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The efficacy of 0.12% chlorhexidine mouthrinse compared with 0.2% on plaque accumulation and periodontal parameters: a systematic review

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Abstract

Objectives: The aim of this systematic review was to evaluate the effects of 0.12% chlorhexidine (CHX) mouthrinse compared with 0.2% on plaque and periodontal parameters.

Materials and methods: MEDLINE-PubMed and the Cochrane Central Register of Controlled Trials were searched for (randomized) clinical trials and cohort studies. Plaque scores, parameters of periodontal inflammation and periodontal attachment loss were selected as primary outcome parameters.

Results: Screening of 409 titles and abstracts identified eight eligible publications. A meta-analysis of seven studies using the same plaque index showed a significant difference between 0.2% and 0.12% CHX ($p = 0.008$). The Weighted Mean Difference for plaque based on the Quigley & Hein Plaque Index (1968) was 0.10 (95%CI [0.03–0.17]) (heterogeneity $I^2 = 0\%$, $p = 0.87$). Three studies that compared 0.12% and 0.2% CHX mouthrinse products provided data on gingival inflammation. No difference in the effect of gingivitis between the two concentrations was found in these studies. No studies could be found that compared the two CHX concentrations and evaluated the probing pocket depth and/or the periodontal attachment level.

Conclusions: In comparing 0.12% and 0.2% CHX, information concerning the effect on gingival inflammation was sparse and no studies could be found that compared the two CHX concentrations and evaluated the probing pocket depth and/or the periodontal attachment level. With respect to plaque inhibition, the results showed a small but significant difference in favour of the 0.2% CHX concentration. However, the clinical relevance of this difference is probably negligible.

Key words: chlorhexidine; concentration; gingivitis; mouthrinse; mouthwash; plaque; systematic review

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After almost 40 years of use by the dental profession, chlorhexidine (CHX) digluconate is recognized as the gold standard in chemical plaque control and is known to be an effective anti-plaque and anti-inflammatory agent (Löe & Schiott 1970, Hull 1980, Addy 1986, Kornman 1986a, b, Lang & Brecx 1986, Mandel 1988, Gjermo 1989, Addy et al. 1992). The benefits of CHX, a cationic biguanide, are based on the high intra-oral substantivity of this product (Addy 1986, Kornman 1986a, b) and its bactericidal and bacteriostatic activities (Denton 1991). CHX exhibits a wide spectrum of antibacterial activities that target both gram-positive and gram-negative bacteria, as well as yeast,

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dermatophytes and some lipophilic viruses (Denton 1991). When delivered orally, CHX is free from systemic toxicity and microbial resistance, and supra-infections do not occur (Van Strydonck et al. 2005).

Many indications for the use of this antiseptic have been suggested. After periodontal surgery and implant therapy, plaque control is one of the most important factors for proper healing (Sanz & Herrera 1998, Lang et al. 2000, Quirynen et al. 2002). Adequate mechanical oral hygiene can be an insurmountable problem, not only in post-surgical situations where oral hygiene is difficult, but also for handicapped and elderly patients who are less able to perform adequate oral hygiene procedures (Swallow et al. 1969, Francis et al. 1987, Kalaga et al. 1989, Persson et al. 1991, Laher & Cleaton-Jones 1996). For these patients, an alternative method of plaque control would be desirable (Keijser et al. 2003). The long-term use of CHX rinses among physically and mentally handicapped individuals has been advocated for the last three decades (Jenkins 1996).

CHX plaque inhibition is dose-dependent. Similar levels of plaque inhibition can be achieved with larger volumes of lower concentration solutions (Bonesvoll & Gjermo 1978). One of the most common side effects accompanying CHX mouthrinses is the perturbation of taste. Therefore, some brands have lowered the concentration of CHX in their mouthrinses. In some brands, the ethanol has also been removed in order to eliminate side effects such as soreness and to improve acceptability (Bolanowski et al. 1995). In Europe, a 0.2% CHX solution was developed, which became the standard international concentration (Hase et al. 1998, Neto et al. 2008). A lower concentration of CHX (0.12%) has been tested in several studies and has also been shown to confer clinical benefits (Keijser et al. 2003, Van Strydonck et al. 2005). The optimum dose of CHX is generally considered to be about 20 mg twice daily (Cumming & Löe, 1973, Agerbaek et al. 1975, Jenkins et al. 1994), which balances efficacy against local side effects and user acceptability (Flötra et al. 1971). Concentrations of 0.12% CHX have been found to be similarly effective as 0.2% if the volume of the rinse was increased from 10 to 15 ml, yielding an 18 mg dose on each occasion (Keijser et al. 2003, Van Strydonck et al. 2005).

The aim of this study was to systematically assess, considering the existing literature, whether or not there exists a difference in the inhibition of plaque and improvement in the parameters of gingivitis and periodontitis between mouthrinses with concentrations of 0.12% or 0.2% CHX.

Materials and methods

Focused question

What is the effect of 0.12% compared with 0.2% CHX mouthrinse on the accumulation of plaque and on periodontal parameters in adult patients?

Search strategy

Two sources of evidence were selected for this study: The National Library of Medicine, Washington, DC (MEDLINE-PubMed) and the Cochrane Central Register of Controlled Trials (CENTRAL). Reference lists of potentially relevant studies and review papers were also hand searched. Both sources were searched up to February 2010 using the following terms:

[⟨({Agent} AND {vehicle}) AND {concentration}⟩ AND {outcome}]

[⟨({ *Agent:* 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} AND

{*Vehicle:* Mouthwashes [MeSH] OR Mouthwashes OR Mouthwash OR mouthwash* OR mouthrinses OR mouthrinse})

AND

{*Concentration:* 0.12% OR 0.2%}⟩

AND

{*Outcome:* [MeSH terms/all subheadings] gingivitis OR gingival haemorrhage OR periodontal diseases OR gingival pocket OR periodontal pocket [text words] gingivitis OR gingivit* OR gingival bleeding OR gingival haemorrhage OR gingival diseas* OR gingival index OR gingival inflammation OR bleeding on probing OR papillary bleeding OR bleeding index OR sulcus bleeding index OR periodontitis OR pocket depth OR gingival pocket OR periodontal pocket OR periodontal diseas* OR pockets OR probing depth OR probing-depth OR probing-pocket-depth OR probing pocket depth OR pocket-depth OR periodontal attachment loss 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.

Eligibility criteria

At first, titles and abstracts resulting from the search as described above were screened independently by two reviewers (C.E.B., G.A.W.). Subsequently, full text papers were screened and selected (C.E.B., G.A.W.). The following eligibility criteria were taken into account:

- Randomized Controlled Clinical Trials (RCTs) or Controlled Clinical Trials (CCTs);
- Conducted in humans:
  - Subjects ⩾18 years of age;
  - In good general health (no systemic disorders);
- Intervention: 0.12% CHX mouthrinse;
- Comparison: 0.2% CHX mouthrinse;
- Clinical parameters: plaque scores, bleeding scores, gingivitis scores, probing pocket depth, periodontal attachment level.

Only papers written in English were accepted for this review. Case reports, letters and narrative reviews were excluded from the search. Papers without abstracts whose title suggested that they were related to the objectives of this review were also selected so that the full text could be screened. Studies that had only one of the two CHX concentrations or that lacked a comparison were excluded. CHX mouthrinses containing NaF were excluded due to a possible interaction between these ingredients (Mendieta et al. 1994, Quirynen et al. 2001). Vehicles other than mouthrinses, including sprays, gels or dentifrices, were not included in this review. Any disagreements between the reviewers were resolved by discussion.

Quality assessment

Methodological quality was assessed by combining the proposed criteria of the RCT checklist of the Dutch Cochrane Center, the Consort-statement (Moher et al. 2001a–d), and approaches as recommended by Esposito et al. (2001) and Needleman et al. (2005). This combina-

tion resulted in the quality criteria that are listed in Table 1. The study was considered to exhibit a low risk of bias when it was characterized as having a random allocation, defined inclusion/exclusion criteria, and if it was double-blinded regarding patient and examiner, featuring balanced experimental groups, and an identical treatment protocol between groups except for the intervention, and when a follow-up report was included. When the study lacked one of these five criteria, it was classed as having a moderate risk of bias. The absence of two or more of these criteria resulted in a high risk of bias. In addition, the ''Levels of Evidence'' of the Center of Evidence Based Medicine (CEBM) were used to assess methodological quality.

Assessment of heterogeneity

Factors that were recorded to investigate the heterogeneity of the primary outcomes across studies were as follows:

- Study design and evaluation period;
- Number, age and age range of subjects;
- Oral prophylaxis before the study;
- Intervention and control group;
- Regimens;
- Clinical parameters;
- Smoking and Industry funding.

Statistical analyses

Data extraction

Data were processed for analysis from papers that met the eligibility criteria. Data were extracted with regard to the effectiveness of 0.12% CHX compared with 0.2% CHX. Mean values and standard deviations (SD) were extracted by the authors C.E.B. and D.E.S. From one selected study (Quirynen et al. 2001), the original dataset was requested from the author because the published paper only provided descriptive data for bleeding scores.

Data analysis

The data presentation is largely descriptive. Where appropriate, a meta-analysis was performed and Weighted Mean Differences (WMD) were calculated by means of the Review Manager 4.2 software using a ''random effect'' model (RevMan version 4.2 for Windows, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2003). Because all studies started with a thorough prophylaxis, it may be assumed that at the baseline of each study, the intervention group was similar to the control group. For that reason, the meta-analysis was performed using available data from the end-trial assessments.

Results

Search and selection results

The MEDLINE-PubMed search returned 402 papers and the Cochrane CENTRAL search yielded 246 papers (Fig. 1). A total of 239 papers were identical. In total, 409 titles and abstracts were screened. The screening of titles and abstracts resulted initially in nine full-text papers. Two of these papers had to be excluded because the intervention was compared with a CHX spray (Francetti et al. 2004) or no plaque, bleeding or gingivitis scores were provided (Addy et al. 1991). The study of Van Steenberghe et al. (2001) was excluded because the same dataset was used as in the study of Quirynen et al. (2001), which had already been included in this systematic review. Two additional papers were obtained from the reference lists (Segreto et al. 1986 and Harper et al. 1995). Consequently, eight studies were identified to be eligible for inclusion according to the defined criteria in terms of study design, participants, type of intervention and outcome measures. As the studies reported by Harper et al. (1995) and Quirynen et al. (2001) used more than one 0.12% CHX mouthrinse, it was decided that the results of each mouthrinse would be entered separately. Consequently, the results of the 0.2% CHX experiments of these two studies were entered twice. In total, 10 experiments were used for the analysis.

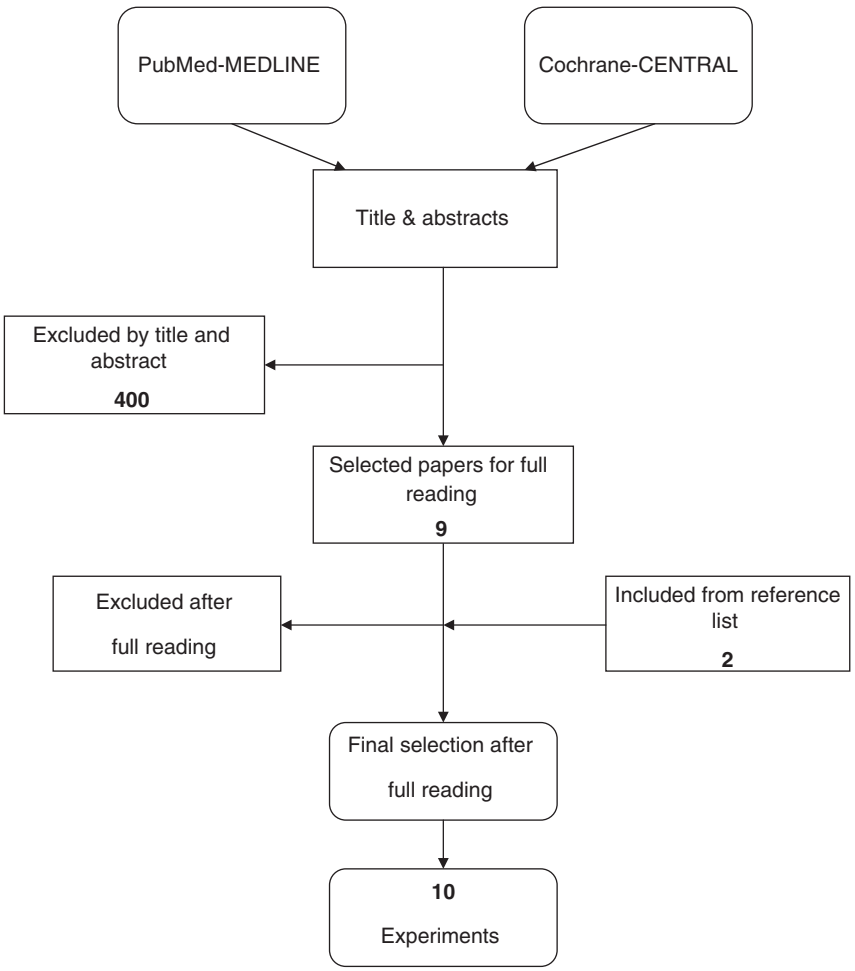

Fig. 1. Search and selection results.

Assessment of study quality and heterogeneity

The quality assessment is summarized in Table 1. Five studies were considered to exhibit a low estimated risk of bias and three exhibited a moderate potential estimated risk of bias. The level of evidence (CEBM) was 1b for two studies (II, VIII) and 2b for six studies (I, III, IV, V, VI and VII).

After a preliminary evaluation of the selected papers, considerable heterogeneity was observed as described below. Information regarding the study characteristics is listed in Table 2.

Study design and evaluation period

Three of the studies used a parallel design (II, VI and VIII) and five used a crossover design (I, III, IV, V and VII). Of the selected studies, two had an evaluation period of 3 days per regimen (II, VIII) and three had a 4-day evaluation period (I, IV and VII). The studies conducted by Neto et al. (2008) (III), Quirynen et al. (2001) (V) and Segreto et al. (1986) (VI) had the longest experimental periods of 14 days, 11 days and 3 months, respectively.

Number, age, and range of subjects

The number of subjects varied per group and study ranging from 10 to 597 subjects. In three papers, the mean age was reported and it ranged from 21.6 to 25.7 years (II, IV and V). Three papers did not mention the age of the participants at all (I, VI and VIII). Two studies enrolled participants who wore removable dental appliances (V, VI). Five papers mentioned having selected participants with good general health (I, II, IV, VII and VIII). Medications that could interfere with the intervention were considered to be the exclusion criteria in four studies (I, IV, VII and VIII). Neto et al. (2008) mentioned that subjects had no systemic condition that may have influenced oral health. In the study of Segreto et al. (1986), the investigators tried to determine whether the medical history of the subjects was unfavourable. Finally, three papers mentioned no exposure to systemic antibiotic treatment as an inclusion criterion (III, V and VI).

Oral prophylaxis before the study

At baseline in all of the selected trials, the participants underwent a thorough prophylaxis treatment consisting of supragingival scaling and polishing to remove all plaque, stain and calculus. Plaque was stained for a second time in two studies using an erythrosine disclosing solution and cotton swabs, to ensure that all visible plaque was removed (II, VIII).

Intervention and control group

The study by van Strydonck et al. (2005) (VIII) used Perio-aid for the 0.12% CHX treatment. This new formula also contains cetylpyridiniumchloride (CPC). Quirynen et al. (2001) (V) used the old formula as well as the new formula. To make these results comparable with those of Van Strydonck et al. (2005) (VIII), the new formula was incorporated in the analysis.

Two other studies by Keijser et al. (2003) (II) and Smith et al. (1995) (VII) used Oral-B for the 0.12% CHX group. The study by Pizzo et al. (2006) (IV) used Eburos for the 0.12% CHX group. Five of the studies used Corsodyl for the 0.2% CHX group (II, IV, V, VII and VIII). Neto et al. (2008) (III) used Hibitane Dental for the 0.12% and 0.20% CHX groups. Harper et al. (1995) (I) used two mouthrinses, Parodex and Prexidine, for the 0.12% concentration and Hibident for the 0.2% concentration. Segreto et al. (1986) (VI) did not mention which brand they used for the mouthrinses.

Regimens

In all but two (IV and VI) of the studies, the volume of the mouthrinses used was 15 ml for the 0.12% CHX and 10 ml for the 0.2% CHX. In the study by Pizzo et al. (2006) (IV), the volume for the daily rinses was 10 ml for both the control and the test groups, whereas Segreto et al. (1986) (VI) used 15 ml for both.

In three studies (II, V and VIII), 0.12% CHX was used twice daily for 30 s and the 0.20% CHX was used twice daily for 60 s. In four other studies (I, III, IV and VII), the CHX mouthrinse was used twice daily for 60 s for both concentrations. Segreto et al. (1986)

Table 1. Quality assessment of the included studies

Quality criteria		Study							
		I	II	III	IV	V	VI	VII	VIII
Internal validity	Random allocation	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	Allocation concealment	?	?	?	?	?	?	?	?
	Blinded to patient	Yes	No	Yes	Yes	Yes	Yes	Yes	No
	Blinded to examiner	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	Blinding during statistical analysis	?	?	?	?	?	?	?	?
	Balanced experimental groups	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	Reported loss to follow up	Yes	Yes	?	Yes	?	Yes	Yes	Yes
	#(%) of drop-outs	0	0	?	0	?	143 (24%)	0	1 (0.025%)
	Treatments identical, except for intervention	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
External validity	Representative population group	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	Eligibility criteria defined	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Statistical validity	Sample size calculation and power	?	?	?	?	?	?	?	?
	Point estimates and measures of variability presented for the primary outcome	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	Included an intention- to-treat analysis	Yes	Yes	?	Yes	?	?	Yes	No
Authors' estimated risk of bias		Low	Moderate	Low	Low	Low	Low	Low	Moderate
Levels of evidence Centre for Evidence-based Medicine (2009)		2b	1b-	2b	2b	2b	2b	2b	1b-

Table 2. Overview of the studies

#	Authors (year)	Title	Design, Blinded, Evaluation period (Washout period)	# Subjects, Gender, Age (mean and range) & Oral prophylaxis	Intervention group Control group	Outcome of the study
I	Harper et al. (1995)	An approach to efficacy screening of mouthrinses: studies on a group of French products (II). Inhibition of salivary bacteria and plaque in vivo	RCT Cross- over Double blind 4 days (2.5 days)	21 healthy volunteers ♀: ? ♂: ? Yes	0.12% (Parodex) 15 ml 60 s twice daily 0.12% (Prexidine) 15 ml 60 s twice daily 0.2% (Hibident) 10 ml 60 s according to the manufacturers' recommended regimen twice daily	No significant difference between three groups
II	Keijser et al. (2003)	Comparison of 2 commercially available chlorhexidine mouthrinses	RCT Parallel Single blind 3 days	80 healthy subjects ♀: 40 ♂: 40 Mean age: 25.7 yrs Age range: 25–45 yrs Yes	0.12% (Oral-B) 15 ml 30 s twice daily 0.2% (Corsodyl) 10 ml 60 s twice daily	No significant difference between two groups
III	Neto et al. (2008)	Comparative analysis of the effect of two chlorhexidine mouthrinses on plaque accumulation and gingival bleeding	RCT Cross-over Double blind 14 days (7 days)	10 dental students ♀: 3 ♂: 7 Mean age: ? Age range: 20–25 yrs Yes	0.12% (Hibitane Dental) 15 ml 60 s twice daily 0.2% (Hibitane Dental) 10 ml 60 s twice daily	No significant difference between two groups
IV	Pizzo et al. (2006)	The effects of antimicrobial sprays and mouthrinses on supragingival plaque regrowth: a comparative study	RCT Cross-over Single blind 4 days (10 days)	15 healthy subjects ♀: 7 ♂: 8 Mean age 23.5 yrs Age range: 22–27 yrs Yes	0.12% (Eburos) 10 ml 60 s twice daily 0.2% (Corsodyl) 10 ml 60 s twice daily No other oral hygiene measures in connection with scorable tooth sites were allowed. Toothbrushing with a fluoride toothpaste without sodium lauryl sulfate and the use of unwaxed dental floss were allowed on the other teeth, with the exception of the first upper premolars	No significant difference between two groups
V	Quirynen et al. (2001)	Effect of different chlorhexidine formulations in mouthrinses on de novo plaque formation	RCT Cross-over Double blind 11 days (3 weeks)	16 dental students ♀: 9 ♂: 7 Mean age 21.6 yrs Age range: ? Yes	0.12% (Perio-aid) 15 ml 30 s twice daily 0.2% (Corsodyl) 10 ml 60 s twice daily	Rinsing with 0.12% CHX gives an equal reduction of plaque as the 0.2% CHX mouth rinse
VI	Segreto et al. (1986)	A comparison of mouthrinses containing two concentrations of chlorhexidine	RCT Parallel Double blind 3 months	597 ♀: 363 ♂: 234 Mean age: ? Age range: ? Yes	0.12% CHX gluconate in a flavored mouthrinse base 15 ml 30 s twice daily 0.20% CHX gluconate in a flavored mouthrinse base 15 ml 30 s twice daily	No significant difference between two groups

Table 2. (Contd.)

#	Authors (year)	Title	Design, Blinded, Evaluation period (Washout period)	# Subjects, Gender, Age (mean and range) & Oral prophylaxis	Intervention group Control group	Outcome of the study
VII	Smith et al. (1995)	Comparative staining in vitro and plaque inhibitory properties in vivo of 0.12% and 0.2% chlorhexidine mouthrinses	RCT Cross-over Double blind 4 days (⩾10 days)	24 healthy subjects ♀: 9 ♂: 15 Mean age: ? Age range: 20–50 yrs Yes	0.12% (Oral B) 15 ml 60 s twice daily 0.2% (Corsodyl) 10 ml 60 s twice daily	No significant difference between two groups The 0.12% can be used as the 0.2% is recommended and used
VIII	Van Strydonck et al. (2005)	Plaque inhibition of two commercially available chlorhexidine mouthrinses	RCT Parallel Single blind 3 days	40 healthy subjects ♀: ? ♂: ? Mean age: ? Age range: ? Yes	0.12% (Perio-aid) 15 ml 30 s twice daily 0.2% (Corsodyl) 10 ml 60 s twice daily	No significant difference between two groups

(VI) asked the participants to rinse for 30 s with both concentrations.

In all but one study (VI), the subjects were requested subsequently to refrain from their normal oral hygiene methods and to only use the rinses provided. In one study, only sextant 2 was assessed. Tooth brushing with a fluoride toothpaste that was free of sodium lauryl sulphate and the use of unwaxed dental floss were allowed on the other teeth (IV), with the exception of the first upper premolars. Segreto et al. (1986) (VI) used a longer evaluation period; therefore, besides rinsing, soft toothbrushes and sodium fluoride dentifrice were provided to the participants according to the individual's habits.

Clinical parameters

Plaque

For plaque scoring, studies used the Quigley & Hein Plaque Index (Quigley & Hein 1962) (III), the Turesky et al. (1970) (18) modification of the Quigley & Hein Plaque Index (1962) (I, IV, V, VI and VII), the Turesky et al. (1970) (18) modification of the Quigley & Hein Plaque Index (1962) and further modified by Lobene et al. (1982) (II, VIII) and the Silness & Löe Plaque Index (Silness & Löe 1964) (III).

Bleeding

Three studies assessed gingival bleeding. One study used bleeding upon marginal probing (van der Weijden et al. 1994, Lie et al. 1998) (III). Quirynen et al. (2001) (IV) used two indices, namely the Sulcus Bleeding Index by Mühlemann & Son (1971) and the Papillary Bleeding Index by Saxer & Mühlemann (1975). One study focused on grades 2 and 3 from the Gingival Index (Löe 1967) to assess bleeding (VI).

Gingivitis

Segreto et al. (1986) (VI) assessed gingivitis with the Papillary-Marginal-Gingivitis Index (de la Rosa & Sturzenberger 1976).

No studies could be found that compared the two CHX concentrations and evaluated the probing pocket depth and/or the periodontal attachment level.

Smoking and industry funding

None of the selected papers indicated the smoking status of the participants. Four studies mentioned that the study products had been provided by the manufacturers (II, VI, VII and VIII). No additional industry support was declared.

Study outcomes

*Within groups (comparison baseline **versus** end of study)*

Plaque (Table 3). Owing to the baseline oral prophylaxis treatment, all subjects started with no visible plaque; therefore, the increment was equal to the end score.

Bleeding and gingivitis (Tables 4 and 5). None of the studies mentioned whether or not there was a significant difference between baseline and end scores.

Between groups

The descriptive analysis is presented in Table 6. None of the eight studies showed a statistical difference in terms of plaque scores for either of the concentrations. The studies that assessed bleeding revealed no statistical difference between the 0.12% and 0.20% CHX groups (III, V and VI). Neither did Segreto et al. (1986) find a significant difference between the two concentrations with respect to visual signs of inflammation.

Meta-analysis

From the collective data, it was possible to perform a meta-analysis for plaque scores (Fig. 2). The Quigley & Hein Plaque Index (Quigley & Hein 1962) data were scored in seven studies (I, II, III, IV, VII and VIII) and there was a significant difference in the effect on plaque between 0.12% CHX and 0.2% CHX. The WMD was 0.10 in favour of the 0.2% CHX mouthrinse with a 95% confidence interval (CI: [0.03–0.17]). The test for overall effect showed a p-value of 0.008. The test for heterogeneity was $I^2 = 0\%$ ($p = 0.87$).

As there appeared to be heterogeneity in terms of volume, rinsing time, other active ingredients, brand and index used, it was decided to conduct separate subgroup meta-analyses for each of these variables (Table 7).

Duration. In the meta-analysis, the available data for 30 and 60 s of rinsing are analysed separately. However, the study of Pizzo et al. (2001) was not included because it was the only study that used a 10 ml volume for the 0.12% CHX rinse instead of the 15 ml used in all other studies. After 30 s of rinsing, the WMD was 0.11 (95% CI: [− 0.01 to

Table 3. Mean (SD) end plaque index scores for the different intervention groups

#	Index	Intervention groups	Mean (SD)
I	Turesky et al. (1970) modification of the Quigley and Hein plaque index (1962)	0.12% CHX parodex 0.12% CHX prexidine 0.20% CHX	1.68 (0.31) 1.67 (0.36) 1.56 (0.33)
II	Turesky et al. (1970) modification of the Quigley and Hein plaque index (1962) and further modified by Lobene et al. (1982)	0.12% CHX 0.20% CHX	1.65 (0.31) 1.60 (0.40)
III	Quigley & Hein Plaque Index (1962)	0.12% CHX 0.20% CHX	0.25 (0.16) 0.23 (0.26)
	Silness & Löe Plaque Index (1964)	0.12% CHX 0.20% CHX	0.12 (0.10) 0.11 (0.11)
IV	Turesky et al. (1970) modification of the Quigley and Hein plaque index (1962)	0.12% CHX 0.20% CHX	1.41 (0.41) 1.09 (0.49)
V	Turesky et al. (1970) modification of the Quigley and Hein plaque index (1962)	0.12% CHX ALC 0.12% CHX CPC 0.20% CHX	1.75 ◇ (0.44 ◇) 1.74 ◇ (0.39 ◇) 1.59 ◇ (0.53 ◇)
VI	Turesky et al. (1970)	0.12% CHX 0.20% CHX	1.01 (?) 1.14 (?)
VII	Turesky et al. (1970) modification of the Quigley and Hein plaque index (1962)	0.12% CHX 0.20% CHX	2.10 (0.33) 2.05 (0.35)
VIII	Turesky et al. (1970) modification of the Quigley and Hein Plaque Index (1962) and further modified by Lobene et al. (1982)	0.12% CHX 0.20% CHX	0.97 (0.46) 0.78 (0.31)

◇ = calculated by the authors.
? = not mentioned.

Table 4. Mean (SD) bleeding index scores for the different intervention groups

#	Index	Intervention groups	Baseline mean (SD)	End mean (SD)	Difference baseline-end	Significant difference
III	Gingival Bleeding Index van der Weijden et al. (1994)	0.12% CHX 0.20% CHX	3.56% (3.60%) 3.43% (3.43%)	14.93% (6.68%) 13.95% (9.24%)	+11.37% +10.52%	? ?
V	Sulcus Bleeding Index Mühlemann & Son (1971)	0.12% CHX ALC 0.12% CHX CPC 0.20% CHX	0.03 (0.04) 0.02 (0.03) 0.02 (0.03)	0.01 (0.03) 0.01 (0.02) 0.01 (0.02)	− 0.02 − 0.01 − 0.01	? ? ?
	Papillary Bleeding Index Saxer & Mühlemann (1975)	0.12% CHX ALC 0.12% CHX CPC 0.20% CHX	0.10 (0.09) 0.10 (0.08) 0.10 (0.08)	0.09 (0.10) 0.09 (0.11) 0.09 (0.13)	− 0.01 − 0.01 − 0.01	? ? ?
VI	Bleeding scores as extracted from the Gingival Index (Löe 1967)	0.12% CHX 0.20% CHX	? ?	0.041 ◇ 0.053 ◇	? ?	? ?

For abbreviations see Table 3.

Table 5. Mean (SD) gingivitis index scores for the different intervention groups

#	Index	Intervention groups	Baseline mean (SD)	End mean (SD)	Difference baseline-end	Significant difference baseline-end
VI	*Papillary-Marginal-Gingivitis Index de la Rosa & Sturzenberger (1976)*					
	Occurrence	0.12% CHX	0.55 ◇	0.27 ◇	− 0.28 ◇	?
		0.20% CHX	0.56 ◇	0.29 ◇	− 0.27 ◇	?
	Severity	0.12% CHX	0.68 ◇	0.30 ◇	− 0.38 ◇	?
		0.20% CHX	0.72 ◇	0.32 ◇	− 0.40 ◇	?

For abbreviations see Table 3.

0.22], $p = 0.07$) and after 60 s, the WMD was 0.07 (95% CI: [– 0.02 to 0.17], $p = 0.14$). Although it was not attempted to statistically compare the two subgroups, the difference was numerically small.

Alcohol versus no alcohol. The 0.12% CHX mouthrinses can be divided into alcohol-containing and alcohol-free products. In the subgroup with alcohol, the WMD was 0.09 (95% CI: [0.01–0.16], $p = 0.03$) and in the group without alcohol, the WMD was 0.18 (95% CI: [– 0.02–0.37], $p = 0.08$).

Brand. The data allowed for a meta-analysis with a subdivision of two different brands. For Oral-B, 0.12% CHX as compared with 0.2% CHX yielded a WMD that was 0.05 (95% CI: [– 0.07 to 0.17], $p = 0.42$). For Perio-aid, 0.12% CHX as compared with 0.2% CHX yielded a WMD that was 0.06 (95% CI: [– 0.13 to 0.26], $p = 0.54$). However, the data did not allow for a side-by-side comparison between the different brands.

Hence, the results of this analysis fail to suggest that either one of these variables contributed to the observed WMD and CI data.

Table 6. Overview of results

#	Effect on plaque inhibition	Effect on bleeding	Effect on gingivitis	Comparison
I1	○	□	□	0.2%
I2	○	□	□	0.2%
II	○	□	□	0.2%
III	○	○	□	0.2%
IV	○	□	□	0.2%
V1	○	○	□	0.2%
V2	○	○	□	0.2%
VI	○	○	○	0.2%
VII	○	□	□	0.2%
VIII	○	□	□	0.2%

For abbreviations see Table 3.
○, No significant difference.
□, not assessed.

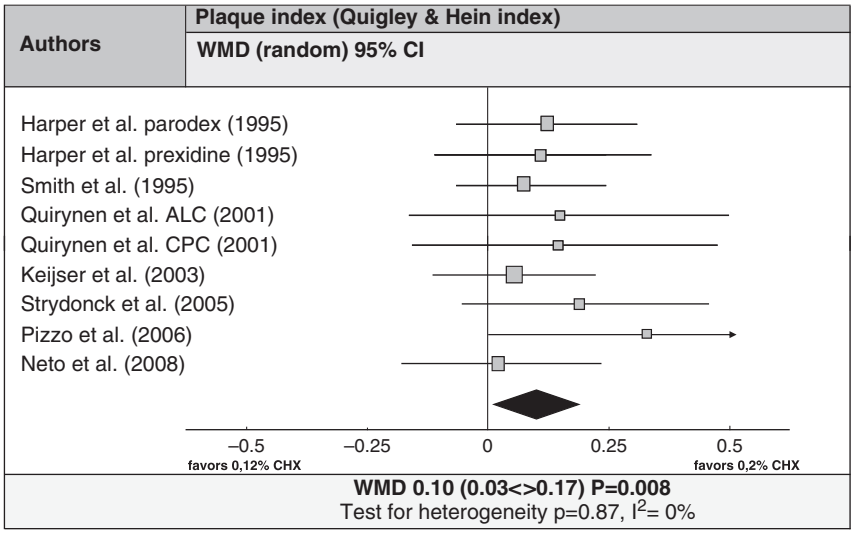

Fig. 2. Meta-analyses Plaque Index comparing 0.12% *versus* 0.2% chlorhexidine.

Discussion

This review aimed to establish the differential effects of two CHX concentrations (0.12% and 0.2%). The papers selected for use in this study came from two databases and provided information that was relevant to the question of interest.

Meta-analysis

None of the individual experiments showed a statistical difference between the 0.12% CHX and the 0.2% CHX mouthrinses. When summarizing the results with respect to Quigley & Hein plaque scores using a meta-analysis, there appeared to be a significant WMD of 0.10 in favour of the 0.2% CHX mouthrinse. Importantly, one should regard this result in light of the plaque index used. The Quigley & Hein Index (Quigley & Hein 1962) is scored on a 6-point scale from 0 to 5 to determine the extent of plaque covering the tooth surface. As the actual WMD is rather small (0.10), one must question the clinical relevance of this result. ''Clinical difference'' is not a statistical issue but is decided based on clinical arguments. Often, the magnitude of the difference in plaque scores will not be reflected in a difference in gingival inflammation. Although the information

Table 7. Results of the subgroup meta-analysis

Subgroups	Studies	WMD (random)	Test for overall effect	95% CI	Test for heterogeneity	
30 s	II, V1, V2, VIII	0.11	$p = 0.07$	[– 0.01, 0.22]	$p = 0.78$	$I^2 = 0\%$
60 s	I1, I2, III, VII	0.07	$p = 0.05$	[– 0.02, 0.17]	$p = 0.60$	$I^2 = 0\%$
Alcohol-containing	I1, I2, II, III, IV, V1, VII	0.09	$p = 0.03$	[0.01, 0.16]	$p = 0.79$	$I^2 = 0\%$
Alcohol-free	V2, VIII	0.18	$p = 0.08$	[– 0.02, 0.37]	$p = 0.85$	$I^2 = 0\%$
Perio-Aid	V2, VIII	0.06	$p = 0.54$	[– 0.13, 0.26]	$p = 0.50$	$I^2 = 0\%$
Oral-B	II, VII	0.05	$p = 0.42$	[– 0.07, 0.17]	$p = 1.00$	$I^2 = 0\%$

WMD, Weighted Mean Difference.
CI, Confidence Interval.

is limited, the bleeding scores data support this assumption.

Power

The present meta-analysis included 182 and 183 subjects in each group. Sample size calculations using a pooled weighted standard deviation (as taken from the present data) of 0.47, an α of 0.05, a β of 0.8 and a WMD of 0.10 predicted that an individual study would have required 174 subjects in each group for sufficient statistical power. Power is the chance of detecting a real treatment effect as statistically significant, which helps to reject hypotheses with appropriate certainty.

Often, individual studies are too small to detect small effects, but when several are combined, there is a higher chance of detecting a treatment effect (Higgins & Green 2009). This indicates the value of a meta-analysis, which helps to increase power. With the present knowledge, one may conclude that the individual studies that aimed to assess the difference between 0.12% and 0.2% CHX suffered from inadequate power.

Study design

The studies in this systematic review consisted of either parallel or crossover designs. The advantage of a crossover design, which was used in the studies by Harper et al. (1995) (I), Neto et al. (2008) (III), Pizzo et al. (2006) (IV), Quirynen et al. (2001) (V) and Smith et al. (1995) (VII), over a parallel design, which was used in the studies by Keijser et al. (2003) (II) and Van Strydonck et al. (2005) (VIII), is that comparisons of treatments are not influenced by variability between subjects because the comparison is carried out within each individual (Dallal 2007). However, there is the possible disadvantage of a carry-over effect between treatments (Altman 1999), which appears to be dealt with adequately in these five studies using a sufficient wash-out period. The wash-out periods varied from 2.5 days to 3 weeks (see Table 1).

Duration, alcohol *versus* no alcohol, CPC

In the meta-analysis, the data for 30 and 60 s of rinsing were analysed separately. Nevertheless, the difference between the two subgroups was numerically small and these results confirmed the studies of Keijser et al. (2003) and Van der Weijden et al. (2005). These researchers concluded that, in order to be effective, a 30-s rinsing time was sufficient for both the 0.12% and 0.2% chlorhexidine solutions. In support of this, Bonesvoll et al. (1974a) showed that there was a rapid binding of CHX in the mouth during the first 15 s of rinsing. They observed that, compared with a 60-s rinse, approximately half of the CHX was retained after the first 15 s and approximately 75% within 30 s.

Van Strydonck et al. (2005) and Quirynen et al. (2001) tested Perio-aid, which is an alcohol-free CHX product. However, this formulation did contain 0.5% CPC. The existing evidence suggests that CPC mouthrinses, when used as adjuncts to either supervised or unsupervised oral hygiene, provide a small but significant additional benefit in reducing plaque accumulation and gingival inflammation (Haps et al. 2008). Therefore, the CPC may have compensated for a possible effect of the alcohol. Hence, a firm conclusion regarding alcohol-free rinses cannot be drawn.

Availability

One problem encountered in this review of the literature is that no information could be found on the availability of CHX in the various commercial products. ''In vitro'' work has shown a discrepancy in the availability of CHX of some products (Sheen & Addy, 2003). This may have an effect on the potential of some rinses to provide the expected plaque inhibitory activity for which they were formulated.

Probing pocket depth

Gjermo (1977) concludes in his review on CHX in periodontal disease that ''established destructive periodontitis with pocket formation and subgingival plaque seems unaffected by CHX''. The FDA (2008) states that: ''CHX rinse is indicated for use between dental visits as part of a professional programme for the treatment of gingivitis as characterized by redness and swelling of the gingivae, including gingival bleeding upon probing''. In clinical practice, however, the major use of CHX mouthrinses is to improve outcomes of non-surgical and surgical periodontal therapy. Indeed, a recent study (Feres et al. 2009) has shown the potential effect that CHX may have in the clinical outcome of non-surgical therapy. Comparable study protocols in which also the two CHX concentrations were compared are lacking.

Perturbation of taste

CHX mouthrinses can have a variety of side effects. As stated earlier, one of the most common side effects of CHX mouthrinses is taste perturbations. The study by Van Strydonck et al. (2005) concluded that the perturbation of taste perception after using 0.12% CHX is significantly lower than that after using 0.2% CHX. The study by Pizzo et al. (2006) also supported this notion. On the other hand, the studies by Keijser et al. (2003) and Quirynen et al. (2001) concluded that there was no significant difference in terms of taste perception, duration of taste and alteration of taste. Accordingly, a definite conclusion with respect to taste perception cannot be drawn.

Conclusions

Three studies provided data on the comparison of 0.12% and 0.2% CHX mouthrinse products with respect to gingival inflammation. The summary of this sparse information shows no difference in the effect of gingivitis between the two concentrations of CHX. No studies could be found that compared the two CHX concentrations and evaluated the probing pocket depth and/or the periodontal attachment level. With respect to plaque growth inhibition, the results show a small but significant difference in favour of the 0.2% CHX concentration. However, the clinical relevance of this difference is probably negligible.

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Clinical Relevance

Scientific rationale: At present, CHX is by far the most effective mouthrinse for reducing plaque and gingivitis and is available in two concentrations, 0.12% and 0.2%.

Principal findings: There is a small but statistically significant difference (0.10 Quigley and Hein Plaque Index units) in the effect on plaque between the 0.2% and 0.12% CHX concentrations, but the limited research that is available indicates no difference between the two concentrations in reducing gingivitis.

Practical implications: When provided with a choice, our results suggest that 0.2% CHX concentration has a small but statistically significant advantage in terms of plaque reduction, but not in terms of gingivitis reduction. However, considering the magnitude of the difference, which was 0.10, as scored on a 0–5 point scale, one may question the clinical relevance. The clinically detectable difference in product performance is probably negligible.