Send orders for print-reprints and e-prints to reprints@benthamscience.net

Current Pharmaceutical Design, **2020**, *26*, 1-11 1

META-ANALYSIS ARTICLE

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

Beáta Kerémi[1], Katalin Márta[2], Kornélia Farkas[2,3], László Márk Czumbel[1], Barbara Tóth[4], Zsolt Szakács[2], Dezső Csupor[4], József Czimmer[5], Zoltán Rumbus[2], Péter Révész[6], Adrienn Németh[6], Gábor Gerber[7], Péter Hegyi[2,8] and Gábor Varga[1]

[1]Depratment of Oral Biology, Faculty of Dentistry, Semmelweis University, Budapest, Hungary; [2]Institute for Translational Medicine, Medical School, University of Pecs, Pecs, Hungary; [3]Institute of Bioanalysis, Medical School, University of Pecs, Pecs, Hungary; [4]Department of Pharmacognosy, Interdisciplinary Excellence Centre, University of Szeged, Szeged, Hungary; [5]Division of Gastroenterology, First Department of Medicine, Medical School, University of Pecs, Pecs, Hungary; [6]Department of Otorhinolaryngology (ENT), Medical School, University of Pecs, Pecs, Hungary; [7]Department of Anatomy, Histology and Embryology, Faculty of Medicine, Semmelweis University, Budapest, Hungary; [8]Szentágothai Research Centre, University of Pecs, Pecs, Hungary

ARTICLE HISTORY

Received: March 6, 2020
Accepted: April 29, 2020

DOI:
10.2174/1381612826666200515134450

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^2-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.

Keywords: Chlorine dioxide, plaque index, gingival index, oral hygiene, mouthwash, systematic review, meta-analysis.

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-

*Address correspondence to this author at the Department of Oral Biology, Semmelweis University, Budapest, Hungary, Nagyvárad tér 4, Budapest 1089, Hungary; Tel: +36-1-210-4415; Fax: +36-1-210-4421;
E-mail: varga.gabor@dent.semmelweis-univ.hu

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, Clinical Trials.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.

PubMed
("chlorine dioxide"[Supplementary Concept] OR "chlorine dioxide"[All Fields]) AND ("mouth"[MeSH Terms] OR "mouth"[All Fields] OR "oral"[All Fields])
Scopus
*((**chlorine** AND **dioxide**) AND **oral)***
Web of Science
((chlorine dioxide) AND oral)
EBSCO
(chlorine dioxide) AND oral
Clinicaltrials.gov
"chlorine dioxide" AND "oral"
EMBASE
'chlorine dioxide' AND oral
Cochran Library
'(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 mutants, 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 date (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), Clinical Trials.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)

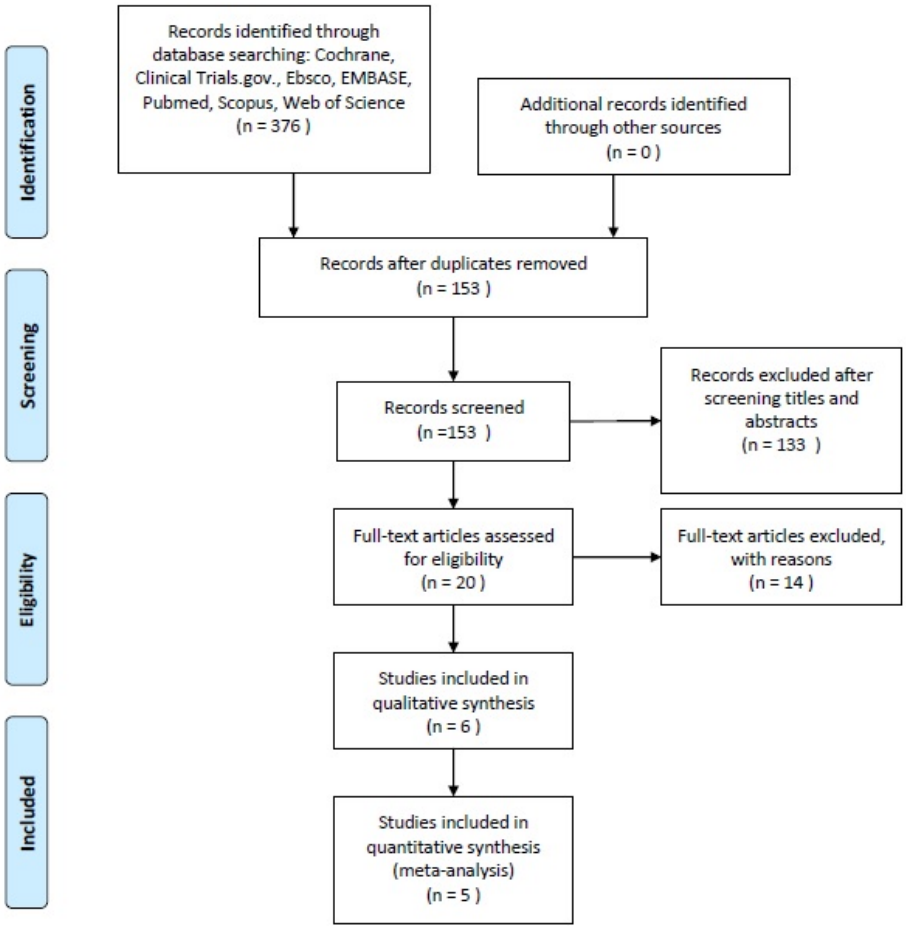

Fig. (1). PRISMA 2009 flow diagram for identification of relevant studies.

[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**: o**ne 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^0 of patients	N^0 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	Freshclore	chlorine dioxide	
Yeturu	2016	RCT, single-blind, parallel	India	undergoing fix orthodon-tic 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	Freshclore	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

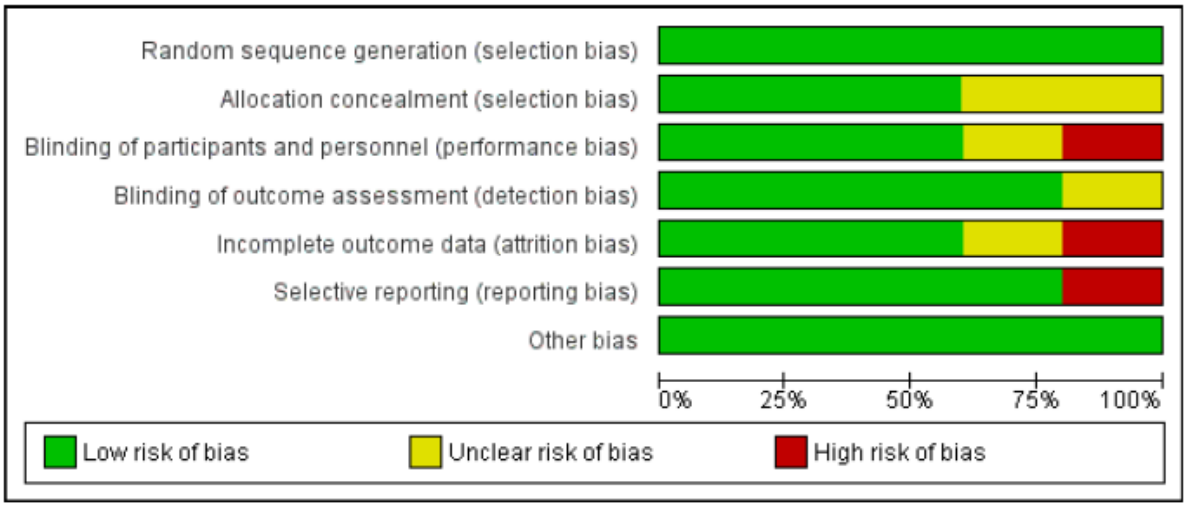

Fig. (2). Risk of Bias graph.

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 7th, 14th and 21st days after treatment initiation [75, 77]. Pham *et al.* collected data on the 14th day [79], Yeturu *et al.* on the 15th day, Shinada *et al.* [78] on the 7th day. Hence we pooled and analyzed data before treatment and after treatment irrespective of the duration of treatments.

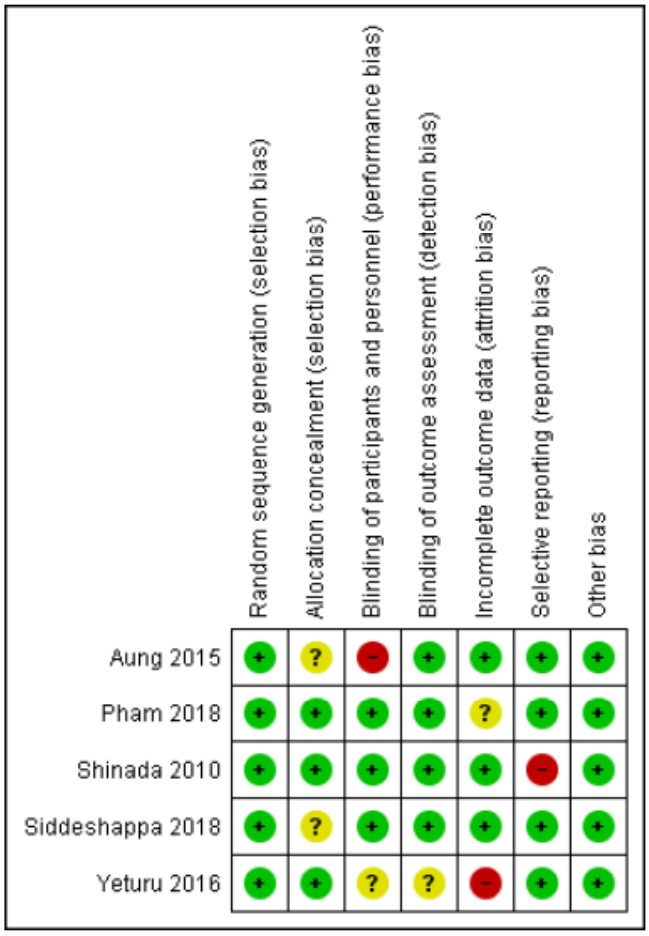

Fig. (3). Risk of bias summary.

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^{-2} to 12.1×10^{-2} CFU (SD: 1.36506, $p<0.001$), while a herbal mouth rinse evoked a decrease from 17.6×10^{-2} to 10.1×10^{-2} 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].

Group by Subgroup within study		Subgroup within study	Statistics for each study				
			Std diff in means	Standard error	Lower limit	Upper limit	p-Value
chlorine dioxide	Aung	chlorine dioxide	0.554	0.277	0.010	1.097	0.046
chlorine dioxide	Yeteru	chlorine dioxide	0.668	0.202	0.272	1.064	0.001
chlorine dioxide	Pham	chlorine dioxide	0.708	0.271	0.177	1.240	0.009
chlorine dioxide	Siddeshappa	chlorine dioxide	0.868	0.262	0.354	1.383	0.001
chlorine dioxide	Shinada	chlorine dioxide	0.986	0.431	0.141	1.830	0.022
chlorine dioxide			0.720	0.119	0.487	0.952	0.000
positive control	Yeteru	positive control	0.668	0.202	0.272	1.064	0.001
positive control	Yeteru_b	positive control	0.749	0.226	0.305	1.193	0.001
positive control	Siddeshappa	positive control	0.868	0.262	0.354	1.383	0.001
positive control			0.745	0.131	0.489	1.001	0.000
negative control	Pham	negative control	0.044	0.213	-0.374	0.462	0.838
negative control	Shinada	negative control	0.067	0.378	-0.675	0.809	0.859
negative control			0.049	0.186	-0.315	0.413	0.791

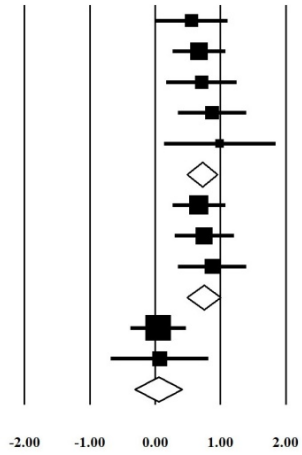

Fig. (4). Plaque index alteration between the chlorine dioxide, other effective treatments and placebo group.
Standardized difference in means ± standard error with 95% CI

Group by Subgroup within study		Subgroup within study	Statistics for each study				
			Std diff in means	Standard error	Lower limit	Upper limit	p-Value
chlorine dioxide	Pham	chlorine dioxide	0.514	0.258	0.008	1.020	0.046
chlorine dioxide	Yeteru	chlorine dioxide	0.668	0.202	0.272	1.064	0.001
chlorine dioxide	Siddeshappa	chlorine dioxide	0.868	0.262	0.354	1.383	0.001
chlorine dioxide	Shinada	chlorine dioxide	1.060	0.442	0.194	1.926	0.016
chlorine dioxide			0.712	0.130	0.457	0.967	0.000
positive control	Yeteru	positive control	0.668	0.202	0.272	1.064	0.001
positive control	Yeteru_b	positive control	0.749	0.226	0.305	1.193	0.001
positive control	Siddeshappa	positive control	0.868	0.262	0.354	1.383	0.001
positive control			0.745	0.131	0.489	1.001	0.000
negative control	Shinada	negative control	0.181	0.381	-0.566	0.928	0.635
negative control	Pham	negative control	0.296	0.218	-0.131	0.723	0.175
negative control			0.267	0.189	-0.103	0.638	0.157

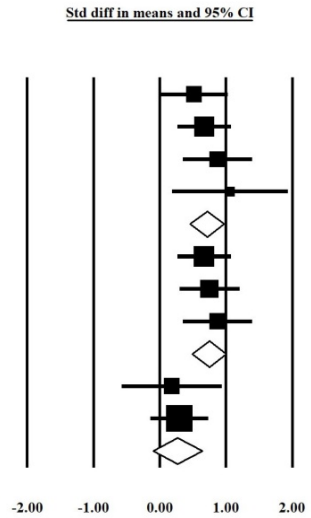

Fig. (5). Gingival index alteration between the chlorine dioxide, other effective treatments and placebo group.
Standardized difference in means ± standard error with 95% CI

Group by Subgroup within study	Study name	Subgroup within study	Statistics for each study				
			Std diff in means	Standard error	Lower limit	Upper limit	p-Value
chlorine dioxide	Aung	chlorine dioxide	0.554	0.277	0.010	1.097	0.046
chlorine dioxide	Pham	chlorine dioxide	0.974	0.294	0.397	1.551	0.001
chlorine dioxide	Shinada	chlorine dioxide	1.425	0.502	0.441	2.408	0.005
chlorine dioxide			0.880	0.240	0.410	1.350	0.000
negative control	Pham	negative control	0.424	0.223	-0.012	0.860	0.057
negative control	Shinada	negative control	1.146	0.487	0.193	2.100	0.018
negative control			0.618	0.282	0.065	1.172	0.029

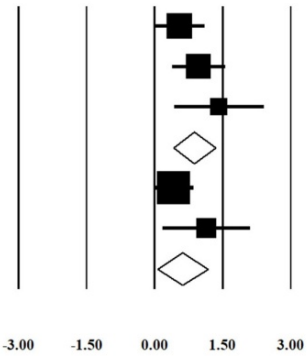

Fig. (6). Tongue coating index modified by Winkel alteration between the chlorine dioxide, other effective treatments and placebo group.
Standardized difference in means ± standard error with 95% CI

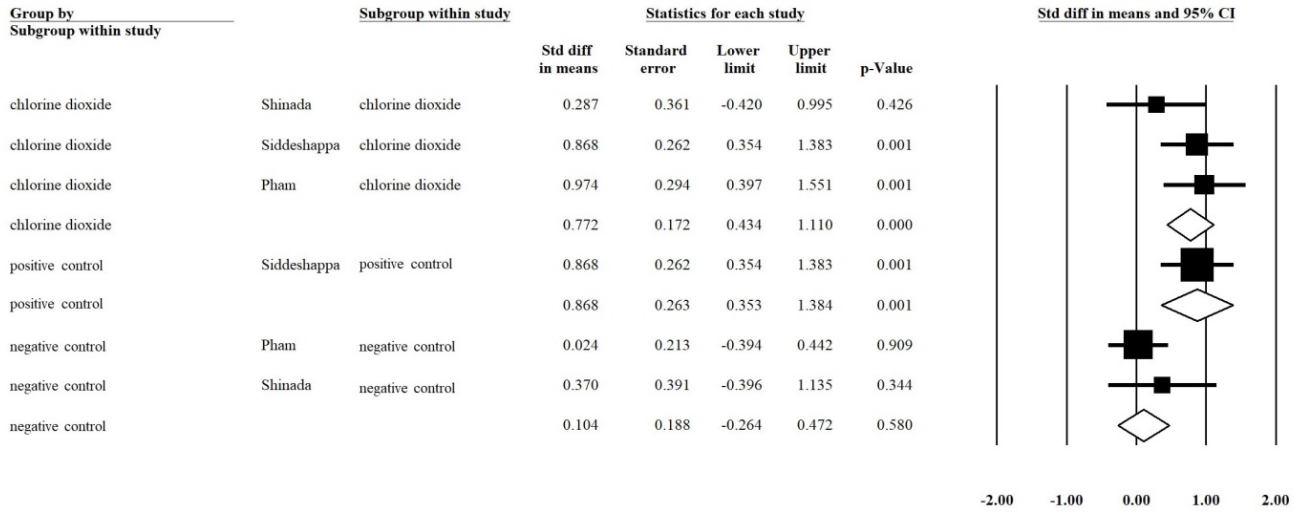

Fig. (7). *Tannerrella forsythia* count alteration between the chlorine dioxide, other effective treatments and placebo group. Standardized difference in means ± standard error with 95% CI

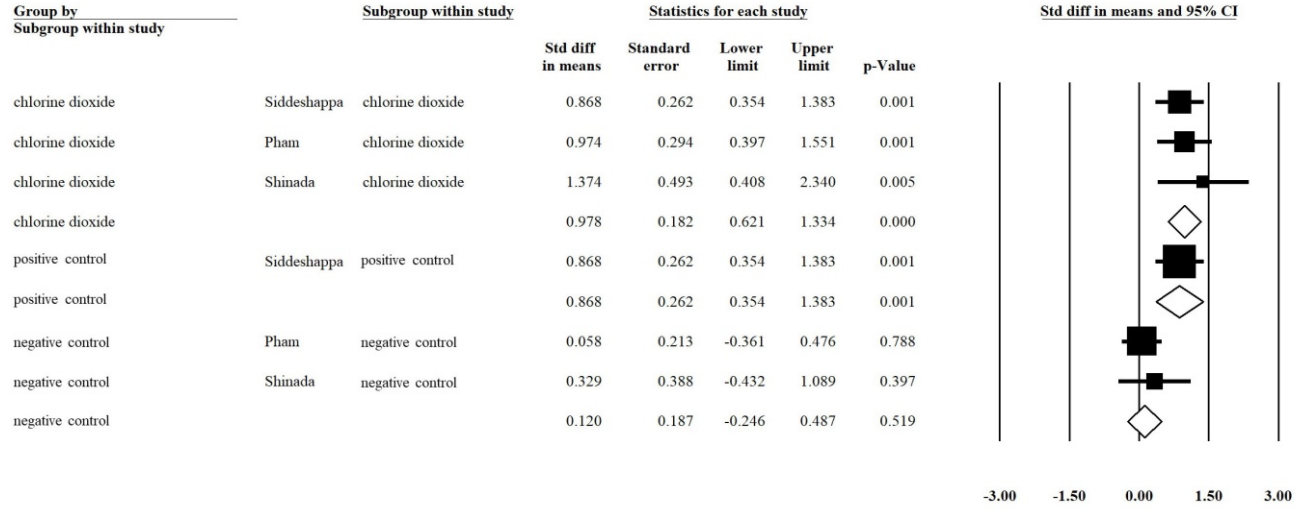

Fig. (8). *Fusobacterium nucleatum* count alteration between the chlorine dioxide, other effective treatments and placebo group. Standardized difference in means ± standard error with 95% CI

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 antifungicidal 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 (NaClO2)-containing mouthwash and 0.10% (w/w) chlorine dioxide (ClO2) [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 Siddeshappa et al. used Freshclor® (Group Pharmaceuticals Ltd., Bangalor, 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.

FUNDING

None.

CONFLICT OF INTEREST

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

ACKNOWLEDGEMENTS

The authors gratefully acknowledge the fundings by the Hungarian Human Resources Development Operational Program (EFOP-3.6.2-16-2017-00006 and EFOP-3.6.3-VEKOP-16-2017-00009), an Economic Development and Innovation Operative Program Grant (GINOP 2.3.2-15- 2016-00048) and an Institutional Developments for Enhancing Intelligent Specialization Grant (EFOP-3.6.1-16-2016-00022) of the National Research, Development and Innovation Office. Additional support was received by the Excellence Program of the Ministry for Innovation and Technology in Hungary, within the framework of the Therapy thematic program of the Semmelweis University.

REFERENCES

[1] Keremi B, Beck A, Fabian TK, *et al.* Stress and Salivary Glands. Curr Pharm Des 2017; 23(27): 4057-65. http://dx.doi.org/10.2174/1381612823666170215110648 PMID: 28215154

[2] Lohinai Z, Burghardt B, Zelles T, Varga G. Nitric oxide modulates salivary amylase and fluid, but not epidermal growth factor secretion in conscious rats. Life Sci 1999; 64(11): 953-63. http://dx.doi.org/10.1016/S0024-3205(99)00021-1 PMID: 10201644

[3] Márton K, Boros I, Varga G, *et al.* Evaluation of palatal saliva flow rate and oral manifestations in patients with Sjögren's syndrome. Oral Dis 2006; 12(5): 480-6. http://dx.doi.org/10.1111/j.1601-0825.2005.01224.x PMID: 16910919

[4] Márton K, Madléna M, Bánóczy J, *et al.* Unstimulated whole saliva flow rate in relation to sicca symptoms in Hungary. Oral Dis 2008; 14(5): 472-7. http://dx.doi.org/10.1111/j.1601-0825.2007.01404.x PMID: 18938274

[5] Racz R, Nagy A, Rakonczay Z, Dunavari EK, Gerber G, Varga G. Defense Mechanisms Against Acid Exposure by Dental Enamel Formation, Saliva and Pancreatic Juice Production. Curr Pharm Des 2018; 24(18): 2012-22. http://dx.doi.org/10.2174/1381612824666180515125654 PMID: 29769002

[6] Földes A, Kádár K, Kerémi B, *et al.* Mesenchymal Stem Cells of Dental Origin-Their Potential for Antiinflammatory and Regenerative Actions in Brain and Gut Damage. Curr Neuropharmacol 2016; 14(8): 914-34. http://dx.doi.org/10.2174/1570159X14666160121115210 PMID: 26791480

[7] Grimm WD, Dannan A, Becher S, *et al.* The ability of human periodontium-derived stem cells to regenerate periodontal tissues: a preliminary in vivo investigation. Int J Periodontics Restorative Dent 2011; 31(6): e94-e101. PMID: 22140674

[8] Grimm WD, Dannan A, Giesenhagen B, *et al.* Translational Research: Palatal-derived Ecto-mesenchymal Stem Cells from Human Palate: A New Hope for Alveolar Bone and Cranio-Facial Bone Reconstruction. Int J Stem Cells 2014; 7(1): 23-9. http://dx.doi.org/10.15283/ijsc.2014.7.1.23 PMID: 24921024

[9] Kadar K, Kiraly M, Porcsalmy B, Molnar B, Racz GZ, Blazsek J, *et al.* Differentiation potential of stem cells from human dental origin - promise for tissue engineering. Journal of Physiology and Pharmacology: an official journal of the Polish Physiological Society 2009; 60(Suppl 7): 167-75.

[10] Keremi B, Lohinai Z, Komora P, Duhaj S, Borsi K, Jobbagy-Ovari G, *et al.* Antiinflammatory effect of BPC 157 on experimental periodontitis in rats. Journal of Physiology and Pharmacology: an official journal of the Polish Physiological Society 2009; 60(Suppl 7): 115-22.

[11] Racz GZ, Kadar K, Foldes A, Kallo K, Perczel-Kovach K, Keremi B, *et al.* Immunomodulatory and potential therapeutic role of mesenchymal stem cells in periodontitis Journal of Physiology and

Pharmacology: an official journal of the Polish Physiological Society 2014; 65(3): 327-9.

[12] Wilder RS, Bray KS. Improving periodontal outcomes: merging clinical and behavioral science. Periodontol 2000 2016; 71(1): 65-81.
http://dx.doi.org/10.1111/prd.12125 PMID: 27045431

[13] Kornman KS. Contemporary approaches for identifying individual risk for periodontitis. Periodontol 2000 2018; 78(1): 12-29.
http://dx.doi.org/10.1111/prd.12234 PMID: 30198138

[14] Yadav SR, Kini VV, Padhye A. Inhibition of tongue coat and dental plaque formation by stabilized chlorine dioxide vs chlorhexidine mouthrinse: A randomized, triple blinded. J Clin Diagn Res 2015; 9(9): ZC69-74.
http://dx.doi.org/10.7860/JCDR/2015/14587.6510 PMID: 26501017

[15] Jones CG. Chlorhexidine: is it still the gold standard? Periodontol 2000 1997; 15: 55-62.
http://dx.doi.org/10.1111/j.1600-0757.1997.tb00105.x PMID: 9643233

[16] McCoy LC, Wehler CJ, Rich SE, Garcia RI, Miller DR, Jones JA. Adverse events associated with chlorhexidine use: results from the Department of Veterans Affairs Dental Diabetes Study. J Am Dent Assoc 2008; 139(2): 178-83.
http://dx.doi.org/10.14219/jada.archive.2008.0134 PMID: 18245686

[17] Gürgan CA, Zaim E, Bakirsoy I, Soykan E. Short-term side effects of 0.2% alcohol-free chlorhexidine mouthrinse used as an adjunct to non-surgical periodontal treatment: a double-blind clinical study. J Periodontol 2006; 77(3): 370-84.
http://dx.doi.org/10.1902/jop.2006.050141 PMID: 16512751

[18] Supranoto SC, Slot DE, Addy M, Van der Weijden GA. The effect of chlorhexidine dentifrice or gel versus chlorhexidine mouthwash on plaque, gingivitis, bleeding and tooth discoloration: a systematic review. Int J Dent Hyg 2015; 13(2): 83-92.
http://dx.doi.org/10.1111/idh.12078 PMID: 25059640

[19] Varoni E, Tarce M, Lodi G, Carrassi A. Chlorhexidine (CHX) in dentistry: state of the art. Minerva Stomatol 2012; 61(9): 399-419.
PMID: 22976567

[20] Frank ME, Gent JF, Hettinger TP. Effects of chlorhexidine on human taste perception. Physiol Behav 2001; 74(1-2): 85-99.
http://dx.doi.org/10.1016/S0031-9384(01)00558-3 PMID: 11564456

[21] Grover R, Frank ME. Regional specificity of chlorhexidine effects on taste perception. Chem Senses 2008; 33(4): 311-8.
http://dx.doi.org/10.1093/chemse/bjm095 PMID: 18263592

[22] Wang MF, Marks LE, Frank ME. Taste coding after selective inhibition by chlorhexidine. Chem Senses 2009; 34(8): 653-66.
http://dx.doi.org/10.1093/chemse/bjp047 PMID: 19703921

[23] James P, Worthington HV, Parnell C, *et al.* Chlorhexidine mouthrinse as an adjunctive treatment for gingival health. Cochrane Database Syst Rev 2017; 3CD008676
http://dx.doi.org/10.1002/14651858.CD008676.pub2 PMID: 28362061

[24] Kamath NP, Tandon S, Nayak R, Naidu S, Anand PS, Kamath YS. The effect of aloe vera and tea tree oil mouthwashes on the oral health of school children. Eur Arch Paediatr Dent 2019.
PMID: 31111439

[25] Mathur A, Gopalakrishnan D, Mehta V, Rizwan SA, Shetiya SH, Bagwe S. Efficacy of green tea-based mouthwashes on dental plaque and gingival inflammation: A systematic review and meta-analysis. Indian Journal of Dental Research: official publication of Indian Society for Dental Research 2018; 29(2): 225-32.

[26] Diefenbach AL, Muniz FWMG, Oballe HJR, Rösing CK. Antimicrobial activity of copaiba oil (Copaifera ssp.) on oral pathogens: Systematic review. Phytother Res 2018; 32(4): 586-96.
http://dx.doi.org/10.1002/ptr.5992 PMID: 29193389

[27] Van Leeuwen MP, Slot DE, Van der Weijden GA. The effect of an essential-oils mouthrinse as compared to a vehicle solution on plaque and gingival inflammation: a systematic review and meta-analysis. Int J Dent Hyg 2014; 12(3): 160-7.
http://dx.doi.org/10.1111/idh.12069 PMID: 24720368

[28] Wirthlin MR, Roth M. Dental unit waterline contamination: a review of research and findings from a clinic setting. Compendium Of Continuing Education In Dentistry (Jamesburg, NJ: 1995) 2015; 36(3): 216-9.

[29] Praeger U, Herppich WB, Hassenberg K. Aqueous chlorine dioxide treatment of horticultural produce: Effects on microbial safety and produce quality-A review. Crit Rev Food Sci Nutr 2018; 58(2): 318-33.
http://dx.doi.org/10.1080/10408398.2016.1169157 PMID: 27196114

[30] Sowerby LJ, Rudmik L. The cost of being clean: A cost analysis of nasopharyngoscope reprocessing techniques. Laryngoscope 2018; 128(1): 64-71.
http://dx.doi.org/10.1002/lary.26770 PMID: 28815686

[31] Watamoto T, Egusa H, Sawase T, Yatani H. Clinical evaluation of chlorine dioxide for disinfection of dental instruments. Int J Prosthodont 2013; 26(6): 541-4.
http://dx.doi.org/10.11607/ijp.3465 PMID: 24179967

[32] Kuroyama I, Osato S, Nakajima S, Kubota R, Ogawa T. Environmental monitoring and bactericidal efficacy of chlorine dioxide gas in a dental office. Biocontrol Sci 2010; 15(3): 103-9.
http://dx.doi.org/10.4265/bio.15.103 PMID: 20938095

[33] Anna H, Barnabás P, Zsolt L, Romána Z. Tracking of the degradation process of chlorhexidine digluconate and ethylenediaminetetraacetic acid in the presence of hyper-pure chlorine dioxide in endodontic disinfection. J Pharm Biomed Anal 2019; 164: 360-4.
http://dx.doi.org/10.1016/j.jpba.2018.11.005 PMID: 30439663

[34] Ballal NV, Khandewal D, Karthikeyan S, Somayaji K, Foschi F. Evaluation of Chlorine Dioxide Irrigation Solution on the Microhardness and Surface Roughness of Root Canal Dentin. Eur J Prosthodont Restor Dent 2015; 23(4): 173-8.
PMID: 26767238

[35] Cobankara FK, Ozkan HB, Terlemez A. Comparison of organic tissue dissolution capacities of sodium hypochlorite and chlorine dioxide. J Endod 2010; 36(2): 272-4.
http://dx.doi.org/10.1016/j.joen.2009.10.027 PMID: 20113788

[36] Fráter M, Braunitzer G, Urbán E, Bereczki L, Antal M, Nagy K. In vitro efficacy of different irrigating solutions against polymicrobial human root canal bacterial biofilms. Acta Microbiol Immunol Hung 2013; 60(2): 187-99.
http://dx.doi.org/10.1556/AMicr.60.2013.2.9 PMID: 23827750

[37] Herczegh A, Ghidan A, Friedreich D, Gyurkovics M, Bendő Z, Lohinai Z. Effectiveness of a high purity chlorine dioxide solution in eliminating intracanal Enterococcus faecalis biofilm. Acta Microbiol Immunol Hung 2013; 60(1): 63-75.
http://dx.doi.org/10.1556/AMicr.60.2013.1.7 PMID: 23529300

[38] Herczegh A, Gyurkovics M, Ghidan Á, Megyesi M, Lohinai Z. Effect of dentin powder on the antimicrobial properties of hyper-pure chlorine-dioxide and its comparison to conventional endodontic disinfecting agents. Acta Microbiol Immunol Hung 2014; 61(2): 209-20.
http://dx.doi.org/10.1556/AMicr.61.2014.2.10 PMID: 25046882

[39] Lundstrom JR, Williamson AE, Villhauer AL, Dawson DV, Drake DR. Bactericidal activity of stabilized chlorine dioxide as an endodontic irrigant in a polymicrobial biofilm tooth model system. J Endod 2010; 36(11): 1874-8.
http://dx.doi.org/10.1016/j.joen.2010.08.032 PMID: 20951304

[40] Ablal MA, Adeyemi AA, Jarad FD. The whitening effect of chlorine dioxide--an in vitro study. J Dent 2013; 41(Suppl. 5): e76-81.
http://dx.doi.org/10.1016/j.jdent.2013.05.006 PMID: 23707537

[41] Li Y, Greenwall L. Safety issues of tooth whitening using peroxide-based materials. Br Dent J 2013; 215(1): 29-34.
http://dx.doi.org/10.1038/sj.bdj.2013.629 PMID: 23846062

[42] Torres CRG, Bonício GC, Crastechini É, Mailart MC, Borges AB. Effect of whitening mouthrinses on enamel toothbrush abrasion. Am J Dent 2018; 31(6): 285-9.
PMID: 30658373

[43] Soolari N, Soolari A. Closure of an open wound associated with bisphosphonate-related osteonecrosis of the jaw in a breast cancer patient. Open Dent J 2011; 5: 163-7.
http://dx.doi.org/10.2174/1874210601105010163 PMID: 22135700

[44] Valente JH, Jay GD, Zabbo CP, Reinert SE, Bertsch K. Activated chlorine dioxide solution can be used as a biocompatible antiseptic wound irrigant. Adv Skin Wound Care 2014; 27(1): 13-9.
http://dx.doi.org/10.1097/01.ASW.0000439060.79822.b3 PMID: 24343388

[45] Alleyn CD, O'Neal RB, Strong SL, Scheidt MJ, Van Dyke TE, McPherson JC. The effect of chlorhexidine treatment of root sur-

faces on the attachment of human gingival fibroblasts in vitro. J Periodontol 1991; 62(7): 434-8.
http://dx.doi.org/10.1902/jop.1991.62.7.434 PMID: 1920010

[46] Barnhart BD, Chuang A, Lucca JJ, Roberts S, Liewehr F, Joyce AP. An in vitro evaluation of the cytotoxicity of various endodontic irrigants on human gingival fibroblasts. J Endod 2005; 31(8): 613-5.
http://dx.doi.org/10.1097/01.don.0000153840.94227.87 PMID: 16044047

[47] Nishikiori R, Nomura Y, Sawajiri M, Masuki K, Hirata I, Okazaki M. Influence of chlorine dioxide on cell death and cell cycle of human gingival fibroblasts. J Dent 2008; 36(12): 993-8.
http://dx.doi.org/10.1016/j.jdent.2008.08.006 PMID: 18819741

[48] Tonzetich J. Production and origin of oral malodor: a review of mechanisms and methods of analysis. J Periodontol 1977; 48(1): 13-20.
http://dx.doi.org/10.1902/jop.1977.48.1.13 PMID: 264535

[49] Ratcliff PA, Johnson PW. The relationship between oral malodor, gingivitis, and periodontitis. A review. J Periodontol 1999; 70(5): 485-9.
http://dx.doi.org/10.1902/jop.1999.70.5.485 PMID: 10368052

[50] Fedorowicz Z, Aljufairi H, Nasser M, Outhouse TL, Pedrazzi V. Mouthrinses for the treatment of halitosis. Cochrane Database of Systematic Reviews 2008; (4):
http://dx.doi.org/10.1002/14651858.CD006701.pub2

[51] Frascella J, Gilbert RD, Fernandez P, Hendler J. Efficacy of a chlorine dioxide-containing mouthrinse in oral malodor.Compendium Of Continuing Education In Dentistry (Jamesburg, NJ: 1995) 2000; 21(3): 241.

[52] Krespi YP, Shrime MG, Kacker A. The relationship between oral malodor and volatile sulfur compound-producing bacteria. Otolaryngol Head Neck Surg 2006; 135(5): 671-6.
http://dx.doi.org/10.1016/j.otohns.2005.09.036 PMID: 17071291

[53] Silness J, Löe H. Periodontal disease in pregnancy, II Correlation between oral hygiene and periodontal condition. Acta Odontol Scand 1964; 22: 121-35.
http://dx.doi.org/10.3109/00016356408993968 PMID: 14158464

[54] Löe H, Silness J. Periodontal diesase in pregnancy. I Prevalence and severity. Acta Odontol Scand 1963; 21: 533-51.
http://dx.doi.org/10.3109/00016356309011240 PMID: 14121956

[55] Lundgren T, Mobilia A, Hallström H, Egelberg J. Evaluation of tongue coating indices. Oral Dis 2007; 13(2): 177-80.
http://dx.doi.org/10.1111/j.1601-0825.2006.01261.x PMID: 17305619

[56] Winkel EG, Roldán S, Van Winkelhoff AJ, Herrera D, Sanz M. Clinical effects of a new mouthrinse containing chlorhexidine, cetylpyridinium chloride and zinc-lactate on oral halitosis. A dual-center, double-blind placebo-controlled study. J Clin Periodontol 2003; 30(4): 300-6.
http://dx.doi.org/10.1034/j.1600-051X.2003.00342.x PMID: 12694427

[57] Moher D, Shamseer L, Clarke M, *et al.* PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev 2015; 4: 1.
http://dx.doi.org/10.1186/2046-4053-4-1 PMID: 25554246

[58] Higgins JPT GSe. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011 Available from http://handbookcochraneorg 2011

[59] Cochran WG. The combination of estimates from different experiments. Biometrics 1954; 10: 101-29.
http://dx.doi.org/10.2307/3001666

[60] DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986; 7(3): 177-88.
http://dx.doi.org/10.1016/0197-2456(86)90046-2 PMID: 3802833

[61] Czumbel LM, Kerémi B, Gede N, *et al.* Sandblasting reduces dental implant failure rate but not marginal bone level loss: A systematic review and meta-analysis. PLoS One 2019; 14(5)e0216428
http://dx.doi.org/10.1371/journal.pone.0216428 PMID: 31050690

[62] Tóth B, Hegyi P, Lantos T, *et al.* The Efficacy of Saffron in the Treatment of Mild to Moderate Depression: A Meta-analysis. Planta Med 2019; 85(1): 24-31.
http://dx.doi.org/10.1055/a-0660-9565 PMID: 30036891

[63] Eunike MC, Fauziah E, Suharsini M. Antibacterial effects of 0.1% chlorine dioxide on actinomyces sp. as an agent of black stain. International Journal of Applied Pharmaceutics 2017; 9(Special Issue 2): 79-82.

[64] Ambalavanan S, Ganapathy D. The role of antibiotic mouth rinses in oral health care. Journal of Pharmaceutical Sciences and Research 2016; 8(4): 244-6.

[65] Kuroyama I, Osato S, Ogawa T. The bactericidal effects of an acidified sodium chlorite-containing oral moisturizing gel: a pilot study. J Oral Implantol 2013; 39(6): 689-95.
http://dx.doi.org/10.1563/AAID-JOI-D-11-00087 PMID: 21905903

[66] Yates R, Moran J, Addy M, Mullan PJ, Wade WG, Newcombe R. The comparative effect of acidified sodium chlorite and chlorhexidine mouthrinses on plaque regrowth and salivary bacterial counts. J Clin Periodontol 1997; 24(9 Pt 1): 603-9.
http://dx.doi.org/10.1111/j.1600-051X.1997.tb00236.x PMID: 9378830

[67] Uludamar A, Özyeşil AG, Ozkan YK. Clinical and microbiological efficacy of three different treatment methods in the management of denture stomatitis. Gerodontology 2011; 28(2): 104-10.
http://dx.doi.org/10.1111/j.1741-2358.2009.00354.x PMID: 20545775

[68] Mohammad AR, Giannini PJ, Preshaw PM, Alliger H. Clinical and microbiological efficacy of chlorine dioxide in the management of chronic atrophic candidiasis: an open study. Int Dent J 2004; 54(3): 154-8.
http://dx.doi.org/10.1111/j.1875-595X.2004.tb00272.x PMID: 15218896

[69] Rossato MB, Unfer B, May LG, Braun KO. Analysis of the effectiveness of different hygiene procedures used in dental prostheses. Oral Health Prev Dent 2011; 9(3): 221-7.
PMID: 22068177

[70] Chapek CW, Reed OK, Ratcliff PA. Management of periodontitis with oral-care products. Compendium (Newtown, Pa) 1994; 15(6): 740, 2, 5 passim.

[71] Goultschin J, Green J, Machtei E, *et al.* Use of a metastabilized chlorous acid/chlorine dioxide formulation as a mouthrinse for plaque reduction. Isr J Dent Sci 1989; 2(3): 142-7.
PMID: 2490928

[72] Myneni Venkatasatya SR, Wang HH, Alluri S, Ciancio SG. Phosphate buffer-stabilized 0.1% chlorine dioxide oral rinse for managing medication-related osteonecrosis of the jaw. Am J Dent 2017; 30(6): 350-2.
PMID: 29251459

[73] Paraskevas S, Rosema NA, Versteeg P, Van der Velden U, Van der Weijden GA. Chlorine dioxide and chlorhexidine mouthrinses compared in a 3-day plaque accumulation model. J Periodontol 2008; 79(8): 1395-400.
http://dx.doi.org/10.1902/jop.2008.070630 PMID: 18672988

[74] Grootveld M, Silwood C, Gill D, Lynch E. Evidence for the microbicidal activity of a chlorine dioxide-containing oral rinse formulation in vivo. J Clin Dent 2001; 12(3): 67-70.
PMID: 11505963

[75] Siddeshappa ST, Bhatnagar S, Yeltiwar RK, Parvez H, Singh A, Banchhor S. Comparative evaluation of antiplaque and antigingivitis effects of an herbal and chlorine dioxide mouthwashes: A clinicomicrobiological study. Indian J Dent Res 2018; 29(1): 34-40.
http://dx.doi.org/10.4103/ijdr.IJDR_391_16 PMID: 29442084

[76] Yeturu SK, Acharya S, Urala AS, Pentapati KC. Effect of Aloe vera, chlorine dioxide, and chlorhexidine mouth rinses on plaque and gingivitis: A randomized controlled trial. J Oral Biol Craniofac Res 2016; 6(1): 54-8.
http://dx.doi.org/10.1016/j.jobcr.2015.08.008 PMID: 26937371

[77] Aung EE, Ueno M, Zaitsu T, Furukawa S, Kawaguchi Y. Effectiveness of three oral hygiene regimens on oral malodor reduction: a randomized clinical trial. Trials 2015; 16(1): 31.
http://dx.doi.org/10.1186/s13063-015-0549-9 PMID: 25622725

[78] Shinada K, Ueno M, Konishi C, *et al.* Effects of a mouthwash with chlorine dioxide on oral malodor and salivary bacteria: a randomized placebo-controlled 7-day trial. Trials 2010; 11: 14.
http://dx.doi.org/10.1186/1745-6215-11-14 PMID: 20152022

[79] Pham TAV, Nguyen NTX. Efficacy of chlorine dioxide mouthwash in reducing oral malodor: A 2-week randomized, double-blind, crossover study. Clin Exp Dent Res 2018; 4(5): 206-15.
http://dx.doi.org/10.1002/cre2.131 PMID: 30386642

[80] Herczegh A, Gyurkovics M, Agababyan H, Ghidán A, Lohinai Z. Comparing the efficacy of hyper-pure chlorine-dioxide with other oral antiseptics on oral pathogen microorganisms and biofilm in vitro. Acta Microbiol Immunol Hung 2013; 60(3): 359-73. http://dx.doi.org/10.1556/AMicr.60.2013.3.10 PMID: 24060558

[81] Noszticzius Z, Wittmann M, Kály-Kullai K, *et al.* Chlorine dioxide is a size-selective antimicrobial agent. PLoS One 2013; 8(11)e79157 http://dx.doi.org/10.1371/journal.pone.0079157 PMID: 24223899

[82] Anitha V, Rajesh P, Shanmugam M, Priya BM, Prabhu S, Shivakumar V. Comparative evaluation of natural curcumin and synthetic chlorhexidine in the management of chronic periodontitis as a local drug delivery: a clinical and microbiological study. Indian Journal of Dental Research: official publication of Indian Society for Dental Research 2015; 26(1): 53-6. http://dx.doi.org/10.4103/0970-9290.156806

[83] Gupta D, Gupta RK, Bhaskar DJ, Gupta V. Comparative evaluation of terminalia chebula extract mouthwash and chlorhexidine mouthwash on plaque and gingival inflammation - 4-week randomised control trial. Oral Health Prev Dent 2015; 13(1): 5-12. PMID: 25386630

[84] Haydari M, Bardakci AG, Koldsland OC, Aass AM, Sandvik L, Preus HR. Comparing the effect of 0.06% -, 0.12% and 0.2% Chlorhexidine on plaque, bleeding and side effects in an experimental gingivitis model: a parallel group, double masked randomized clinical trial. BMC Oral Health 2017; 17(1): 118. http://dx.doi.org/10.1186/s12903-017-0400-7 PMID: 28821290

[85] Shah SS, Nambiar S, Kamath D, *et al.* Comparative Evaluation of Plaque Inhibitory and Antimicrobial Efficacy of Probiotic and Chlorhexidine Oral Rinses in Orthodontic Patients: A Randomized Clinical Trial. Int J Dent 2019; 20191964158 http://dx.doi.org/10.1155/2019/1964158 PMID: 30930947

[86] Gupta RK, Gupta D, Bhaskar DJ, Yadav A, Obaid K, Mishra S. Preliminary antiplaque efficacy of aloe vera mouthwash on 4 day plaque re-growth model: randomized control trial. Ethiop J Health Sci 2014; 24(2): 139-44. http://dx.doi.org/10.4314/ejhs.v24i2.6 PMID: 24795515

[87] Chhina S, Singh A, Menon I, Singh R, Sharma A, Aggarwal V. A randomized clinical study for comparative evaluation of Aloe Vera and 0.2% chlorhexidine gluconate mouthwash efficacy on de-novo plaque formation. J Int Soc Prev Community Dent 2016; 6(3): 251-5. http://dx.doi.org/10.4103/2231-0762.183109 PMID: 27382543

[88] Manipal S, Hussain S, Wadgave U, Duraiswamy P, Ravi K. The Mouthwash War - Chlorhexidine vs. Herbal Mouth Rinses: A Meta-Analysis. J Clin Diagn Res 2016; 10(5): ZC81-3. http://dx.doi.org/10.7860/JCDR/2016/16578.7815 PMID: 27437366