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Masters Program in Public Health, Universitas Sebelas Maret

Meta-analysis

Meta-Analysis the Effect of Chlorhexidine and Povidone Iodine Mouthwashes on Viral Load SARS-CoV-2-Saliva

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ABSTRACT

Background: The strategy to reduce the risk of transmission of COVID-19 is to reduce the salivary SARS-CoV-2 viral load. Chlorhexidine and povidone iodine mouthwash are common active ingredients in oral antiseptics that have efficient viral activity against salivary SARS-CoV-2. This study aims to combine the results of several effect sizes regarding the effect of using chlorhexidine and povidone iodine mouthwash on the salivary SARS-CoV-2 viral load from various countries.
Subject and Method: This study is a meta-analysis with the following PICO model, P: COVID-19 patients. I: use of chlorhexidine and povidone iodine mouthwash. C: no mouthwash. O: salivary SARS-CoV-2 viral load. A search for the articles used in this study was carried out using the keywords “COVID-19” OR “SARS-CoV-2” OR “viral load” OR “SARS-Cov-2 viral load” OR “Chlorhexidine mouthrinse” OR “Povidone Iodine mouthrinse ” OR “Randomized Controlled Trial” OR “RCT” between 2012-2022 from the PubMed, Springerlink, Elsevier, Google Scholar and Wiley Online Library databases. The inclusion criteria used in this study were full-text articles using a Randomized Controlled Trial (RCT) design. The analysis used was multivariate with Standardized Mean Difference (SMD). The articles collected were then critically reviewed using the PRISMA checklist, then the data were analyzed using the Review Manager 5.4 tool.
Results: This meta-analysis examined 10 articles with a Randomized Controlled Trial (RCT) study design originating from Singapore, Saudi Arabia, Iran, Brazil, Italy, South Korea and Malaysia. A meta-analysis of 7 articles showed that the use of chlorhexidine mouthwash could reduce salivary SARS-CoV-2 viral load by 0.12 units lower than without the use of mouthwash (SMD= -0.12; 95% CI= -0.33 to 0.09; p=0.250). Meanwhile, 7 articles showed that the use of povidone iodine mouthwash could reduce the salivary SARS-CoV-2 viral load by 0.64 units lower than without the use of mouthwash (SMD= -0.64; 95% CI= -1.51 to 0.23; p=0.150).
Conclusion: The use of chlorhexidine and povidone iodine mouthwashes can reduce the amount of salivary SARS-CoV-2 viral

Keywords: mouthwash, chlorhexidine, povidone iodine, COVID-19, salivary SARS-CoV-2 viral load.

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BACKGROUND

Prior to the COVID-19 outbreak, there were four types of corona virus that could infect humans, namely alphacoronavirus 229E, betacoronavirus HKU1, alphacoronavirus NL63 and betacoronavirus OC43 which are known to cause the common cold in humans. In 2002 a new corona virus was discovered, namely SARS-CoV (Severe Acute Respiratory Illness Coronavirus) and in 2012 MERS-CoV (Middle East Respiratory Syndrome Coronavirus) was discovered which causes severe acute respiratory infections. At the end of 2019 the novel coronavirus appeared in Wuhan, China (Fang et al., 2020).

WHO declared an epidemic, namely a health emergency, in January 2020. As of April 16, 2020, the coronavirus infection has spread throughout the world, causing more than 2 million cases and more than 137 thousand deaths. Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) is classified under the Betacoronavirus genus of the Coronaviridae family. The outbreak of coronavirus disease 2019 (COVID-19) has been declared by WHO and is of international concern. COVID-19 spreads worldwide rapidly and mostly cause acute respiratory disorders (Elzein et al., 2020).

Before this writing was published, WHO data stated that there were 500,-186,525 cases globally and 948,865 cases in 24 hours. The United States is the country with the highest positive confirmed cases in the world, namely 78,050,838. then under the United States, namely India, Brazil, France, Germany and the United Kingdom (WHO, 2022). Indonesia is in the second highest position in Asia after India. Positive cases of COVID-19 in Indonesia as of 14 April 2022 were 6,037,742 and 833 cases within 24 hours and 155,794 of them died (WHO, 2022).

SARS-CoV-2 infection causes acute respiratory distress and is transmitted through droplets produced by infected people when they sneeze, talk, cough or exhale (Singh et al., 2021). Prevention of infection by cross-contamination is carried out by washing hands, using masks, maintaining distance and mass vaccination (Seneviratne et al., 2021).

In the saliva of patients infected with SARS-CoV-2, ACE2 receptors were found in the epithelial cells lining the ducts of the salivary glands. Angiotensin Converting Enzyme 2 (ACE2) is the main cellular receptor for SARS-CoV-2 that interacts with the spike protein. ACE2 was higher in the tongue compared to other oral tissues and was found to be higher in the minor salivary glands of the lungs (Xu et al., 2020). This shows that the oral cavity, especially saliva, has a high risk of transmitting SARS-CoV-2. Strategies to reduce salivary SARS-CoV-2 viral load can reduce the risk of transmission. The use of mouthwash with an antiseptic that has virucidal activity can be done (Ferrer et al., 2021).

Povidone iodine and chlorhexidine mouthwash are common active ingredients in oral antiseptics that have efficient viral activity against SARS-CoV-2 (Ferrer et al., 2021). The use of povidone iodine mouthwash can inactivate the virus so that it is effective in reducing the concentration of the virus in aerosol action. Chlorhexidine mouthwash has broad spectrum antibacterial properties and is effective at low or high concentrations (Yoon et al., 2020).

Prevention of infection that has been carried out to avoid infection with the COVID-19 virus has been widely applied, even though the transmission of SARS-CoV-2 transmission is most at risk to dental professionals. Patients need to remove the mask during dental examinations and procedures that generate aerosols (Eduardo et al., 2021). A study conducted by (To et al., 2020) stated that there was the presence of SARS CoV-2 in the saliva of COVID-19 patients with a viral load of 1.2 x 106 to 9.9 x 106 infective copies/ml in the patients tested. The highest viral loads were in the nasopharynx and saliva. Although the amount of SARS-CoV-2 viral load increases 2-4 hours after use of mouthwash, this procedure can help reduce the concentration of virus in aerosols to reduce the risk of cross-contamination (Yoon et al., 2020).

SUBJECTS AND METHOD

1. Study Design

This research was conducted using a systematic review and meta-analysis between 2012 and 2022. Searching for this research article through databases, including: PubMed, Springerlink, Cochrane Database, Hindawi, Elsevier, Google Scholar and Wiley Online Library using the search keyword "COVID -19" OR "SARS-CoV-2" OR "viral load" OR "SARS-Cov-2 viral load" OR "Chlorhexidine mouthrinse" OR "Povidone Iodine mouthrinse" OR "Randomized Controlled Trial" OR "RCT"

2. Steps in Conducting Meta-Analysis

Meta-analysis was conducted through five steps, as follow:

a. Defining the research questions with PICO (Population, Intervention, Comparisson, Outcome) form.
b. Searching for primary study articles from various electronic databases such as Google Scholar, PubMed, Cochrane, Scopus and Science Direct as well as non-electronic.
c. Conducting screening and Critical Appraisal toward the primary studies articles.
d. Conducting data extraction and synthesizing the effect estimates into RevMan 5.4.
e. Interpreting and making conclusion.

2. Inclusion Criteria and Exclusion Criteria

The inclusion criteria used in this study were full-text articles using a Randomized Controlled Trial (RCT) design. The analysis used was multivariate with Standardized Mean Difference (SMD).

The exclusion criteria in this study were articles published before 2012 and articles that did not include the mean SD.

3. Study Variables

The independent variables is Chlorhexidine and Povidone iodine mouthwash. The dependent variable is Salivary SARS-CoV-2 viral load.

4. Operational Definition of Variables

Chlorhexidine mouthwash is a bis-biguanite derivative mouthwash which has a broad spectrum and low toxicity. The properties of chlorhexidine are bactericidal, viricide and fungicide.

Povidone iodine mouthwash is a mouthwash with a broad spectrum antimicrobial consisting of iodine and polyvinyl pyrrolidone polymer. Iodine release is slow and gradual so as to minimize the toxicity and inactivation of the virus

Salivary SARS-CoV-2 viral load is the number of SARS-CoV-2 virus particles in the saliva sample.

5. Study Instrument

This study is guided by PRISMA flow diagrams and quality assessment of research articles using the Critical Appraisal Checklist for Randomized Controlled Trial (RCT) tool. The following are the 12 questions used in the checklist (Tables 3 and 4):

1. Does this research address a clear research focus?
2. Is the Randomized Controlled Trial research method suitable for answering research questions?
3. Were there enough subjects in the study to establish that the findings were not made by chance?
4. Were subjects randomly allocated to the experimental and control groups?
5. Were inclusion/exclusion criteria used?
6. Were the two groups comparable at study entry?
7. Were objective and unbiased outcome criteria used?
8. Were objective and validated measurement methods used to measure the results?
9. Is the effect size practically relevant?

10. How precise is the estimated effect? Are there confidence intervals?
11. Could there be confounding factors that have not been taken into account?
12. Are the results applicable to your research?

7. Data Analysis

The articles collected are processed using the Review Manager application (RevMan 5.4). Data processing was carried out by calculating effect sizes and heterogeneity values to determine the combined research model and form the final meta-analysis results which were presented in the form of forest plots and funnel plots.

RESULTS

The article review process using a database based on PRISMA flowchart diagram can be seen in Figure 1. The initial search process in the database gave 1085 results, then through the process of deleting duplicate articles as many as 12 articles with 1073 articles filtered of which qualified for further full text review. The results of the articles were reviewed again and there were 10 articles originating from 7 Asian continents, 2 South American continents and 1 from the European continent, can be seen in Figure 2.

The total number of primary research included in this meta-analysis synthesis was 10 articles originating from Singapore, Saudi Arabia, Iran, Brazil, Italy, South Korea and Malaysia.

The primary study for the use of chlorhexidine mouthwash used 7 randomized controlled trial (RCT) studies from Singapore, Saudi Arabia, Iran, Brazil and Italy. Meanwhile, the use of povidone iodine mouthwash used 7 randomized controlled trial (RCT) studies from Lebanon, Italy, South Korea, Iran, Malaysia and Brazil.

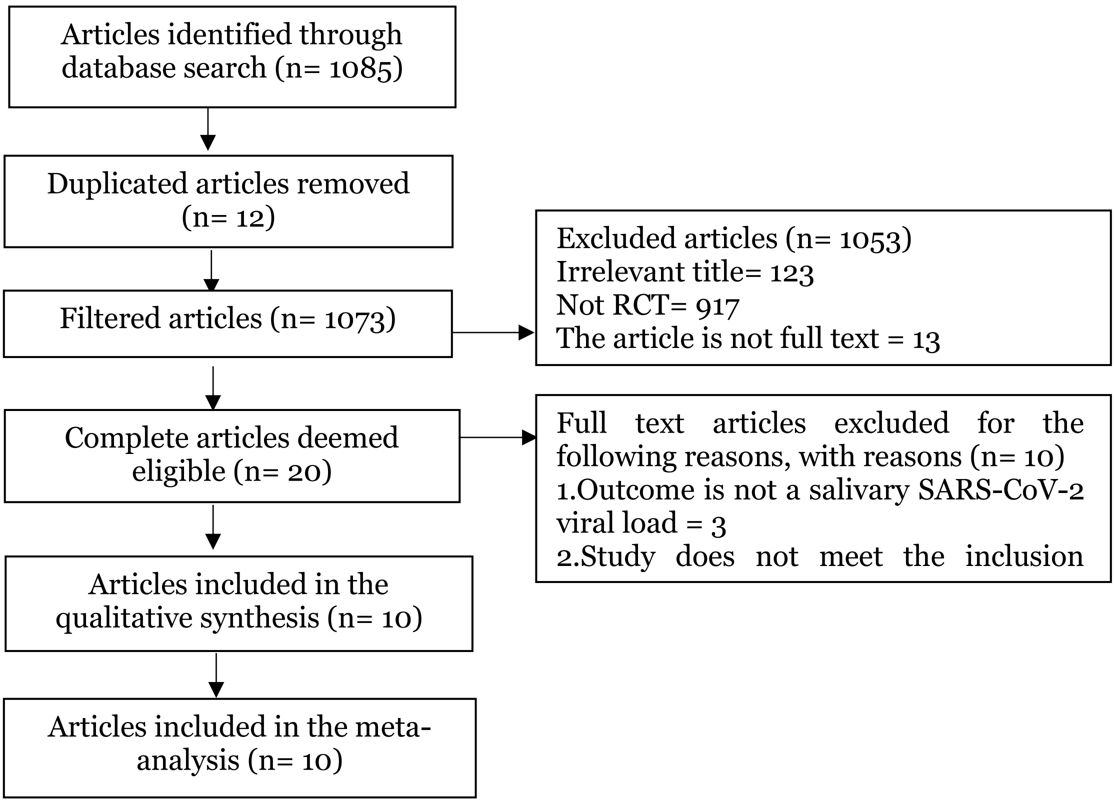

Figure 1. PRISMA Flow Diagram

Table 1. Primary Study Description of Chlorhexidine Mouthwash Included in the Meta-Analysis

Author (Year)	Country	Study Design	Sample	P Population	I Intervention	C Comparison	O Outcome	Chlorhexidine		No Mouthwash	
								Mean	SD	Mean	SD
Seneviratne et al., 2021	Singapore	RCT	Interven-tion: 6 Control: 2	COVID-19 patient	Mouthwash chlorhexidine, povidone iodine and cetylpyridinium chloride	Distilled water	Viral load SARS-CoV-2 saliva	3.5	0.8	2	2
Natto et al., 2022	Saudi Arabia	RCT	Interven-tion: 15 Control: 15	COVID-19 patients being treated at the hospital	Chlorhexidine and povidone iodine mouthwash	Saline	Viral load SARS-CoV-2 saliva	1.48	4.41	0.17	7.67
Ghasemi et al., 2022	Iran	RCT	Interven-tion: 40 Control: 40	COVID-19 patients hospitalized at the hospital	Chlorhexidine mouthwash, povidone iodine, Hydrogen Peroxide	Saline	Viral load SARS-CoV-2 saliva	1.96	0.83	2.2	0.8
Costa et al., 2021	Brazil	RCT	Interven-tion: 55 Control: 55	COVID-19 patient reporting at health center	Chlorhexidine mouthwash	Distilled water	Viral load SARS-CoV-2 saliva	32.38	4.73	32.26	4.64
Eduardo et al, 2021	Brazil	RCT	Interven-tion: 12 Control: 12	COVID-19 patient	Mouthwash chlor-hexidine for 1 minute	Distilled water	Viral load SARS-CoV-2 saliva	2.1	1.5	1.6	0.2
Fantozzi et al., 2022	Italy	RCT	Interven-tion: 8 Control: 11	COVID-19 patient	Mouthwash chlorhexidine, povidone iodine and hydrogen peroxide	Sodium chloride	Viral load SARS-CoV-2 saliva	35	32.6	36.1	32.7
Mukhtar et al., 2021	Saudi Arabia	RCT	Interven-tion: 45 Control: 44	COVID-19 patient	Mouthwash chlorhexidine and H2O2 2%	Distilled water	Viral load SARS-CoV-2 saliva	2.6	0.7	2.9	0.4

Table 2. Description of the Primary Study of Povidone Iodine Mouthwash Included in the Meta-Analysis

Author (Year)	Country	Study Design	Sample	P Population	I Intervention	C Comparison	O Outcome	Povidone Iodine		No Mouthwash	
								Mean	SD	Mean	SD
Elzein et al., 2021	Lebanon	RCT	Interven-tion: 25 Control: 9	COVID-19 patient	Chlorhexidine and povidone iodine mouthwash	Distilled water	Viral load SARS-CoV-2 saliva	4.72	0.89	6.37	1.08
Seneviratne et al., 2021	Italy	RCT	Interven-tion: 4 Control: 2	COVID-19 patient	Mouthwash chlorhexi-dine, povidone iodine and cetylpyridinium chloride	Distilled water	Viral load SARS-CoV-2 saliva	24.2	8.08	25.3	2.17
Natto et al., 2022	South Korea	RCT	Interven-tion: 15 Control: 15	COVID-19 patient	Chlorhexidine and povidone iodine mouthwash	Saline	Viral load SARS-CoV-2 saliva	4.43	4.78	0.17	7.67
Ghasemi et al., 2022	Iran	RCT	Interven-tion: 40 Control: 40	COVID-19 patient	Chlorhexidine mouth-wash, povidone iodine, hydrogen peroxide	Saline	Viral load SARS-CoV-2 saliva	27.15	6.03	31.23	3.96
Mohamed et al., 2020	Malaysia	RCT	Interven-tion : 5 Control: 5	Patients who have COVID-19 for 5 days	Povidone iodine mouthwash and essential oils	Distilled water	Viral load SARS-CoV-2 saliva	32	13	25	5
Fantozzi et al., 2022	Italy	RCT	Interven-tion: 8 Control: 11	COVID-19 patient	Mouthwash chlorhexi-dine, povidone iodine and hydrogen peroxide	Sodium chloride	Viral load SARS-CoV-2 saliva	35.7	32.7	36.1	32.7
Choudhury et al., 2021	Brazil	RCT	Interven-tion: 303 Control: 303	COVID-19 patient	Povidone iodine mouthwash, nose and eye drops	Warm water	Viral load SARS-CoV-2 saliva	2	0.66	14	4.62

Table 3. Quality Assessment of Randomized Controlled Trial (RCT) Effect of Using Chlorhexidine Mouthwash on Salivary SARS-CoV-2 Viral Load

No.	Questions of Checklist	Costa et al., 2021	Eduardo et al, 2021	Mukhtar et al., 2021	Seneviratne et al., 2021	Natto et al., 2022	Ghasemi et al., 2022	Fantozzi et al., 2022
1.	Does this research address a clear research focus?	2	2	2	2	2	2	2
2.	Is the Randomized Controlled Trial research method suitable for answering research questions?	2	2	2	2	2	2	2
3.	Were there enough subjects in the study to establish that the findings were not made by chance?	1	1	1	2	2	2	2
4.	Were subjects randomly allocated to the experimental and control groups?	2	2	2	2	2	2	2
5.	Were inclusion/exclusion criteria used?	2	2	2	2	2	2	2
6.	Were the two groups comparable at study entry?	0	0	0	1	1	2	2
7.	Were objective and unbiased outcome criteria used?	2	2	2	2	2	2	2
8.	Were objective and validated measurement methods used to measure the results?	2	2	2	2	2	2	2
9.	Is the effect size practically relevant?	0	0	2	2	2	2	2
10.	How precise is the estimated effect? Are there confidence intervals?	2	0	0	2	2	2	2
11.	Could there be confounding factors that have not been taken into account?	2	0	2	1	1	1	1
12.	Are the results applicable to your research?	2	2	2	2	2	2	2
	Total	19	15	19	20	22	23	23

Answer 0=hesitant, 1=No, 2=Yes

Table 4. Randomized Controlled Trial (RCT) quality assessment of the effect of using povidone iodine mouthwash on salivary SARS-CoV-2 viral load

No.	Questions of Checklist	Choudhury et al., 2021	Elzein et al., 2021	Seneviratne et al., 2021	Natto et al., 2022	Ghasemi et al., 2022	Mohamed et al., 2020	Fantozzi et al., 2022
1.	Does this research address a clear research focus?	0	2	2	2	2	2	2
2.	Is the Randomized Controlled Trial research method suitable for answering research questions?	2	2	2	2	2	2	2
3.	Were there enough subjects in the study to establish that the findings were not made by chance?	0	2	2	2	2	2	2
4.	Were subjects randomly allocated to the experimental and control groups?	2	2	2	2	2	2	2
5.	Were inclusion/exclusion criteria used?	2	2	2	2	2	2	2
6.	Were the two groups comparable at study entry?	2	1	1	1	2	2	2
7.	Were objective and unbiased outcome criteria used?	2	2	2	2	2	2	2
8.	Were objective and validated measurement methods used to measure the results?	2	2	0	2	2	2	2
9.	Is the effect size practically relevant?	0	2	2	2	2	2	2
10.	How precise is the estimated effect? Are there confidence intervals?	0	2	2	2	2	2	2
11.	Could there be confounding factors that have not been taken into account?	0	1	1	1	1	1	1
12.	Are the results applicable to your research?	2	2	2	2	2	2	2
	Total	14	20	20	22	23	23	23

Answer 0=hesitant, 1=No, 2=Yes

Figure 2. Research area map of the use of chlorhexidine mouthwash for SARS-CoV-2 Saliva Viral Load

1. The Effect of Using Chlorhexidine Mouthwash on Salivary SARS-CoV-2 Viral Load

	Chlorhexidine			Non chlorhexidine				Std. Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	Year
Mukhtar et al., 2021	2.6	0.7	45	2.9	0.4	44	24.5%	-0.52 [-0.94, -0.10]	2021
Seneviratne et al., 2021	3.5	0.8	6	2	2	2	1.4%	1.19 [-0.61, 2.99]	2021
Eduardo et al., 2021	2.1	1.5	12	1.6	0.2	12	6.6%	0.45 [-0.36, 1.26]	2021
Costa et al., 2021	32.38	4.73	55	32.26	4.64	55	31.3%	0.03 [-0.35, 0.40]	2021
Fantozzi et al., 2022	35	32.6	8	36.1	32.7	11	5.3%	-0.03 [-0.94, 0.88]	2022
Natto et al., 2022	1.48	4.41	15	0.17	7.67	15	8.5%	0.20 [-0.51, 0.92]	2022
Ghasemi et al., 2022	1.96	0.83	40	2.2	0.8	40	22.5%	-0.29 [-0.73, 0.15]	2022
Total (95% CI)			**181**			**179**	**100.0%**	**-0.12 [-0.33, 0.09]**	

Heterogeneity: Chi² = 9.36, df = 6 (P = 0.15); I² = 36%
Test for overall effect: Z = 1.16 (P = 0.25)

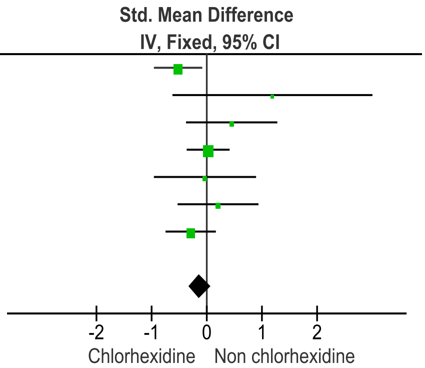

Figure 3. Forest Plot of Use of Chlorhexidine Mouthwash for SARS-CoV-2 Saliva Viral Load

a. Forest Plot

The forest plot in Figure 3 shows the effect of using chlorhexidine mouthwash on the salivary SARS-CoV-2 viral load. The use of chlorhexidine mouthwash can reduce the salivary SARS-CoV-2 viral load by 0.12 units lower than without the use of mouthwash, but not statistically significant (SMD= -0.12; 95% CI= -0.33 to 0.09; p=0.250). The forest plot in Figure 3 also shows homogeneity between studies (I^2= 36%) so that the analysis uses the Fixed Effect Model.

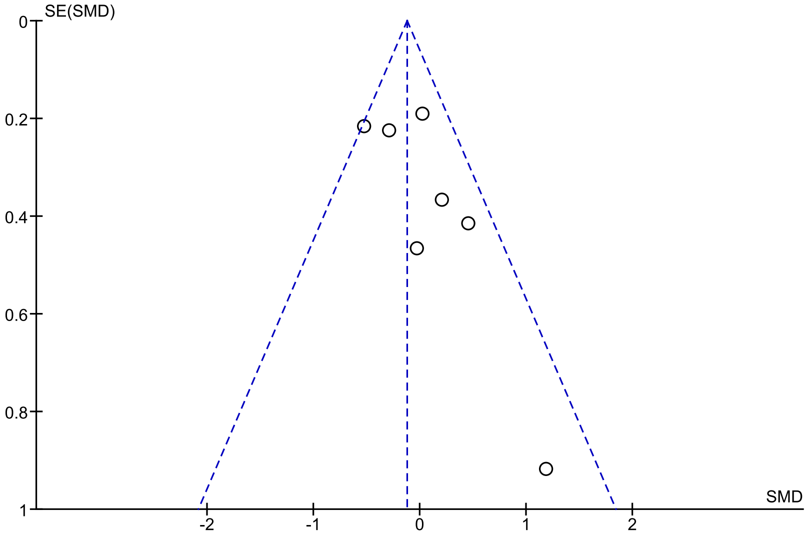

Figure 4. Funnel Plot Effect of Using Chlorhexidine Mouthwash on the Viral Load of SARS-CoV-2 Saliva

b. Funnel plot

The funnel plot of Figure 4 indicates the unequal distribution of effect estimates across the 7 studies. There are 2 plots on the left and 5 plots on the right. The funnel plot in Figure 4 regarding the effect of using chlorhexidine mouthwash on the SARS-CoV-2-saliva viral load shows an asymmetrical triangle. This indicates the presence of publication bias. Because the publication bias is in the opposite direction to the location of the diamonds in the forest plot, the publication bias tends to understate a similar effect (underestimate).

2. The Effect of Using Povidone Iodine Mouthwash on the SARS-CoV-2 Saliva Viral Load

Study or Subgroup	Povidone iodine Mean	SD	Total	Non povidone iodine Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI	Year
Mohamed et al., 2020	32	13	5	25	5	5	13.0%	0.64 [-0.65, 1.93]	2020
Seneviratne et al., 2021	24.2	8.08	4	25.3	2.17	2	10.8%	-0.12 [-1.83, 1.58]	2021
Elzein et al., 2021	4.72	0.89	25	6.37	1.08	9	15.4%	-1.71 [-2.59, -0.84]	2021
Choudhury et al., 2021	2	0.66	10	14	4.62	10	11.9%	-3.48 [-4.97, -1.99]	2021
Natto et al., 2022	4.43	4.78	15	0.17	7.67	15	16.2%	0.65 [-0.09, 1.39]	2022
Ghasemi et al., 2022	27.15	6.03	40	31.23	3.96	40	17.4%	-0.79 [-1.25, -0.34]	2022
Fantozzi et al., 2022	35.7	32.7	8	36.1	32.7	11	15.2%	-0.01 [-0.92, 0.90]	2022
Total (95% CI)			**107**			**92**	**100.0%**	**-0.64 [-1.51, 0.23]**	

Heterogeneity: Tau² = 1.08; Chi² = 37.71, df = 6 (P < 0.00001); I² = 84%
Test for overall effect: Z = 1.45 (P = 0.15)

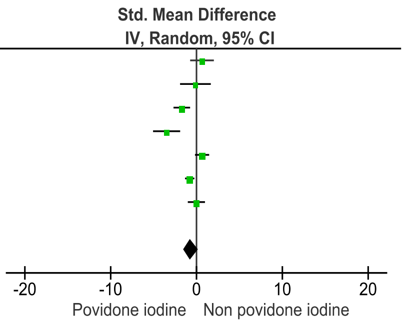

Figure 5. Forest Plot Effect of Using Povidone Iodine Mouthwash on the Viral Load of SARS-CoV-2 Saliva

a. Forest Plot

The forest plot in Figure 5 shows that there is an effect of using chlorhexidine mouthwash on the salivary SARS-CoV-2 viral load. According to the results of the analysis, the use of povidone iodine mouthwash can reduce the salivary SARS-CoV-2 viral load by 0.64 units lower than without the use of mouthwash, but this is not statistically significant (SMD= -0.64; 95% CI= -1.51 to 0.23; p=0.150). The forest plot in Figure 5 also shows heterogeneity between studies (I^2= 84%) so that the analysis uses the Random Effect Model.

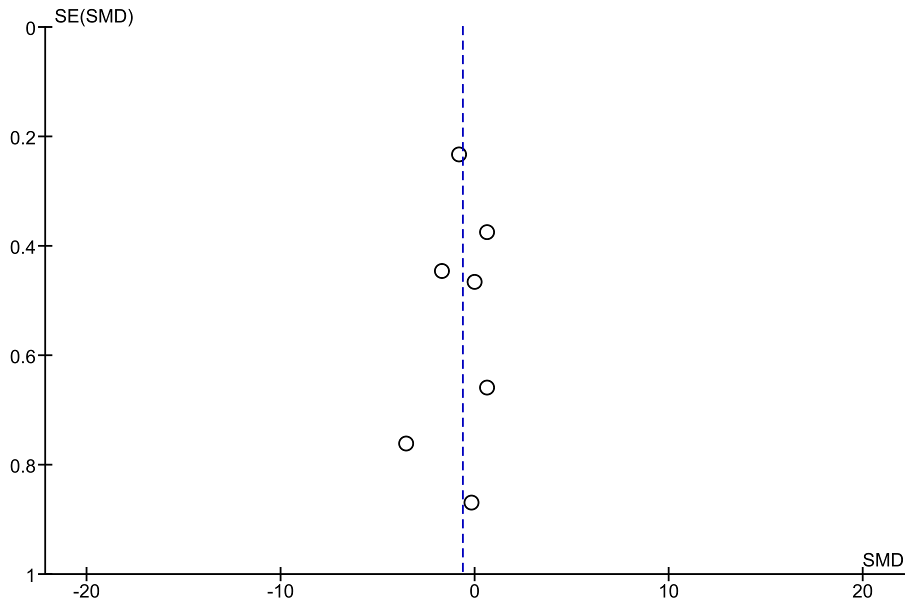

Figure 6. Funnel Plot Effect of Using Povidone Iodine Mouthwash on SARS-CoV-2 Saliva Viral Load

b. Funnel Plot

The funnel plot in Figure 6 indicates an unequal distribution of effect estimates across the 7 studies. There are 3 plots on the left and 4 plots on the right. The funnel plot in Figure 6 regarding the effect of using povidone iodine mouthwash on the SARS-CoV-2-saliva viral load shows an asymmetrical triangle. The location of the diamonds in the opposite direction in the forest plot indicates that publication bias tends to underestimate the true effect (underestimate).

DISCUSSION

This systematic review and meta-analysis study discusses the effect of using chlorhexidine and povidone iodine mouthwash on the salivary SARS-CoV-2 viral load. The independent variable used in this study was the use of chlorhexidine and povidone iodine mouthwash. Meanwhile, the dependent variable used was the salivary SARS-CoV-2 viral load.

1. The Effect of Using Chlorhexidine Mouthwash on the SARS-Cov-2-Saliva Viral Load

Based on an analysis of 7 primary studies with a Randomized Controlled Trial (RCT) study design conducted with a systematic review and meta-analysis of the effect of using chlorhexidine mouthwash on the SARS-CoV-2 salivary viral load, it shows that the use of chlorhexidine mouthwash can reduce the SARS-CoV-2 viral load. Salivary CoV-2 was 0.12 units lower than without using mouthwash but not statistically significant (SMD= -0.12; 95% CI= -0.33 to 0.09; p=0.250).

This is due to limited research with a small population. The total population in this study was 360 patients. So it is necessary to carry out further research with a larger population so that the results obtained are more representative.

The study by Meister et al., 2020 stated that the different chains of SARS-CoV-2 could be efficiently deactivated with chlorhexidine so that its use is recommended to reduce virus transmission via aerosols

(Alzein., et al 2021). Research conducted by Yoon et al., 2020 showed that chlorhexidine mouthwash significantly reduced salivary SARS-CoV-2 viral load in a short period of time, namely for 2 hours after rinsing. A recent study found that chlorhexidine mouthwash could have an anti-SARS-CoV-2 effect (Eduardo et al., 2021).

2. **Effect of Using Povidone Iodine Mouthwash on the SARS-Cov-2-Saliva Viral Load**

Based on an analysis of 7 primary studies with a Randomized Controlled Trial (RCT) study design that was carried out with a systematic review and meta-analysis of the effect of using povidone iodine mouthwash on the salivary SARS-CoV-2 viral load. This research article shows that the use of povidone iodine mouthwash can reduce the salivary SARS-CoV-2 viral load 0.64 units lower than without the use of mouthwash but not statistically significant (SMD = -0.64; 95% CI = -1.51 to 0.23; p = 0.150).

This is due to limited research with a small population. The total population in this study was 199 patients. So it is necessary to carry out further research with a larger population so that the results obtained are more representative.

Povidone iodine mouthwash has broad spectrum antimicrobial properties. Its use has been since 60 years as a skin disinfectant, hands, mucosal surfaces and wound healing. In vitro studies show the effectiveness of povidone iodine against enveloped and non-enveloped viruses (Alzein et al., 2020). The use of povidone iodine mouthwash is recommended to reduce salivary SARS-CoV-2 viral load in patients infected with COVID-19, especially the first week from the onset of symptoms when the viral load is highest in these circumstances (To et al., 2020).

Oral and nasal decontamination with povidone iodine mouthwash can reduce the amount of aerosolized virus particles (Chopra et al., 2021). Study of Lamas et al. (2020) reported a significant reduction in SARS-CoV-2 viral load after gargling with 1% povidone iodine for 1 minute with a clinical effect lasting 3 hours (Lamas et al., 2020).

The limitation of this study is that there is a research bias because it only uses 7 databases, namely PubMed, Springerlink, Cochrane Database, Hindawi, Elsevier, Google Scholar, Wiley Online Library, thus ignoring research from other databases. In this study there is also a language bias because only the selected articles are published in English, thus ignoring articles published in other languages.

AUTHORS CONTRIBUTION

Danti Narulita is the main researcher who selects topics, searches for and collects study data. Setyo Sri Rahardjo and Bhisma Murti played a role in analyzing the data reviewing study documents.

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CONFLICT OF INTEREST

There is no conflict of interest in this study

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