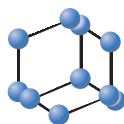


## SYSTEMATIC REVIEW ARTICLE


**BENTHAM  
SCIENCE**

## Effects of Chlorine Dioxide on Oral Hygiene - A Systematic Review and Meta-analysis



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**Abstract: Background:** Effective and selective oral rinses are required in the daily medical and dental practice. Currently mouthwashes used have substantial side effects.

**Objectives:** Our aim was to evaluate the efficacy of chlorine dioxide-containing mouthwashes in comparison with other previously established mouth rinses in healthy adults using oral hygiene indices.

**Methods:** This work was registered in PROSPERO (CRD42018099059) and carried out using multiple databases and reported according to the PRISMA statement. The search terms used were “chlorine dioxide” AND “oral”, and only randomised controlled trials (RCTs) were included. The primary outcome was the alteration of the plaque index (PI), while the secondary outcomes were the gingival index (GI) and bacterial counts. For the risk of bias assessment, the Cochrane Risk of Bias Tool was used. Statistical analysis for data heterogeneity was performed by Q-value and I<sup>2</sup>-tests.

**Results:** 364 articles were found in the databases. After the selection process, only five RCTs were eligible for meta-analysis. Data heterogeneity was low. There were no statistical differences in effectiveness between chlorine dioxide and other effective mouth rinses in PI (0.720±0.119 vs 0.745±0.131; 95% confidence intervals (CIs): 0.487-0.952 vs 0.489-1.001, respectively) and GI (0.712±0.130 vs 0.745±0.131; 95% CIs: 0.457-0.967 vs 0.489-1.001, respectively) and also in bacterial counts.

**Conclusion:** Chlorine dioxide reduces both plaque and gingival indices and bacterial counts in the oral cavity similar to other routinely used oral rinses, however, the evidence supporting this outcome is very limited. Therefore, further large scale RCTs are needed to decrease the risk of bias.

### ARTICLE HISTORY

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### 1. INTRODUCTION

Good oral hygiene is a key factor in the maintenance of oral health. In healthy conditions, the primary elements serving maintenance of oral health are the antimicrobial and acid neutralization components of saliva [1-5]. However, to maintain healthy conditions in the mouth, additional instruments and substances are needed, especially during the onset of gingivitis and consequently periodontitis [6-11]. The maintenance of good oral hygiene can be challenging for most patients. In the tooth-cleaning process, besides tooth-brushing, other cleaning devices and mouthwashes are also frequently used. Mouthwashes can inhibit the development and maturation of dental plaque, which is a key causative factor in the formation of dental caries, and is also involved in the inflammatory process leading to gingivitis and periodontitis [12, 13].

Mouthwashes usually contain antimicrobial agents. Among them, chlorhexidine is regarded to be the gold standard nowadays. [14] However, chlorhexidine might not be the best possible option [15], since chlorhexidine-containing mouthwashes cause substantial

side effects [16], including teeth and tongue surface discoloration [17-19], disturbances in taste sensation [20-22], and also mucosal irritation and burning sensation [23]. Because of these side effects, researchers have been testing other effective alternatives such as aloe vera [24], green tea [25] and essential oils [26, 27] to substitute chlorhexidine.

A novel, recently emerging oral disinfectant is chlorine dioxide. Its application in dental waterline is well accepted for infection control [28]. Its solution is also used for the disinfection of surgical [29, 30] and dental instruments [31]. Its antibacterial effects were also demonstrated, applying it as a gas in the air of dental offices [32]. Additionally, in the last decade, the direct dental application of chlorine dioxide has gained substantial interest. The compound was investigated as a root canal irrigant *in vitro* [33-39]. The whitening effect of chlorine dioxide was evaluated *in vitro* [40] and *in vivo* [41, 42]. Its wound-healing action was also suggested [43, 44]. Besides its very strong antibacterial effects, its effects on eukaryotic cells are very mild. Cell viability tests demonstrated that it is toxic only in very high concentrations, for human gingival fibroblasts [45-47].

The effect of chlorine dioxide was investigated in halitosis. Halitosis is an oral malodor caused by oral bacteria [48] that can break down sulfur-containing proteins and volatile sulphur com-

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pounds. Therefore, these bacteria are responsible for the formation of unpleasant odor [49]. Chlorine dioxide was shown to inhibit the growth of bacteria involved in the formation of halitosis [50-52].

Therefore, based on the above described information, the aim of the present systematic review and meta-analysis was to investigate the efficacy and safety of chlorine dioxide on oral hygiene based on randomised controlled trials (RCTs). Our goal was to compare the effect of chlorine dioxide and other routinely used disinfectants against oral hygiene indices such as gingival index, plaque index, modified Winkel Tongue Coating Index and bacterial counts.

## 2. MATERIALS AND METHODS

The following PICO (patients, intervention, comparison, outcome) format was applied: P: healthy adults; I: chlorine dioxide-containing mouthwashes; C: other, routinely used mouth rinses used in dental practice; and O: changes in index values (Plaque Index [53], Gingival Index [54], and modified Winkel Tongue Coating Index [55, 56]) for oral hygiene. In the outcome, our plan included the examination of microbes most commonly occurring in the oral cavity (cariogenic bacteria such as *Streptococcus mutans*, *Lactobacilli*; periodontal pathogenic bacteria such as *Tannerella forsythia*, *Fusobacterium nucleatum*, fungi - *Candida albicans*).

### 2.1. Protocol and Registration

Our systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) Statement [57]. The protocol was registered in International Prospective Register of Systematic Reviews (PROSPERO) a priori with the registration number CRD42018099059.

### 2.2. Information Sources and Search Strategy

Literature search was conducted until 31st May, 2019, using the following search strategy: for MEDLINE (via PubMed); in Title Abstract Keyword for Cochrane Central Register of Controlled Trials (CENTRAL); Web of Science, ClinicalTrials.gov., Ebsco, Scopus. No language, publication date or publication status restrictions were applied. The reference lists of all identified articles were inspected for further possible eligible studies (Table 1).

**Table 1. Search terms in different databases.**

<u>PubMed</u>
("chlorine dioxide"[Supplementary Concept] OR "chlorine dioxide"[All Fields]) AND ("mouth"[MeSH Terms] OR "mouth"[All Fields] OR "oral"[All Fields])
<u>Scopus</u>
(( <i>chlorine</i> AND <i>dioxide</i> ) AND <i>oral</i> )
<u>Web of Science</u>
(( <i>chlorine dioxide</i> ) AND <i>oral</i> )
<u>EBSCO</u>
( <i>chlorine dioxide</i> ) AND <i>oral</i>
<u>Clinicaltrials.gov</u>
"chlorine dioxide" AND "oral"
<u>EMBASE</u>
'chlorine dioxide' AND oral
<u>Cochran Library</u>
'chlorine dioxide' and oral in Title, Abstract, Keywords in Trials'

### 2.3. Eligibility Criteria and Study Selection

Randomized, placebo-controlled trials evaluating the effects of chlorine dioxide-containing mouthwashes in adult patients with mild-to-moderate gingivitis were included. Abstracts, case series,

case reports were excluded. The EndNote X6 software was used for record management. After removing duplicates, the remaining records were screened for eligibility based on the title at first and in the second round on the abstracts. Inclusion criteria were randomized controlled trials, healthy patients without periodontal problems, except gingivitis. We investigated plaque index (PI) and gingival index (GI) and also the number of bacterial colonies before and days or weeks after the application of oral rinsing solutions. Exclusion criteria involved the following: *in vitro* models, studies not investigating the oral cavity, hypochlorous acid application, studies on volatile sulphur compounds, investigations on chlorine dioxide applied for dental waterline disinfection, reviews and abstracts with not available detailed results. The adequacy of the full texts to the eligibility criteria was investigated by two independent authors. Disagreements between two reviewers were resolved by discussion (BK, LMC) or, if it was impossible, they were consulted with the third reviewer (GV).

### 2.4. Data Collection Process

The following data items were extracted from the included papers: study design, characteristics of the patient population and sample size, intervention details, type of comparator(s), outcome measures and overall results. PI (based on Silness-Löe or other), (GI) (based on Löe-Silness or other), sulcular bleeding index, modified Winkel tongue-coating index, and a number of bacteria such as *Streptococcus mutans*, *Tannerella forsythia*, *Fusobacterium nucleatum*, *Lactobacilli* were extracted as outcomes.

### 2.5. Risk of Bias in Individual Studies

For risk of bias assessment the Cochrane Risk of Bias Tool was used which includes the following domains: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias) and other potential bias [58]. Disagreements between two independent reviewers for quality of studies were resolved by discussion. Risks of bias graph and bias summary were generated by Review Manager 5.3 software.

### 2.6. Statistical Analyses and Synthesis of Results

To compare the effect of the different oral rising agents, we calculated standardized differences in means in case of all eligible outcomes. We pooled those articles, where the mean values with standard deviation at the baseline and the end of the investigation, and also the corresponding p-values were available. If there were more time-point values, we used the latest one.

Heterogeneity was tested by Q-value and I-squared tests [58, 59]. Random effect model by DerSimonian and Laird [60] was used for all meta-analytical calculations as described previously [61, 62]. Results of the meta-analysis were displayed graphically using Forest plots. Data analysis was performed with Comprehensive MetaAnalysis software Version3 provided by the Biostat Inc., Engelwood, MJ, USA.

## 3. RESULTS

### 3.1. Study Selection

The literature search was conducted through the Cochrane Central Register of Controlled Trials (n=24), ClinicalTrials.gov (n=13), Ebsco (n=25), EMBASE (n=87), PubMed (n=85), Scopus (n=96), Web of Science (n=46). 376 articles were imported to the EndNote Program. After removing duplicates, the search yielded a total of 153 potentially relevant reports. After screening titles and abstracts, 20 publications remained, from which 14 articles were excluded due to lack of randomization.

Among these, one study applied a bacterial viability test, which was fundamentally different from our outcome (oral hygiene tests)

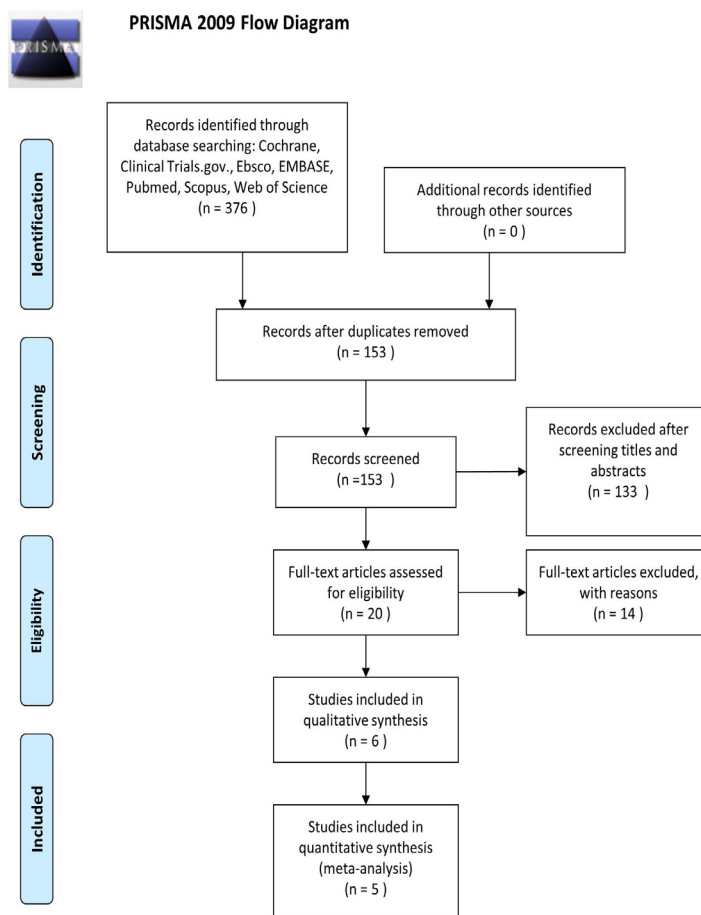


Fig. (1). PRISMA 2009 flow diagram for identification of relevant studies.

[63], another study did not cover our aim [12], one described the antibacterial mouth rinses, but without any quantitative data [64]. Two studies assessed acidified sodium chlorite, not chlorine dioxide [65, 66], two others measured *Candida albicans* count [67, 68]; one investigated denture wearing population [69], one investigated patients with periodontal pockets [70]. Two papers were reviews [71, 72]. One used very distinctive index types [73]. Lastly, one work was excluded because of its fundamentally distinctive study protocol (a plaque regrowth model was applied in this study) [14].

Furthermore, out of the six selected studies, we had to exclude one more article as it was not an RCT and some crucial data were missing from that article [74]. Finally, five articles were eligible for systematic review and meta-analysis [75-79] (Fig. 1).

### 3.2. Characteristics of the Included Studies

One work was placebo controlled [78], another one used physiological saline as control [79] (i.e. having negative controls) and two other studies used herbal mouthwash [75], aloe vera and chlorhexidine [76] as positive controls. One investigation had a parallel design of which we only used the chlorine dioxide group in our work [77]. All of these five randomized trials were included in the quantitative analysis (Table 2).

### 3.3. Risk of Bias within Studies

During Risk of Bias assessment, we tested the quality of randomization, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other scores of bias. The evaluated publications could receive 3 qualifications for each question: low (green), unclear (yellow) and high (red) risk of bias. The risk of

bias assessment graph (Fig. 2) and summary (Fig. 3) shows the results.

The methodological quality of the included trials was acceptable, mostly with low or unclear risk of bias. All studies described the methods of randomization. Pham and coworkers performed a double-blind, crossover study [79]. Randomization was only described partially; therefore, this article has a low risk of bias. In two studies [75, 77], there was no information about allocation concealment, yielding unclear risks of bias. Two studies were single-blinded trials: one had an unclear risk of performance bias [76], the other had a high risk of performance bias [77], because the patients knew which group they belonged to. The blinding of outcome assessment was not described by Yeturu *et al.*; therefore, this study was judged to have an unclear risk of detection bias [76]. Yeturu and coinvestigators lost 5 participants in the follow-up period due to noncompliance of high risk [76], while Pham and coworkers lost only one patient so the attrition bias was unclear [79]. One paper was judged to have unclear risk as it did not have a registration number as a clinical trial [75]. Finally, another study had a high risk of reporting bias because some participants noted side effects in their diaries [78]. There was no other identified bias.

### 3.4. Results of Individual Studies

Altogether 201 patients were included in the qualitative analysis. The demographic data of participants reported no significant difference, all patients were healthy young people with normal gingiva or only moderate gingivitis. In two studies, the participants were males [77, 78]. Females were excluded by Shinada *et al.*, because “their menstrual cycle might affect oral malodour”, which was investigated in this publication [78]. The volunteers in the

Table 2. Included studies characteristics.

Publication Data				Demography							Care Product	Main Content	Investigated Parameters
First Author	Year of Publication	Design	Country	Population	Age (years)			Sex (Female/Male)	N <sup>o</sup> of Patients	N <sup>o</sup> of Patients/Groups			
					Mean	SD	Range						
Pham	2018	RCT, double-blind, crossover	Vietnam	healthy students with malodour	-	-	19-23	19/20	39	17	TheraBreath	0.1% chlorine dioxide	SL PI, LS GI, mWtci, T.f., F.n., P.g., T.d.
					-	-				22	placebo	0.9% sodium chloride	
Siddeshappa	2018	RCT, double-blind,	India	mild to moderate gingivitis	-	-	20-50	16/24	40	20	HiOra	Herbal mouth-wash	SL PI, LS GI, SBI, S.m., T.f., F.n.
					-	-				20	Freshlore	chlorine dioxide	
Yeturu	2016	RCT, single-blind, parallel	India	undergoing fix orthodontic treatment (mild to moderate gingivitis)	21,53	3,41	-	18/12	85	30	-	aloe vera	SL PI, LS GI,
					21,72	4,67	-	11/14		25	-	chlorhexidine	
					21,7	3,01	-	16/14		30	Freshlore	chlorine dioxide	
Aung	2015	RCT, single-blind, parallel	Japan	healthy	19,8	2,9	-	0/30	30	15	Fresh	chlorine dioxide	SL PI, SBI, mWtci,
Shinada	2010	RCT, double-blind, crossover	Japan	healthy	22,9	6,2	19-38	0/15	15	8	Clo2 Fresh	0.1% chlorine dioxide	SL PI, LS GI, mWtci, T.f., F.n., P.g., T.d.
										7	-	placebo	

RCT: randomised clinical trials; SL PI: Silness-Löe Plaque index; LS GI: Löe-Silness Gingival index; SBI: sulcular bleeding index; mWtci: modified Winkel tongue coating index; T.f.: *Tannerella forsythia*, F.n.: *Fusobacterium nucleatum*; P.g.: *Prphyromonas gingivalis*, T.d.: *Treponema denticola*; S.m.: *Streptococcus mutans*; SD: standard deviation.

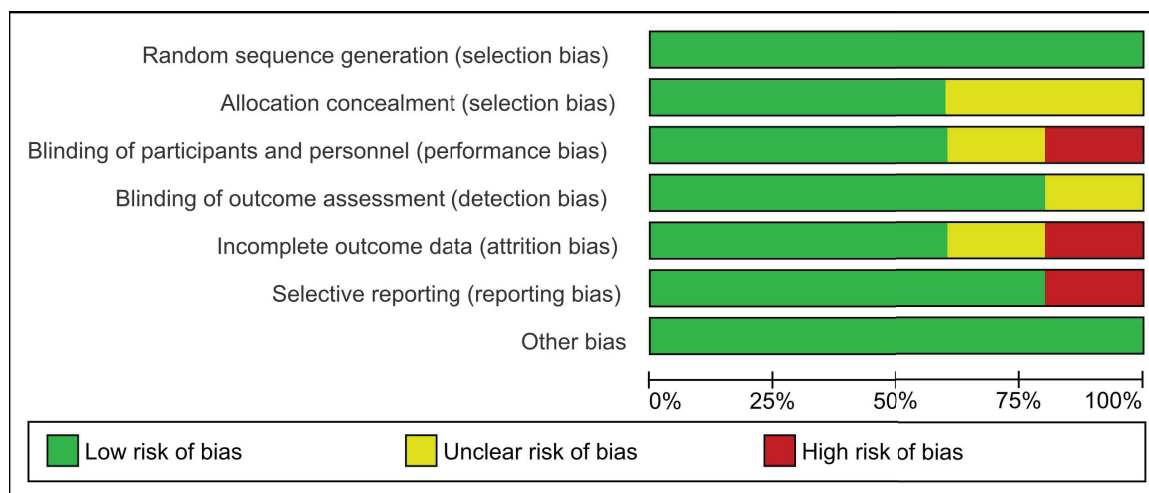


Fig. (2). Risk of Bias graph.

Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

study of Aung *et al.* were monks [77]. Altogether 112 participants received chlorine dioxide, 50 got herbal (20) or aloe vera (30) treatments, and 25 participants chlorhexidine containing oral rinses and, finally, only 7 participants received placebo mouth rinse, while 39 participants got physiological saline. Data (see below) were obtained before and after the use of mouth rinses. The length of

outcome period varied among studies. Siddeshappa *et al.* and Aung *et al.* carried out measurements on the 7<sup>th</sup>, 14<sup>th</sup> and 21<sup>st</sup> days after treatment initiation [75, 77]. Pham *et al.* collected data on the 14<sup>th</sup> day [79], Yeturu *et al.* on the 15<sup>th</sup> day, Shinada *et al.* [78] on the 7<sup>th</sup> day. Hence we pooled and analyzed data before treatment and after treatment irrespective of the duration of treatments.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Aung 2015	+	?	-	+	+	+	+
Pham 2018	+	+	+	+	?	+	+
Shinada 2010	+	+	+	+	+	-	+
Siddeshappa 2018	+	?	+	+	+	+	+
Yeturu 2016	+	+	?	?	-	+	+

Fig. (3). Risk of bias summary.

Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Our primary outcome was PI, the secondary outcome was GI, and tertiary outcome was tongue-coating index modified by Winkel. For the description of oral hygiene, the Silness-Löe PI and Löe-Silness GI were used in four articles [75, 76, 78, 79], Aung *et al.* applied the debris index of the Oral Hygiene Index and, for the description of gingival inflammation, bleeding on probing index [77]. Because bleeding on probing index is not comparable with GI, we could not calculate on these results as secondary outcomes. As a result of the different measurement ways, we could only calculate the standardized difference in means and 95% confidence interval, but not the overall effect. Three articles investigated the tongue-coating index modified by Winkel [77-79].

We created two subgroups on the control side. The placebo and physiological saline treatment groups served as negative controls, while the established effective mouth rinses (chlorhexidine, aloe vera and herbal extract) served as positive controls. The data heterogeneity might not be important, ranging 0 to 33% in the various subgroups, suggesting that the data were homogeneous. Because the number of the involved papers was low, neither the Q value nor p value was calculated.

The alteration of PI was investigated comparing chlorine dioxide treatment to the positive controls (chlorhexidine, aloe vera and herbal extracts) and the negative controls (placebo and physiological saline). There was no statistical difference between the chlorine dioxide and the positive control, but the PIs in both groups were statistically different from the negative control values. Standardized

difference in means ± standard error was 0.720 ± 0.119 vs 0.745 ± 0.131 (chlorine dioxide vs positive control) vs 0.049 ± 0.186 (negative control) (p<0.01). 95% CIs were 0.487–0.952 vs 0.489–1.001 (chlorine dioxide vs positive control) vs -0.315–0.413 (negative control) (Fig. 4).

Regarding the secondary outcome, GI was investigated comparing chlorine dioxide treatment again to the positive controls (chlorhexidine, aloe vera and herbal extracts) and the negative controls (placebo and physiological saline), similar to PI evaluation. In GI, there was no statistical difference between the chlorine dioxide treatments and the positive control treatments. Additionally, GI values were statistically not different for either the chlorine dioxide treated or the positive control group *versus* the negative control group values, only some tendencies for changes could be observed. The difference in means ± standard error was 0.712 ± 0.130 vs 0.745 ± 0.131 (chlorine dioxide group vs positive control) vs 0.267 ± 0.189 (negative control). The 95% confidence intervals were 0.457-0.967 vs 0.489–1.001 (chlorine dioxide group vs positive control) vs -0.103–0.638 (negative control) (Fig. 5).

In the case of the third outcome, tongue-coating index, modified by Winkel, only the chlorine dioxide treated group and the negative controls could be compared for the lack of comparable data of the positive controls, chlorhexidine, aloe vera and herbal extracts. Here we found no statistical difference between the chlorine dioxide and the negative control groups, means ± standard errors were 0.880 ± 0.240 vs 0.618 ± 0.282 (chlorine dioxide group vs placebo group) (p>0.05). The 95% confidence intervals were 0.410–1.350 vs 0.065–1.172 (chlorine dioxide group vs placebo group) (Fig. 6).

The reported microbial results were not enough for complex statistical analysis but we could present the data on forest plots. The *Tannerella forsythia* (*T.f.*) counts were investigated after the use of chlorine dioxide or positive controls (chlorhexidine, aloe vera and herbal extracts) or negative controls (placebo, physiological saline) mouth rinsing. No statistical difference was found between either group. Standardized difference in means ± standard error was 0.772 ± 0.172 vs 0.868 ± 0.263 (chlorine dioxide group vs positive control) vs 0.104 ± 0.188 (negative control). 95% CIs were 0.434–1.110 vs 0.353–1.384 (chlorine dioxide group vs positive control) vs -0.264–0.472 (negative control) (Fig. 7). The confidence intervals of the negative control group overlapped with the results of the chlorine dioxide treated group and the positive controls, but the tendency for changes can be seen (Fig. 7). When *Fusobacterium nucleatum* (*F.n.*) counts were investigated, no statistical difference was found between the chlorine dioxide group and the positive or negative controls. Standardized difference in means ± standard error was 0.978 ± 0.182 vs 0.868 ± 0.262 (chlorine dioxide group vs positive control) vs 0.120 ± 0.187 (negative control). The 95% CIs were 0.621–1.334 vs 0.354–1.383 (chlorine dioxide group vs positive control) vs -0.246–0.487 (placebo group) (Fig. 8).

A single study described that colony forming unit (CFU) counts of *Streptococcus mutans* (*Str. m.*) decreased significantly in the chlorine dioxide group and in the one treated with herbal mouth wash stated in the study of Shideshappa [75]. Chlorine dioxide induced a decrease in bacterial counts from 16.7 × 10<sup>2</sup> to 12.1 × 10<sup>2</sup> CFU (SD: 1.36506, p<0.001), while a herbal mouth rinse evoked a decrease from 17.6 × 10<sup>2</sup> to 10.1 × 10<sup>2</sup> CFU (SD: 1.38506, p<0.001). On the other hand, *Porphyromonas gingivalis* and *Treponema denticola* counts did not change significantly in response to similar treatments in two studies [75, 78].

Adverse effects were not investigated quantitatively in our systematic review and meta-analysis, because the articles did not report them, except the paper of Shinada and coworkers in which three out of the 15 involved participants in the chlorine dioxide group had disturbances in taste and smell sensation [78].



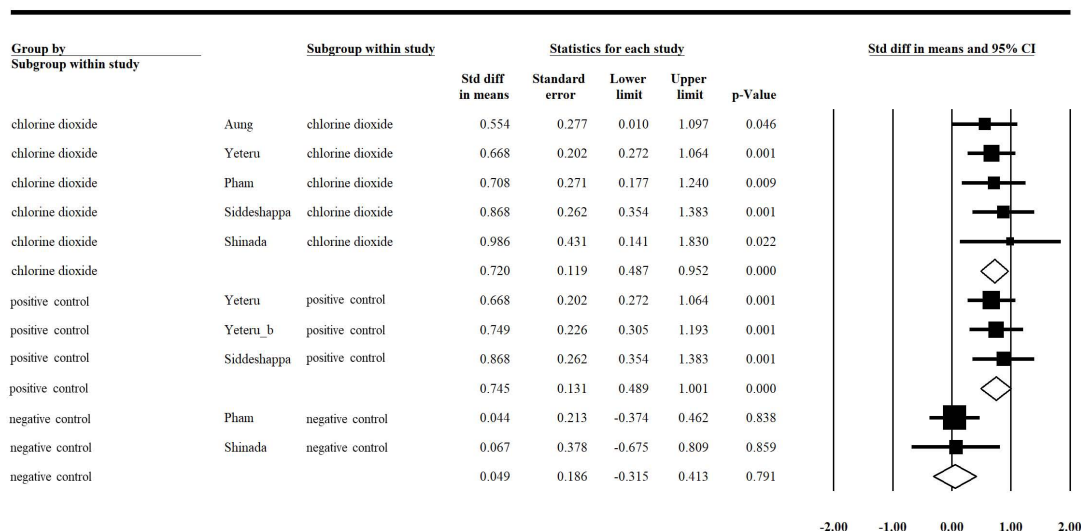


Fig. (4). Plaque index alteration between the chlorine dioxide, other effective treatments and placebo group. Standardized difference in means ± standard error with 95% CI.

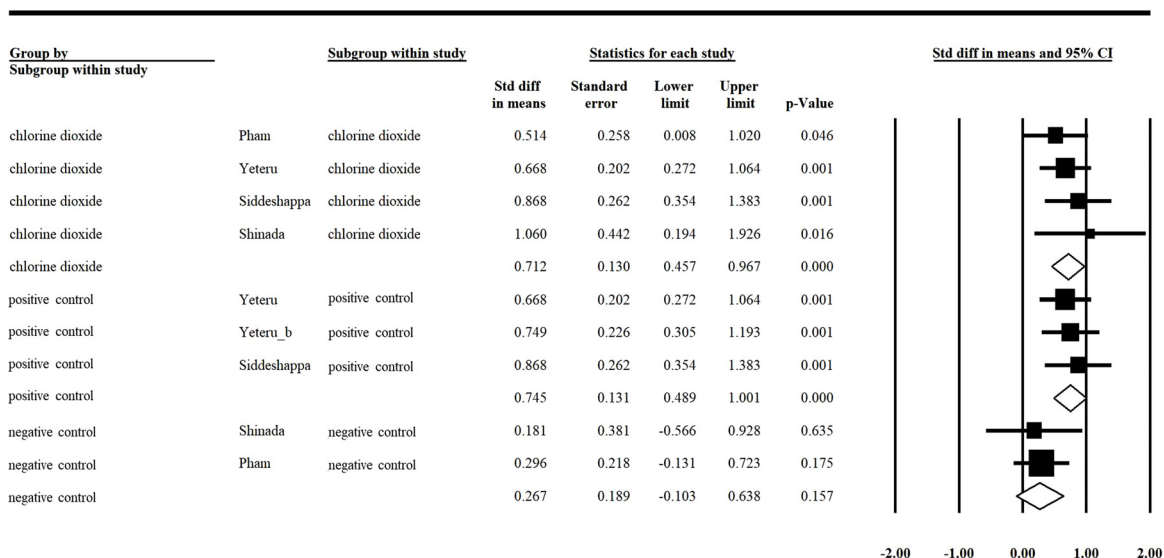


Fig. (5). Gingival index alteration between the chlorine dioxide, other effective treatments and placebo group. Standardized difference in means ± standard error with 95% CI.

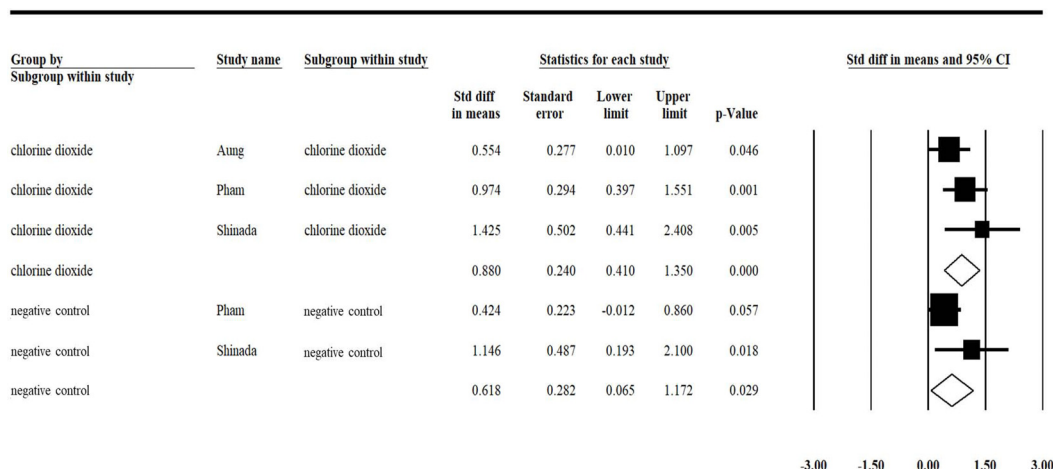


Fig. (6). Tongue coating index modified by Winkel alteration between the chlorine dioxide, other effective treatments and placebo group. Standardized difference in means ± standard error with 95% CI.

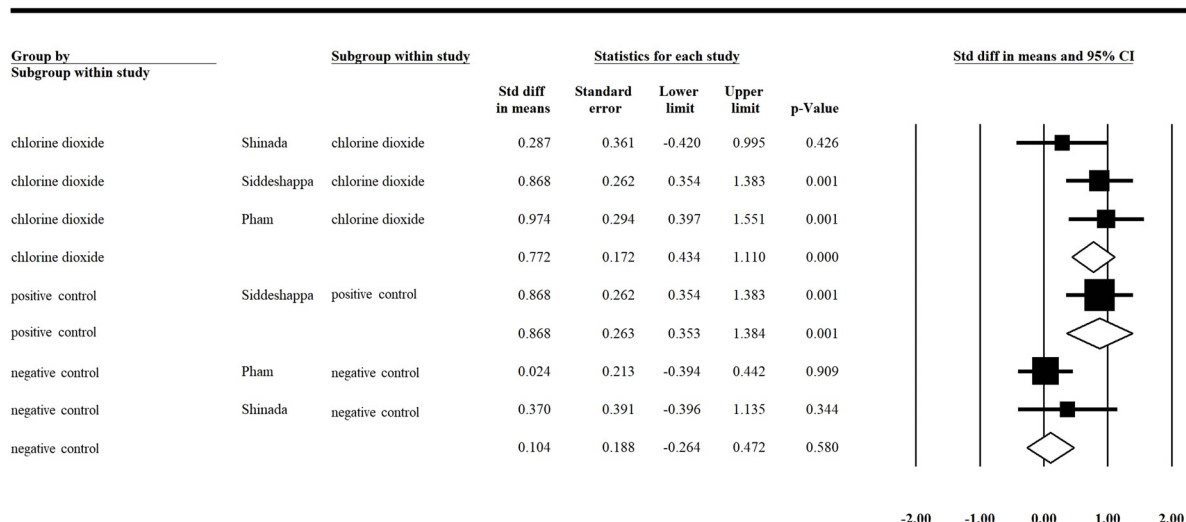


Fig. (7). *Tannerella forsythia* count alteration between the chlorine dioxide, other effective treatments and placebo group. Standardized difference in means ± standard error with 95% CI.

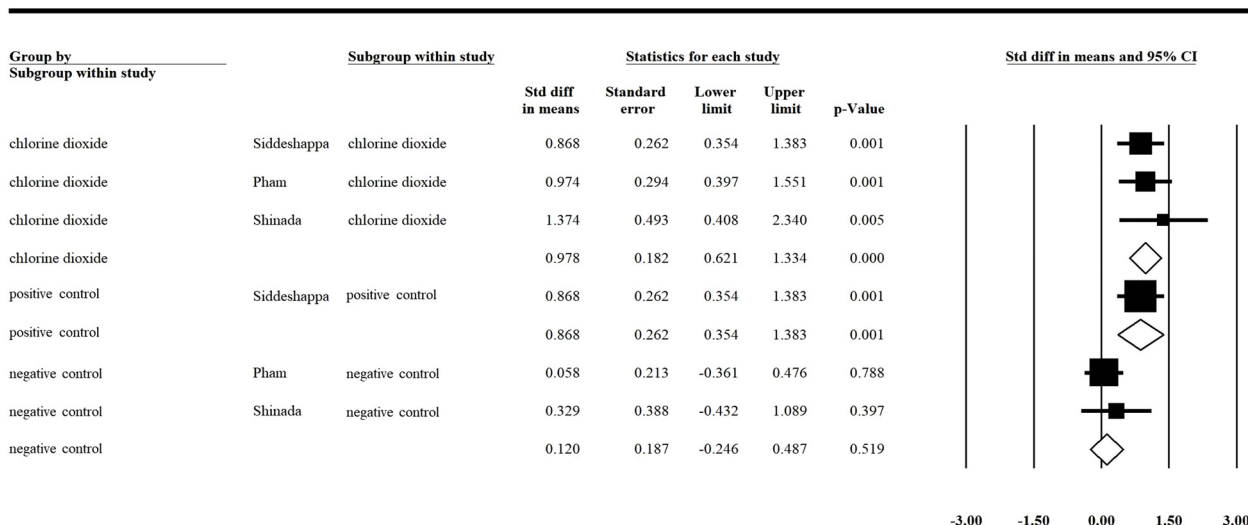


Fig. (8). *Fusobacterium nucleatum* count alteration between the chlorine dioxide, other effective treatments and placebo group. Standardized difference in means ± standard error with 95% CI.

4. DISCUSSION

Up till now, no meta-analysis or systematic review has investigated the possible effects of chlorine dioxide on oral hygiene. Only one qualitative review was published focusing on the effect of chlorine dioxide on halitosis [50]. In the present work, we performed a systematic review. The low number of high quality RCTs did not permit to perform a full scale meta-analysis on all parameters investigated. Our data clearly suggested that chlorine dioxide has a very similar effect on oral hygiene as other, well established mouthwashes containing chlorhexidine, aloe vera and herbal extracts, which were used as positive controls in the present work. This is in line with those basic findings of the five included RCTs [75-79], but in contrast to the work of Paraskevas and coworkers who found that chlorine dioxide was less effective than chlorhexidine based on the alteration in plaque index PI after a very short period of time, only 3 days of use [73]. On the other hand, *in vitro* studies demonstrated that chlorine dioxide was, in fact, more effective than chlorhexidine, when chlorine dioxide was applied as a root canal irrigant [33, 36-38, 80]. These positive *in vitro* results support our present findings.

Chlorine dioxide is well soluble in water and penetrates well through biofilms [74, 81]. It has antibacterial, antiviral and antifungal properties [14, 74, 81]. Additionally, it is suggested that it has size-selective antimicrobial properties, that is, it is toxic in non-eukaryotic microorganisms in much lower concentrations than in eukaryotic ones [81]. Other similar chlorine containing compounds such as acidified sodium chlorite and chlorous acid were also previously characterized but the potential beneficial effects of those are far behind chlorine dioxide [65, 66, 71].

Chlorhexidine is still widely used as a gold standard in various procedures of dental disinfection [82-85]. Similar efficacy of aloe vera on oral hygiene was also shown by well-designed clinical studies [86, 87]. Likewise, various other herbal extracts have a similar effect on chlorhexidine against plaque formation and oral disinfection [88]. In the present work, when these remedies were pooled together as positive controls, chlorine dioxide proved to be equally effective in oral hygiene as these previously well-established treatments.

#### 4.1. Summary of Evidence

Patient population involved in the included studies represents patients requiring dental treatment. Mild or moderate gingivitis without periodontal involvement is typical for the oral hygiene of an average patient. Patients receiving orthodontic treatment (with fixed braces) have an increased plaque formation risk. This can be explained by the complex surfaces of the fixed devices and the difficulty in cleaning.

#### 4.2. Limitations

Our systematic review and meta-analysis have several limitations. First is the low number of included articles: we found only five eligible RCTs. We included only these controlled studies for our analysis to avoid uncertainties and biases of observational investigations. In these RCTs 201 patients were involved altogether, which is a relatively low number. Second, each included study was performed in Asia, and thus our results in systematic review and meta-analysis based on Asian people only.

Additionally, the duration of the follow-up times was not precisely defined in the individual studies. Our aim was to evaluate the effectiveness of antibacterial agents compared to baseline values. Only “before treatment” and “after treatment” data were examined.

The study designs also varied in the included studies. Aung *et al.* used a parallel study design, they did not have a control group. They investigated the effect of tooth brushing in the 1st week, and subsequently the patients used mouthwash. Therefore, one week’s data were considered to be the starting point, since it preceded the use of mouthwash [77]. Shinada *et al.* used 0.16% (w/w) sodium chloride (NaClO<sub>2</sub>)-containing mouthwash and 0.10% (w/w) chlorine dioxide (ClO<sub>2</sub>) [78]. Aung *et al.* used Fresh® Mouthwash (Bio-Cide International Inc., Oklahoma, USA and Pine Medical Co., Tokyo, Japan), but unfortunately no data are available on the composition of the mouthwash applied [77]. Yeturu *et al.* and Sidde-shappa *et al.* used Freshchlor® (Group Pharmaceuticals Ltd., Bangalore, India) a stabilized chlorine dioxide mouthwash, in which the presence of some unknown additional components is suspected [75, 76]. Pham *et al.* used TheraBreath® Mild Mint Oral Rinse (TheraBreath, Los Angeles, California, USA) containing 0.10% (w/w) chlorine dioxide [79]. Thus, a high level of heterogeneity might influence the strength of our conclusions. The application of compounds was similar in the studies. Participants were rinsed with 10-15ml of solution twice daily (morning and evening) for 30-30 sec, except participants included in the studies by Yeturu *et al.* (1 min rinsing) [76] and Pham *et al.*, where rinsing was followed by 15 sec gargling [79].

#### CONCLUSION

Our systematic review and meta-analysis revealed that chlorine dioxide has similar beneficial effects on oral hygiene as most of the commonly used, established mouthwashes in dentistry. In the included studies, chlorine dioxide had no adverse reactions or considerably fewer than other compounds. Thus, it may serve as a good alternative to chlorhexidine and other presently used antibacterial mouthwashes. Nevertheless, all currently available RCTs [75-79] agreed on the need for more randomized controlled clinical trials with the same or similar design and with longer follow-up time to confirm the evidence regarding the applicability of chlorine dioxide. Our meta-analysis supports the use of chlorine dioxide, however, it highlights the lack of sufficient clinical data regarding its use in dental care.

#### CONSENT FOR PUBLICATION

Not applicable.

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#### CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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