Antiviral efficacy of Chlorhexidine mouthwash versus Povidone Iodine mouthwash in SARS CoV 2 infected adults – A Meta-Analysis

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KEYWORDS
chlorhexidine, povidone iodine, SARS CoV 2, antiviral efficacy

ABSTRACT
Background: SARS CoV 2, the virus which causes covid19, is a global disease which has become a major concern. Ever since the outbreak, many significant research on its therapeutic and preventive methods have emerged. Oral cavity being the major source of viral load transmission, an antimicrobial mouthrinse will be effective in reduction of the viral load. It also aids in preventing cross-contamination. So it's crucial to analyse the antiviral efficacy of 0.2 % Chlorhexidine mouthwash over 1% Povidone iodine mouthwash.
Objective: To assess the antiviral efficacy of Chlorhexidine mouthwash over Povidone iodine mouthwash in SARS CoV2 infected adult patients.
Data Sources: Systematic search analysis was done till june 2024 through PubMed and Google Scholar.
Study Selection: All published randomised controlled trials that involved the antiviral efficacy of chlorhexidine mouthwash and povidone iodine mouthwash in SARS CoV2 infected adult patients were included in meta analysis.
Data Extraction: A predetermined checklist was used as a guide for data extraction
Analytical Approach: RevMan 5 software has been used to measure the mean length of pre-treatment viral load and post-treatment viral load of both Chlorhexidine and Povidone iodine . The values were pooled from the selected studies. To compare the antiviral efficacy of Chlorhexidine mouthwash over Povidone iodine mouthwash in SARS CoV2 infected adult patients, fixed –effect model was used. Data analyses were performed in June 2024.
Main Outcomes and Measures: The primary outcome was a comparison of pre-treatment viral load and post treatment viral load of the groups with use of chlorhexidine mouthwash and Povidone iodine.
Results: The initial search producd 687 articles of which 6 articles were selecctd for full-text screening , which recognized four articles with randomized controlled trials were included. The findings did not favour any particular antimicrobial mouthwash in providing antiviral efficacy. The usage of chlorhexidine mouthwash versus Povidone iodine mouthwash provides equal antiviral efficacy. (MD = 1.74, 95% CI -.1.35 – 4.84, p = 0.42). An insignificant Q statistic (p = 0.27) indicated the absence of heterogeneity (I2 =0%).
Conclusion: This systematic review and meta-analysis demonstrated that Antiviral efficacy of chlorhexidine mouthwash and povidone iodine mouthwash are same in reduction of viral load in SARS CoV 2 infected adults.

1. Introduction

Corona virus disease-2019 (Covid19) which causes respiratory disorder is caused by SARS CoV-2, a new member of human corona virus from the coronaviridae family and belongs to the genus Betacoronavirus, sub-genus Sarbecovirus and subfamily orthocoronavirinae[1,2]. This disease is a rapidly spreading and a highly infectious respiratory syndrome which has been matter of global concern. This contagious disease mainly spreads through direct or indirect close contact with saliva and respiratory secretions of infected patients produced by coughing , sneezing or talking. A high viral load in saliva leads to high infectivity of the SARS CoV-2. The angiotensin-converting enzyme-II (ACE-2), a main receptor of SARS CoV-2, is intensely present in the mucosa of oral cavity particularly in the epithelium of the tongue[3,4]. Studies too shows that viral load will be higher in initial stages of the disease. Therefore, besides performing hand hygiene and other protective measures, in order to reduce the viral load an antimicrobial mouth rinse is essential. There are studies emphasising the efficacy of Chlorexidine mouthwash and povidone iodine mouthwash in reducing the viral load in the

oral cavity[5,6]. Hence we intended to do a meta-analysis in order to determine the antiviral efficacy of chlorhexidine mouthwash over povidone iodine.

2. Methods

The present study protocol was prospectively registered with PROSPERO and adhered completely to the reporting parameters outlined in the "Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) guidelines." As a systematic review, this study heterogeneity was present within an acceptable range, hence a meta-analysis was performed.

Eligibility criteria

Inclusion criteria

1. Adults above 18 years of age.
2. 0.2 % chlorhexidine as intervention versus povidone iodine
3. Outcome indicators: pretreatment viral load and post treatment viral load
4. Double blinded, Randomized controlled trial with two groups randomized to receive chlorhexidine or povidone iodine
5. Articles published in English language from the year 2020 till June 2024.

Exclusion criteria

1. The study designs like Case control study, cross sectional study/ observational study and open label randomized controlled trials.
2. Articles with insufficient data
3. Studies involving animals.

Search strategy

To perform a meta-analysis, the primary step is setting up the meta-data. All the literature retrieved using electronic retrieval method. A complete systematic literature search was done in the following databases Medical Subject Headings (MeSH), controlled vocabulary and keywords through databases which includes PubMed and Google Scholar for studies from the year 2020 to june 2024. The keyword used was “chlorhexidine”, “povidone iodine”. “SARS CoV 2”, “adults”, “Randomised controlled trial”. Moreover, reference list of articles which are relevant were manually searched from the topics which are selected and the articles which are relevant to the topic were also included. The study was registered prospectively in the PROSPERO database.

Study Selection

Our study selection involved screening in two stages. All the search results were uploaded in Rayyan software, a systematic review program to carry out the study selection. Our study included population above 18 years, articles with 0.2% as intervention group versus povidone iodine, studies with outcome indicator and articles that are published from the year 2020 till june 2024. Double-blinded, randomized controlled studies were also included.

Two authors (R.G, K.R) independently searched the literature and scrutinized the title, abstract, and selected keywords of all the studies. The abstract and full texts were thoroughly screened individually by two authors (R.G, K.R) to select the studies which meets the relevance of our review. During the entire selection process, all the difference of opinion and conundrums were resolved through common consent and consultation with third author (S.P). The fourth and fifth reviewer (K.S, R.G) performed as a moderator to come to a common solution in case of conflicts among reviewer.

Data extraction and management

The first and co-author individually obtained the appropriate study characteristics for the review which related to outcome measure from the included studies. A checklist was made prior consisting of first author last name, published year, total sample size, gender, study design, intervention, participants age with SARA.CoV2 were made for data extraction.

The obtained data transferred into the software Review Manager (RevMan_5.3) by the first author (R.G).A thorough screening of data entry was done by the second author (K.R) by comparing the data presented in the review and included the reports.

Outcome measure for the study:

The outcome was comparison of chlorhexidine versus povidone iodine mouth rinse in SARS CoV 2 infected adults in both intervention and control groups.

Quality Assessment

The risk of bias and the quality of the articles which are selected was evaluated using the Revised Cochrane risk-of-bias tool for randomized trials (RoB 2). All the studies was classified as follows: "low-risk," "some concerns," or "high-risk" of bias.

3. Statistical analysis

A qualitative analysis was made extensively. All the computations were made using RevMan_5.3 for quantitative Meta-analysis. In case of studies with multiple antimicrobial rinse in a single trial, only the suitable arms were included for the analysis. A logistic-normal-random-effect model was done due to heterogeneity among studies. For study-specific and overall pooled prevalence, 95% Confidence Interval (CI) was done. I^2 statistics was used to evaluate the heterogeneity. Significant heterogeneity was considered if p-value <0.05 or I^2>50% among the studies.

Study specific and pooled estimates were shown graphically with the help of forest plot. Sensitivity analysis was performed to evaluate the reliability of the obtained estimate in the meta-analysis.

4. Results

Study selection and characteristics:

Totally 687 articles were identified initially. After a thorough screening, 342 studies were found to be duplicates and excluded. Out of which 6 were assessed with respect to inclusion criteria. Finally, 4 studies fulfilled all the criteria for inclusion and eventually included for the qualitative and quantitative analysis. Fig 1 shows **t**he PRISMA flowchart for the study selection.

The included four studies were evaluated using Cochrane risk-of-bias tool. After assessment it showed low risk of bias in two studies and the remaining two studies showed some concerns**.** The main drawback of the study is small sample size. Baseline characteristics were equal in intervention as well as control groups in all the included studies. Finally, the results were not statistically significant in all the four studies even though there were variations in pre treatment viral load and post treatment viral load.

Characteristics of the study population

Totally, 89 study population were in the intervention group and 93 were in the control group from all the four included studies. The mean age of all the cohorts included in this study ranged above 18 years. All the studies used chlorhexidine and povidone mouth rinse for measurement of pre treatment viral load and post treatment viral load. Initially, 687 records were searched. Out of which 6 articles went through full-text evaluation. Finally, 4 articles with randomized controlled trials were found and included. The findings did not favour any particular antimicrobial mouthwash in providing antiviral efficacy[7,8]. The usage of chlorhexidine mouthwash versus Povidone iodine mouthwash provides

similar antiviral efficacy. (MD = 1.74, 95% CI -.1.35 – 4.84, p = 0.42). An insignificant Q statistic (p = 0.27) indicated the absence of heterogeneity (I2 =0%).

Methodological quality of the included studies

All the four studies which were included for the final review were double- blinded Randomised controlled trials with povidone iodine as control group and chlorhexidine mouthwash as interventional group. The selected articles were published between 2020 and 2021 where the clinical trials done in the hospital setting.

5. Discussion

Covid-19, a global disease, affected millions of people worldwide. It is a respiratory disorder and it's highly infectious which mainly spreads through salivary droplets produced by coughing, sneezing and even talking. In order to curb the risk of transmission mainly for healthcare professionals, many strategies have been implemented [9, 10]. One such recommendation from dental professionals is the usage of antimicrobial mouthwash such as 0.2% Chlorhexidine mouthwash and 1% Povidone iodine as it reduces the viral load of SARS CoV-2[11,12]. Therefore, a systematic review with meta-analysis has been done to analyze the anti-viral efficacy of Chlorhexidine mouthwash over Povidone iodine.

Overall, in the four randomized control trials included in the meta-analysis, it is demonstrated that patients receiving antimicrobial mouthwash have an significant decrease in the viral load. Though both chlorhexidine mouthwash and povidone iodine mouthwash have good outcome in antiviral efficacy [13, 14], it shows equal results in reducing the viral load. (MD = 1.74, 95% CI -.1.35 – 4.84, p = 0.42). An insignificant Q statistic (p = 0.27) indicated the absence of heterogeneity (I2 =0%).

Moreover, the use of mouthwashes with anti-viral properties can be more beneficial for health care workers especially for the Dental professionals who are at risk [15, 16]. Pre-procedural mouthwash can potentially decrease the viral load and hence the risk of cross-contamination will be low [17-20].

Even though our study has a positive aspect of having higher quality of double blinded randomized control trial, it also has its own limitation since the sample size is less and only four trials were included.

6. Conclusion

Use of anti microbial mouthwash in covid-19 patients is essential mainly for health care providers. The results of our Meta-analysis shows that Chlorhexidine mouthwash and povidone iodine produces antiviral efficacy equally and shows decrease in viral load in post treatment population in both control and interventional groups. Even though it has similar properties as antiviral, both the mouthwash are effective in reducing viral load in the oral cavity. Despite the promising results, more such researches are needed in future to manage viral infections especially in dental settings.

7. Footnotes

Author contributions

Drs Geetha R and Karthik Ragupathy S R had a full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Drs Mohan R and Mary JJF analysed and did data interpretation. Dr Sanjay P and Dr Krithika sivaranjani contributed equally.

Study concept, design and methodology: Geetha R, Karthik Ragupathy S R

Data collection and entry of the data: Sanjay P, Kiruthika Shriranjani

Analysis and interpretation of data: Geetha R, Kiruthika Shriranjani

Drafting of the manuscript: Kiruthika Shriranjani

Critical revision of the manuscript and supervision: Sanjay P

Statistical analysis: Geetha R

Administrative, technical, or material support: Sanjay P, Kiruthika Shriranjani

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Tables and Figures

Table 1: Characteristics of included studies and outcome

Sl. NO.	First Author	Year of publication	Journal	Study setting	Study design	Blinding	Study period	Study population	Sampling strategy	Intervention group	Type of comparator	Type of analysis (PP/ITT)	Intervention (mean and SD or median (IQR))	Control (mean and SD or median (IQR))	Intervention	Control	Pre treatment viral load	Post treatment viral load	Pre treatment viral load	Post treatment viral load
1	Denis Damiao Costa *et al.*	2021	Oral Diseases	Hospital	A randomized controlled clinical trial	Double blind	2 Months	Adults	Randomization	Chlorhexidine gluconate	Placebo	Not mentioned	40.5(13.48)	38.48(11.89)	50	50	2.19(4.30)	2.45(3.88)	0.40(3.87)	0.76(4.41)
2	Farmaha JK *et al.*	2022	British Dental Journal	Hospital	A randomized controlled trial	Double blind	5 Months	Adults	Randomization	Chlorhexidine gluconate	Povidone Iodine	Not mentioned	38.8(8.1)	41.9(10.8)	6	8	16.4(22.5)	53.8(32.8)	11.9(14.7)	43.9(32.0)
3	Fantozzi PJ *et al.*	2021	American Journal of Otolaryngology--Head and Neck Medicine and Surgery	Hospital	A prospective randomized placebo-controlled pilot study	Double blind	6 Months	Adults	Randomization	Chlorhexidine gluconate	Povidone Iodine	Not mentioned	24.7 (5.3)	24. I (5.1)	8	8	34.9	33.9	36.3	38.8
4	Rola Elzein *et al.*	2020	The Journal of Evidence-based Dental Practice	Hospital	A randomized controlled trial	Double blind	4 Months	Adults	Randomization	Chlorhexidine gluconate	Povidone Iodine	Not mentioned	47(15.4)	39.9(14.2)	25	27	27.69(7.16)	33.9(7.08)	29.88(6.2)	34.36(6.3)

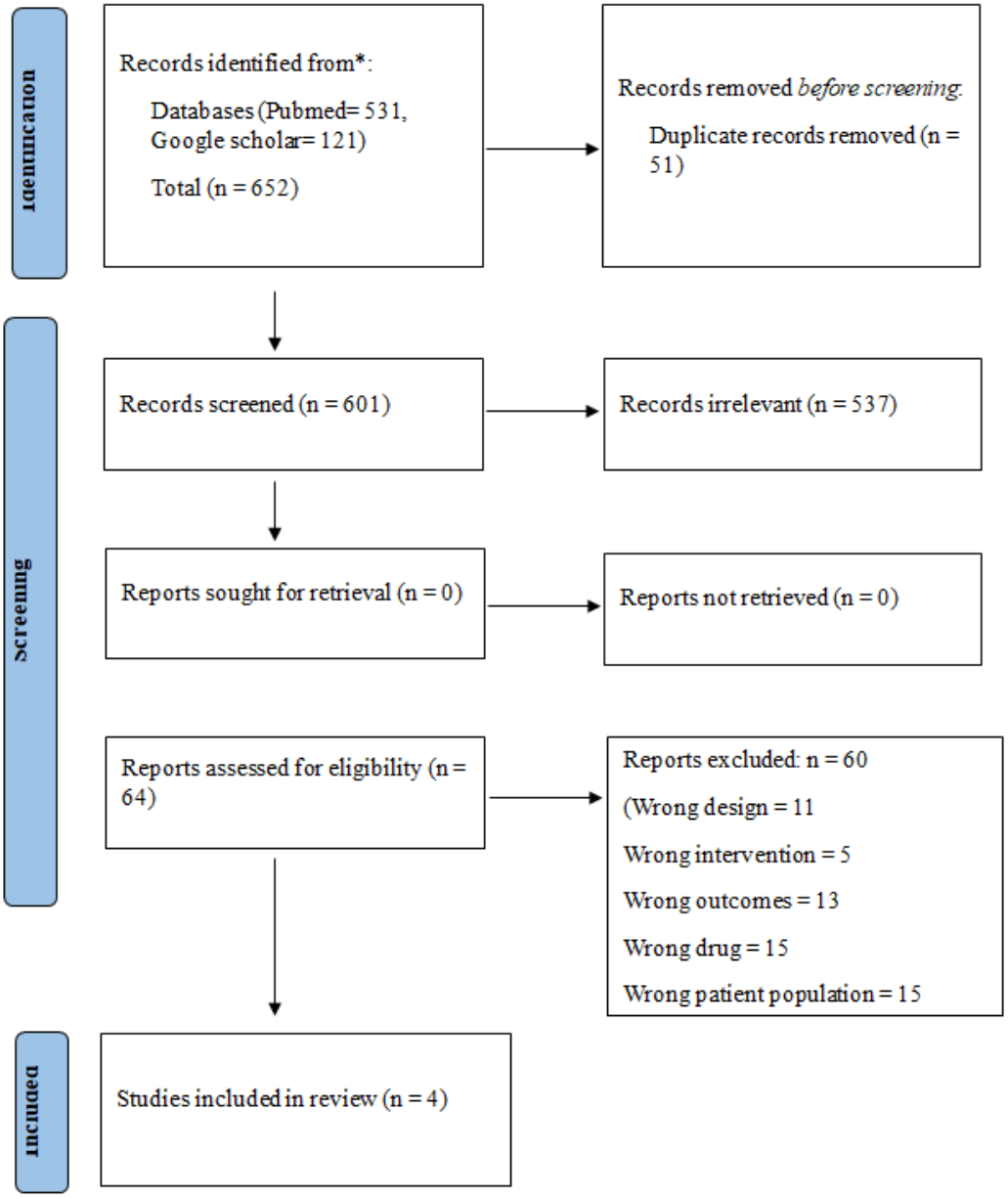

Fig 1 - PRISMA flow diagram of the study selection process

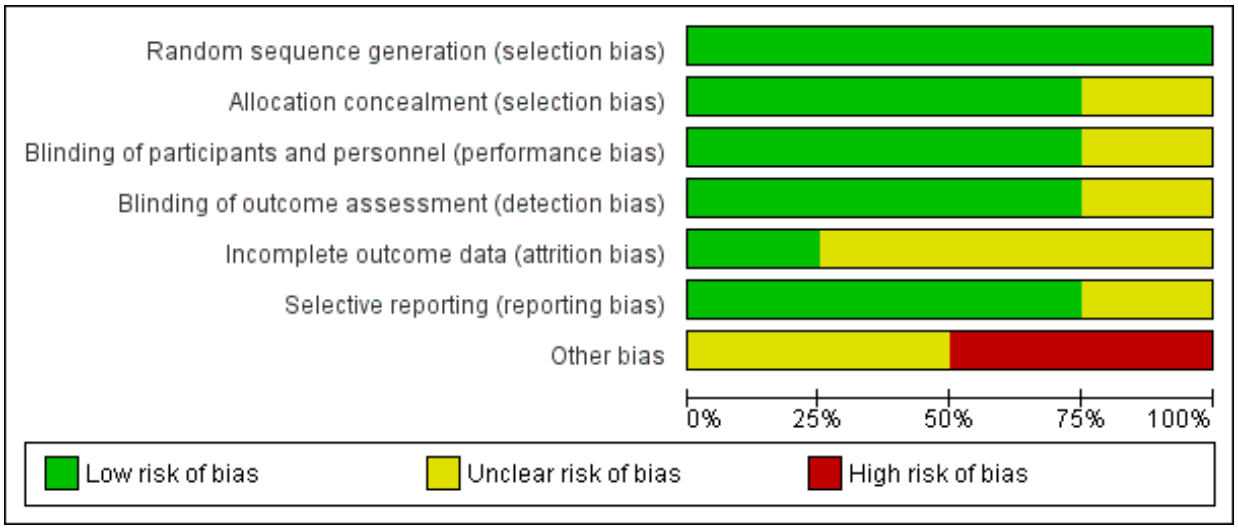

Figure 2: Risk of bias

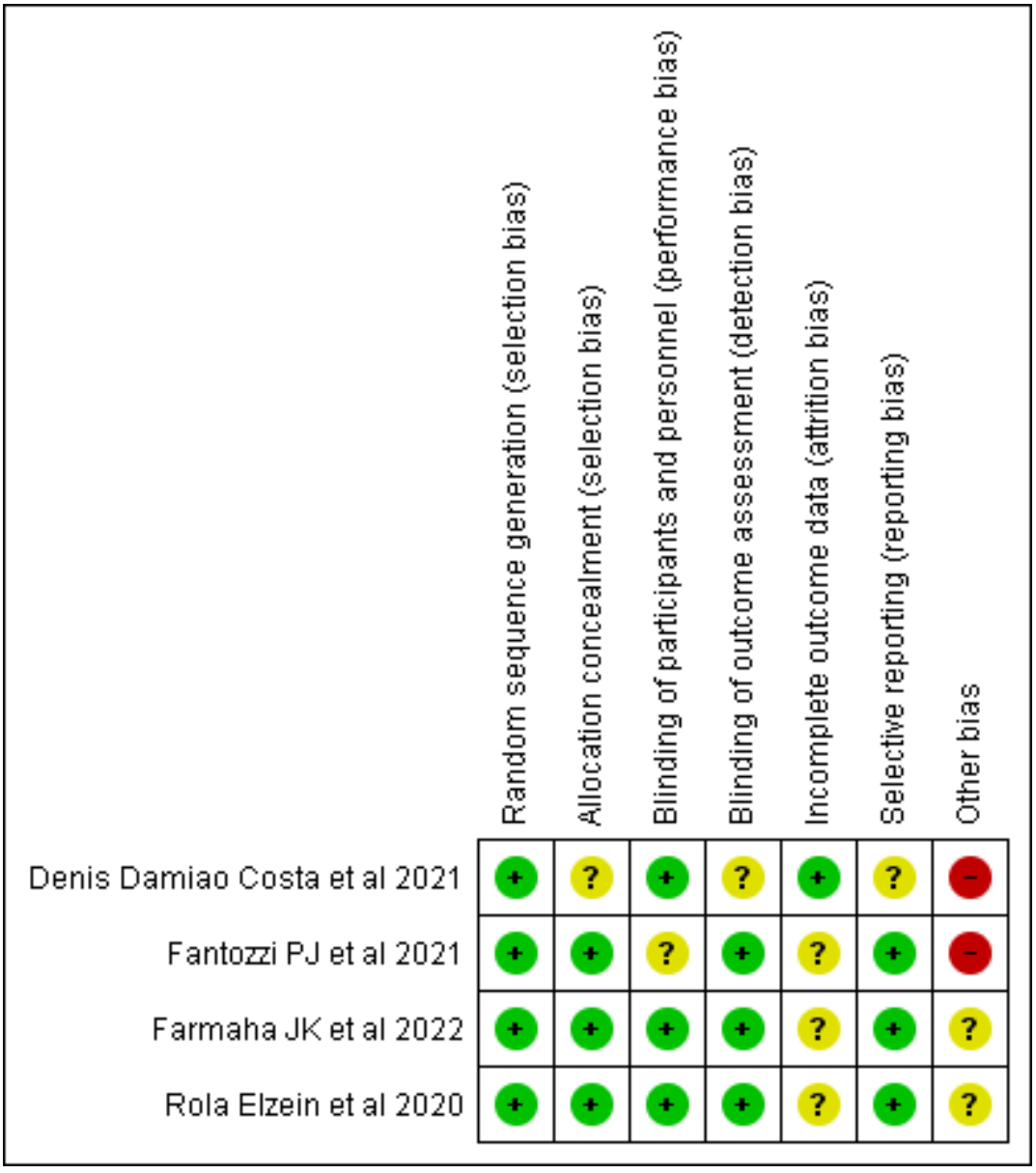

Figure 3: Summary

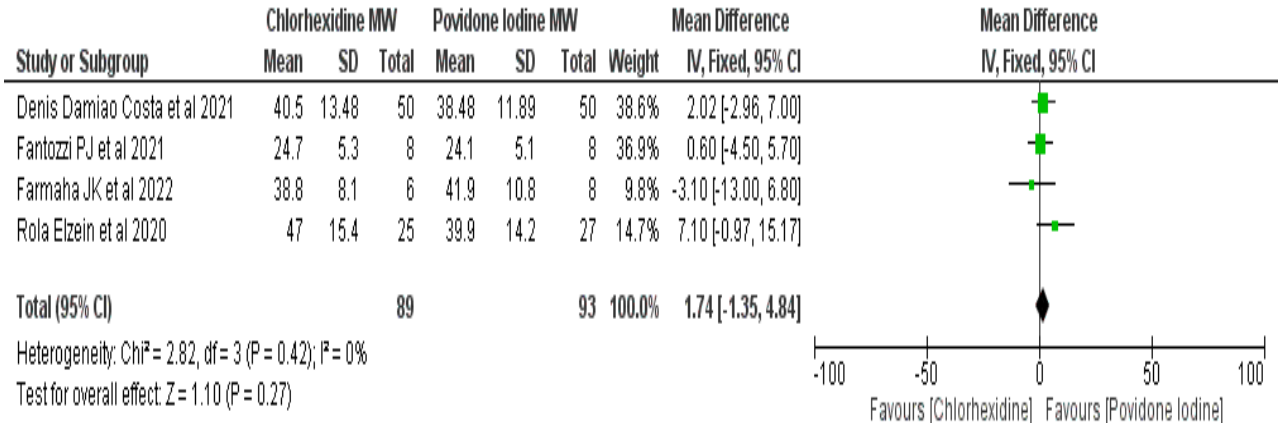

Figure 4: Forest plot