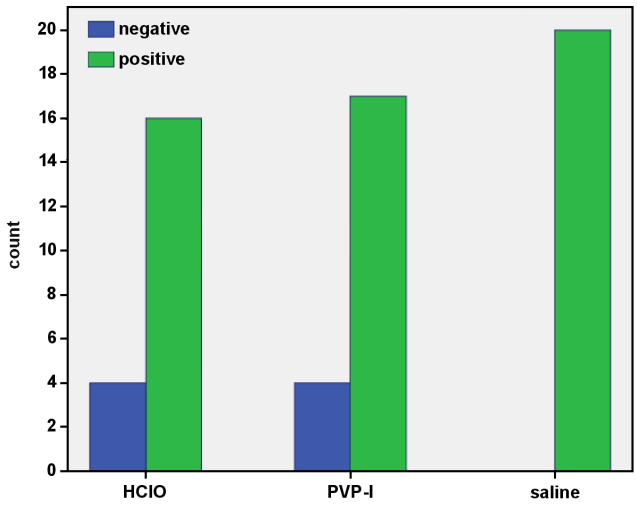


Fig. 2. Number of negative and positive samples as determined by real-time reverse transcription polymerase chain reaction (RT-PCR) post-gargle by groups ($p < 0.05$)

Table 1. Distribution of age, gender and the cycle threshold (*Ct*) values at baseline and post-gargle

Patient No.	HClO group (*n* = 20)					PVP-I group (*n* = 21)					Saline group (*n* = 20)				
	age [years]	gender	B	PG	PG result	age [years]	gender	B	PG	PG result	age [years]	gender	B	PG	PG result
1	47	F	17.24	18.70	+	43	F	32.20	25.48	+	20	M	24.53	25.43	+
2	20	F	29.82	23.99	+	58	M	24.55	40.00	–	75	F	25.76	25.30	+
3	47	M	29.41	27.82	+	78	F	29.90	28.50	+	79	F	33.17	34.09	+
4	52	F	24.25	19.59	+	30	M	30.65	31.09	+	61	F	22.64	22.66	+
5	72	F	21.90	21.15	+	35	F	23.83	23.37	+	74	F	24.13	25.32	+
6	33	F	26.76	27.88	+	50	M	33.15	40.00	–	83	F	28.54	27.68	+
7	40	M	29.38	23.77	+	51	M	24.12	25.33	+	87	M	21.70	25.62	+
8	60	M	30.39	30.31	+	45	M	29.02	40.00	–	53	F	29.80	31.75	+
9	40	M	24.30	23.10	+	32	M	30.18	40.00	–	35	M	32.06	35.92	+
10	56	M	28.70	40.00	–	35	M	21.84	20.76	+	57	F	22.58	20.38	+
11	40	F	22.90	27.61	+	33	F	26.30	27.00	+	61	M	26.67	27.37	+
12	33	M	37.50	40.00	–	20	M	20.63	24.14	+	33	F	28.54	27.68	+
13	65	M	30.47	33.56	+	68	F	27.78	26.96	+	65	M	20.86	24.82	+
14	70	F	33.36	40.00	–	77	F	28.97	28.71	+	70	M	27.85	30.75	+
15	81	F	32.94	31.05	+	54	M	27.29	26.63	+	67	M	23.12	21.63	+
16	48	F	29.52	28.27	+	55	M	30.32	32.30	+	48	M	27.29	26.63	+
17	68	F	35.43	35.43	+	66	F	27.01	25.57	+	20	F	22.48	20.99	+
18	30	M	34.17	40.00	–	59	F	23.12	21.63	+	30	M	25.66	26.89	+
19	20	F	22.34	19.38	+	68	F	30.72	30.82	+	20	M	31.13	31.88	+
20	83	F	31.64	30.57	+	40	M	32.22	31.96	+	45	F	25.78	26.68	+
21			NA			44	F	29.03	31.34	+			NA		
M ±*SD*	50.57 ±18.39		28.62 ±5.15	29.11 ±7.24		49.57 ±16.08		27.75 ±3.58	29.60 ±6.08		54.28 ±21.23		26.29 ±2.63	26.30 ±4.64	
p-value	–	–	–	–	<0.05*	–	–	–	–	<0.05*	–	–	–	–	>0.05

M – mean; *SD* – standard deviation; B – *Ct* value at baseline; PG – *Ct* value post-gargle; M – male; F – female; + SARS-CoV-2-positive; – SARS-CoV-2-negative; NA – not applicable; * statistically significant (Kruskal–Wallis test).

Table 2 shows the distribution of the SARS-CoV-2 RT-PCR *Ct* values among the groups which gargled with different solutions. Although there was an increase in the mean *Ct* values of the patients who gargled with PVP-I, no statistically significant differences were found between the groups before and after gargling ($p > 0.05$). It was also observed that there were no statistically significant differences in the values within the groups ($p > 0.05$) (Fig. 3,4).

Table 2. Comparison of the mean cycle threshold (*Ct*) values among the groups

Time point	*Ct* values			*p*-value†
	HClO group ($n = 20$)	PVP-I group ($n = 21$)	Saline group ($n = 20$)	
Baseline	28.62 ±5.15	27.75 ±3.58	26.29 ±3.63	>0.05
Post-gargle	29.11 ±7.24	29.60 ±6.08	26.30 ±4.64	>0.05
p-value‡	>0.05	>0.05	>0.05	–

Data presented as *M* ±*SD*. † one-way ANOVA test; ‡ paired-samples *t* test.

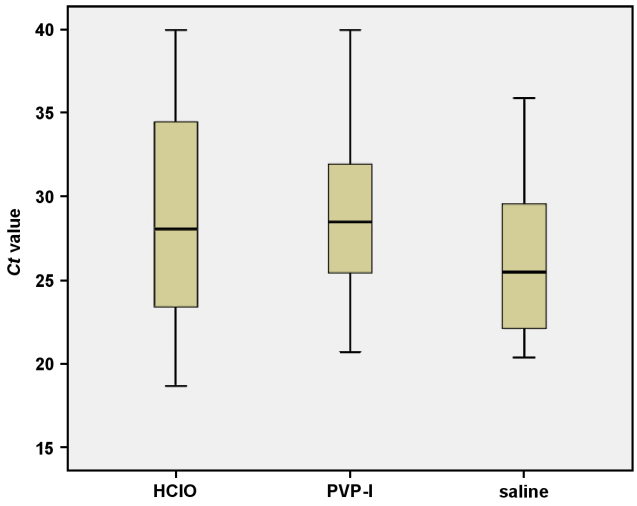


Fig. 3. Cycle threshold (*Ct*) values of the groups at baseline as determined by real-time RT-PCR ($p > 0.05$)

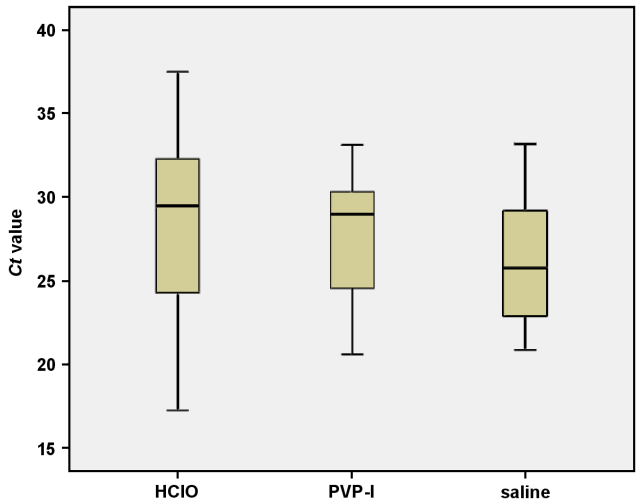


Fig. 4. Cycle threshold (*Ct*) values of the groups post-gargle as determined by real-time RT-PCR ($p > 0.05$)

No adverse clinical events related to the antiseptics were reported (burning in the mouth, allergy, taste disorder, or a dry mouth).

Discussion

The aim of this study was to investigate and compare the effectiveness in reducing the SARS-CoV-2 oral viral load of two different solutions of HClO and PVP-I with isotonic saline. The data from this clinical study is consistent with the null hypothesis: there was no statistically significant difference in reducing the SARS-CoV-2 viral load in either the HClO group or the PVP-I group as compared to the saline group. However, there were statistically significant differences in the number of patients who were SARS-CoV-2-negative after gargling in both groups as compared to the control group.

A recent study reported that the application of oral antiseptics in the oropharyngeal region, one of the viral replication centers in the early asymptomatic stages of COVID-19, had the potential to reduce viral load in the oropharynx.[21] It is known that the envelope of SARS-CoV-2 is highly sensitive to chemical agents that disrupt lipid biomembranes.[22] Therefore, chemical antisepsis is important to decontaminate the open surfaces of the body, such as the mouth. Povidone-iodine has often been suggested for usage as an antiseptic before dental procedures.[23–28] However, in a clinical study conducted by Seneviratne et al., it was found that there was no significant difference in the *Ct* values in the COVID-19 patient group using PVP-I as compared to control.[9] In this respect, it is compatible with our study. Unlike our study, Seneviratne et al. repeated sampling at different time intervals, and also investigated fold changes. The fold change of the PVP-I group was significantly increased at 6 h, whereas no change was observed in the control group.[9] In another clinical study, Chaudhary et al. reported that there was no statistically significant decrease in viral load at both 15 and 45 min in the PVP-I group as compared to the isotonic saline group.[29] These findings are also consistent with the present study. The results of only one of the comprehensive clinical studies investigating viral load in COVID-19 patients were not compatible with our research.[24] Both the sampling technique and time could be counted as the reasons for the disagreement. Like other viruses, SARS-CoV-2 replicates in living cells. Although the applied antiseptics could affect the viral particles outside the cell, they might have not been able to affect the viral particles inside the cell. Therefore, it is thought that antiseptics are effective in the first stage of contamination, before they enter the cell in the early period. This could be the reason why we did not detect any differences in the SARS-CoV-2 RT-PCR *Ct* values before and after the antiseptic application, since this study was conducted on hospitalized patients, i.e., advanced patients. However, it should be noted that RT-PCR positivity cannot be considered as the evidence of an infective virus.

To the best of our knowledge, there has been no published clinical study on the oral antiseptic HClO against SARS-CoV-2 so far. This is the first study to clinically investigate HClO as an oral antiseptic against the SARS-CoV-2 viral load, adding new information to the literature. To date, there are only in vitro studies evaluating the virucidal effect of HClO on SARS-CoV-2.[30–32]

SARS-CoV-2 has been detected in asymptomatic patients with the viral load reported to be similar to that in symptomatic patients.[33] Since patients with no or minimal symptoms often report for dental treatment, they are a danger to clinicians just as much as individuals with symptoms. In addition, hospitalized patients were chosen for the study group because of a high viral load due to an increase in the severity of the disease. It was preferred to collect SARS-CoV-2 samples from the patients in the early morning on the 1st day of hospitalization. Studies have reported that the viral load studied in samples is the highest at 4–8 days, when symptoms appear.[34,35] Furthermore, some authors have suggested the use of the throat gargle sampling method, which shows a higher viral load than a nasopharyngeal swab and an oropharyngeal swab.[36,37] When this sampling technique is used, it is easily tolerated by the patient, not affected by anatomy and less dependent on the specially trained people to collect specimens. When the patient is given written or verbal instructions, they can apply the instructions on their own. There is a minimal risk of contamination, as the method does not require close contact. In addition, it has been reported that the saliva collection method had a sensitivity of 79%, while the saline mouth and throat gargle method had a sensitivity of 98%.[38]

Limitations

This study has several limitations. SARS-CoV-2 was detected in only 61 of the 75 samples obtained. The reason for negative results is the sensitivity of saliva samples. In a study using the same kit as ours, SARS-CoV-2 RNA positivity in the saliva samples of COVID-19 patients was found at the level of 60%,[39] and it was 70% in another study performed with a different kit.[40] The fact that 80% of the samples were positive in our study shows that the sample quality was good. Both positive and negative controls were included in each run to generate a valid result. All of the analyses were carried out in the COVID-19 reference laboratory by the staff experienced in molecular methods. The Bio-Speedy SARS-CoV-2 Double Gene RT-qPCR test has been approved by the U.S. Food and Drug Administration (FDA) and added to the Emergency Use Authorization (EUA) list; it provides results with 99.6% sensitivity and 100.0% specificity according to the manufacturer's package insert. The applied standards limited the number of samples acquired for the research. Furthermore, since the RT-PCR *Ct* value was used for the detection of the SARS-CoV-2 viral load (together with live and non-infective viral particles), the viability of the virus could not be evaluated. It would be useful to culture SARS-CoV-2 in a cell culture for active virus replication; however, this requires special laboratory conditions, such as biosafety level 4. For that reason, we conducted a preliminary study that used a semi-quantitative and feasible method to measure viral load in the samples. Another limitation of the study is that it was conducted on symptomatic hospitalized patients. When a similar analysis is performed on asymptomatic patients, different results might be obtained.

Conclusions

In line with the obtained results, it was determined that gargling with oral antiseptics for 30 s is not sufficient to reduce the viral load of SARS-CoV-2. Gargling with an oral antiseptic before dental procedures can provide a false sense of security, so proper personal protective equipment (PPE) should always be worn before any aerosol-generating procedures in the dental clinic, and four-handed dentistry, the use of a rubber dam or high evacuation suction are advisable to minimize droplet splashing.

Trial registration

This study was registered at ClinicalTrials.gov (NCT 05214196).

Ethics approval and consent to participate

This study was approved by the Institutional Review and Ethics Board of Erzurum Regional Training and Research Hospital (approval No. 2021/16-237) and conducted according to the 2008 Declaration of Helsinki with later amendments. The written informed consent was obtained from all participants.

Data availability

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Consent for publication

Not applicable.

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