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REVIEW ARTICLE

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The efficacy of chlorhexidine dentifrice or gel on plaque, clinical parameters of gingival inflammation and tooth discoloration: a systematic review

Abstract: *Aim:* Based on the existing scientific literature, the effect of chlorhexidine (CHX) dentifrice/gel as compared to a regular or placebo dentifrice/gel is established in healthy adults on the primary outcome parameters of plaque and gingivitis scores. As secondary parameter, tooth surface discoloration was evaluated as a side effect. *Materials and methods:* MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials were searched up to July 2013 to identify eligible studies. Included were (randomized) controlled clinical trials, regarding self-performed brushing by adults without periodontitis with a minimum duration of 4 weeks. *Results:* Independent screening of 389 unique titles and abstracts resulted in 16 comparisons. Of these, nine evaluated CHX dentifrice (0.4–1.0%) and 7 CHX gel (0.2–2.0%). It was not possible to perform a meta-analysis; therefore, a descriptive analysis was carried out. Regarding plaque score reduction, the majority of the experiments using a CHX dentifrice provided a significant positive effect. All studies assessing gingival bleeding as parameter for gingivitis observed a significant reduction in favour of CHX dentifrice over placebo dentifrice. Tooth surface discoloration was more pronounced with CHX dentifrice. The combined data concerning parameters of interest for CHX gel compared with a placebo did not show a trend towards a beneficial effect on plaque and bleeding scores. *Conclusions:* Within the limitations of this analysis, it may be concluded that toothbrushing with a CHX gel does not provide conclusive evidence. Brushing with a CHX dentifrice can be effective with regard to the control of plaque and gingivitis. Tooth surface discoloration was observed as side effect, which potentially can have a negative impact on patients' compliance.

Key words: chlorhexidine; CHX dentifrice; CHX gel; CHX toothpaste; plaque; systematic review; tooth staining

Introduction

Removal of plaque by the individual continues to be considered as the foremost effective tool to control and prevent gingivitis (1, 2). The most reliable methods currently used for plaque removal are toothbrushing and other mechanical cleaning procedures (for review, see 3). As adequate plaque control is difficult to attain by most people, research efforts have

been directed towards the development of safe and efficacious chemical antiplaque agents (2, 4).

Löe and Schiött (5) reported on the inhibition of plaque formation and gingival inflammation in students rinsing twice daily with a 0.2% solution of chlorhexidine (CHX). Ever since, the effect of CHX digluconate has been of interest in dental research and various modes of administration have been studied. CHX mouthrinse as adjunct to mechanical oral hygiene versus placebo or control mouthrinse provides significant reductions in plaque and gingivitis scores. This has recently been established by Van Strydonck and co-workers (6) established in a systematic review of the existing scientific literature that in gingivitis patients, the corollary is a significant increase in tooth surface discoloration score. Discoloration of tooth surfaces, restorations and the dorsum of the tongue, desquamation and soreness of the oral mucosa (7, 8) are all well-known side effects of CHX. Another systematic review has recently been published on medicated chewing gum (9). The meta-analysis showed that CHX provides a beneficial effect on plaque inhibition.

It would be ideal to incorporate CHX in a dentifrice formulation (2) as most patients daily use a dentifrice. The potential of this has been shown in a non-brushing study where the use of CHX dentifrice resulted in significant less plaque and gingivitis as compared to the placebo (10). At present, a systematic evaluation has not yet been performed on the effect of toothbrushing with a CHX dentifrice or gel on clinical parameters of plaque and gingivitis, evaluating the side effects and tooth surface discoloration. Therefore, this paper systematically evaluated the current scientific literature on brushing with CHX dentifrice or gel to add 'evidence-based' knowledge.

Materials and methods

This systematic review was conducted in accordance with the guidelines of Transparent Reporting of Systematic Reviews and Meta-analyses (11, 12).

Focused question

What is the effect of brushing with chlorhexidine (CHX) dentifrice or gel versus a placebo/control dentifrice or gel on parameters of plaque, gingival inflammation and tooth surface discoloration in adult patients with gingivitis?

Search strategy

Three Internet sources of evidence were used to search for appropriate papers that satisfied the study purpose. These included the National Library of Medicine, Washington, DC. (MEDLINE-PubMed), the Cochrane Central Register of Controlled Trials (CENTRAL) and EMBASE (Excerpta Medical Database by Elsevier). All databases were searched starting from their earliest records until 01 July 2013. The structured search strategy was designed to include any published paper that evaluated the effect of CHX dentifrice and/or gel on plaque and the parameters of gingival health. The search strategy was customized according to each database that was searched (for details on the used search terms, see Box 1).

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 being used taking into account differences in controlled vocabulary and syntax rules.

The following terms were used in the search strategy:

[<{*Agent*: [MeSH terms/all subheadings] chlorhexidine OR [textwords] chlorhexidine OR chlorhexidine phosphanilate OR chlorhexidine di-gluconate OR chlorhexidine gluconate OR chlorhexidine di-acetate OR zinc-chlorhexidine OR chlorhexidine gluconate lidocaine hydrochloride OR CHX OR CHX formulations}

AND

{*Vehicle*: [MeSH terms/all subheadings] Toothpaste OR Dentifrices OR [text words] toothpaste OR toothpastes OR dentifrices OR dentifrice OR gel}>

AND

{Outcome/disease: [MeSH terms/all subheadings] gingivitis OR gingival hemorrhage [text words] gingivitis OR gingivit* OR gingival bleeding OR gingival hemorrhage OR gingival diseas* OR gingival index OR gingival inflammation OR bleeding on probing OR papillary bleeding OR bleeding index OR sulcus bleeding index OR plaque index OR dental plaque OR plaque OR interdental plaque OR interproximal plaque OR dental deposit* OR stain OR discoloration OR calculus OR tartar}]

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

Screening and selection

Two reviewers (DES & GAW) independently screened the titles and abstracts for eligible papers. 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. When the abstract was not clear or no abstract was available but the title seemed to be relevant, the paper was selected for full-text reading. After selection, the full-text papers were read in detail by two reviewers (CEB & DES). Any disagreement between the two reviewers was resolved after additional discussion. If a disagreement persisted, the judgement of a third reviewer (GAW) was decisive. Papers that fulfilled all selection criteria were processed for data extraction. All reference lists of the selected studies were handsearched by two reviewers (CEB & DES) for additional published work that could possibly meet the eligibility criteria of the study. Unpublished work was not sought.

The eligibility criteria were as follows:

- Randomized controlled clinical trials (RCTs) or controlled clinical trials (CCTs).
- Conducted in humans:
  - ≥16 years of age.
  - Good general health.
  - Participants with gingivitis/no periodontitis patients.

- Intervention: toothbrushing with CHX dentifrice and/or gel.
- Control group: toothbrushing with placebo dentifrice and/or gel.
- Supragingival use of CHX dentifrice and/or gel.
- Clinical outcome parameters: plaque, gingivitis, bleeding upon probing and tooth surface discoloration.
- No dental implants, orthodontic treatment or (partial) dentures.
- Duration of ≥4 weeks [for rationale, see Adjunctive Dental Therapies for the Reduction of Plaque and Gingivitis (13)].
- Manuscripts written in the English language.

Assessment of heterogeneity

Factors that were recorded to evaluate the heterogeneity of the primary outcome across studies were as follows:

- Characteristics of the participants.
- Characteristics of the interventions.
- Characteristics of the trial settings and investigators.

Quality assessment

Two reviewers (CEB & DES) scored the methodological qualities of the included studies. This was assessed according to the method that has been described in detail by Keukenmeester *et al.* (14). For the criteria listed, see online Appendix S2. In short, when random allocation, defined eligibility criteria, blinding of examiners, blinding of patients, balanced experimental groups, identical treatment between groups (except for the intervention) and reporting of follow-up were present, the study was classified as having a low risk of bias. When one of these seven criteria was missing, the study was considered to have a moderate risk of bias. When two or more of these criteria were missing, the study was considered to have a high risk of bias, as proposed by Van der Weijden *et al.* (15).

Statistical analyses

Data extraction

From the papers that met the eligibility criteria, data were extracted with regard to the effectiveness of CHX gel and/or dentifrice by two reviewers (CEB & DES). Mean values and standard deviations (SDs) of baseline, end and incremental scores on the parameters of interest were extracted from the text. For studies that presented intermediate assessments, the baseline and final evaluations were used for this review. Some of the studies provided standard errors of the mean. Where possible, the authors calculated standard deviation based on the sample size ($SE = SD/\sqrt{N}$). For those articles that provided insufficient data to be included in the analysis, the first or corresponding authors were contacted whether xthey could provide additional data. This warrants a precise estimate because any data approximation in figures was avoided.

Data analysis

Studies were analysed for similarities and suitability for meta-analysis. After a preliminary evaluation of the selected papers, it was found that considerable heterogeneity was present in the study designs, characteristics, outcome variables and results. It was therefore not possible to perform a quantitative analysis of the data and subsequent meta-analysis. The pooled data were analysed in a descriptive format by vote counting.

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 rank the evidence emerging from this review (16, 17) regarding CHX dentifrice and CHX gel. Two reviewers (DES & 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 searches of the three databases resulted in 389 unique papers (for details, see Fig. 1). In total, 363 papers were excluded based on title and/or abstract. Of the 26 remaining papers selected for full-text evaluation, 15 papers were not suitable in relation to the focused question. Reasons for exclusion are detailed in the online Appendix S1. In total, 11 publications were considered eligible and were processed for assessment of heterogeneity. These provided 12 experiments and 16 comparisons, of which nine evaluated CHX dentifrice and seven CHX gel.

Assessment of study quality and heterogeneity

Table 1 provides a brief overview of the design details of the 11 included studies. Evaluation of the selected papers showed considerable heterogeneity, which is described below.

Characteristics of the participants

Information about the number, gender and age of participants is given in Table 1 (study number in Roman numerals). Selection criteria of the included studies for the level of gingivitis were clinical evidence of gingivitis (GI > 0.7) (IV), a mean GI of ≥0.5 (VI), a GI of ≥2 in a minimum number of teeth in each quadrant (II) and a bleeding index ≥30% (I). The other studies provided no specific information of the participants' gingival status (II, V, VII, VIII, IX, XI). Claydon (2006) (II) and Yates

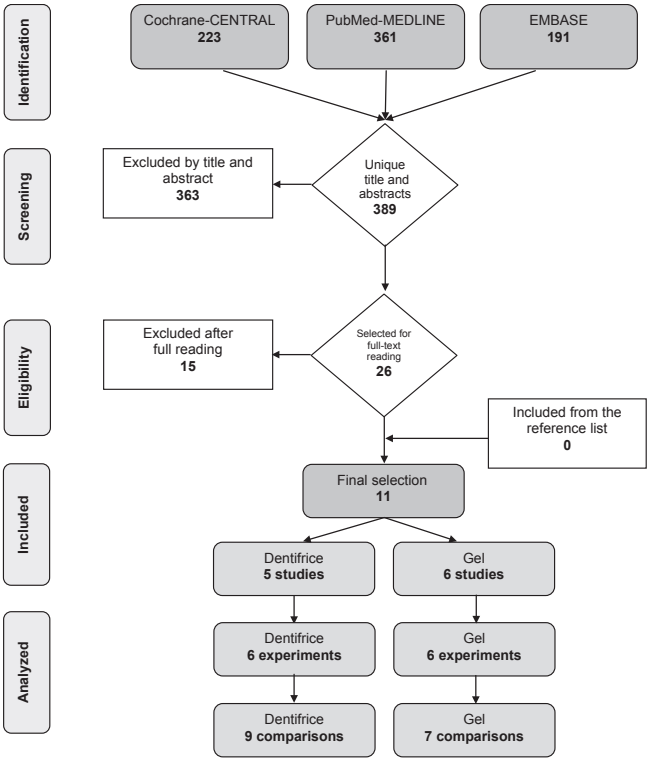

Fig. 1. Search, selection and analysis process.

et al. (1993) (VI) were the only authors who mentioned the number of smokers in their groups. Claydon (II) mentioned that a randomization schedule was used which stratified for smokers, and Soukoulos *et al.* (2004) (III) and Pereira *et al.* (2013 (I) selected only non-smokers.

Characteristics of the interventions

Oral prophylaxis prior to the study

Six studies performed oral prophylaxis at baseline consisting of scaling and polishing (II, IV, V, VI, X, XI). Five studies did not perform a dental prophylaxis or did not specifically mention whether an oral prophylaxis was performed (I, III, VII, VIII, IX). One of these mentioned that no dental prophylaxis, that is, scaling and polishing the teeth, was carried out before and during the trial, except for treatment of some carious lesions (VII). Another study mentioned that when tooth surface discoloration became unacceptable, participants could attend the study dental hygienist involved in the study to have tooth surface discoloration removed by polishing (VII). Teeth were polished on the last day of the experiment after the indices were recorded in one study (I).

Side effects

All included studies reported on observed side effects, both local and systemic. Apart from the taste (bitter or alteration) (II, VII, VIII) and tooth surface discoloration, no other side effects were reported.

Characteristics of the trial settings and investigators

Industry funding source and publication bias

Five of 11 papers mentioned involvement of a third party. This was described as 'supported by' (II, VI, VII, IX, XI) or as co-authors being related to industry (II, IV). The studies I and V share co-authors, and the studies IX, X and XI all are from the same research group in Oslo Norway.

Study quality and risk of bias assessment

Quality assessment values, including the internal, external and statistical validity, are presented in online Appendix S2. Based on a summary of these criteria, the estimated potential risk of bias is low for five studies (I, III, IV, VI, IX), moderate for three studies (V, VII, XI) and high for three studies (II, VIII, X).

Comparison between groups upon completion of the study

Mean (SD) scores for the different intervention groups with various indices and their modifications and within-group analysis are presented in online Appendix S2. Table 2 presents a summary of the descriptive data concerning significant differences with respect to scores of plaque, gingival index, bleeding on probing and tooth surface discoloration as presented separately for CHX dentifrice and gel.

Six of the nine comparisons using CHX dentifrice evaluated the effect on plaque scores. The CHX dentifrices with concentration of 0.4%, 0.6%, 0.8% and 1% all had a significant positive effect on plaque inhibition compared with the placebo (IV, VI, VIII, XI). In addition, three of six comparisons with the CHX dentifrice found a significant improvement in the gingival index in favour of the CHX dentifrice (IV, VI). Moreover, all four CHX dentifrice comparisons that assessed gingival bleeding found a significant effect in favour of the CHX dentifrice (III, VI, VIII). Tooth surface discoloration following the use of CHX dentifrice was reported as a corollary effect (II, VI, X). One comparison (III) did not show increased tooth surface discoloration.

Two of the seven comparisons using CHX gel did not find a significant effect as compared to a placebo. In the five comparisons evaluating CHX gel, two studies (I, V) found a significant effect in favour of the CHX gel on plaque score reduction. Only one of three studies assessing the bleeding scores showed a significant effect (I). Two comparisons (II) showed significantly more tooth surface discoloration, whereas one (IX) showed no increased staining.

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 (16, 17). Because the data are rather inconsistent for CHX gel, with on average a 'moderate estimated risk of bias', and the studies' results are not generalizable as daily oral care products, the strength of the recommendation to use CHX gel is 'weak' to 'very weak'. For

Table 1. **Overview of the studies processed for data extraction**

# Authors (year)	Study design, duration	# Participants baseline (end), gender, age (mean/range), oral prophylaxis (OP)	Groups	Regimen: use and instruction	Conclusions of the authors of the original papers
I Pereira *et al.* (2013) (33)	RCT Parallel Double blind 3 months	20 (20) ♀: ? ♂: ? Mean age: ? Age range: ? No OP	CHX gel 2% Placebo gel	Brush 3× daily for 1 min CHX gel: a full toothbrush head Placebo gel: a full toothbrush head No special brushing technique	At day 90, there was a statistically significant difference in PI and BI scores between the control and test group
II Claydon *et al.* (2006) (34)	RCT Parallel Single blind 6 weeks	164 (157) ♀: ? ♂: ? Mean age: ? Age range: ? OP	CHX gel 1% CHX gel 1% reduced Fluoride dentifrice	Brush 2× daily for 1 min Reduced: 2× brushing of which one time with CHX gel CHX gel: a full toothbrush head Fluoride dentifrice: a full toothbrush head No special brushing technique No interdental cleaning was allowed	A low dose of CHX gel at night and a whitening paste in the morning produced a significant amount of stain that 30% of participants considered unacceptable
III Soukoulis & Hirsch (2004) (35)	RCT Parallel Double blind 8 weeks	33 (?) ♀: 17 ♂: 16 Mean age: 45.6 Age range: 23–63 No OP	CHX gel 0.2% (Periogard, Colgate, NSW, Australia) Placebo gel	The gel was to be used as a dentifrice for a minimum of 2 min daily One toothbrush length of the gel OHI: pamphlet, making sure that it made contact with gingival tissues adjacent to the teeth No other dentifrice or interdental cleaning was allowed No rinsing, eating or drinking was allowed for 30 min after gel application	No statistical difference in plaque scores and gingivitis scores between the groups
IV Sanz *et al.* (1994) (2)	RCT Parallel Double blind 6 months	137◊ (125◊) ♀: 81 ♂: 56 Mean age: 32.3◊ Age range: 18–65 OP	CHX dentifrice 0.4% + placebo mouthrinse Placebo dentifrice + placebo mouthrinse	Brushing 2× daily Rinsing 2× daily with placebo rinse No additional OHI	CHX-containing dentifrice was effective in reducing plaque accumulation and gingival inflammation over a 6-month period
V Smith *et al.* (1994) (36)	RCT Parallel Single blind 6 weeks	120 (114) ♀: ? ♂: ? Mean age: ? Age range: ? OP	CHX gel 0.2% Regular dentifrice	Brush 2× daily for 1 min OHI: ? No other dentifrice or interdental cleaning was allowed	0.2% CHX gel significantly reduced the amount of plaque formed compared with regular dentifrice over a period of 6 weeks

(Continued)

Table 1. ***(Continued)***

# Authors (year)	Study design, duration	# Participants baseline (end), gender, age (mean/range), oral prophylaxis (OP)	Groups	Regimen: use and instruction	Conclusions of the authors of the original papers
VI Yates *et al.* (1993) (37)	RCT Parallel Double blind 6 months	296 (269) ♀: 197 ♂: 99 Mean age: ? Age range: 18–61 OP	CHX dentifrice 1% CHX dentifrice 1% + NaF Placebo dentifrice	Brushing 2× daily for 1 min Using sufficient paste to cover the head of the brush No OHI No use of other oral hygiene products allowed	Plaque, gingival and bleeding scores improved significantly in the active groups
VII Emilson & Fornell (1976) (38)	RCT Parallel Double blind 12 months	37 (36) ♀: 13 ♂: 24 Mean age: 23 Age range: 21–28 No OP	CHX gel 0.5% Placebo gel	Brush once a day for 2 min One toothbrush length strip of the gel ± 0.5 g No OHI No use of any other dentifrice besides the gel	The active gel did not markedly influence plaque formation, gingival conditions as compared to placebo gel treatment
VIII Saxton *et al.* (1976) (39)	CCT Parallel Double blind 4 weeks	40 (29) ♀: ? ♂: ? Mean age: ? Age range: 18–30 OP?	CHX dentifrice 0.8% Placebo dentifrice	?	0.8% CHX dentifrice significantly reduced the bleeding and the plaque after 4 weeks
IX Hansen *et al.* (1975) (8)	RCT Cross-over Double blind 4 weeks	36 (36) ♀: ? ♂: ? Mean age: 18 Age range: 16–21 No OP	1% CHX gel Placebo gel	Brush in the evening One toothbrush length of the gel No OHI Additional toothbrushing to the test brushing was performed with a standard commercial dentifrice without abrasives or fluoride	CHX-containing gel seemed to have no effect on gingivitis and only a slight inhibitory effect on plaque formation. Furthermore, an increase in the degree and frequency of tooth discoloration of the tooth surfaces related to the use of active gel was observed.
X Johansen *et al.* (1975) (40)	RCT Parallel Double blind 2 years	73 (60) ♀: ? ♂: ? Mean age: ? Age range: 19–23 OP	CHX dentifrice Abr 1%‡ CHX dentifrice Abr 0.4%‡ Placebo dentifrice Abr‡ CHX dentifrice 0.4%‡ Placebo dentifrice‡	Brushing 2× daily 1 g dentifrice No OHI	No differences were found in the PI and the GI indices between the active and the placebo dentifrices. Discolorations of anterior teeth and fillings were the only side effects observed.
XI Gjermo & Rölla (1971) (41)	RCT Parallel Double blind 2 months	53 (52) ♀: ? ♂: ? Mean age: 23 Age range: ? OP	CHX dentifrice 0.8%‡ CHX dentifrice 0.6%‡ Dentifrice‡	Brush 2× daily for 2 min 1 g dentifrice No particular instructions concerning toothbrushing methods were given No interdental cleaning was allowed	Dentifrice as a vehicle for CHX might be of value in the general preventive application of the agent

OP, at initial appointment, all teeth were thoroughly scaled and polished; ◊, calculated by the authors of this review based on the presented data in the selected paper; ?, unknown/not given;

‡Agents known to interfere with the antibacterial activity of CHX (sulphates, phosphates) were excluded from the dentifrices.

CHX dentifrice, being a product that one could use for daily oral care, the strength is considered to be 'moderate'.

Discussion

By virtue of common usage, the ideal vehicle for the carriage of plaque control agents is a dentifrice (55). A number of ingredients are added to dentifrices to influence the consistency and stability of the product or its function (55). The inclusion of cationic antiseptics, such as CHX, in a dentifrice formulation poses problems (56). Notably, antiseptics can be inactivated by other ingredients, including detergents, for example sodium lauryl sulphate (SLS) (57). The Addy *et al.* (56) study showed that a CHX toothpaste can be formulated, albeit at the expense of available CHX. Nevertheless, CHX has been formulated, successfully, into dentifrices, although few products have reached or lasted in the marketplace. A reason for this might be the observed side effects (2, 37).

The aim of this systematic review was to establish the differential effects of CHX dentifrice or gel versus placebo dentifrice/gel. The selected papers were derived from three databases and provided information that was relevant to the focused question. Evaluating the studies by vote counting showed that a CHX-containing dentifrice can be effective with regard to the control of plaque and gingivitis. For CHX gel, such an effect could not be established. Consequently, brushing with CHX gel was not found to provide a benefit. Tooth surface discoloration was observed as a side effect with both gels and dentifrices that potentially can have a negative impact on patients' compliance (6).

One study (X) does not support the clinical benefit of CHX dentifrice. The explanation brought forward by the authors is that the experimental participants in this study were highly selected being young dental students with good oral hygiene, healthy gingiva and low caries activity. Moreover, influenced by the environment of a dental school, and possibly by experiment itself, their oral hygiene improved during the first 6 months of the study, then stayed relatively constant for the next 12 months. When the students at this time started their clinical training, a further drop in the plaque index values was observed in all groups. Thus, it seems conceivable that a plaque-inhibiting effect of CHX dentifrice in this study design may have been masked by the excellent mechanical tooth cleaning performed by the test participants (40).

Risk of bias assessment

Today, practitioners are under increasing pressure to make sound decisions based on scientific evidence. Partly as a consequence of this daunting challenge, a growing number of organizations have developed ways to arrange our thinking about information and its quality in recent years. These organizations have created evidence, grading schemes to generate dependable systematic reviews of evidence. These schemes or systems continue efforts to reduce the bias that can enter reviews (58). The risk of bias assessment as performed in the present review included all relevant aspects and was a compilations of items as found in various available checklists. The presented high and moderate risk of bias can be a result of poor reporting instead of introducing risk factors during the trial itself. For instance, only three papers (I, II, III) were published during the last decade, while the other papers have been published up to 40 years ago. Therefore, using a modern assessment tool based on the current reporting methodological quality items may lead to on overestimation of the risk of bias. For example, if as suggested to the Cochrane collaboration, 'allocation concealment' (59) was used as a discriminating criterion, this would have had a major impact on the estimated risk of bias and would subsequently reduce the level of all included studies by one step.

Table 2. **A descriptive summary of statistical significance of CHX dentifrice/gel to a comparison**

Study #	Intervention	CHX%	PS	GI	BS	SI	Comparison
X	CHX dentifrice	0.4	0	0	□	−	Placebo dentifrice
	CHX dentifrice	0.4	0	0	□	0	Placebo dentifrice
IV	CHX dentifrice	0.4	+	+	+	−	Placebo dentifrice
XI	CHX dentifrice	0.6	+	□	□	?	Placebo dentifrice
	CHX dentifrice	0.8	+	□	□	?	
VIII	CHX dentifrice	0.8	+	□	+	□	Placebo dentifrice
X	CHX dentifrice	1.0	0	0	□	−	Placebo dentifrice
VI	CHX dentifrice	1.0	+	+	+	−	Placebo dentifrice
	CHX NaF dentifrice	1.0	+	+	+	−	
V	CHX gel	0.2	+	□	□	□	Placebo dentifrice
III	CHX gel	0.2	0	0	?	□	Placebo gel
VII	CHX gel	0.5	0	0	□	?	Placebo gel
II	CHX gel	1.0	□	□	□	−	Placebo dentifrice
	CHX gel reduced	1.0	□	□	□	−	
IX	CHX gel	1.0	0	□	0	0	Placebo gel
I	CHX gel	1.0	+	□	+	□	Placebo gel

PS, plaque scores; GI, gingival index; BS, bleeding scores; SI, staining index; +, significant difference in favour of test group; −, significant difference in favour of control group; 0, no significant difference; □, no data available; ?, inconclusive data that do not allow to draw conclusions concerning statistical significance; NaF, natrium fluoride.

Table 3. **GRADE body of evidence profile for impact of CHX gel and dentifrice compared with the placebo on plaque, clinical parameters of gingival inflammation and tooth discoloration from the presented systematic review**

		CHX gel	
GRADE	CHX dentifrice PS, GI, BS, stain	PS, GI	BS, stain
Risk of bias	Low to moderate	Low to moderate	Low to moderate
Consistency	Consistent	Consistent	Inconsistent
Directness	Indirect	Indirect	Indirect
Precision	Moderate	Low	Low
Publication bias	Not detected	Not detected	Not detected
Body of evidence	Moderate	Weak	Very weak

For abbreviations, see Table 2.

Side effects

CHXs' most clinically undesirable effect is its propensity to stain teeth on prolonged use. It has been reported that CHX may also interfere with the taste function. Another objectionable feature of the antimicrobial is a very bitter taste and CHX can enhance calculus formation (60). Although tooth surface discoloration with CHX products may be an unwelcome side effect, lack of tooth surface discoloration with CHX products would suggest lack of clinical activity as is commonly stated *'If it does not stain it does not work'* (61). Former research evaluating CHX mouthrinses which claimed not to produce tooth surface discoloration was subsequently shown to lack clinical activity (62). Also, results from this systematic review point in the same direction where the two studies (IX, X) providing experiments without a significant increase in tooth surface discoloration also were ineffective for any of the parameters. Based on a recent systematic review, there is moderate evidence that alternately using CHX and oxygenating mouth rinses reduces tooth surface discoloration without interfering with plaque growth inhibition (63). The explanation being that the oxidizing agent probably does not interfere with the CHX but removes food dyes and chromogens which bind to surfaces (for review, see 64), leaving a greyish tooth surface discoloration (65).

Limitations

One limitation is examiner/patient blinding. Because the CHX experimental groups with a long observational period will reveal themselves by tooth surface discoloration, this may have affected the examiner and patient blinding to a certain extent. This is a particular limitation related to CHX that cannot be overcome.

The ADA requirements for a seal of acceptance Chemotherapeutic Products for Control of Gingivitis are a study period of 4 weeks to evaluate both the efficacy and safety of chemical agents as well as patients' compliance (13). According to Gunsolley (66), intermediate-length trials (2 weeks to 2 months), which allow for the assessment of gingivitis, have limitations in that they may not reflect the patients' actual long-term use of the product. However, two studies on CHX dentifrice extended up to 6 months (IV, VI) and both showed a significant effect in favour of the CHX product. Two included CHX dentifrice studies provided data up to 1–2 years (VII, X), both failed to show a positive effect. But, as discussed before, this may find its origin in other factors such as a highly dentally motivated group of participants.

With respect to the gels and dentifrices in the included studies, no exact information on the formulation of each of these products was provided. This is a major factor when considering the physical–chemical properties and the vehiculation of the active ingredients with detergents, given that CHX is a very reactive cation, components from which pastes and gels are usually formulated are sometimes anionic and thus interfere with the action (bioavailability) of the CHX.

Effectiveness of CHX in non-brushing studies

Previous work using a non-brushing model showed that application of CHX with a tray for 3 weeks allowing for experimental gingivitis to develop resulted in a significant reduction in plaque and gingivitis when comparing the specially formulated CHX dentifrice to a placebo (10). More recent work using a 3-day non-brushing model shows that 0.12% CHX dentifrice–gel applied in a tray did not differ on plaque accumulation as compared to a regular dentifrice (67). Using this same model results showed that a 1% CHX gel significantly inhibits plaque formation as compared to a 0.12% CHX dentifrice–gel or a regular dentifrice. In addition, the 1% CHX gel also was comparably effective as a 0.2% CHX mouthwash (68).

This is in agreement with Francis *et al.* 1987 (69) who showed that CHX gel, applied in trays to physically handicapped children, resulted in comparable reductions in buccal and lingual, plaque and gingivitis similarly to a 0.2% CHX mouthrinse.

Various other studies have allowed subjects to apply a pea-sized amount of CHX gel on the teeth gums with the index finger and leaving it undisturbed for approximately 5 min before rinsing. This resulted in significant improvement (as evaluated in studies 6–24 weeks) over the placebo gel group on plaque scores and the gingival index (22–25). The outcome of these studies taken together with the result of this review indicates that CHX gel is not effective in combination with toothbrushing but is effective when applied with a finger to teeth and gums. The studies did not provide an explanation for this observation, but hypothetically the local dose/concentration appears to be a factor in efficacy. This is supported by the study with a positive effect for the 2% CHX gel (I) as compared to three studies using a lower concentration not finding an effect. Also, the plaque inhibitory effect of CHX is derived from the antiseptic adsorbed onto tooth surfaces [for review, see (70)]. An earlier study indicated that the CHX gel did not readily break up and dissolve in saliva and then adsorb onto other tooth surfaces. This investigation, often described as the 'buccal brushing study', also has (71) revealed that brushing a 1% CHX gel on the buccal sur-

faces of teeth had no effect on plaque growth on lingual and palatal tooth surfaces. Therefore, local (finger) application may be the best method for obtaining a benefit from CHX gels.

Conclusion

Within the limitations of this analysis, it may be concluded that toothbrushing with a CHX gel does not provide conclusive evidence. Brushing with a CHX-containing dentifrice is effective with regard to the control of plaque and gingivitis. Tooth surface discoloration was observed as a negative side effect, which potentially may have a negative impact on patients' compliance.

Clinical relevance

Scientific rationale for the study

Plaque control is essential in the control of gingivitis. CHX may be useful when individuals are unable to maintain adequate levels of plaque using mechanical methods alone.

Principle findings

When a CHX-containing dentifrice is used during mechanical oral hygiene procedures, reductions in plaque, gingivitis and bleeding are obtained when compared to a placebo/control. For CHX gel, this could not be established. However, the effect could not be quantified via a meta-analysis and tooth surface discoloration as a side effect is an obstacle to the generalized use of CHX dentifrice or gel.

Practical implications

CHX dentifrice may contribute to a plaque reduction and improvement in gingival health. Tooth surface discoloration is observed as a negative side effect, which potentially can have an impact on patients' compliance limiting the usefulness in daily practice. CHX gel should not be used in combination with toothbrushing.

Practical limitation

CHX dentifrice usually does not contain fluoride and may therefore be a poor alternative for daily oral home care.

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Conflict of interest

The authors declare that they have no conflict of interest.

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Implications for future research

CHX-containing dentifrices with an antidiscoloration system are available on the market. This could improve patients' compliance. However, their clinical beneficial effect and side effects need to be properly evaluated.

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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. Overview of the studies and reason for rejection that were excluded after full-text reading.

Appendix S2. Methodological quality and risk of bias scores of the included studies.

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