Original Article

A Comparison of the Effects of Chlorhexidine and Sodium Bicarbonate Mouthwashes on COVID-19–Related Symptoms

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Abstract

Background: Some studies have reported that mouthwashes can decrease the viral load in the mouth, but there is not much information about the effectiveness of mouthwashes on coronavirus disease 2019 (COVID-19). This study was conducted to compare the impact of using two types of mouthwash, chlorhexidine and sodium bicarbonate, on COVID-19 symptoms and infection. **Materials and Methods:** The present three-group, double-blind clinical trial examined 116 operating room nurses and anesthesia personnel of certain hospitals of Isfahan University of Medical Sciences, Isfahan, Iran. The participants were randomly assigned to three groups: intervention group 1 (chlorhexidine mouthwash), intervention group 2 (sodium bicarbonate mouthwash), and the control group (placebo). Mouthwash was used twice a day (morning and night) for 2 weeks. The participants were monitored in terms of COVID-19–related symptoms for 4 weeks, from the first day of mouthwash use. **Results:** Fisher's exact test indicated a significant difference between the chlorhexidine and control groups in terms of the onset of COVID-19–related symptoms (p = 0.02). There was no significant difference in the symptoms of COVID-19 between the groups, but the groups were significantly different in terms of all symptoms at a 4-week interval (p = 0.04). Furthermore, headache was less observed in the chlorhexidine (p = 0.007) and sodium bicarbonate (p = 0.03) groups compared to the control group. **Conclusions:** The use of 0.2% chlorhexidine mouthwash can decrease the onset of COVID-19–related symptoms in health-care workers. In addition, this mouthwash can partially reduce the symptoms of this disease in comparison to the control and sodium bicarbonate groups.

Keywords: *Chlorhexidine, COVID-19, medicine, mouthwashes, nursing, operating room, Persian, sodium bicarbonate*

Introduction

In all countries, coronavirus disease 2019 (COVID-19) has caused a crisis and severe damage.[1] The World Health Organization (WHO) declared COVID-19 a pandemic on March 12, 2020. High mortality rates, high hospitalization costs, and the ineffectiveness and dangerous complications of some proposed drugs for treating COVID-19 indicate the need for safe treatment and prevention.[2] The transmission of this disease occurs primarily through aerosol, saliva, coughing, sneezing, and inhalation of virus-infected droplets.[3] A healthy lifestyle, boosting the immune system, observing hand and face hygiene, wearing a mask, and social distancing protect individuals against the damages caused by COVID-19.[2,4] Due to the presence of coronavirus (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]) in individuals' saliva and contamination by aerosol, the oral cavity has been introduced as a potential reservoir for the transmission of COVID-19. Angiotensin-converting enzyme 2 (ACE2) has been identified as a coronavirus receptor. ACE2 levels are high in the lungs, heart, saliva, end part of the small intestine, kidney, and bladder;[5,6] the number of positive cases of COVID-19 can reach 91.7% in the saliva samples, and live virus grows in saliva.[7]

The best way to prevent this disease is to reduce its prevalence in society. Vaccines are the most reliable way to manage COVID-19 and can decrease the mortality rate caused by this virus. According to previous studies, vaccination cannot guarantee the prevention of coronavirus,

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but can minimize its complications and mortality.[8,9] Using mouthwash is an effective and recommended method to reduce the viral load in the mouth. According to some studies, the virus may be destroyed in the early stages of the disease in the upper respiratory system, but the safety and effectiveness of mouthwashes on COVID-19 are unclear.[10] Mouthwashes prevent coronavirus transmission through reduction of virus accumulation in the mouth by washing and removing the virus. They also inhibit virus attachment to the receptor, exhibit virucidal and virostatic properties, and make the biological environment of the oral cavity unsuitable for viruses.[11,12]

Chlorhexidine is a biguanide antimicrobial that is effective against gram-positive and gram-negative bacteria, obligate anaerobes, aerobes, and yeast. It deactivates viruses at some specific concentrations and can be used as a mouthwash and a posterior pharyngeal spray. The results of the study by Jain *et al*.[13] indicate that chlorhexidine digluconate at a concentration of 0.2% kills more than 99.9% of SARS-CoV-2 in the shortest possible time, and it seems to be a reliable and effective virus inactivator. The side effects of chlorhexidine include the possibility of tooth discoloration, supragingival mass formation, and changes in taste perception.[14] Sodium bicarbonate, with the formula of $NaHCO_3$, is a sodium salt in combination with carbonic acid. As a common household substance (e.g., 7.5%–8.4%), in Persian medicine, sodium bicarbonate solution has become a suitable mouthwash, which is easily accessible, has minimal abrasiveness, is safe, and has antibacterial properties and almost no side effects as a mouthwash.[15-17] Studies have reported the different effects of sodium bicarbonate on COVID-19, and most of them have investigated sodium bicarbonate fumigation.[17,18] Health-care workers are the main groups at risk of infection during the present COVID-19 outbreak. One study reported that the risk of infection with COVID-19 among health-care workers was 10 times higher than that in the general population.[19] Since the operating room nurses and anesthesia personnel are in close contact with patients, they may be infected even after vaccination. According to a study that investigated the prevalence of COVID-19 in health-care workers after vaccination, even though vaccination can be very effective, this infection can still occur and may be asymptomatic and dangerous for the vulnerable population.[20]

Considering the susceptibility of the oral cavity to COVID-19 infection and based on the results of some articles, which indicated that no vaccine provided complete immunity,[21,22] preventive measures must also be taken in addition to vaccine injection. As there were few studies on the impact of mouthwashes on the prevention and treatment of COVID-19, the present study was conducted with the aim to compare the impact of mouth washing with chlorhexidine and sodium bicarbonate mouthwashes on COVID-19–related symptoms in operating room nurses and anesthesia personnel in the operating rooms of certain hospitals of Isfahan University of Medical Sciences in the year 2022.

Materials and Methods

The present study was a three-group, double-blind clinical trial, including two intervention groups, which received chlorhexidine and sodium bicarbonate mouthwashes, and a control group that received a placebo. It was conducted on operating room nurses and anesthesia personnel in the operating rooms of certain hospitals of Isfahan University of Medical Sciences, Isfahan, Iran, from July to October 2022. This trial was registered in the Iranian Registry of Clinical Trial (IRCT) with the registration code of IRCT20220328054364N1.

Receiving at least two doses of vaccine, being under 60 years of age, not having been infected with COVID-19 in the last 2 months,[23] having no symptoms of systemic infection, not receiving immunosuppressive drugs, having no history of allergy to mouthwash solutions, observing the minimum 2 weeks after the injection of the second dose,[24] not being pregnant, and not breastfeeding were the inclusion criteria. The exclusion criteria included unwillingness to continue participating in the research, not using the mouthwash solution properly for any reason, and using the mouthwash for less than 7 days.

Operating room nurses and anesthesia personnel were enrolled in the study using convenience sampling and according to the study inclusion criteria and were then randomly allocated to three groups. For randomization, first, we allocated a number to each sample, and then, using the table of random numbers, registered samples into three groups. Considering a 95% confidence interval, $z1 = 1.96$, $z2 = 0.84$, and $d = 1$, and taking into account a 10% loss of samples, a sample size of 120 individuals was obtained. A number was assigned to each eligible person. The individuals were placed in an intervention group with chlorhexidine solution, an intervention group with sodium bicarbonate solution, and a control group using the random numbers table. Sampling continued until the required number of samples had been collected. Finally, the data related to 116 eligible individuals (36 individuals in the chlorhexidine mouthwash group, 40 individuals in the sodium bicarbonate mouthwash group, and 40 individuals in the control group) were analyzed. Figure 1 shows the CONSORT diagram.

The research data were collected at the seventh peak of COVID-19. Checklists 1 and 2 were used for data collection. Checklist 1 consisted of three parts. the first was a demographic characteristics form, including questions on gender, age, education level, body mass index (BMI), type of injected vaccine, history of taking complementary medicines and vitamin D in the last month, history of underlying diseases, history of respiratory failure, history

of smoking, hospital name, date of receiving mouthwash, and contact number, the second was the type of mouthwash solution, and the third included the COVID-19–related symptoms, including runny nose, lethargy, fever, body aches, headache, dizziness, wheezing, weakness, fatigue, ear inflammation and infection, loss of appetite, tears, sneezing, cough, dyspnea, sore throat, diarrhea, vomiting, skin rash, red and irritated eyes, and lower senses of smell and taste.[25,26] The researcher completed the first and second parts of this checklist by questioning the participants according to the mouthwash they used. The third part was completed by collecting checklist 2 during the self-reporting of COVID-19 symptoms. Checklist 2 was prepared to record symptoms and the course of daily use of mouthwash. It included all COVID-19–related symptoms and was completed at 1-week intervals. Furthermore, a table was designed for recording the use of mouthwash, and the staff recorded their mouthwash use twice a day, in the morning and at night. Mouthwash use and symptoms were completed through self-report in this checklist.

Given that chlorhexidine compounds are effective against lipid-coated viruses, they were used as a mouthwash in this research. Some studies indicate that if cells are in an alkaline state (i.e., pH >7), the entry of the virus into the cell is reduced, but the viral load is increased in the host cell in acidic conditions (i.e., pH <7). Sodium bicarbonate increases the pH, it was used during the Spanish flu pandemic, and it is an available and safe option; hence, sodium bicarbonate was the second mouthwash used in this study.[27,28]

Initially, the researcher explained the research objectives to the participants and obtained written informed consent forms from them. For blinding, uniform dark-colored medicine glass bottles were prepared and filled with sodium bicarbonate, chlorhexidine, and drinking water. After coding the solutions, the bottles were given to personnel along with a medicinal scale and a symptom registration sheet. The type of solution provided to each staff member and their characteristics were recorded in checklist 1. The mouthwash use method and other pertinent information were written on the bottles and also explained verbally. Each participant received two 250-ml dark glass bottles containing mouthwash solution; the first bottle of medicine was used in the first week and the second bottle was given to the staff at the end of the first week for use in the second week.

Ready and colorless 0.2% chlorhexidine solution (Vi-One, Tehran, Iran) was the standard concentration of this mouthwash. It was obtained from a pharmacy and poured into bottles prepared by the researcher. The sodium bicarbonate powder (production of Sabzkooh Iran company) was obtained from a sales unit. A 7.5% mouthwash solution was prepared by the researcher[28] using a precise scale and graduated glass. Thus, 7.50 g of sodium bicarbonate was weighed after setting the scale to zero and was diluted with water to make 100 ml of solution. After dissolution, it was poured into glass bottles.

Placebo was the third mouthwash. Drinking water was used for placebo due to its use in the preparation of sodium bicarbonate solution. The colors of all three

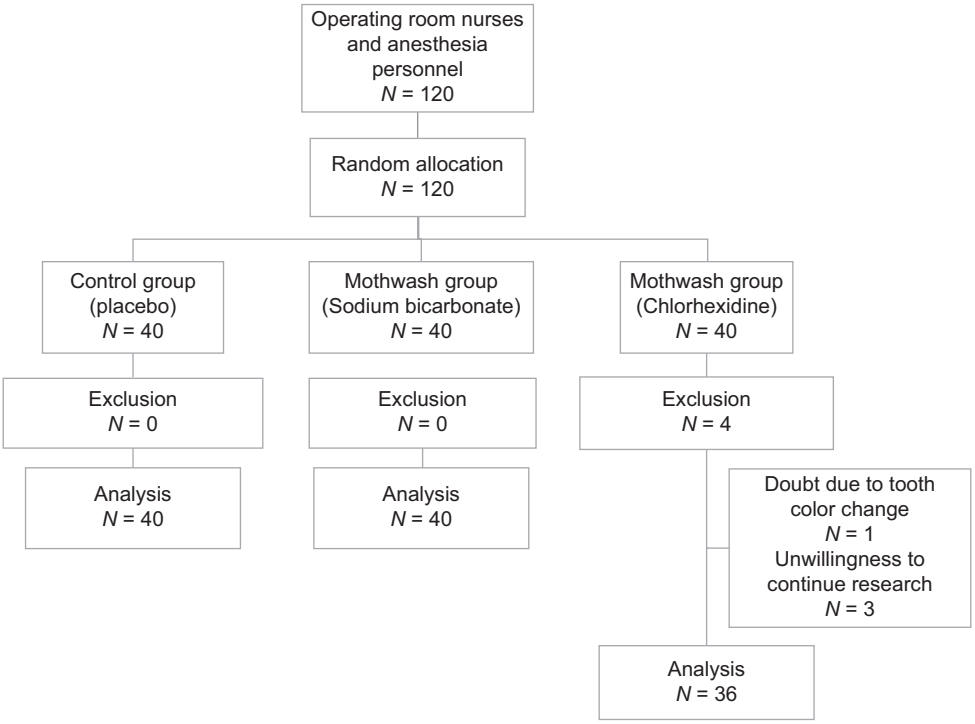

Figure 1: CONSORT diagram of participants

solutions were similar according to the rules of placebo and the double-blind nature of the research, but essential oils were not added owing to their potential effect on the antimicrobial properties of the solutions. According to the instructions on the chlorhexidine mouthwash bottle and a previous study, the method of use was 15 ml once in the morning and once at night for 1 min and over a 2-week period.[29] The instructions included the following: avoid eating and drinking for at least half an hour after using the mouthwash, keep it at room temperature and away from direct sunlight, avoid continuous use for more than 3 weeks, brush your teeth before use, and the mouthwash solution is not edible. Given the antimicrobial properties of some types of toothpaste, the researcher provided the participants with simple toothpaste. After using the mouthwash, its use was stopped for 2 weeks, and the participants were followed for 4 weeks to examine the onset of symptoms of COVID-19 from the first day of using mouthwash (because the effects of mouthwash might be transient)[13] as well as COVID-19–related symptoms in them. In this study, the emergence of at least two of the above-mentioned symptoms was considered an infection with COVID-19.[25]

During the 4 weeks of monitoring the participants, they recorded and reported their symptoms once a week on the Symptom Recording Checklist (checklist 2). In the case of any suspicious symptoms, they wrote them in the checklist rather than symptom recording at 1-week intervals. Moreover, three virtual groups were created by the researcher based on the specific type of mouthwash solution used by the participants to remind them to use mouthwash every day. Furthermore, at the same intervals, all three groups received a short clip with mouthwash usage instructions. The participants were asked to report any suspected symptoms of COVID-19 to be recorded by the researcher. The data were analyzed using the Statistical Package for the Social Sciences (SPSS) software (version 22; IBM Corp., Armonk, NY, USA) at a significance level of < 0.05.

Ethical considerations

The present research was conducted after obtaining an ethical code (IR.MUI.NUREMA.REC.1401.044) from the ethics committee of Isfahan University of Medical Sciences, a letter of recommendation from the research deputy of the School of Nursing and Midwifery of the same university, and approval of the officials of each hospital. The researcher explained the research objectives to the participants and obtained written informed consent forms from them. Moreover, all of the participants were free to withdraw from the study whenever they wanted.

Results

According to the results of the Chi-square test, Kruskal–Wallis, and one-way analysis of variance (ANOVA), there was no significant difference between the groups in terms of gender, education level, age, and BMI. All participants were vaccinated at least twice. The Kruskal–Wallis test did not indicate any significant difference between the groups in terms of the numbers of vaccinations received. Table 1 summarizes the demographic information of the participants.

Cochran's test indicated no significant changes in symptoms in the groups over time, but the headache symptom was

Table 1: Demographic variables in the research groups

Variables	Group *n* (%)			Statistic (χ^{2}*/H**)	*p*
	Chlorhexidine	Sodium bicarbonate	Control		
Gender					
Male	6 (16.70)	2 (5.00)	3 (7.50)	3.28*	0.19
Female	30 (83.30)	38 (95.00)	37 (92.50)		
Age (years)					
20–30	12 (33.30)	13 (32.50)	14 (35.00)	0.020*	0.98
30–40	18 (50.00)	21 (52.50)	18 (45.00)		
40–50	5 (13.90)	3 (7.50)	6 (15.00)		
50–60	1 (2.80)	3 (7.50)	2 (5.00)		
Education level					
Associate degree	2 (5.60)	5 (12.50)	7 (17.50)	3.59*	0.16
Bachelor's	31 (86.10)	33 (82.50)	32 (80.00)		
Master's	2 (5.60)	2 (5.00)	1 (2.50)		
Ph.D.	1 (2.80)	0 (0)	0 (0)		
BMI*					
Weight loss	4 (11.10)	1 (2.50)	3 (7.50)	4.55**	0.10
Normal weight	18 (50.00)	23 (57.50)	29 (72.50)		
Overweight	12 (33.30)	13 (32.50)	8 (20.00)		
Obesity	2 (5.60)	3 (7.50)	0 (0)		

*Chi-square test. **Kruskal–Wallis test. ***BMI=body mass index

less observed and there was a significant change in this symptom in the chlorhexidine (p = 0.007) and sodium bicarbonate (p = 0.03) groups.

According to the Kruskal–Wallis test, there was no significant difference between the groups at different times, but there was a significant difference between the groups in terms of the total number of symptoms at a 4-week interval (H = 6.30, p = 0.04). Table 2 summarizes the relevant data.

A comparison of the chlorhexidine and control groups using the Mann–Whitney test indicated a significant difference between the two groups in the first week (Z= −2.20, p = 0.02) and the fourth week (Z = −1.96, p = 0.04). As can be seen in Table 3, a significant difference was also observed between the two groups in terms of symptoms (Z = −2.29, p = 0.02).

A comparison of the sodium bicarbonate and control groups using the Mann–Whitney test indicated no significant difference at any time (p > 0.05), but a P value of 0.06 was obtained in the third week for the mean total of symptoms, which was close to the significance level.

A comparison of the chlorhexidine and sodium bicarbonate groups using the Mann–Whitney test revealed no significant difference at any time (p > 0.05).

A total of seven (19.40%) participants in the chlorhexidine group, 18 (45%) in the control group, and 11 (27.50%) in the sodium bicarbonate group were infected with COVID-19. The Chi-square test indicated a significant difference between the groups in terms of the onset of COVID-19–related symptoms (χ^2 (2) = 6.13, p = 0.04). A pairwise group comparison was performed to accurately examine the difference between the groups. Fisher›s exact test indicated a significant difference between the chlorhexidine and control groups in terms of the onset of COVID-19–related symptoms (p = 0.02), but no significant difference was seen between the control and sodium bicarbonate groups. Fisher›s test indicated no significant difference between the chlorhexidine and sodium bicarbonate intervention groups in this regard [Table 4].

Discussion

The results of the present study indicated a significant difference in the onset of COVID-19–related symptoms between the chlorhexidine and control groups (p = 0.02). This study confirmed the results of a study by Huang and Huang (2021), indicating that chlorhexidine mouthwash is a simple and safe additive to current guidelines for the prevention of COVID-19 with significant effects on outbreak control. When chlorhexidine is used along with vaccination, appropriate social distancing, wearing a mask, and hand washing, it may help prevent the disease effectively.[8]

The present study indicated that 18 (45%) participants in the control group and seven (19.40%) participants in the chlorhexidine group were infected with COVID-19 in 4 weeks, showing a significant difference between

Table 2: A comparison of the mean total of symptoms in different groups

Time/group	Chlorhexidine	Control	Sodium bicarbonate	H*	*p*
First week					
Mean (SD)	0.22 (1.17)	1.22 (3.14)	0.70 (1.84)	5.29	0.07
Minimum	0	0	0		
Maximum	7	17	8		
Second week					
Mean (SD)	0.66 (2.05)	1.50 (2.63)	0.87 (2.26)	2.48	0.28
Minimum	0	0	0		
Maximum	10	10	12		
Third week					
Mean (SD)	0.86 (2.66)	0.97 (2.16)	0.20 (0.72)	3.67	0.16
Minimum	0	0	0		
Maximum	11	10	4		
Fourth week					
Mean (SD)	0.05 (0.23)	0.92 (2.58)	0.75 (2.43)	3.82	0.14
Minimum	0	0	0		
Maximum	1	14	13		
Total					
Mean (SD)	1.80 (3.67)	4.62 (7.37)	2.52 (4.99)	6.30	0.04
Minimum	0	0	0		
Maximum	13	31	18		

*Kruskal–Wallis statistic

Table 3: A comparison of the mean amounts of symptoms in chlorhexidine and control groups

Time/group	Chlorhexidine	Control	*Z**	*p*
Time/group				
Mean (SD)	0.22 (1.17)	1.22 (3.14)	−2.20	0.02
Minimum	0	0		
Maximum	7	17		
Second week				
Mean (SD)	0.66 (2.05)	1.50 (2.63)	−1.51	0.13
Minimum	0	0		
Maximum	10	10		
Third week				
Mean (SD)	0.86 (2.66)	0.97 (2.16)	−1.09	0.27
Minimum	0	0		
Maximum	11	10		
Fourth week				
Mean (SD)	0.05 (0.23)	0.92 (2.58)	−1.96	0.04
Minimum	0	0		
Maximum	1	14		
Total				
Mean (SD)	1.80 (3.67)	4.62 (7.37)	−2.29	0.02
Minimum	0	0		
Maximum	13	31		

*Mann–Whitney test. SD=Standard deviation

Table 4: Comparison of the onset of COVID-19–related symptoms (infection) in the research groups

Group	Number (%)	χ^2*	df	*p*
Chlorhexidine	7 (19.40)	6.13	2	0.04
Control	18 (45.00)			
Sodium bicarbonate	11 (27.50)			

*Chi-square. COVID-19=coronavirus disease 2019, df=degrees of freedom

these two groups ($p = 0.02$), while a research[30] indicated that COVID-19 was an enveloped virus and 0.12% chlorhexidine gluconate had little or no effect on viruses compared to other mouthwashes. This significant difference between these two studies might be due to the difference in the concentration of chlorhexidine mouthwash. The present study was consistent with a study by Moosavi *et al*.,[11] which indicated that chlorhexidine mouthwash had a wide range of antimicrobial effects, and antiviral mouthwashes played important roles in decreasing the viral load of saliva.

The results of a study by De Paula Eduardo *et al*.[31] on SARS-CoV-2 load reduction in saliva using mouthwash indicated that chlorhexidine mouthwash caused a significant reduction in viral SARS-CoV-2 load in saliva up to 60 min after washing, but its effect was transient. Therefore, it appears that chlorhexidine solution decreased infection by reducing the salivary viral load, which is consistent with the present study.

Huang and Huang conducted a study in 2021 on the effect of chlorhexidine mouthwash and posterior oral oropharyngeal spray use on the prevention of COVID-19 among medical staff in Los Angeles and California.[8] The results indicated that there were no cases of SARS-CoV-2 infection in the intervention group. Furthermore, the infection rate of COVID-19 in the control group was close to 50% in the same period. The results of this study were consistent with those of our research.

A comparison of the sodium bicarbonate and control groups indicated no significant difference in symptoms and infection of COVID-19 at any time ($p > 0.05$). The results of a study by Kumar *et al*.[28] indicated that gargling with 7.5% sodium bicarbonate solution might be ineffective in achieving initial SARS-CoV-2 clearance in mild COVID-19 patients, and thus, its results were consistent with our study.

Zamani *et al*.[17] indicated that inhalation of sodium bicarbonate could have a significant positive effect on respiratory complications caused by the coronavirus. This finding was inconsistent with the present study. The difference in these two studies might be due to the difference in the way sodium bicarbonate was used; mouthwash was used in the present study, but Zamani *et al*.[17] used a nebulized form of sodium bicarbonate. Another reason for inconsistency in these two studies could be the difference in disease severity. The current study used sodium bicarbonate to prevent the mild form of the disease, whereas Zamani *et al*.[17] used it to prevent the severe form of the disease and those who required tracheal intubation.

A comparison of the sodium bicarbonate and control groups indicated no significant difference in the symptoms and infection of COVID-19 at any time ($p > 0.05$). Siahpoosh *et al*.[18] conducted a study on the effectiveness of inhalation of baking soda (sodium bicarbonate) on improving respiratory symptoms in COVID-19 patients. They reported that inhaling the nebulized form of sodium bicarbonate decreased the severity of respiratory system inflammation by increasing the airway blood flow and decreasing sputum stickiness. However, sodium bicarbonate molecules were not emitted from the evaporation of sodium bicarbonate solution during home fumigation, and its fumigation worked like hot water fumigation. Sodium bicarbonate fumigation was theoretically unsuitable for inflammation and COVID-19 infection. Furthermore, the nebulized form of sodium bicarbonate might increase the transmission rate of infectious aerosol in patients with COVID-19. The findings of Siahpoosh *et al*. are in line with the present study in that sodium bicarbonate solution has no effect when used as a home fumigant, and doubts remain about its effectiveness when used in the nebulized form.

Mir *et al*.[16] conducted a study titled "Lysosomotropic properties of sodium bicarbonate and COVID-19" and showed that the entry of the novel coronavirus into host cells depends on pH. Sodium bicarbonate plays a role in neutralizing the acidic state and can be considered a safe

and available option for possible preventive and therapeutic interventions against the proliferation of SARS-CoV-2. However, comparison of the sodium bicarbonate and control groups in the present study indicated no significant difference in symptoms and infection of COVID-19 at any time ($p > 0.05$). The difference in the results of these two studies might be due to their methods and the fact that the study by Mir *et al*.[16] was a laboratory study.

As a limitation of the study, despite daily and constant reminders to participants in a virtual group, there was the possibility of forgetting, and the researcher could not observe all points. This is due to the fact that it was impossible to follow the participants for each use. In addition, that why sodium bicarbonate not provided the desired result was probably due to its number of uses per day or its concentration, which could be increased to achieve the desired result.

Conclusion

Although the separate comparison of symptoms in the groups at different times did not show any significant differences, 0.2% chlorhexidine mouthwash decreased the symptoms. In the present study, 0.2% chlorhexidine mouthwash was more effective than sodium bicarbonate mouthwash and placebo. The symptoms and complications of COVID-19 are considered a serious challenge for health-care workers. The use of chlorhexidine mouthwash is recommended as a way to reduce the salivary viral load, reduce infection, and ultimately reduce the occurrence of disease symptoms. It is suggested that larger-scale research with more samples be conducted in multiple care centers. It is also recommended that these two solutions be compared at different concentrations.

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Conflicts of interest

Nothing to declare.

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