

The effect of chlorhexidine dentifrice or gel versus chlorhexidine mouthwash on plaque, gingivitis, bleeding and tooth discoloration: a systematic review

摘要

目的

本研究以系統性文獻回顧，評估Chlorhexidine 牙粉或凝膠、漱口水三種劑型，在牙菌斑、牙齦出血、牙齦發炎以及牙齒變色等相關指標的效果差異

研究方法

本研究搜尋PubMed-MEDLINE, Cochrane-CENTRAL and EMBASE databases 共2256篇研究，共5篇符合研究分析標準。

研究結果

比較5篇研究的異質性，3篇研究指出Chlorhexidine漱口水對於牙菌斑指標改善具有正向效果，但是對於牙齦出血、牙齦發炎指標改善則無明顯差異。值得一提的是，Chlorhexidine 漱口水的牙齒變色指標比牙粉或凝膠更加明顯。

本研究進行對五篇研究結果進行統合分析(Meta-analysis)後發現，Chlorhexidine 凝膠可以成功抑制牙菌斑的形成的程度，但是抑制範圍並無漱口水廣。

當Chlorhexidine 牙粉或凝膠應用在未刷牙的族群，其牙菌斑抑制效果相較於漱口水不佳。但是，在刷牙後直接將凝膠以手指塗上患部，其牙菌斑及牙齦發炎指標改善，比漱口水更好。

結論

雖然漱口水牙齒變色作用明顯，但是若日常的口腔清潔無法落實，第一選擇還是使用含Chlorhexidine的漱口水。



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The effect of chlorhexidine dentifrice or gel versus chlorhexidine mouthwash on plaque, gingivitis, bleeding and tooth discoloration: *a systematic review*

Abstract: *Objective:* To systematically review and evaluate the available scientific evidence on the effectiveness of chlorhexidine dentifrice or gel (CHX DF/gel) compared to chlorhexidine mouthwash (CHX MW) on plaque, bleeding, gingival inflammation and tooth discoloration scores. *Material and methods:* PubMed-MEDLINE, Cochrane-CENTRAL and EMBASE databases were searched to identify appropriate studies. *Results:* Independent screening of the 2256 unique titles and abstracts resulted in five publications that met the eligibility criteria. Considerable heterogeneity was found between the studies. Three of the five studies showed a positive effect on plaque scores in favour of the CHX MW. With respect to gingival index and bleeding scores, no significant differences were found. Chlorhexidine mouthwash, however, showed a significantly more tooth discoloration than the CHX DF/gel. A meta-analysis of the effect on 'de novo' plaque formation of CHX DF/gel versus CHX MW resulted in a difference in means of 0.27 [95% CI: 0.14; 0.39] ($P < 0.0001$). *Conclusion:* Chlorhexidine gel can be successfully formulated and will inhibit plaque growth to some degree, but not to the same extent, as a CHX MW. When CHX DF/gel is used in a non-brushing model, it is significantly less effective in plaque inhibition compared to CHX MW. Based on one study when CHX gel was applied with a finger after brushing, it is significantly more effective on plaque scores and the gingival index. The only brushing study also with a long follow-up showed that there is no significant difference between CHX DF and CHX MW. However, as a corollary, significantly more tooth discoloration was observed with the CHX MW. Altogether, the data show that when daily oral hygiene cannot be performed, CHX MW is the first product of choice.

Key words: bleeding; chlorhexidine; dentifrice; gel; gingivitis; mouthwash; oral hygiene; plaque; systematic review; tooth discoloration

Introduction

Dental plaque is a multispecies biofilm of microorganisms that grows on hard and adjacent soft tissues in the oral cavity. It has a well-established role as an aetiological factor in chronic gingivitis and periodontitis (1–3). As such, plaque control through daily oral hygiene is key to the

prevention of these conditions (4). The most reliable methods currently used for plaque removal are tooth brushing and, when indicated, interdental cleaning (5).

In conjunction with mechanical plaque control, chemotherapeutic agents have the potential to inhibit plaque growth, reduce gingivitis and improve oral health beyond tooth brushing alone (6). Of the chemical plaque control agents, chlorhexidine (CHX) is the most studied and effective antimicrobial agent in oral care (7). Recently, a systematic review of the existing scientific literature established that, in patients with gingivitis, CHX mouthwash (MW), as an adjunct to mechanical oral hygiene, provided significant reductions in plaque and gingivitis scores (8). The corollary was a significant increase in tooth discoloration. In another systematic review, it was concluded that tooth brushing with a CHX-containing dentifrice (DF) was effective in the control of plaque and gingivitis but again that tooth surface discoloration was an apparent side effect (9). To our knowledge, no head-to-head comparison of CHX DF or gel with CHX MW has been made in a systematic manner. Therefore, the aim of this systematic review was to summarize and evaluate the available evidence on the effectiveness of CHX DF or gel (CHX DF/gel) compared with CHX MW when used as intervention products in one and the same investigation on plaque, gingivitis and tooth discoloration scores.

Materials and methods

This systematic review was conducted in accordance with the guidelines of Transparent Reporting of Systematic reviews and Meta-Analyses (10, 11).

Focused question

What is the effect of CHX DF/gel compared to CHX MW in patients with gingivitis on plaque, bleeding, gingival inflammation and tooth discoloration scores?

Search strategy

Three Internet sources were used to search for appropriate papers satisfying the study purpose: the National Library of Medicine, Washington, D.C. (MEDLINE-PubMed), the Cochrane Central Register of Controlled Trials (CENTRAL) and EMBASE (Excerpta Medical Database by Elsevier). All databases were searched for studies conducted up to September 2013. The search was designed to include any published study that evaluated the effect of CHX DF/gel and CHX MW within the same experiment for details see Box 1. All reference lists of the selected studies were hand-searched for additional papers that could meet the eligibility criteria of this study. Case reports, letters and narrative/historical reviews were not included in the search. Papers without abstracts but with titles suggesting that they were related to the objectives of this review were also selected so that the full text could be screened for eligibility.

Box 1. Search terms used for PubMed-MEDLINE, Cochrane-CENTRAL and EMBASE. The search strategy {<[Agent] AND [vehicle]> AND <[outcome/disease]>} was customized appropriately for each of the additional databases used taking into account differences in controlled vocabulary and syntax rules.

The following terms were used in the search strategy:

Active ingredients: {<(chlorhexidine [MeSH] OR chlorhexidine OR chlorhexidine phosphanilate OR chlorhexidine di-gluconate OR chlorhexidine gluconate OR zinc-chlorhexidine OR chlorhexidine gluconate lidocaine hydrochloride OR CHX OR CHX formulations [textwords])

AND

Vehicle: (Mouthwashes OR Toothpaste OR Dentifrices [MeSH] OR Mouthwashes OR Mouthwash OR mouthwash* OR mouthrinses OR mouthrinse OR gel OR Toothpaste OR Toothpastes OR Dentifrices OR Dentifrice [textwords])>

AND

Outcome: <Search gingivitis [MeSH] OR gingivitis OR gingivit* OR gingival pocket OR gingival bleeding OR gingival inflammation OR gingival disease* OR gingival index OR gingival hemorrhage OR bleeding on probing OR bleeding-on-probing OR papillary bleeding index OR bleeding index OR sulcus bleeding index OR plaque removal OR plaque index OR dental plaque OR plaque OR removal OR interdental plaque OR interproximal plaque OR dental deposit* OR stain OR discoloration OR pseudo pocket OR pseudopocket OR periodontal index OR oral tissue OR calculus OR tartar [textwords]>

The asterisk (*) was used as a truncation symbol.

Screening and selection

The papers were screened independently by two reviewers (SCS and GAW), first by title and abstract. If the eligibility aspects were present in the title, the paper was selected. If none of the eligibility aspects were mentioned in the title, the abstract was read in detail to screen for suitability. After selection, full-text papers were read in detail by two reviewers (DES and SCS). Those papers that fulfilled all selection criteria were processed for data extraction. Disagreements were resolved by discussion. If disagreement persisted, the judgement of a third reviewer (GAW) was decisive. Two reviewers (DES and SCS) hand-searched the reference lists of all included studies for additional articles.

The eligibility criteria were:

- Randomized controlled trials (RCTs) or controlled clinical trials (CCTs).
- Studies conducted in human adults ≥ 18 years old in good general health without dental implants or (partial) dentures.
- Intervention: chlorhexidine dentifrice or gel (CHX DF/gel).
- Comparison: chlorhexidine mouthwash (CHX MW).
- CHX DF/gel and CHX mouthwash compared in the same experiment.
- Topical supragingival use of the CHX DF or gel.
- Evaluation parameters: plaque, gingivitis, bleeding and tooth discoloration scores.
- Manuscripts written in the English or Dutch language.

Assessment of heterogeneity

The heterogeneity across studies was detailed according to the following factors:

- Study design, evaluation period, oral prophylaxis and industry funding.
- Participant characteristics.
- Chlorhexidine: brand, dosage and regimen.

Quality assessment

Two reviewers (DES and SCS) scored the methodological qualities of the included studies. This was assessed according to the method which has been described in detail by Keukenmeester *et al.* (12,13). For the criteria listed, see Appendix S1.

Statistical analyses

Data extraction

From the collection of papers that met the inclusion criteria, data were extracted with regard to the effectiveness of CHX DF/gel versus CHX MW by two reviewers (DES and SCS). Mean values and standard deviations (SDs) of baseline, end and incremental scores on the parameters of interest were extracted from the text (DES and SCS). For studies that presented intermediate assessments, the baseline and final evaluations were used for this review. Also, the within-group statistical analyses and between-study groups were obtained if presented.

Data analysis

Only baseline data and end-trial assessments were available. Where possible, a meta-analysis was performed and the difference in means (DiffM) was calculated using the Review Manager 5.1 software (RevMan version 5.1 for Windows, Copenhagen, Denmark; Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011). Difference in means values between test and control at both baseline and end was calculated using a fixed-effects model. Heterogeneity was tested by chi-square test and the I^2 statistic. When a study had multiple CHX DF/gel treatment arms, data from the CHX MW group were used in more than one comparison, the number of subjects (n) in this group was divided by the number of comparisons. Only two studies could be included for this quantitative analysis of the total body of evidence. Therefore additionally, data were also summarized using vote counting in a descriptive manner.

Grading the 'body of evidence'

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system as proposed by the GRADE

working group was used to grade the evidence emerging from this review (14, 15). Two reviewers (DES and GAW) rated the quality of the evidence as well as the strength of the recommendations according to the following aspects: risk of bias of the individual studies; consistency and precision among the study outcomes; directness of the study results; and detection of publication bias. Any disagreement between the two reviewers was resolved after additional discussion.

Results

Summary of included studies

The search resulted after removing the duplicates in 2256 papers (for details, see Fig. 1). The screening of titles and abstracts initially resulted in 12 full-text articles. Seven papers were excluded because of insufficient data presentation on the clinical parameters. The reasons for exclusion are specified in Appendix S2. No additional papers emerged from hand-searching of the reference lists. Consequently, five studies were identified as eligible for inclusion in this review according to defined criteria for study design, participants, intervention and outcome. These five trials, all experimental clinical studies, were processed for data extraction.

Assessment of quality and heterogeneity

Considerable heterogeneity was observed in the five included clinical trials regarding study design, participants, evaluation period, oral prophylaxis, intervention regimen, outcome variables and results. Information regarding the study characteristics including study population (number, gender and age of participants) interventions and regimens is displayed in Table 1. In this review, different indices and their modifications are used. Three studies (III, IV and V) used a non-brushing design. Two studies used a brushing design (I and II); in study I, the CHX DF was used as a dentifrice during brushing, while in study II the participants performed brushing with their normal toothpaste and applied additionally the CHX gel with a finger thoroughly in the oral cavity.

Study design, evaluation period, oral prophylaxis and industry funding

All studies excluded patients with systemic disorders that might interfere with the outcome of the study, such as diabetes mellitus, known allergies or haematological disorders (II) or the use of antibiotics during the trial or 3 months prior to commencing (III). None of the studies considered smoking as an exclusion. Study duration differed among studies: 3 days (IV, V), 6 weeks (II), 6 months (I) and 5 days per leg of each regimen within the cross-over design done by Addy 1989 (III). In most studies, oral prophylaxis was performed at the start of each experiment (I, III, IV, V), except for one (II). Not one of the studies presented information regarding industrial funding.

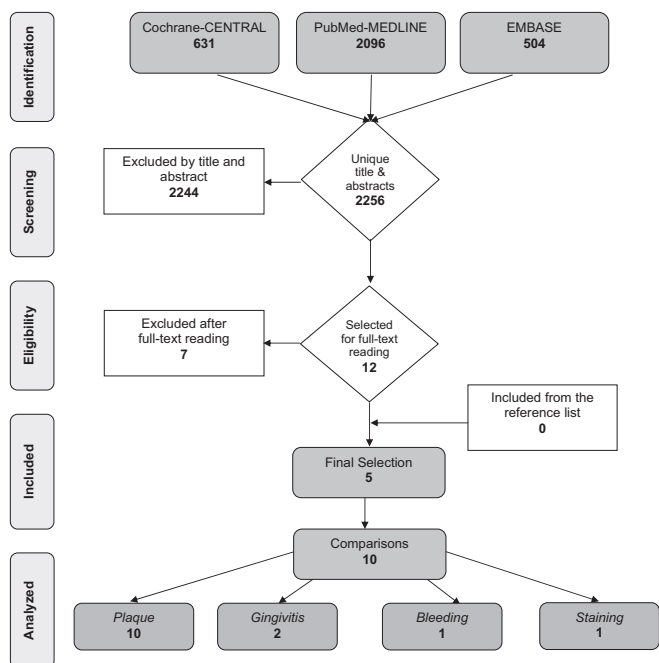


Fig. 1. Search, selection and analysis process.

Only III acknowledges Colgate-Palmolive for help and (financial) support for the study.

Study quality and risk of bias assessment

Quality assessment values, including external, internal and statistical validity, are presented in Appendix S1. Based on a summary of these criteria, the estimated potential risk of bias is low in four of the five studies (I, III, IV and V) and moderate for one study (II).

Study outcomes

Comparison baseline – end (results within groups)

Appendix S3 A–D shows the results from the data extraction. Statistically significant improvements between baseline and end data were not part of the report in any of the selected studies.

Comparison between groups

Table 2 shows the individual outcomes of the studies with respect to differences between the CHX DF/gel and the CHX MW. The non-brushing studies all showed a significant difference in plaque scores in the favour of the CHX MW over the various CHX DF/gel formulations (III, IV, V). With the exception of the 1% CHX DF/gel product there was no statistical significant difference with the 0.2% CHX MW product used in V. The only study assessing bleeding scores (I) showed no significant difference between the CHX DF/gel and CHX MW. Only study II with a 6-week duration showed a signifi-

cant difference in favour of the CHX DF/gel on both plaque and gingivitis scores. The 6-month brushing study (I) did not reveal a significant difference in plaque and gingivitis scores; moreover, this was the only study that showed data on tooth discoloration where significantly more staining was found for the use of the CHX MW compared to the CHX DF/gel.

Meta-analysis

From the collective data of the studies, a meta-analysis only appeared possible on 'the novo' plaque accumulation studies after 3 days of non-brushing (IV, V). Figure 2 shows a significant effect in favour of the CHX MW (DiffM 0.27 ($P < 0.0001$), 95% CI: [0.14;0.39]) as compared to the CHX DF/gel. Test for heterogeneity was not significant ($P = 0.21$).

Grading the 'body of evidence'

Table 3 shows a summary of the various aspects which were used to rate the quality of evidence and strength of recommendations according to GRADE (14, 15). Tooth discoloration and bleeding scores were not weighted because there was only one publication providing information on both these aspects. Because the data are on average fairly consistent, including studies that had a 'low-to-moderate estimated risk of bias', overall results are generalizable as daily oral care products, but the data are imprecise with the possibility of a publication bias. Taken as a whole, the strength of the recommendation emerging from this systematic review is therefore considered to be 'moderate' for plaque scores and low for the gingival index outcome.

Discussion

The bisbiguanide antiseptic CHX is the most thoroughly investigated antiplaque substance. It has been clinically tested and successfully used in dentistry for various clinical applications for more than 40 years (16). It has excellent plaque inhibitory properties with an immediate antibacterial effect as well as a prolonged bacteriostatic effect on the oral flora (17). Clinical studies ranging from 3-month up to 2-year duration with CHX-containing mouth rinses have demonstrated significant reductions in plaque and gingivitis (8). Long-term clinical studies have also confirmed the excellent safety profile of CHX formulations (18).

The observed plaque inhibitory action of CHX has yet to be superseded (19, 20). Encouraging results from experimental CHX-containing dentifrices have been obtained (21, 22). It has also been apparent, however, that the activity of a CHX MW is difficult to equal (23). The antimicrobial and antiplaque properties of CHX may be compromised by components contained in any formulation including anionic detergents, some dentifrice abrasives, calcium ions and sodium monofluorophosphate, all of which may reduce the availability of CHX in a DF. This is why most of the earlier studies showed no efficacy for CHX DFs mainly because the CHX had been

Table 1. Overview of the brushing/non-brushing/finger application studies processed for data extraction

Authors (year) Title	Design, blinding, test period	Subjects (follow-up), gender age (mean and range)	Groups, brand	Regimen	Conclusion
Brushing Used with a toothbrush (I) Sanz et al. (1994) (36)	RCT Parallel Double-blind 6 months	<i>Participants with gingivitis</i> (GI > 0.7) 140♂ (127♂) ♀ 84♂ ♂ 56♂ Mean age: 32.3♂ Range: 18–61 years	Experimental-DF (CHX 0.4%) + placebo-MW DF + CHX MW (0.12%) Peridex™ Procter & Gamble, USA	Brushing Rinsing/twice daily	No significant difference between CHX 0.4% DF and 0.12% CHX MW. CHX 0.4% DF will contribute less staining compared with using a 0.12% CHX MW.
Finger application (II) Pai et al. (2004) (37)	RCT Parallel ? 6 weeks	? 24♂ (24♂) ♀ ? ♂ ? Mean age: ? Range: 25–39	CHX gel (0.2%) CHX MW (0.2%) Rexidine Centaur Labs, India	Applying 1 g with index finger throughout the oral cavity/twice daily Rinsing/10 ml/ twice daily/1 min	Better therapeutic efficacy can be achieved using CHX gel for treating oral infections than conventional treatment using a CHX MW.
Non-brushing (III) Addy et al. (1989) (23)	RCT Cross-over Single-blind 5 days per regimen	<i>Participants with a high standard oral hygiene and gingival health</i> 15 (15) ♀ 10 ♂ 5 Mean age: 23♂ Range: 19–28 years	DF Colgate® Palmolive, USA (0.5% CHX + 0.525% betaine) DF Colgate® Palmolive, USA (0.5% CHX + 0.76% miranol C ₂ M) DF Colgate® Palmolive, USA (0.5% CHX + 2% Tween 20) DF Colgate® Palmolive, USA (0.5% CHX + 0.5% Emphos) DF Colgate® Palmolive, USA (0.5%CHX Emphos + monofluorophosphate) CHX MW (0.2%) Corsodyl® GlaxoSmithKline, UK	Rinsing with slurry (3 g + 10 ml water)/ twice daily/1 min Rinsing/10 ml/ twice daily/1 min	All CHX 0.5% DFs were less effective than a 0.2% CHX MW.
(IV) Slot et al. (2007) (27)	RCT Parallel Single-blind 3 days	<i>Non-periodontitis patients</i> 69♂ (67♂) ♀ 53♂ ♂ 14♂ Mean age: 21.7♂ Range: 18–39	CHX DF gel (0.12%) Perio-Aid® DentaId, Spain CHX MW (0.12%) Perio-Aid® DentaId, Spain	Applying gel in fluoride tray/ twice daily/2 min Rinsing/15 ml/ twice daily/1 min	0.12% CHX MW is significantly more effective than the application of 0.12% CHX DFG via a tray.
(V) Slot et al. (2010) (26)	RCT Parallel Single-blind 3 days	<i>Non-periodontitis patients</i> 83♂ (82♂) ♀ 64♂ ♂ 18♂ Mean age: 22.2♂ Range: 18–31	CHX DF gel (0.12%) Perio-Aid® DentaId, Spain CHX gel (1%) Corsodyl® GlaxoSmithKline, UK CHX MW (0.2%) Corsodyl® GlaxoSmithKline, UK	Applying gel in fluoride tray/ twice daily/2 min Rinsing/10 ml/ twice daily/1 min	The effect of a 1% CHX gel application is significantly greater than that of 0.12% CHX DF gel. The 1% CHX gel applied via a tray and 0.2% CHX MW rinse were comparably effective

RCT, randomized clinical trial; CHX, chlorhexidine; CHX MW, chlorhexidine mouthwash; CHX DFG, chlorhexidine dentifrice gel; CHX gel, chlorhexidine dentifrice gel; Placebo-MW, placebo mouthwash; DF, dentifrice?; not specified/unknown.

Table 2. A descriptive summary of statistical significance between the intervention and the comparison

Method	Author(s) #	Intervention	Concentration (%)	Plaque scores	Gingival index	Bleeding scores	Tooth discoloration scores	Comparison	Concentration (%)
Brushing Used with a toothbrush	(I)	CHX DF + placebo-MW	0.4	O	O	O	+	CHX MW + DF	0.12
Finger application	(II)	CHX gel	0.2	+	+	□	□	CHX MW	0.2
Non-brushing	(III)	CHX DF/betaine	0.5	–	□	□	□	CHX MW	0.2
		CHX DF/miranol	0.5	–	□	□	□	CHX MW	0.2
		CHX DF/Tween	0.5	–	□	□	□	CHX MW	0.2
		CHX DF/Emphos	0.5	–	□	□	□	CHX MW	0.2
		CHX DF/Emphos + MFP	0.5	–	□	□	□	CHX MW	0.2
	(IV)	CHX DF gel	0.12	–	□	□	□	CHX MW	0.12
	(V)	CHX DF gel	0.12	–	□	□	□	CHX MW	0.2
		CHX gel	1	O	□	□	□	CHX MW	0.2

For abbreviations, see Table 1: +, significant difference in favour of intervention group; –, significant difference in favour of comparison group; O, no significant difference; □, no data available.

inactivated in the formulation. It is therefore not possible to extrapolate results from the use of active ingredients in a simple mouthwash formulation to effects achievable with complex vehicles such as toothpastes (23).

CHX dose, delivery and activity

Discussing the findings of this systematic review and the results of the individual studies revealed that it is necessary to consider factors relevant to the plaque inhibitory action of CHX. In an extensive narrative review of the literature pertaining to CHX, it was established that when delivered as a rinse, plaque inhibition is dose dependent (24). Moreover, it was concluded that the plaque inhibitory effect of CHX is derived from the antiseptic adsorbed to the tooth surface and not from the originally hypothesized slow release from an oral reservoir. This explains why small doses of CHX applied directly to the teeth, for example from a spray, provide a similar plaque inhibitory effect as compared to much larger doses from mouth rinses (25). Extrapolating this further, it becomes apparent that the mode of CHX

delivery is important to ensure contact of the antiseptic with all tooth surfaces as is the activity of CHX within any formulation.

Considering the delivery method, a previous systematic review found that brushing with a CHX gel compared to a regular dentifrice was not effective against plaque and gingivitis, but when the CHX is incorporated in a DF, it can be effective (9). Brushing produced evidence showing poor distribution of CHX from the gel over tooth surfaces and much better results have been reported when the CHX gel was delivered in trays (for review, see 24). This is consistent with the comparable findings for the 1% CHX gel in trays and 0.2% CHX MW used in the study of Slot *et al.* (26). The lack of similar findings for the 0.12% CHX DF/gel delivered in trays compared to the 1% CHX gel in trays and 0.2% CHX MW in this study (26) could be the CHX dosage. A similar conclusion, concerning dosage, could be drawn for the related study (27), where the same 0.12% CHX DF/gel was less effective than a 0.12% CHX MW.

Two hypotheses go against dose as the only explanation for the results of these two studies. When estimating the dose of

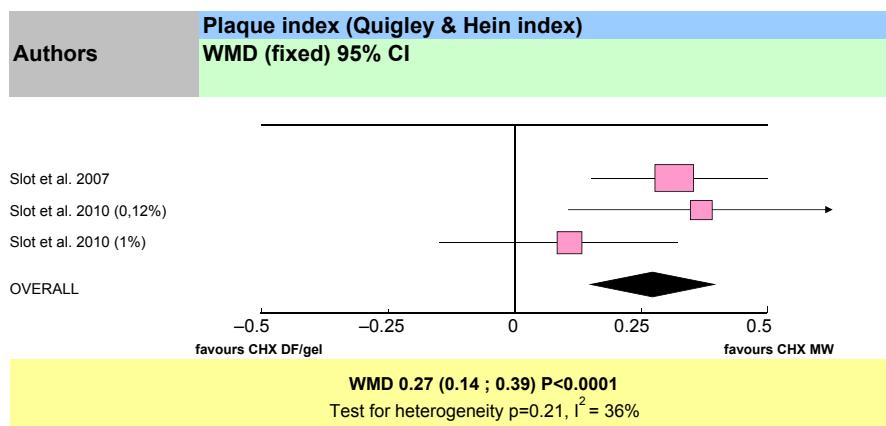


Fig. 2. Meta-analysis on plaque scores for non-brushing studies.

Table 3. GRADE evidence profile, for the impact of CHX MW compared to CHX DF/gel on plaque, clinical parameters of gingival inflammation and tooth discoloration from the presented systematic review

	Risk of bias	Consistency	Directness	Precision	Publication bias	Strength of recommendation
Plaque scores	Low to moderate	Moderate	Partly generalizable	Imprecise	Possible	Moderate
Gingival index	Low to moderate	Inconsistent	Indirect	Imprecise	Possible	Low

CHX MW, chlorhexidine mouthwash; CHX DF/gel, chlorhexidine dentifrice or gel.

CHX from the DF/gel at 7–9 mg, which was approximately half that of the 0.12% MW (27) and one-eighth that of the 1% CHX gel (26), such a dose applied directly to the teeth is still high on the CHX dose–response curve for plaque inhibition and certainly higher than employed in studies using 0.2% CHX sprays (for review, see 24). However, the 0.12% CHX DF/gel in both studies (26, 27) did not provide a significant difference compared to a conventional fluoride toothpaste. Taking both study results into account, the data suggest that the CHX DF/gel was partially or totally inactive in respect of CHX. A similar argument can be employed in respect of the findings of the Addy *et al.*'s (23) study to explain the findings of the reduced plaque inhibitory effects of the CHX DF/gel formulations compared to CHX MW. A similar argument can be found in the discussion section of the published paper. Essentially, the authors pointed out that the various CHX DF/gel formulations were used at a dose of 15 mg twice per day, which was well within the effective range for CHX delivered as a MW. This together with the finding of greater plaque inhibition than the placebo DF but no difference from the triclosan zinc citrate DF suggests a significant inactivation of CHX in the various CHX DF/gel formulations used in this study III (23).

The two brushing studies on plaque and gingivitis (I, II) are more difficult to discuss in respect of the action of the experimental CHX DF/gel formulations used. Both studies used test formulations in a 'normal tooth brushing' model in which additionally the Hawthorne effect of improved mechanical cleaning can be expected (for review, see 24). The improved mechanical oral hygiene narrows the margin to demonstrate benefits derived from chemical adjuncts such as CHX. In study I, a Hawthorne effect was apparent as plaque and gingivitis scores decreased in both the CHX groups and the control group. To further interpret the results however, one has to make two assumptions as to the use of the various formulations because exact details were not specified. Firstly, the amount of DF used on the brush was similar to that reported for 'usual' tooth brushers, namely 1–1.2 g. Secondly, the CHX MW product in the positive control group was used as recommended by the manufacturer, namely 15 ml rinsed for 30 s. If these assumptions are correct, the CHX DF/gel would deliver a dose of 4–5 mg of CHX and the MW 18 mg of CHX. While this is a large difference in dose, one has to remember that the CHX DF/gel was delivered directly to the teeth but the MW was used throughout the mouth. Combined with an expected Hawthorne effect, this could explain the findings for the CHX DF/gel similar to the CHX MW on plaque and

gingivitis, particularly because both were significantly more effective than the control group of DF with a placebo rinse. Unfortunately, it does not explain the increased tooth staining in favour of the CHX MW over the CHX DF/gel; CHX activity in the latter does not appear in question as staining was greater than in the control group.

Study II is perhaps more difficult to interpret. Nevertheless, as with study I, a Hawthorne effect was apparent with improvements in plaque and gingivitis in all groups including the control group. Surprisingly however, the 0.2% CHX DF/gel was significantly more adjunctive to tooth brushing with toothpaste than 0.2% CHX MW despite the fact that the gel delivered 2 mg CHX throughout the mouth on a finger compared to 20 mg CHX from the rinse product. Possible inactivity of the CHX MW is not out of the question and has been reported for a well-known European mouth rinse (for review, see 24), although this is unlikely to have been the complete explanation as the CHX MW group was significantly better than control. The observed efficacy of the CHX gel was suggested to be the result of the mucoadhesive property of the carbopol, which was used as a gelling agent. Carbopol has the property to stay in the oral cavity for an extended period, thereby permitting drug release for a prolonged duration (28, 29). This is unlikely to explain the findings because the substantivity of CHX from MW is in itself more than 12 h, and as stated, the mechanism of action is from CHX adsorbed to teeth and not derived from a slow-release mechanism (for review, see 24). The tray application used in study IV and study V is a research model to test the potential of CHX gel or dentifrice without the mechanical interference of a toothbrush. Finger application as performed by study II is not a representative oral hygiene intervention. This item is addressed in the methodological quality and risk of bias scores (Appendix S1). However, it is not taken into account for estimating the authors' estimated risk of bias.

Series of papers

The present review is the last one out of a series of four studies addressing the efficacy of CHX dentifrice or gel. The first investigation evaluated a 0.12% CHX DF/gel product (27) marketed for long term, according to the manufacturer's instruction to be used twice daily, on a toothbrush. The study showed that within the limitations of the 3-day non-brushing design, application of 0.12% CHX dentifrice gel in a prefab fluoride tray was not significantly different from a similar application of a regular fluoride DF on plaque accumulation. Use of a 0.12% CHX MW,

however, proved to be significantly more effective than that of the 0.12% CHX DF/gel (27). In the Netherlands, a 1% CHX gel is available, intended according to the manufacturer's instruction for short-term use up to a maximum of 15 days. A second study (26) using a fluoride tray for application comparing the previous 0.12% CHX DF/gel, a 1% CHX gel, a 0.2% CHX MW and a regular fluoride toothpaste also in a 3-day non-brushing design showed a significantly greater plaque inhibition by the 1% gel and the 0.2% CHX MW than by the 0.12% CHX DF/gel and no significant difference between the 1% gel and 0.2% CHX MW products. Again, the 0.12% CHX DF/gel was not significantly different from the fluoride toothpaste against plaque. Slot *et al.* (9) recently performed a systematic review to evaluate the effect of tooth brushing with a CHX DF or gel on clinical parameters of plaque, gingivitis and tooth staining. From the collective evidence, it was concluded that tooth brushing with a CHX gel did not provide a significant effect on plaque scores and gingival inflammation. The evidence for brushing with a CHX DF, however, indicated that a DF formulation can be effective with regard to the control of plaque and gingivitis. As expected, the known side effect of tooth staining with these CHX products was observed, and the authors of the review repeated concerns over the negative impact that this may have in patient compliance with their use (9). The present review has shown that compared to CHX MW, the CHX DF/gel or CHX DF is less effective with regard to plaque scores and no difference in bleeding scores or the gingival index data was observed. Recently with respect to CHX MW, a systematic review was performed. It was concluded that in patients with gingivitis, CHX MW together with oral hygiene versus placebo or control MW provides significant reductions in plaque and gingivitis scores, but also as a corollary significant increase in staining scores (8). The present systematic review comparing CHX DF/gel to CHX MW also found an increased tooth surface discoloration with the CHX MW in the reports of the selected papers.

Side effects

Reversible local side effects such as staining of teeth, fillings, the tongue, impaired taste sensation (30), increased formation of supragingival calculus and occasionally mucous membrane irritation and desquamation (31) are associated with the prolonged use of CHX mouth rinse. To a varying degree, all these factors may adversely affect patient compliance. Therefore, it would be ideal to incorporate CHX in a dentifrice formulation, thus combining mechanical cleaning (and hence reducing its side effects), fluoride delivery, antiplaque benefit and resulting antigingivitis benefit with no added discomfort for patients (23). Irrespective of which type of vehicle is used, the extrinsic staining effect remains problematic. To reduce this tendency, a number of strategies could be suggested: reduce the overall oral dosage of the gel, use the product just before retiring to bed and use a whitening dentifrice (32). The use of the whitening paste has been shown to reduce CHX-induced staining and may be expected to have a beneficial

effect (33). The findings of a study by Claydon *et al.* (32) highlighted the significant problem of staining seen with the use of CHX products. But even when used at reduced dosage as the last effort before bedtime and when used in conjunction with the whitening dentifrice, 30% of the participants still found the staining unacceptable (32).

Limitations

- One limitation is patient blinding, because both CHX experimental groups used different products with their own application method. And whether a brushing or a non-brushing model is used blinding is not feasible.
- The ADA requirements for a seal of acceptance Chemotherapeutic Products for Control of Gingivitis require a study period of 6 months to evaluate both the efficacy and safety of chemical agents as well as patients' compliance (34). Only one study on CHX dentifrice extended up to 6 months (study I) and did not show a significant effect in favour of any product.
- This summary of the evidence is primarily established by vote counting, which does not take into account the variation in scoring indices used. Vote counting procedures probably constitute the most common quantitative technique used in the reviewing of research. Such a technique is appealing because it is easy to use, requires a minimal amount of statistical data from each study to be integrated and permits the merging of analyses from different studies. However, vote counting does not include differences between methods applied within the studies and does not account for differences in the sample size or the actual strengths of the values (12).
- Because there were fewer than four studies, fixed-effects analysis was used, as the estimate of between-study variance is poor for analyses with low numbers of studies (35).

Conclusion

This review has shown that CHX gel can be successfully formulated and will inhibit plaque growth to some degree, but not to the same extent, as a CHX MW. When CHX DF/gel is used in a non-brushing model, it is significantly less effective in plaque inhibition compared to CHX MW. Based on one study when CHX gel was applied with a finger after brushing, it was significantly more effective on plaque scores and the gingival index. The only other long-term brushing study also with a long follow-up showed that there is no significant difference between CHX DF and CHX MW. However, as a corollary, significantly more tooth discoloration was observed with the CHX MW. Altogether, the data show that when daily oral hygiene cannot be performed, CHX MW is the first product of choice.

Clinical relevance

Scientific rationale for the study

Plaque control is essential for the prevention of gingivitis. Chlorhexidine (CHX) may be a useful adjunct to oral hygiene

when individuals are unable to achieve satisfactory plaque control by mechanical methods alone.

Principle findings

Chlorhexidine MW was significantly more effective on plaque scores than CHX DF/gel. Use of the CHX MW resulted in significantly more tooth discoloration than that of the CHX DF/gel.

Practical implications

Chlorhexidine contributes to plaque reduction and improvement of gingival health. CHX MW is a valuable preventive intervention in dentistry for short- to medium-term use in cases where mechanical plaque control is difficult or impossible. There is limited evidence to support the use of CHX DF with tooth brushing. Finger application with CHX gel seems promising. However, the side effect and tooth discoloration is an obstacle to the generalized use of CHX products and potentially can have a negative impact on patients' compliance limiting the usefulness in daily practice.

Declaration of interest and source of funding statement

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♦ Studies included from the search and selection process for this review.

Supporting information

Additional supporting information may be found in the online version of this article.

Appendix S1. Methodological quality and risk of bias scores of the included studies.

Appendix S2. Overview of the excluded studies and reasons for rejection after full-text reading.

Appendix S3. Mean (SD) scores for the different intervention groups with various indices and their modifications. Within groups analysis are presented.

Appendix S4. Meta-analysis on the ‘*the novo*’ plaque accumulation after 3 days non-brushing.