


# The short-term effect of different chlorhexidine forms versus povidone iodine mouth rinse in minimizing the oral SARS-CoV-2 viral load

## An open label randomized controlled clinical trial study

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### Abstract

Several investigations evaluated the possibility of different types of mouth wash rinse in minimizing the SARS-CoV-2 load. However, results still controversial. The study aim is to assess the short-term efficiency of several over-the-counter mouth rinses and lozenges in minimizing the salivary viral load for SARS-CoV-2 in patients with confirmed COVID-19 in comparison to saline. This is a randomized controlled clinical trial with 4 arms. The recruited cases were randomized using a simple randomization technique and were assigned to chlorhexidine digluconate mouth rinse (CHX mouth rinse), 2mg of chlorhexidine digluconate lozenges (CHX lozenges), povidone iodine mouth rinse (PVP-I mouth rinse) or saline as a control group. Saliva were collected from all study subjects by passive drool technique at two time points. First, prior to intervention with mouth rinse or the lozenges, the baseline saliva sample was collected. Second saliva samples were collected immediately after the mouth rinse. Real time PCR was conducted and the value threshold cycle (Ct) for each sample was recorded.

Majority of the participants had an education level of high school or less (60%), were married (68.3), males (58.3%), and non-smokers (58.5%). No statistically significant differences between groups at the two times test ( $P > .05$ ). However, a significant decrease of salivary viral load in all four groups combined ( $P$ -value for E genes = .027, and for S genes = .006), and in PVP-I mouth rinse specifically ( $P = .003$  and  $P = .045$ , respectively). Povidone iodine mouth rinse showed a potential influence on the reduction of the viral load on a short-term basis. However, longer-term studies of the effect of these products should be conducted.

**Abbreviations:** CHX mouth rinse = digluconate mouth rinse, CHX lozenges = chlorhexidine digluconate lozenges, PVP-I mouth rinse = povidone iodine mouth rinse, Ct = threshold cycle, SARS-CoV-2 = Severe Acute Respiratory Syndrome Coronavirus 2, KFGH = King Fahad General Hospital, RT-PCR = Real-time polymerase chain reaction.

**Keywords:** COVID-19, SARS-CoV-2, mouth rinse, chlorhexidine digluconate, povidone iodine

### 1. Introduction

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is known as a leading source of the COVID-19 coronavirus disease.<sup>[1-4]</sup> On March 11, 2020, it was announced by the WHO that SARS-CoV-2 was a global pandemic.<sup>[2,3,5-7]</sup> Since then, coronavirus disease has been widespread, and several ongoing studies have been investigating new methods to prevent or treat SARS-CoV-2.

There are several diagnostic methods for COVID-19. However, molecular testing (PCR) is considered to be the standard and recommended current diagnostic method of diagnosis at the World Health Organization.<sup>[7]</sup> These methods are continuously improving. SARS-CoV-2 appears to be very infectious,

especially given the new variants, and the chances of its transmission with asymptomatic patients is still very high.<sup>[7]</sup> The SARS-CoV-2 incubation period has been reported to range between 1 and 14 days, with most evidence suggested it to be 3 to 7 days.<sup>[5]</sup> Therefore, there is evidence indicating the possibility of infection spreading when patients were unaware about their infection status and asymptomatic.<sup>[8,9]</sup>

Current evidence proved saliva can act as a SARS-CoV-2 reservoir.<sup>[9]</sup> Several reports found that the virus is transmitted through aerosols, which pose a significant possibility for transmission risk of the infection in dental clinics.<sup>[5,7]</sup> So, it is required to decrease this potential risk in dental offices, by minimizing the salivary SARS-CoV-2 load, if possible,

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

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in any suspected or confirmed cases. One of the suggested methods is mouth rinses, which have been used globally to reduce the quantity and quality of oral Microscopic organisms. Few researches investigated the effectiveness of various mouth washes in minimizing the risk of corona virus transmission.<sup>[9,10]</sup> However, the results are still controversial. Therefore, the aim was to assess the short-term efficacy of over-the-counter mouth rinses and lozenges in minimizing the salivary viral load of SARS-CoV-2 in COVID-19 patients when compared with saline.

## 2. Materials and Methods

This is an open label randomized controlled clinical trial which was approved by the ethical committee – Jeddah Health Affairs (#1485) and registered at <https://clinicaltrials.gov> (NCT04941131). It took place at King Fahad General Hospital in Jeddah city, Saudi Arabia, and at Al-Hamra Community Health Center, Jeddah, and the CONSORT guideline was followed (Fig. 1).

### 2.1. Sample

Any participants 18 years or older, whose nasal swabs showed positive RT-PCR assay for SARS Cov-2, were recruited from King Fahad General Hospital (KFGH) for the period from June to July 2021. History of allergy to any material used in the study, known pregnancy, or prior treatment for COVID-19 were considered exclusion criteria. All patients signed consent form

upon recruitment in the study. The study involved an intraoral examination as well.

### 2.2. Sample collection

The recruited cases were selected randomly using a simple randomization technique and were allocated to either chlorhexidine digluconate mouth rinse (CHX mouth rinse) (Lacalut Aktiv, Arcam GmbH, Homburg, Germany), 2 mg of chlorhexidine digluconate lozenges (CHX lozenges) (Septofort), povidone iodine mouth rinse (PVP-I mouth rinse) (Meridiol Meridol, Colgate-Palmolive Company, New York) or saline as a control group (Fig. 1). Instructions to participants were to abstain from drinking, eating, and any oral hygiene measures performance for 30 minutes or more prior to the saliva collection. Three milliliters of saliva were collected by passive drool technique from all participants at two time points. First, prior to intervention with mouth rinse or the lozenges, the baseline saliva sample was collected. After which, they were asked to use the mouth rinse or lozenges, and to use the same mouth rinse/lozenges again after 5 minutes. Patients followed rinse instructions, using 10 mL of non-diluted solution for 30 seconds, then spitting it out. For the lozenge, it was to melt slowly inside the oral cavity.

### 2.3. Data management

Google Forms, a web-based survey tool, was used to collect the data (Google, LLC) and to generate a standard digitally secure

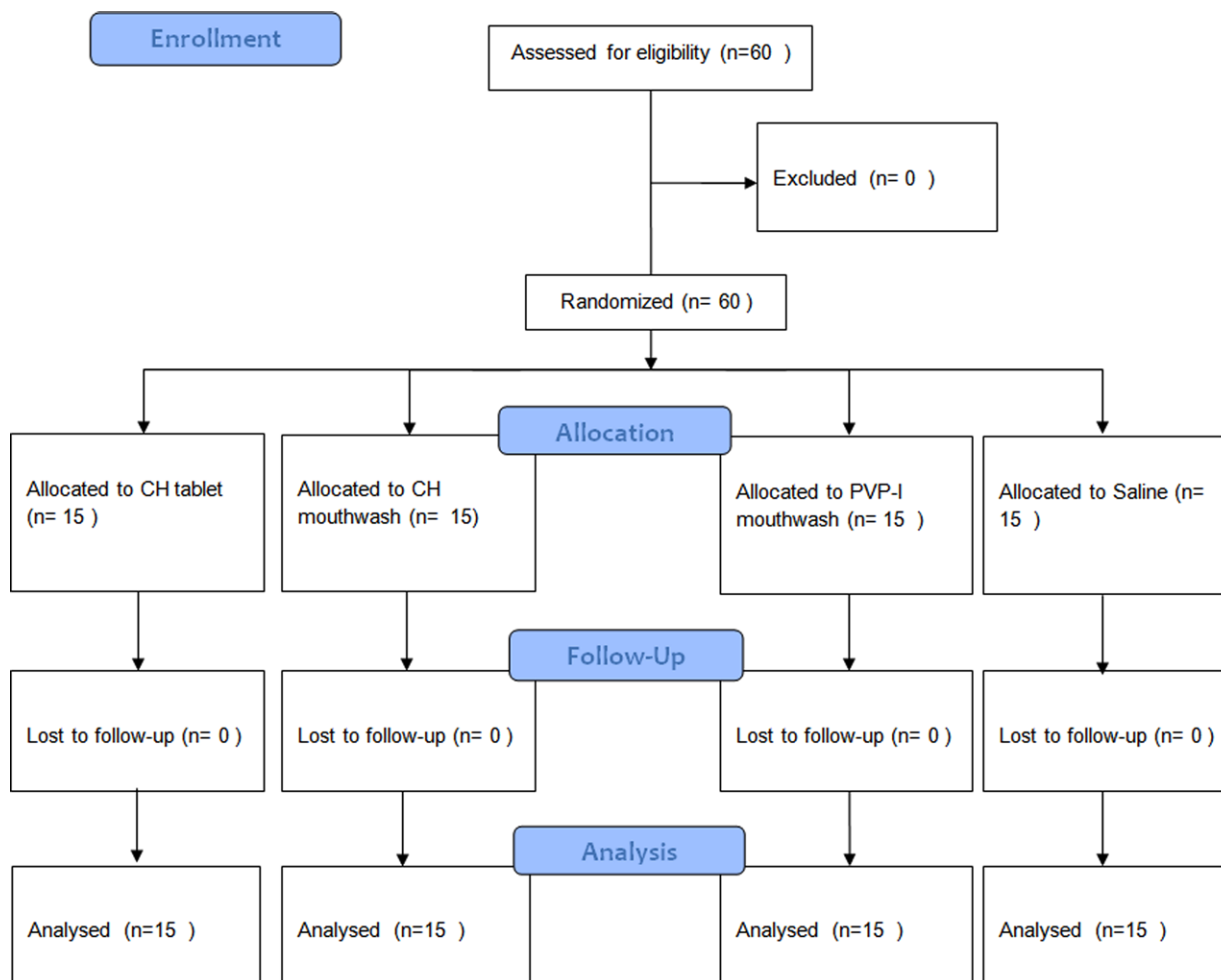


Figure 1. CONSORT flow diagram.

questionnaire link used by the data collector and the participant to fill out each patient form. Prior to completing the form, verbal consent was obtained. The Weqaya Novel Coronavirus Investigation Form was utilized to gather the clinical and demographics characteristics of the participants. This is an official standardized case report form generated by the Saudi Centre of Disease Prevention and Control to be used during the pandemic for surveillance purposes.

**2.4. Real-time polymerase chain reaction**

Saliva samples were transferred—80. RNA extraction was done, and the Real-time polymerase chain reaction (RT-PCR) was completed using LabGun COVID-19 RT-PCR Kit. Primer and probe mixture were used to identify E genes and S genes, which are characteristics of SARS-CoV-2. Thermal cycling was conducted and the threshold cycle (Ct) value for each sample was calculated using the Bio-Radcyler's software.

**2.5. Sample size calculation and statistical analysis plan**

A sample size calculation was conducted using GPower (Version 3.1). Assuming the expected effect size of 1.1,<sup>[9,10]</sup> a sample size of n = 60 (15 in each group) was adequate to obtain a Type I error rate of 5% and a power of 80%.

The SPSS Statistics for Windows version 25, (IBM Corp, Armonk, NY) was used for data analysis. Results were presented in a descriptive form using tables and graphs. After checking the normality, a one-way ANOVA with Bonferroni correction was used to compare the four groups, and a dependent sample t test was used for before and after comparison. P < .05 was considered statistically significant.

**3. Results**

The average age of participants was 37.3 ± 13.2. The majority had an education level of high school or less (60%), married (68.3), males (58.3%), and non-smokers (58.5%) (Table 1). However, these patterns were statistically different between groups. The PVP-I mouth rinse group was more likely to have smokers (80.0%), and the gender was almost equally divided in the CHX mouth rinse group (54.3% females vs 46.7% males) (Table 1).

The mean Ct value of E and S genes was high before and after using any mouth wash rinse/lozenges. No significant difference was found between the groups at the time points

(P > .05) (Table 2). However, in looking within the same group, we found a significant reduction of viral load in all four groups combined (P-value for E genes = .027, and P-value for S genes = .006). Specifically, PVP-I mouth rinse showed a significant reduction in the Ct values for both genes; P = .003 and P = .045, respectively (Table 2). When combining the results of both genes, we found PVP-I mouth rinse again significantly minimized the viral load after the patients used it (P < .001) (Fig. 2). CHX lozenges was able to reduce the viral load as well (Fig. 2).

**4. Discussion**

This study revealed no statistical difference between the four groups in the short term. However, PVP-I mouth rinse showed a potential effect within the same group, and CHX lozenges showed the same pattern if the results of both genes were combined.

CHX mouth rinse showed controversial effects. It was demonstrated previously that a 0.12% CHX mouth rinse might be effective against herpes virus and parainfluenza virus. Hence, it may be effective against SAR-CoV-2 in the mouth.<sup>[11]</sup> It also showed an antiviral effect in some in vitro and case report/case series studies.<sup>[12-14]</sup> Its effect extends up to two hours then the viral load tends to return.<sup>[9]</sup> This raises a question regarding how many times it must be used daily. Moreover, it could not reduce the viral load significantly compared with other products such as essential oils, polyvidone iodine and dequalinium chloride/benzalkonium chloride in other studies.<sup>[15,16]</sup> Therefore, it was proposed that this mouth rinse may inactivate the virus weakly.<sup>[17]</sup> One study used hydrogen peroxide followed by CHX mouth rinse, and this did not show any additional benefit due to washed out effect of hydrogen peroxide and the reduced substantively.<sup>[9,11,14]</sup> However, when the order was switched, it showed better results and the virus was even undetectable in 36.3% of patients.<sup>[9,11,14]</sup>

CHX lozenges showed some beneficial oral effect such as inhibiting plaque.<sup>[18]</sup> It was recommended as an alternative to CHX mouth rinses<sup>[18]</sup> and it may be even more effective against sore throat and upper respiratory tract pathogens.<sup>[18]</sup> It did not show any short-term effect on each SARS-CoV-2 gene in our trial. However, it showed a potential effect when both gene results were combined. These results indicate that more studies are needed to evaluate its effect and mechanism.

PVP-I, however, showed more consistent results in reducing the viral load. It shows destruction ability of the SARS-CoV-2 lipid membrane,<sup>[19]</sup> and it inactivated more than 99.99% of the virus within 30 seconds.<sup>[14]</sup> All the commercial concentrations

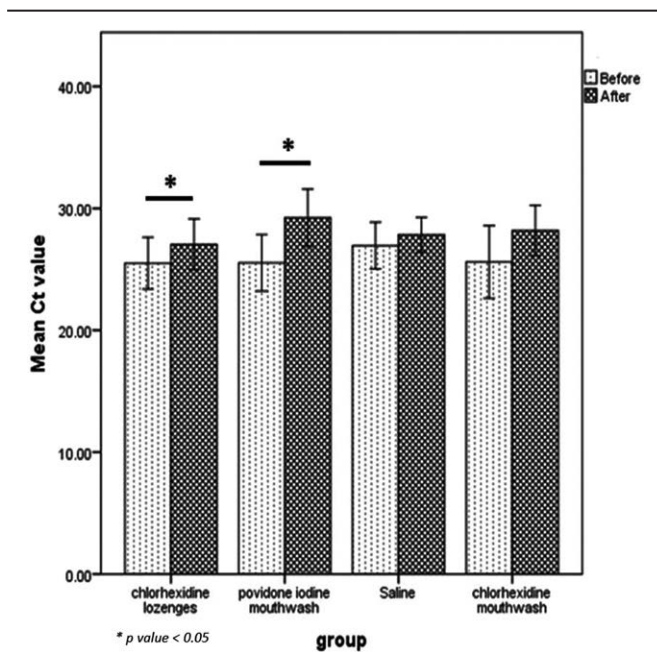
**Table 1**  
Characteristic of study sample at patient level (N = 12 per group).

|                      | Total         | CH lozenges<br>N (%) | CH mouth rinse<br>N (%) | PVP-I mouth rinse<br>N (%) | Saline<br>N (%) |
|----------------------|---------------|----------------------|-------------------------|----------------------------|-----------------|
| Age (mean ± SD)      | 37.40 ± 13.21 | 36.20 ± 13.21        | 37.80 ± 11.24           | 33.86 ± 10.29              | 41.73 ± 17.14   |
| Gender               |               |                      |                         |                            |                 |
| Male                 | 35 (58.30)    | 12 (80.00)           | 8 (53.30)               | 11 (73.30)                 | 11 (73.30)      |
| Female               | 25 (41.70)    | 3 (20.00)            | 7 (46.70)               | 4 (26.70)                  | 4 (26.70)       |
| Education            |               |                      |                         |                            |                 |
| Bachelor or more     | 24 (40.00)    | 6 (40.0)             | 7 (46.70)               | 8 (53.30)                  | 3 (20.00)       |
| High school          | 36 (60.00)    | 9 (60.0)             | 8 (53.30)               | 7 (46.70)                  | 12 (80.00)      |
| Status               |               |                      |                         |                            |                 |
| Single               | 19 (31.70)    | 6 (40.0)             | 3 (20.00)               | 7 (46.70)                  | 3 (20.00)       |
| Married              | 41 (68.30)    | 9 (60.0)             | 12 (80.00)              | 8 (53.30)                  | 12 (80.00)      |
| Smoker               |               |                      |                         |                            |                 |
| Yes                  | 25 (41.70)    | 5 (33.3)             | 3 (20.00)               | 12 (80.00)                 | 5 (33.30)       |
| No                   | 35 (58.30)    | 10 (66.7)            | 12 (80.00)              | 3 (20.00)                  | 10 (66.70)      |
| Co-morbid conditions |               |                      |                         |                            |                 |
| Diabetes             | 2 (3.30)      | 0                    | 1 (6.70)                | 0                          | 1 (6.70)        |
| Hypertension         | 3 (5.00)      | 1 (6.70)             | 1 (6.70)                | 0                          | 1 (6.70)        |

**Table 2**  
Characteristic of study sample at patient level (N = 12 per group).

|                 | Total        | CH lozenges N (%) | CH mouth rinse N (%) | PVP-I mouth rinse N (%) | Saline N (%) | P   |
|-----------------|--------------|-------------------|----------------------|-------------------------|--------------|-----|
| Before          |              |                   |                      |                         |              |     |
| E genes         | 26.44 ± 6.01 | 26.14 ± 5.98      | 26.23 ± 7.37         | 25.85 ± 6.33            | 27.59 ± 5.01 | .89 |
| S genes         | 25.24 ± 5.53 | 24.83 ± 5.13      | 25.03 ± 6.63         | 25.18 ± 6.35            | 26.11 ± 4.04 | .96 |
| After           |              |                   |                      |                         |              |     |
| E genes         | 28.54 ± 5.18 | 27.33 ± 4.90      | 28.50 ± 5.21         | 30.28 ± 6.33            | 27.80 ± 4.00 | .46 |
| S genes         | 27.69 ± 5.30 | 26.74 ± 5.27      | 27.86 ± 5.89         | 28.09 ± 6.37            | 27.87 ± 3.83 | .93 |
| Diff            |              |                   |                      |                         |              |     |
| E genes         | 1.99 ± 6.06  | 1.65 ± 6.26       | 1.48 ± 4.41          | 4.43 ± 4.78             | 0.17 ± 7.67  | .25 |
| S genes         | 2.64 ± 5.98  | 2.67 ± 5.28       | 2.47 ± 6.24          | 3.33 ± 5.60             | 1.85 ± 7.68  | .96 |
| P value E genes | 0.03*        | 0.40              | 0.34                 | <0.01*                  | 0.94         |     |
| P value S genes | <0.01*       | 0.15              | 0.22                 | 0.04*                   | 0.49         |     |

\*P < .05.



**Figure 2.** Mean Ct value for all the genes before and after using the mouth rinse/lozenge.

(0.5%, 1%, and 1.5%) showed the same pattern of inactivation even after 15 seconds.<sup>[20]</sup> Its effect was found to extend up to at least three hours, and it can be used safely for up to 6 months in the oral cavity and 5 months in the nasal cavity.<sup>[21–34]</sup> Our study supports the potential effect of PVP-I mouth rinse in helping with the virus reduction in the oropharyngeal area. This can prevent the spread of infection from patients’ mouths and protect dentists as well as all medical field workers.

Drawback of the present study is its evaluation of short-term effects only, up to 5 minutes. A follow-up study is needed for a duration of at least 10 days since the incubation period of the virus can reach up to 2 weeks and now the isolation for 10 days is enough. Moreover, while RT-PCR is an excellent diagnostic tool, we did not determine the viability of viruses which could have been killed by the mouth rinse but not differentiated by the RT-PCR. Based our findings thus far, however, we can recommend that any patient thought to be a risk should use PVP-1 mouth rinse for at least certain days to eliminate any SARS-CoV-2 from the oral cavity.

**5. Conclusions**

Using povidone iodine mouth rinse following to the manufacturer’s instructions showed a potential short term effect

on minimizing the saliva SARS-Cov-2 viral load, which could decrease the risk of spread between health workers and the public. However, longer-term studies on the effect of these products should be conducted to evaluate their potential efficacy.

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**Author contributions**

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