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"Does Oronasal Administration of Antiseptic Agents Affect on Viral Load in COVID 19 Orthodontic Patients?": A Systematic Review and Meta-analysis

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Abstract

Aim: Droplets and aerosols are the main source of transmission and rapid spread of COVID-19 worldwide. Topical mouthwashes and oronasal irrigation are recommended as ways of preventing airborne transmission to health care professionals.
This meta-analysis aimed to assess the changes of COVID 19 viral load after administration of different mouthwashes.
Methods: An electronic search was undertaken including the following databases: Medline/PubMed, Web of Science, Scopus, and Embase. Search for grey literature, and hand search for relevant studies was also performed. The quality of included randomized clinical trials (RCTs) were assessed using the Cochrane Collaborations. Afterward, the relevant data from the included studies was extracted. Inverse-variance random-effects meta-analysis was performed to compare the effects of different types of mouthwashes on COVID viral presence.
Results: After screening 1437 studies, 10 randomized clinical trials were finally selected. A total of 884 patients were assessed in these studies. The meta-analysis revealed the Cyclic Threshold (CT) values increased after the use of mouthwashes (MD=2.00, 95%CI= 0.51, 3.49, P<0.05). Considering the CT values are inversely correlated to the viral load, the result means the use of mouthwashes decreases the viral load in the saliva. This study also showed that increase of CT values was statistically significant for Povidone Iodine mouthwash (MD=4.08, 95%CI= 0.13, 8.02, P<0.05); however, Cetylpyridinium Chloride and Chlorhexidine Gluconate mouthwashes non-significantly (P value>0.05) reduced viral load in the saliva of patients with COVID 19.
Conclusion: According to the result of this study, the use of mouthwashes reduces the viral load of saliva in patients with COVID 19. In addition to basic precautions for preventing the transmission of COVID 19, using mouthwashes may be a reasonable way to decrease the risk of disease transmission to medical staff.

Keywords: COVID 19, SARS-COV-2, Mouthwashes, Viral load.

1. Background

Corona Virus Disease of 2019 (COVID-19), as the seventh human coronavirus, caused a pandemic and numerous problems in the world with its sudden onset and outbreak in 2019 (1, 2).

Severe acute respiratory syndrome coronavirus 2(SARS-COV 2), like severe acute respiratory syndrome coronavirus (SARS-COV) and middle east respiratory syndrome coronavirus (MERC-COV), causes severe pneumonia with a mortality rate of 2.9%, 9.6% and approximately 36%, respectively (3, 4).

The rapid spread of COVID-19 within a short period indicates its high transmission potential, which is the cause of economic problems, further spread of poverty and damage to education and health care systems in all countries (5, 6).

SARS-COV-2 transmission is highly effective, mainly through the respiratory tract, like other respiratory viruses. Droplets and aerosols are the main routes of transmission (7, 8). Aerosols are solid or liquid particles (<5 μm) that can float in the air for a long time, whereas droplets are larger particles (>5

μm) that are heavier and cannot float in the air for a long time (9, 10). Human-to-human transmission occurs when close contact with an infected person and subsequent exposures to coughs, sneezes, respiratory particles, or airborne particles occur (11), to prevent cross-transmission, infection control-related practices such as hand hygiene, wearing a mask, and social distancing should be adhered to in any society (12).

The Angiotensin-converting enzyme 2 (ACE2) receptor in salivary gland epithelial cells is the primary target of Covid-19. The infection will likely occur in the oral cavity due to the high abundance of this receptor in the tongue (13).

Evidence found that 91.7% of Covid-19 patients had 19 SARS-COV-2 viruses in their saliva (14), and there was approximately 1.2 × 108 (Copies / mL) of the virus in the patients' saliva (15). It has been shown that SARS-COV-2 RNA can be stable in the saliva of Covid-19 patients at 4 °C, room temperature (19 °C), and 30°C for a long time (16). Therefore, considering the vital role of saliva and salivary glands in transmitting the disease, they should be considered a source of infection even in asymptomatic carriers (17). In patients with confirmed Covid-19, the viral load in the saliva may be so high that saliva samples are used as a more sensitive diagnostic method for SARS-COV-2 (18).

Direct contact or airborne transmission puts healthcare professionals at high risk for SARS-COV-2 infection (19). Covid-19 patients show high viral load in the oropharynx, the oral and nasal cavities that are not correlated with their clinical symptoms (20, 21). Therefore, medical staff, including dentists, maxillofacial surgeons, and ear, nose, and throat (ENT) specialists in close contact with these areas, are at risk of getting the infection and being potential carriers (22-25).

It is challenging to ensure a clean, aerosol-free environment to prevent Covid-19 transmission, so many non-emergency treatments such as orthodontics were delayed during the outbreak peak, and many patients were left untreated (26).

One of the methods to reduce the viral load in dental aerosols and during orthodontic appointments is topical mouthwash and spray in the mouth and nose. Antiseptic mouthwashes have been shown to reduce viral load in saliva, prevent airborne transmission of the virus to medical personnel and others, and reduce ventilator-associated pneumonia in Covid-19 patients by increasing oral hygiene adherence and reducing viral load (27).

Various studies have been performed on the antiviral effects of Povidone Iodine (PVI), Chlorhexidine gluconate (CHX), Cetylpyridinium chloride (CPC), Hydrogen peroxide (H2O2), and the oral and nasal viral loads were measured before and at different intervals after application of these compounds.

So, the main aim of this study was to systematically review the literature that assessed the efficacy of different mouthwashes in reducing viral loads in COVID19 patients.

2.Methods

This systematic review is based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Structured questions and PICO analysis

The question was asked, “Is oronasal administration of antiseptic agents successful in decreasing the viral load of SARS-COV-2?” in order to determine whether the use of antiseptic agents is a good option for preventing COVID 19’s transmission to medical staff.

A population, intervention, comparison, and outcome (PICO) structure was followed: (a) population: COVID 19 patients; (b) intervention: antiseptic agents oronasal administration; (c) comparison: no antiseptic agents use; and (d) outcome: changes in viral load amounts in the qRT-PCR test.

Search Strategies

An electronic search restricted to July 30th, 2021 was undertaken in September 2021, including the following databases: Medline/PubMed, Web of Science, Scopus, Chochrane, and Embase. Furthermore, the bibliographies of all downloaded articles were screened manually to identify further relevant studies. The following search strategy was used: ("mouthwash*"[Title/Abstract]) OR ("mouth-rinse*"[Title/Abstract]) OR ("oral antiseptic*"[Title/Abstract]) OR ("chlorhexidine"[Title/Abstract]) OR ("Povidone Iodine*"[Title/Abstract]) OR ("oral rinse*"[Title/Abstract]) OR ("cetylpyridinium chloride*"[Title/Abstract]) OR ("mouth spray*"[Title/Abstract]) OR ("hydrogen peroxide*"[Title/Abstract]) OR ("CHX"[Title/Abstract]) OR ("CPC"[Title/Abstract]) OR ("H2O2"[Title/Abstract]) OR ("PVI"[Title/Abstract])) AND (("Sars-cov-2*"[Title/Abstract]) OR ("COVID-19*"[Title/Abstract]) OR ("viral load*"[Title/Abstract]) OR ("viral transmission*"[Title/Abstract]) OR ("antiviral activity*"[Title/Abstract]) OR ("virucidal effect*"[Title/Abstract]) OR

("aerosol*"[Title/Abstract]) OR ("cross-contamination*"[Title/Abstract])) (Table 1).

Table 1. Databases. Applied search strategy, and numbers of retrieved studies.

Database of published trials, dissertations and conference proceedings	Search strategy used	Hits
MEDLINE searched via PubMed searched on September 7, 2021th, via www.ncbi .nlm.nih.gov/sites	(("mouthwash*"[Title/Abstract]) OR ("mouth-rinse*"[Title/Abstract]) OR ("oral antiseptic*"[Title/Abstract]) OR ("chlorhexidine"[Title/Abstract]) OR ("Povidone Iodine*"[Title/Abstract]) OR ("oral rinse*"[Title/Abstract]) OR ("cetylpyridinium chloride*"[Title/Abstract]) OR ("mouth spray*"[Title/Abstract]) OR ("hydrogen peroxide*"[Title/Abstract]) OR ("CHX"[Title/Abstract]) OR ("CPC"[Title/Abstract]) OR ("H2O2"[Title/Abstract]) OR ("PVI"[Title/Abstract])) AND (("Sars-cov-2*"[Title/Abstract]) OR ("COVID-19*"[Title/Abstract]) OR ("viral load*"[Title/Abstract]) OR ("viral transmission*"[Title/Abstract]) OR ("antiviral activity*"[Title/Abstract]) OR ("virucidal effect*"[Title/Abstract]) OR ("aerosol*"[Title/Abstract]) OR ("cross-contamination*"[Title/Abstract]))	894
ISI web of science Core Collection was searched via web of knowledge on September 7, 2021th, via apps.webofknowledge.com	TS=(mouthwash OR mouth-rinse OR oral antiseptic OR chlorhexidine OR Povidone Iodine OR oral rinse OR cetylpyridinium chloride OR mouth spray OR hydrogen peroxide OR CHX OR CPC OR H2O2 OR PVI) AND TS=(Sars-cov-2* OR COVID-19)	359
EMBASE searched via Ovid on September 6, 2021th, via http://ovidsp.dc2.ovid.com	#1 ((((((('mouthwash'/exp OR mouthwash OR 'mouth rinse'/exp OR 'mouth rinse' OR oral) AND ('antiseptic'/exp OR antiseptic) OR 'chlorhexidine'/exp OR chlorhexidine OR 'povidone'/exp OR povidone) AND ('iodine'/exp OR iodine) OR oral) AND rinse OR 'cetylpyridinium'/exp OR cetylpyridinium) AND ('chloride'/exp OR chloride) OR 'mouth'/exp OR mouth) AND ('spray'/exp OR spray) OR 'hydrogen'/exp OR hydrogen) AND ('peroxide'/exp OR peroxide) OR chx OR cpc OR 'h2o2'/exp OR h2o2 OR pvi #2 'sars cov 2*' OR 'covid 19'/exp OR 'covid 19' #3 #1 AND #2 367 #4 #3 AND 'controlled study'/de 96	96
Scopus searched via Scopus on September 5, 2021th, via https://www.scopus.com	TITLE-ABS-KEY (mouthwash OR mouth-rinse OR oral AND antiseptic OR chlorhexidine OR povidone AND iodine OR oral AND rinse OR cetylpyridinium AND chloride OR mouth AND spray OR hydrogen AND peroxide) AND TITLE-ABS-KEY (sars-cov-2 OR covid-19)	21
Cochrane Central Register of Controlled Trials searched via the Cochrane Library Searched on September 7, 2021th, via www.thecochranelibrary.com	#1 "mouthwashes" 2016 #2 mouth-rinse 637 #3 chlorhexidine 5194 #4 cetylpyridinium chloride 213 #5 povidone iodine 1662 #6 SARS-COV-2 340 #7 Covid-19 7023 #8 #1 OR #2 OR #3 OR #4 OR #5 7779 #9 #6 OR #7 7045 #10 #8 AND #9 67	67
Total		1437

Selection Criteria

The following inclusion and exclusion criteria were applied:

Inclusion criteria

Studies including controlled and randomized clinical trials investigating the COVID-19 viral load

Studies published in English

Exclusion criteria

- Animal studies
- In vitro studies
- Case reports, case series, and literature reviews
- Studies published in languages other than English

Screening and Selection of Papers

After removing duplicates both automatically and manually, the search results' titles and abstracts were initially screened by two independent authors (M.E. and E.B). Studies were evaluated for full text if they met the inclusion criteria at first analysis or if insufficient information was provided in the title and abstract to make a decision. Following the entire assessment, studies were either selected for inclusion or rejected. Discussion with a third review author (A.J.) resolved any disagreement between authors. In papers that included inadequate or limited information about the number of viral load amounts in qRT-PCR, the corresponding authors were contacted via e-mail for clarification and missing data requests. The following data were extracted from the studies selected for inclusion by one of the reviewers (M.E.): the year of publication, the country, the study design, the follow-up period, the number of patients, and the result of the qRT-PCR test result.

Data extraction

Data was extracted from the included studies for the final investigation. They presented the author, publication year, study type, the number of patients, age, sex, follow-up, study summary, changes in the Ct value with different oronasal antiseptics, patients' symptoms, and adverse complications.

Quality and risk of bias assessment of the included studies

Two reviewers (M.E. and E.B) independently assessed the included RCTs for quality assessment using the Revised Cochrane Risk-of-Bias tool for Randomized Trials developed by Sterne et al.

Statistical Analysis

Because of the lack of homogenic studies with similar interventions and outcome measurements, the meta-analyses for adverse effects of mouthwashes and patients' symptoms could not be performed. However, a meta-analysis for comparing the viral CT values (Cyclic Threshold) in the saliva before, and after the use of mouthwashes was performed. Because of the continuous nature of this variable, Mean Differences (MD) with 95% confidence interval was used to measure the outcome. P- value lesser than 0.05 was considered as the threshold for statistical significance. The reported data from the included studies was extracted and then using Review Manager software (version 5.4, Copenhagen, Denmark, Cochrane Collaboration, 2020) an inverse variance random-effects analysis was performed to pool the outcome measurements together. Because of the differences in the type of mouthwashes, intervention methods and the included population in the included studies, random-effects model was used.

A subgroup analysis based on the type of the mouthwashes was also performed. The statistical heterogeneity between studies was obtained by the Cochran's Chi-square test for heterogeneity and I2 statistic. Because of the existence of less than 10 studies included in this meta-analysis, the publication bias could not be evaluated.

3.Results

Characteristics of included studies

1437 studies were retrieved with the initial search strategy from the databases (Table 2). A total of 378 duplicate articles and articles not related to the question raised were removed, and titles and abstracts of all articles were screened independently and in duplicate by two review authors (M.E and E.B). After screening, 146 articles were selected for further analysis. 11 studies were eligible for full-text review. Hand searching of the bibliographies and cross-referencing related to COVID19 within the selected articles resulted in 0 more papers. One study was subsequently excluded due to the lack of sufficient data, and as a result, 10 studies were included in this systematic review (Figure 1).

Table 2. Characteristics of the included Study

	Arefin et al 2021.	Carrouel et al 2021	Di domênico et al 2021	Eduardo et al 2021	Elzein et al 2021	Gottsauner et al. 2020	Guenezan et al 2021	Huang et al.2021	Schürmann et al 2021	Seneviratne et al 2021
Study design	RCT (parallel group)	RCT (parallel group)	RCT (parallel group)	RCT (parallel group)	RCT (parallel group)	prospective clinical pilot study	RCT (parallel group)	Prospective COHORT Double arm	Clinical pilot study	RCT (parallel group)
Number of patients	189	176	35	43	61	12	24	294	34	16
Age (years), Range	43.98 ± 12.67	43.06 ± 5.56	36 to 59	46 to 62	45.3 ± 16.7 17 to 85	55 22 to 81	23 to 68	23 to 89	NR	NR
Sex (female/male)	30/159	96/80	13/22	11/ 32	36/25	6/6	16//8	124/170	NR	1/15
Type of antiseptics	PVP-I*	CDCM£	H_2O_2€	CPC¥ H_2O_2 CHX§ H_2O_2 + CHX	CHX 0.2% PVP-I 1%	H_2O_2	PVP-I	CHX	Linola sept	PVP-I CHX CPC
Administration method	Nasal irrigation (0.4-0.5-0.6 %) Nasal spray (0.5-0.6 %)	Oral rinse 3 times a day.	1% for gargling 3times a day. 0.5% nasal wash (twice a day)	mouthwash	mouthwash	mouth rinse	Mouthwash Gargle and nasal spray	Oral rinse alone or with posterior oropharyngeal spray	Gargle	mouth rinse
Time of outcome assessment	Immediately after use.	3 samples in day 1 and one sample each day for 7 days.	Each day for 7 days.	Immediately after rinse, 30 min and 60 min after rinsing.	5 min after rinsing	30 min after rinsing	day 1 and then every 2 days until day 7	4 days after rinse	5 min after gargling	5 min- 3h and 6 h after rinsing
Method of sample collection	nasopharyngeal swab	Collected salivary samples	monitored in the hospital for symptoms	Unstimulated saliva collection	saliva collection	oropharyngeal specimen by gargling with 0.9% NaCl for 30 s	nasopharyngeal swab	oropharynx swab	pharyngeal swabs	Collected salivary samples
Adverse Events	No adverse event in NS group and 7.4% in NI 0.4% group.	NR	The most common effects were a burning throat (22.2%), nasal burning (16.7%), and the feeling of a thick tongue (18.7%)	No adverse events observed.	NR	NR	All patients exposed to PI experienced unpleasant nasal tingling. Thyroid stimulating hormone elevation was observed in all patients after 5 days of PI exposure	No Adverse event observed.	NR	NR

* povidine-iodine
£ b-cyclodextrinecitrox mouthwash
€ hydrogen peroxide
¥ cetylpyridinium chloride
§ chlorhexidine

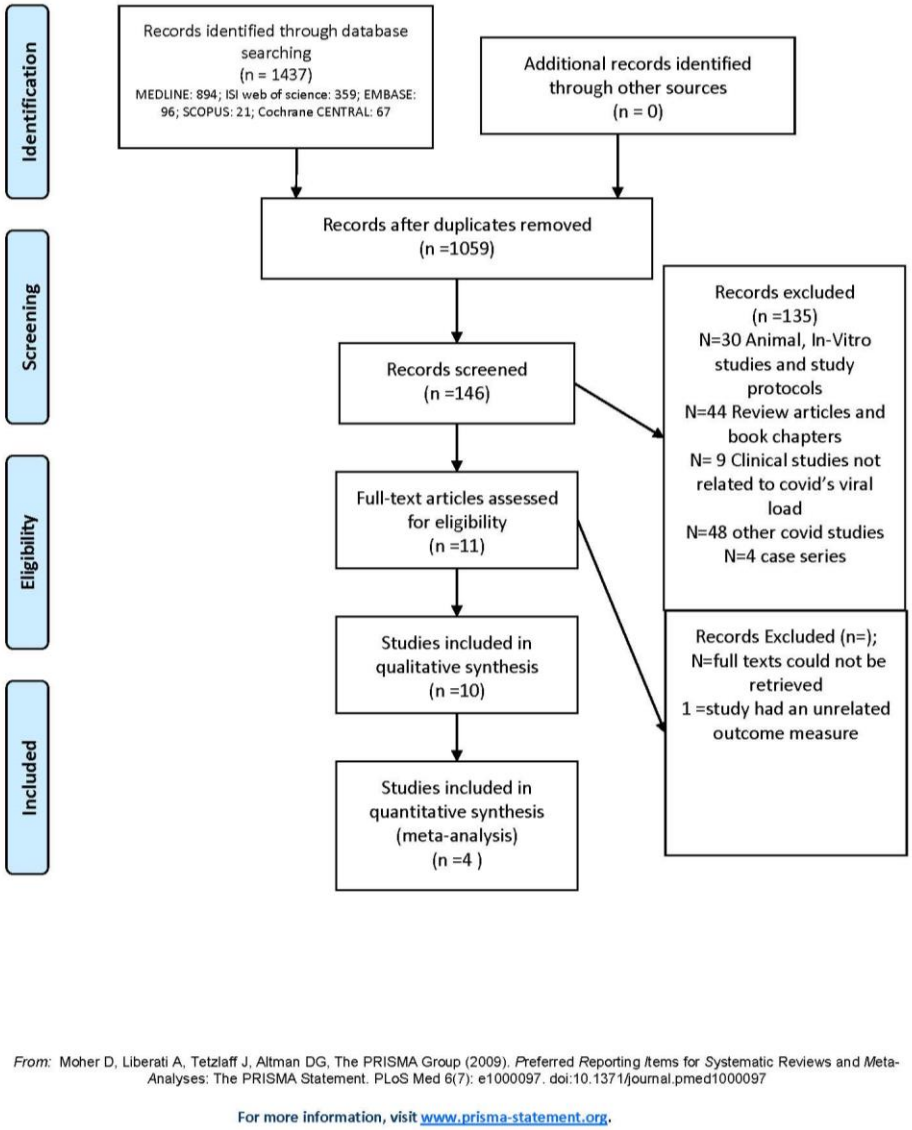

Figure 1. Prisma 2009 flow diagram

Risk of bias

Ten studies were judged to be at low risk of bias as they described the randomization, while four studies did not describe the allocation concealment and thus were judged to be at high risk of bias in this field. As the interventions could be blind for investigators or patients, outcome assessors, and statisticians, triple blinding was included. Nevertheless, four of the studies did not report blinding and were all judged to be at high risk of bias, and one study was double-blinded for outcome assessors. All the studies were rated as low (Table 3).

A total of 884 patients were assessed in the studies; 154 patients from four studies entered quantitative assessment. PVI in the four studies, H2O2 in the three studies, CHX in the four studies, CPC in the two studies, CDCN in one study, and Linola Sept (a commercial mouthwash) in one study were evaluated.

In all studies, the administration method of antiseptics was mouth rinse; in three studies, nasal spray and nasal irrigation were used in two studies.

Regarding viral load values evaluation and performing PCR tests for patients, in four studies, saliva samples were collected, and in four other studies, oropharyngeal swabs were used for sampling.

In one study, NaCl gargling for 30 seconds has been used to sample, and in one other study, just patients' symptoms in hospital after administration of antiseptic have been monitored.

Four of the included studies reported the viral load by RT-PCR based on the CT value, and two of them also reported fold changes related to placebo and baseline. Three other studies reported the viral titer based on the RNA copies/ml, and in two studies, PCR results were reported qualitatively as a positive or negative result.

Adverse effects

Five studies did not report the antiseptics' adverse effects; in two other studies, no adverse effects were observed; in one study for nasal spray (PVI), no adverse effects were observed, and in the nasal irrigation group, 7.4% of adverse effects were observed, including nasal irritation in two patients. In one other study, the most common adverse effects were reported as burning throat in 22.2%, nasal burning in 16.7%, and feeling a thick tongue in 18.7%. In one other study, all of the patients had unpleasant nasal tingling, and the TSH level increased above normal after five days of use, and no change in T3, T4, or creatinine were reported.

Change in patients' symptoms

In one study specifically, the patient's symptoms after antiseptic administration have been evaluated; in this study, in which H2O2 as an antiseptic was used, most comorbidities have been reported in the form of hypertension (48.6%) and diabetes (28.6%). Also, symptoms of cough, sore throat, and dyspnea were evaluated. The most common symptom was cough on the first day (zero), which was significantly reduced in both groups, sore throat disappeared on the second day in both groups, so there were no significant differences in this symptom between the H2O2 and control groups. In one other study, no significant difference in the use of antiseptic agents between the intervention and control groups in terms of symptoms and O2 saturation has been reported.

Viral Load and CT Values

A meta-analysis was performed to compare the viral CT values before and just after the use of mouthwashes in patients with COVID-19. The CT values increased after the use of mouthwash (MD = 2.00, 95%CI = 0.51, 3.49). Considering the CT values are inversely correlated to the viral load in the saliva, this means mouthwashes decrease the viral load in the saliva. This decrease in viral load was statistically significant (P = 0.009), and a low amount of heterogeneity existed between the results of the studies (I2 = 26%).

A subgroup analysis was also performed to compare the effects of different types of mouthwashes (CHX, CPC, and PVI) with rinsing with just water. No statistically significant difference between the effects of using mouthwashes and water on the CT values could be found (P=0.09). Conversely, while the use of water somewhat insignificantly decreased the CT value in patients, the mouthwashes insignificantly (CHX, CPC) and significantly (PVI) increased the CT value (MD=4.08, 95%CI= 0.13, 8.02, P<0.05).

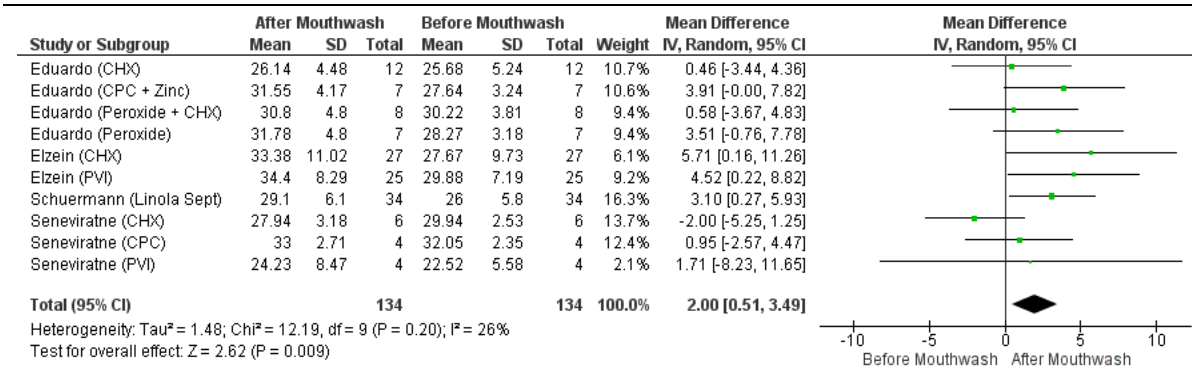

Figure 2. Comparison of CT values before and after using mouthwashes

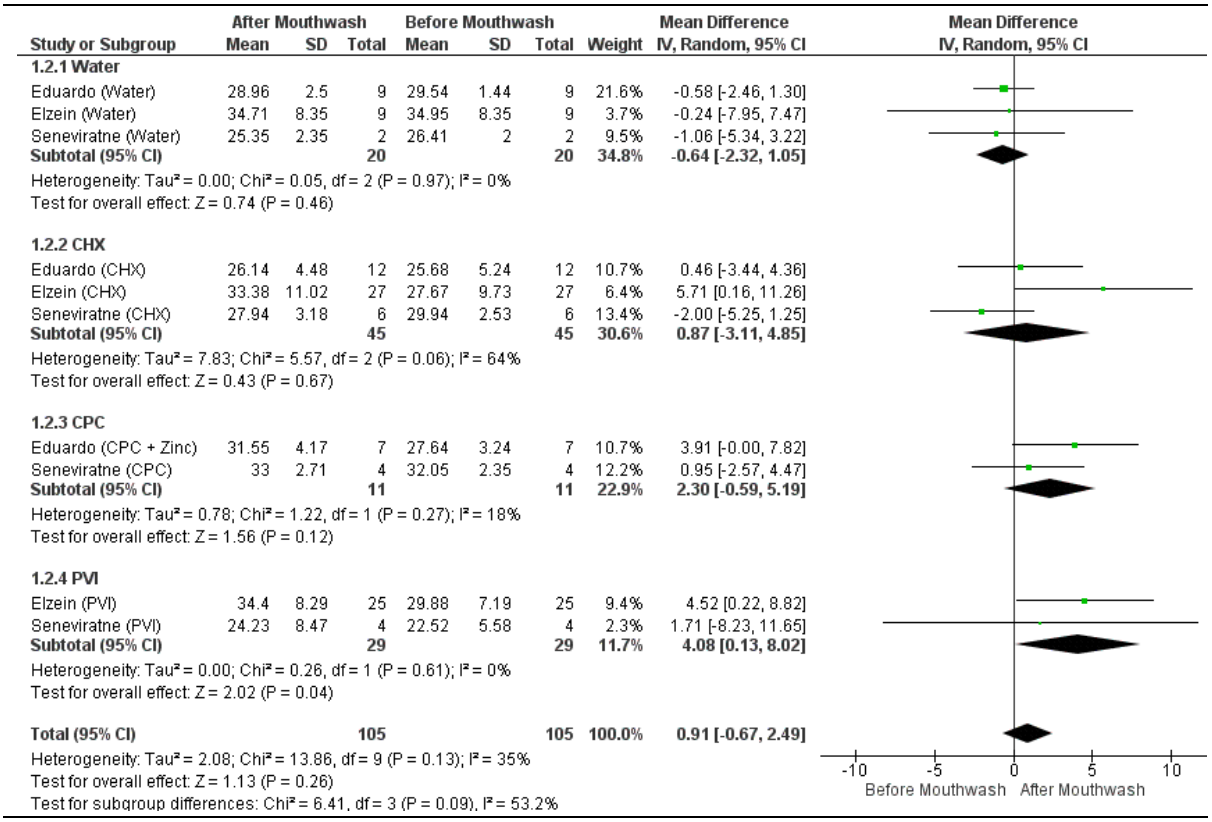

Figure 3. Subgroup comparison of CT Values between using different mouthwashes and water

4. Discussion

Along with all the preventive protocols, quarantines, pervasive restrictions, and nationwide vaccination in many countries, control of the virus is still a global crisis due to successive mutations (28).

Despite the high risk of disease transmission in dental treatments, due to the production of many aerosols and droplets, which are also the main ways of transmitting the disease, these procedures are unavoidable. Therefore, strategies for personal protection and disease prevention must be considered. The use of mouthwashes prior to dental procedures can help to reduce viral load and virus transmission (29).

The results of this meta-analysis revealed that there was an increase in the CT values after the administration of mouthwashes, which indeed advocates a decrease in viral load in the saliva. Instead, the water showed no significant change in CT values.

Based on this result, rinsing the mouth with water alone could somewhat increase the load of viruses in the oral cavity, which could be attributed to the water acting as a carrier for the viruses in the upper airway tract. Meanwhile, mouthwashes could decrease the viral load based on the potential virucidal effects of these substances.

Mouthwashes used in this review study included PVI, CHX, CDCM, H2O2, and CPC, of which CPC, CHX, and PVP were further investigated.

CHX is the standard gold mouthwash in dentistry, effective against a wide range of aerobic and anaerobic gram-positive and harmful bacteria. (30,31) In vitro studies investigating the effect of this mouthwash on viruses have shown the effect of this substance on most viruses; the difference in its effect has also been attributed to differences in the physical or chemical structure of the virus envelope (32).

The present meta-analysis results showed a decrease in viral load after using CHX mouthwash, although this was not statistically significant. A study conducted by Moosavi et al. also showed a more negligible effect in reducing virus load for CHX than for PVI, which is in line with the present study results (30). A systematic review by Marui et al., reviewing 12 studies, showed that CHX, CPC, and essential oil (EO) mouthwashes reduced microorganisms, which decreased more in CHX than in EO, but did not

differ significantly from CPC, which is in line with the present study (10).

CPC is a quaternary ammonium salt that has bactericidal and virucidal effects and is usually used as a mouthwash in concentrations of 0.02-0.07% (33).

In another review study published by Monero et al., a decrease in viral load was observed using this mouthwash, which, like the present study, was less than the decrease in virus load caused by PVI.

Previous laboratory studies have shown that PVI can effectively kill the coronavirus (34). PVI is a bactericidal and antiviral agent that affects the nucleic acid structure of the virus and its surface proteins and prevents the virus from attaching to cells (35). In the present study, a significant reduction in the load of the virus was shown by this mouthwash. Studies in this review have used this substance as a mouthwash and as a nasal rinse. The results of this study are in line with the results of Moosavi et al. (30). This mouthwash in patients has a more significant effect than other mouthwashes and has significantly reduced the virus in droplets and aerosols. Also, in a systematic review by Elmahgoub et al. (36) which examined two in vitro studies, the results showed that PVI 1% and 7% significantly reduced the virus load after 15 seconds. It is noteworthy that the side effects of using this mouthwash, a temporary increase in TSH hormone, and an itchy nose have been observed in nasal use. It is contraindicated in patients with iodine hypersensitivity, hyperthyroidism, or acute thyroid disease. (37) Also, it should be noted that in the studies included in our review, the authors used different concentrations of PVI. Elzein et al. used a 1% PVI solution as their mouthwash while Seneviratne et al. used a 0.5% solution for their intervention. The best concentration of PVI for use in Covid-19 patients is not known, however, the effects of 1% PVI in the Elzein et al. study was statistically significant while the effects for the 0.5% PVI in the Seneviratne et al. study was not statistically significant.

It should be noted that in the studies evaluating the effects of mouthwashes on the viral load for longer periods, the CT value of saliva samples and, therefore, the viricidal effects of these mouthwashes decreased after 30 minutes (38-40).

Most studies have shown the effect of mouthwashes in reducing viral load, although differences in studies can be due to differences in the type of substance, the concentration of the substance used, when and how it is used, or differences in the mean of viral load measurement (38-40).

Due to the reporting of viral load values in copies per mile, several studies were not included several studies were not included in copies/ml. In the study by Gotssauner et al. (41), the results showed that H2O2 (1%) did not reduce intraoral virus loading. In the study by Guenezan et al. (42), the results did not show any changes in the amount of virus RNA over time using PVI.

Heterogeneity of studies can be due to the different types of sampling (saliva collection or swab), the small number of samples in each group, and the different follow-up times for different studies.

Additionally, the quality of included studies, the lack of double-blinding in some studies, and the lack of single blinding and allocation concealment in four studies may be possible limitations for this meta-analysis. Hence, all RCT designs with a control and test group were included in this systematic review to present all the existing evidence. The lack of inclusion of non-English citations might be considered a possible limitation of this study.

Conclusion

This study showed that mouthwash generally reduces the viral load of saliva in patients with COVID 19. In addition, PVI mouthwash reduces viral load by a statistically significant amount, and CPC and CHX mouthwashes non-significantly reduce viral load in the saliva of patients with COVID 19. It should be noted that the use of water as a mouth rinse increased the viral load in the saliva of COVID 19 patients. This study was a review of previous clinical trial studies and, as such, can generalize the findings to clinical situations when compared to previous studies that investigated in-vitro studies.

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