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The effect of cetylpyridinium chloride-containing mouth rinses as adjuncts to toothbrushing on plaque and parameters of gingival inflammation: a systematic review

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Haps S, Slot DE, Berchier CE, Van der Weijden GA. The effect of cetylpyridinium chloride-containing mouth rinses as adjuncts to toothbrushing on plaque and parameters of gingival inflammation: a systematic review.

Abstract: *Objective:* To review the literature concerning cetylpyridinium chloride (CPC) containing mouth rinses as effective adjuncts to toothbrushing in the prevention of plaque accumulation and gingival inflammation. *Materials and methods:* Medline and the Cochrane Central Register of Controlled Trials were searched up to January 2008 to identify appropriate studies. The primary outcome measurements were plaque accumulation and gingivitis. *Results:* Independent screening of titles and abstracts of 3250 papers resulted in eight publications that met the criteria of eligibility. Mean values and standard deviations were obtained by data extraction. Descriptive comparisons are presented for brushing only or brushing and rinsing. Meta-analyses were performed when possible. *Conclusions:* The existing evidence supports that CPC containing mouth rinses, 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.

Key words: bleeding; cetylpyridinium chloride; cetylpyridinium chloride mouth rinse; gingivitis; mouthwash; plaque; systematic review

Introduction

Dental plaque is a multispecies biofilm of microorganisms that grows as an ecosystem on hard and soft tissues in the oral cavity.

Efficient removal of dental plaque is essential for maintaining oral health as plaque has long been identified as a critical factor in the aetiology of caries, gingival inflammation and chronic periodontitis (1–3).

Daily toothbrushing with fluoride-containing dentifrice and flossing are the most frequently recommended methods for removing supragingival plaque (4). Patients' efforts, however, are often compromised by the presence of hard-to-reach areas as well as inadequate skill, poor motivation and lack of compliance. Consequently, the use of antimicrobial mouth rinses as adjuncts to mechanical oral hygiene regimens is considered a means to enhance plaque removal (5, 6).

Mouth rinsing was first practised as an oral hygiene measure in Chinese medicine in 2700 BC (7). It is believed that the earliest mouthwash advocated for dental plaque reduction was the urine of a child, preferably from a newborn baby (8). A well-documented scientific and clinical basis for the use of therapeutic antimicrobial mouth rinses, however, was recorded relatively recently, in the 1960s. A plaque- and calculus-inhibiting effect of the quaternary compound cetylpyridinium chloride (CPC) was first described by Schroeder *et al*. (9). CPC is a cationic surface-active agent and has a broad antimicrobial spectrum, with rapid killing of gram-positive pathogens and yeast in particular (10). It is suggested that interaction with bacteria occurs by the disruption of membrane function, leakage of cytoplasmic material, and ultimately the collapse of the intra-cellular equilibrium (10, 11). The use of CPC has been shown not to introduce a shift from the indigenous gram-positive bacteria to gram-negative anaerobic bacteria, in accordance with the requirements of the American Dental Association (ADA) (10, 12).

Several reviews have been published on the efficacy of CPC mouth rinses (10, 13–15). However, some reviews lack a systematic, transparent approach in their evaluations of CPC mouth rinses and/or do not investigate their efficacy as adjuncts to toothbrushing (13–16). Therefore, the purpose of this review is to provide a comprehensive overview of the effectiveness of CPC containing mouth rinses as adjuncts to daily oral hygiene on the prevention of plaque accumulation and gingivitis in studies with an evaluation period of at least 4 weeks (17).

Materials and methods

Focused question

What is the effect of CPC-containing mouth rinses as adjuncts to toothbrushing when compared with toothbrushing only or toothbrushing plus placebo rinse on the prevention of dental plaque and the parameters of gingival inflammation in adults?

Search strategy

Two internet sources were used in the search for appropriate papers satisfying the study purpose: the National Library of Medicine, Washington, DC (MEDLINE–PubMed) and the Cochrane Central Register of Controlled Trials. Both databases were searched for studies conducted in the period up to and including January 2008.

The search was designed to be inclusive for any published study that evaluated the effect of CPC mouth rinses. All reference lists of the selected studies were screened for additional papers that could meet the eligibility criteria of this study.

Medline and Cochrane search

In the search strategy the following terms were used:
(Intervention)
[MeSH terms/all subheadings] CPC OR Cetylpyridinium chloride OR
[text words] Cetyl pyridinium OR Cetylpyridinium OR Mouthwash OR Mouthwashes OR Mouth rinse OR Mouth rinses OR 1-hexadecylpyridinium chloride OR acetoquat CPC OR ammonyx CPC OR ceepryn chloride OR cepacol OR cepacol chloride OR cetamium OR dobendan OR ipanol OR merothol OR pristacin OR pyrisept OR asept
AND
(Outcome)
[MeSH terms /all subheadings] gingivitis OR gingivitis, necrotizing ulcerative OR gingival hemorrhage OR periodontal index OR
[text words] gingivit* OR gingival bleeding OR gingival hemorrhage OR bleeding on probing OR gingival index OR gingival inflammation OR papillary bleeding OR index gingival bleeding OR bleeding index OR plaque index OR dental plaque OR plaque OR interdental plaque OR interproximal plaque OR dental deposit*.

Eligibility criteria

- Randomized controlled trials.
- Controlled clinical trials.
- Humans in good general health ≥18 years.
- Intervention: CPC mouth rinses.
- Control: toothbrushing only or toothbrushing in conjunction with placebo rinse.

- Parameters mentioned: plaque, bleeding, gingivitis.
- Studies ≥4 weeks duration (17).

Only papers written in English were accepted. Case reports, letters and narrative/historical reviews were not included in the search. Papers without abstracts whose titles suggested that they were related to the objectives of this review were also selected so that the full text could be screened for eligibility.

Screening and selection

The papers were screened independently by two reviewers (SH and GAW), first by title and abstract. Then, full-text papers that fulfilled the eligibility criteria were identified for inclusion in this study. Any disagreement between the two reviewers was resolved after additional discussion.

Assessment of heterogeneity

Factors used to evaluate the heterogeneity of outcomes of different studies are as follows:

- Study design and evaluation period.
- Subjects: number, age range and gender.
- Intervention, industry funding, comparison and regimen.
- Baseline prophylaxis, supervised rinsing and oral hygiene instruction.
- Parameters (plaque and gingivitis levels at baseline and end).
- Side effects and smoking.

Quality of assessment

The quality of methodology of these studies was evaluated based on the following aspects:

- Method of randomization and allocation concealment.
- Blindness of examiners.
- Completeness of follow-up.

Data extraction

From the selection of papers that met the criteria, data were extracted with regards to the effectiveness of self-performed mouth rinsing with CPC mouth rinses in comparison with a control treatment (i.e. toothbrushing only or a control rinse). Mean values and standard deviations (SD) were extracted by SH and DES. Some of the studies provided standard errors (SE) of the mean. If possible, the SD in these studies were calculated by the authors of the present review based on the sample size.

Data analysis

Most papers supplied data only for baseline and end-of-trial assessments. Consequently, it was not possible to perform a meta-analysis (MA) of the difference because the SD of the difference could not be calculated. Therefore, the data for baseline and end-of-trial assessments are presented separately. An analysis for both time points was performed. Weighted mean values were calculated by means of the Review Manager using a random effect model. Review Manager (RevMan) [computer program]. Version 4.2 for windows. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2003.

Results

Search and selection results

The PubMed and the Cochrane searches yielded 2496 papers and 754 papers respectively (Table 1). Initial analysis of these papers narrowed down the candidate pool to 2562 titles and abstracts. The screening of the titles/abstracts initially resulted in 50 full-text articles. Reasons for exclusion after full-text reading are explained in Table 2. After full-text reading, 41 papers were excluded because they failed to fulfill the criteria of this study, whereas one paper (18) was excluded because of insufficient data presentation on the clinical parameters. Additional searching of reference lists of the selected studies resulted no new papers. The final eight articles were processed for data extraction.

Outcome results

Assessment of heterogeneity of studies

Considerable heterogeneity was observed in the interventions, regimens, concentrations of CPC, bio-availability and outcome

Table 1. **Search and selection results**

Selection	PubMed	Cochrane	Identical
Search	2496	754	688
Excluded by title and abstract	2448	752	688
Selected papers for full reading	48	2	0
Excluded after full reading (Table 2)	41		
Included after full reading	9		
Excluded for insufficient data presentation (Table 2)	1		
Included from reference list	0		
Final selection for data extraction	8		

Table 2. **Overview of excluded studies (*n* = 42) and reasons for rejection**

Reason for rejection	References
Evaluation period < 4 weeks	Witt *et al.* (19), Pizzo *et al.* (20), Witt *et al.* (21), Sreenivasan *et al.* (22), Carvalho *et al.* (23), Sheen *et al.* (24), Harper *et al.* (25), Vandekerckhove *et al.* (26), Binney *et al.* (27), Binney *et al.* (28), Ashley *et al.* (29), Llewelyn *et al.* (30) Lobene *et al.* (31), Derdivanis *et al.* (32), Bonesvoll *et al.* (33), Holbeche *et al.* (34), Holbeche *et al.* (35), Ciancio *et al.* (36), Carter *et al.* (37), Lobene *et al.* (38), Volpe *et al.* (39), Sturzenberger *et al.* (40)
Review	Gottehrer *et al.* (41), Pitten *et al.* (10), Princeton Dental Resource Center (42), Fine *et al.* (43), Fleszar *et al.* (44), Eggert *et al.* (45), Overholser *et al.* (46), Lobene *et al.* (47), Satchell *et al.* (48), O'Leary *et al.* (49)
CPC combined with other active ingredient	Cronin *et al.* (50), Ashley *et al.* (51), Rosa *et al.* (52)
Insufficient data	Yates *et al.* (18)
Other clinical parameters	Roberts *et al.* (53),
No CPC	Stallard *et al.* (54), Koch *et al.* (55), Zamet *et al.* (56), Lindhe *et al.* (57), Bakhtadze *et al.* (58)

variables. Furthermore, the number, gender and age of participants also varied among the studies. Information regarding the study characteristics is shown in Table 3.

Study design and evaluation period

All studies conducted a randomized clinical trial and had a parallel design. Three trials (#II, III and IV) were conducted in an evaluation period of 6 months. The other studies had shorter evaluation periods of 4 weeks (#VIII), 6 weeks (#V, VI), 8 weeks (#I) or 3 months (#VII). When intermediate assessments regarding the use of a CPC mouth rinse were presented, the baseline and final evaluation were used for this review.

Subjects: number, age, range and gender

The number of subjects ranged from 63 (66) to 258 (60). The age of the participants ranged from 18 to 66 years. In six studies, both men and women were included. One study (#VIII) investigated only male subjects. Another study (#VII) enrolled only subjects who had previously participated in dental clinical studies conducted by an Institutional Service Company.

Intervention, industry funding, comparison and regimen

Intervention and industry funding

The test mouth rinses used were of various brands, such as Cepacol®; Merrel National Laboratories, Division of Richardson Merrel Inc. Cincinatti, OH, USA (#V, VII and VIII), Crest™; Procter & Gamble Company, Cincinatti, OH, USA (#III), Warner Lambert; Parke-Davis Division of Warner Lambert, Plentypool Wales, UK (#VI) and Procter & Gamble; Procter & Gamble Company, Cincinatti, OH, USA (#II). Study #I used an experimental mouth rinse GlaxoSmithKline; Brenford, UK and for #IV the brand was not mentioned. Consequently, the mouth rinses used in the studies contained different formulations and concentrations of CPC (between 0.05% and 0.10%). Two (#II, III) out of eight studies used formulations with highly bioavailable CPC (72–77%). The remaining studies did not provide any information on this aspect.

Some papers had authors that are industry employees Procter & Gamble (#II, III), Johnson & Johnson Dental Care Company (#VII) and Colgate Palmolive Company; New York, NY, USA (#IV). Funding was mentioned in five papers, one by a Grant of the University of South Dakota Research (V) and four by industry GlaxoSmithKline (I), Johnson & Johnson Dental Care Company (#VII), Colgate Palmolive Company (#IV) and Warner Lambert (#VI).

Comparison and regimen

Two of the studies (#I, VII) compared the effects of CPC mouth rinses with toothbrushing. The other six studies (#II, III, IV, V, VI and VIII) compared CPC to toothbrushing followed by a placebo rinse. The following placebo mouth rinses were used: a rinse with the same colour and flavour as the active rinse but without CPC (#II, VI); coloured flavoured water (#VIII); an alcohol free rinse (#III); a CPC containing rinse (Scope®; Procter & Gamble Company, Cincinatti, OH, USA) diluted in water (1:5)

Table 3. **Studies processed for data extraction**

No.	References	Design and evaluation period	No. of subjects, gender and age	Comparison (BA)	Regimens	Authors' conclusion
I	Zimmer *et al.* (59)	RCT single blind parallel, 8 weeks*	78 Subjects,?♀, ?♂, mean age: 31.7 years, age range: 20.0–64.4 years	A: brushing + 0.01% CPC/F, B: brushing only	Toothbrushing as usual, rinsing for 30 s with a CPC mouth rinse once per day	The 0.1% CPC rinse as an adjunct to toothbrushing is more effective in preventing plaque accumulation than toothbrushing only. With regards to reduction in bleeding, there is no significant difference between the efficacy of the CPC rinse and toothbrushing only
II	Stookey *et al.* (60)	RCT parallel double blind, 6 months*	258 Subjects, 106♀, 152♂, mean age: 34.1 years, age range 18–66 years	A: brushing + 0.075% CPC (72–77%), B: brushing + 0.10% CPC (72–77%), C: brushing + placebo rinse	Toothbrushing, rinsing with water or with 15 ml of a CPC mouth rinse for 30s once per day	0.075% and 0.1% CPC rinses as adjuncts to toothbrushing provide statistically significant antiplaque and antigingivitis benefits over 6 months of use compared to toothbrushing and rinsing with a placebo
III	Mankodi (61)	RCT parallel double blind, 6 months*	119 Subjects, 94♀, 25♂, mean age: 38.2 years, age range 18–65 years	A: brushing + 0.07% CPC (72–77%), B: brushing + placebo rinse	Toothbrushing as usual, rinsing with water or with 20 ml of assigned mouth rinse for 30 s	The 0.07% CPC rinse as an adjunct to toothbrushing provides a significant reduction of plaque, gingival index and bleeding compared to toothbrushing and rinsing with a placebo
IV	Allen *et al.* (62)	RCT parallel double blind, 6 months*	111 Subjects, 63♀, 48♂, mean age: 40.4 years, age range: 18–57 years	A: brushing + 0.05% CPC, B: brushing + control rinse	Toothbrushing for 1 min in customary manner, rinsing with water or with 15 ml of CPC mouth rinse for 30 s twice daily	The 0.05% CPC rinse as an adjunct to toothbrushing exhibited statistically significant reduction in both supragingival plaque and gingivitis compared to toothbrushing and control rinse
V	Nelson (63)	RCT parallel double blind, 6 weeks	±66 Subjects†, ±49♀, ±17♂, mean age: ?, age range: 18–52 years	A: brushing + 0.05% CPC, B: placebo rinse + brushing	Verbal and written instructions for product use according to manufacturer's directions or recommendations	The 0.05% CPC rinse as adjunct to toothbrushing may have limited benefits for controlling gingivitis as there was no significant reduction of the gingival index compared to toothbrushing and rinsing with a placebo
VI	Moran and Addy (64)	RCT parallel double blind, 6 weeks	107 Subjects,?♀, ?♂, mean age:?, age range:?	A: 0.1% CPC + brushing, B: placebo rinse + brushing	Rinsing with 20 ml of CPC mouthwash followed by toothbrushing twice daily	Rinsing with 0.1% CPC mouth rinse before brushing showed no adjunctive benefits to plaque control and gingival health

Table 3. ***(Continued)***

No.	References	Design and evaluation period	No. of subjects, gender and age	Comparison (BA)	Regimens	Authors' conclusion
VII	Finkelstein (65)	RCT, parallel, 3 months	65 Subjects,?♀, ?♂, mean age:?, age range:?	A: brushing + 0.05% CPC, B: brushing only	Toothbrushing *at libitum*, products used according to manufacturer's directions, no other oral hygiene measures were permitted	The 0.05% CPC rinse compared to toothbrushing only: did not significantly improve gingival health; exhibited more plaque reduction; reduced plaque on visible tooth surfaces, but did not penetrate sufficiently between teeth to affect interdental plaque and thus interdental inflammation
VIII	Barnes (66)	RCT parallel single blind, 4 weeks	63 Subjects, 0♀, 63♂, mean age: 18.04 years, age range: 18–21 years	A: brushing + 0.05% CPC, B: brushing + placebo rinse	Usual oral hygiene was continued without change, rinsing with mouthwash at least once daily, use mouthwashes other than the assigned ones were prohibited	The daily use of CPC mouthwashes tested is *partially* effective in reducing existing bacterial plaque accumulations

*Baseline prophylaxis. †Estimation of the number of subjects, male and female participants by the authors based on the published data. ? = not given. BA, bioavailability.

subsequently used contrary to manufacturer's directions to minimize its possible effectiveness (#V); and a rinse without CPC (#IV). Table 3 presents an overview of the comparisons and regimens. The regimens varied substantially in rinsing time and amount of mouth rinse used as well as instruction and supervision of oral hygiene.

Baseline prophylaxis, supervised rinsing and oral hygiene instruction

A baseline prophylaxis was given in four studies (#I, II, III IV). Verbal and/or written instructions were given in all studies. Oral hygiene including rinsing was performed unsupervised in all but one study (#II). In one of these studies (#V), all participants rinsed unsupervised but were given a diary to record their rinsing history in order to monitor the participants' compliance. In study #II, subjects performed rinsing under supervision on weekdays but unsupervised on weekends.

Assessment parameters

The assessment parameters and outcome data are presented in Table 4a–c

Plaque

All but one study (#VII) used the Turesky modification of the Quigley and Hein plaque index (67) to assess plaque. In addition to the Quigley and Hein plaque index, the Modified Proximal Plaque Index (68) was also used in study #I. The Global Plaque Index (69) was used in study #VII.

Gingivitis

Analysis of the selected studies shows that gingivitis was assessed using different indices, namely, the Löe and Silness Gingival Index (GI) (70) (#II, IV, V and VI), the Gingival Severity Index, a Talbott et al. (71) modification of the Löe and Silness GI, the Modified Gingival Index (#III) (72), the Gingival Bleeding Index by Saxton and van der Ouderaa (73) (#III), the Papillary Bleeding Index (PBI) (74) (#I) and the Eastman Interdental Bleeding Index (75) (#VII).

Side effects and smoking

In five studies (#I, II, III, IV and VI), subjects were examined for mucosal pathologies or reactions either via visual investigation performed by the examiner and/or by comments made by

the subjects in a diary. Staining of teeth and tongue was considered as significantly relevant in study #I. Other insignificant side effects that occurred in this study were discomfort in taste, discomfort in sensibility, mouth burning during application and white plaque on the tongue immediately after use (59). In this trial, it was also assumed that smoking did not have a relevant impact on the occurrence of side effects as smokers were represented in approximately the same ratio in the whole group as in the subset with staining.

Quality assessment

Method of randomization and allocation concealment

All studies but one (#VII) performed randomization. Stratification in order to balance treatment groups was performed for gender and PBI (#I); gender and baseline mean GI (#II); gender and baseline smoking (#III); baseline GI (#IV) and PI (#VIII). Regarding allocation concealment, one study (#I) reported that an individual who was not involved in the examination had performed the assignment of subjects to treatment groups. In study #VI, the allocation of mouth rinses was performed through a hospital facility that kept a sealed code breaker.

Blindness of examiners

In all but one study (#VII), information was given on the study blindness. Two studies (#I, VIII) were performed operator-blind. As the operators' blinding could be influenced by clinically visible side effects as staining of tongue/teeth, in study #I, an additional statistical analysis was performed for subjects without visible side effects. The analysis did not reveal any statistical significant changes in the study outcome. The other five studies (#II, III, IV, V and VI) were conducted double-blind.

Completeness of follow-up

Reasons for subject dropout or exclusion that were mentioned medication use outside the study protocol, unavailable patients, non-compliance, adverse events and non-study related medical reasons (#II). Study #VI reported a withdrawal and a malfunctioning data retrieval system software that had led to the data loss of six other participants. Two studies (#III, IV) reported that participants dropped out for reasons unrelated to the use of their assigned mouth rinse. No further clarification for dropout was given in the three remaining studies (#I, V and VII). The remaining study (#VIII) did not report any dropout of participants.

Study outcome

Within groups (baseline scores versus end scores)

Differences between the baseline and end scores are shown in Table 4(a–c). Four out of eight studies (#I, VI, VII and VIII) addressed changes within the groups. In the remaining studies, the data suggested a reduction in the indices assessed. The intra-treatment effect, however, was not addressed by the authors.

Plaque index

Two studies (#VI, VIII) reported a significant improvement in plaque scores for the groups using a CPC mouth rinse. Study #VI observed a significant reduction in the PI for the placebo rinse as well (Table 4a).

Bleeding index

Study #I and VII both reported a reduction in bleeding indices, although the reduction was insignificant (Table 4b).

Gingival index

A significant increase from the baseline and end scores was observed in the GI in study #VI for both the CPC rinse as well as the placebo rinse (Table 4c).

Between groups (CPC rinses versus control)

Differences between CPC mouth rinses and control are presented in Table 4(a–c). Data are presented in a descriptive manner in Table 5.

Plaque index

Both studies that compared a CPC mouth rinse to toothbrushing (#I, VII) showed a significant difference only in favour of the CPC mouth rinse. All but one study (#VI) showed a significant positive change in the plaque index when using the CPC mouth rinse compared to toothbrushing followed by a placebo rinse (Tables 4a and 5).

Bleeding index

There were no significant differences in the gingival indices of the CPC rinse and those of the placebo rinse in one study

Table 4. **Overview of selected studies and parameters of interest (Mean [SD])**

No.	Intervention	Index	Baseline	End	Difference
Plaque index					
I	0.1% CPC/NaF post-brushing	Modified Proximal Plaque Index (1989)	2.22 (0.30)	1.40 (0.49)◇	−0.82◇
	Toothbrushing only		2.20 (0.33)	1.88 (0.50)	−0.32◇
	0.1% CPC/NaF post-brushing	Quigley & Hein (1962)	2.12 (0.34)	1.54 (0.53)◇	−0.58◇
	Toothbrushing only		2.16 (0.41)	2.00 (0.50)	−0.16◇
II	0.75% CPC post-brushing	Quigley & Hein	2.15 (0.38)◇	1.63 (0.499)◇,*	−0.52◇
	0.10% CPC post-brushing rinse	[modified by Turesky *et al.* (67)]	2.10 (3.95)◇	1.60 (0.497)◇,*	−0.50◇
	Placebo post-brushing		2.11 (0.44)◇	1.97 (0.502)◇	−0.14◇
III	0.07% CPC post-brushing	Quigley & Hein	2.73 (0.437)◇	1.97 (0.400)◇,*	−0.76◇
	Placebo post-brushing	[modified by Turesky *et al.* (67)]	2.68 (0.401)◇	2.34 (0.401)◇	−0.34◇
IV	0.05% CPC post-brushing	Quigley & Hein	2.14 (0.34)	1.45 (0.32)*	−0.69◇
	Placebo post-brushing	[modified by Turesky *et al.* (67)]	2.17 (0.34)	2.02 (0.36)	−0.15◇
V	0.05% CPC post-brushing	Quigley & Hein (1962)	2.40 (0.04)	2.43 (0.04)*,‡	+0.03◇
	Placebo prebrushing		2.41 (0.07)	2.53 (0.03)‡	+0.12◇
VI	0.1% CPC prebrushing	Quigley & Hein	2.23 (0.45)	1.92 (0.51)•	−0.31◇
	Placebo prebrushing	[modified by Turesky *et al.* (67)]	2.34 (0.39)	2.0 (0.42)•	−0.34◇
VIII	0.05% CPC post-brushing	Quigley & Hein (1962)	2.02 (0.47)	1.75 (0.53)*,•	−0.27
	Placebo post-brushing		2.04 (0.43)	1.98 (0.47)	−0.06
Bleeding index					
I	0.1% CPC/NaF post-brushing	Papillary Bleeding Index (74)	1.25 (0.45)	0.75 (0.49)	−0.50◇
	Toothbrushing only		1.27 (0.45)	0.89 (0.46)	−0.38◇
II	0.75% CPC post-brushing	Löe & Silness (70)	18.6 (8.86)◇	11.1 (6.15)◇,*	−7.5◇
	0.10% CPC post-brushing rinse		19.9 (9.84)◇	11.6 (6.16)◇,*	−8.3◇
	Placebo post-brushing		20.2 (12.82)◇	15.9 (6.12)◇	−4.3◇
III	0.07% CPC post-brushing	Gingival Bleeding Index (73)	0.106 (0.053)◇	0.040 (0.047)◇,*	−0.066◇
	Placebo post-brushing		0.102 (0.048)◇	0.060 (0.058)◇	−0.042◇
IV	0.05% CPC post-brushing	Löe & Silness, modified by Talbott *et al.* (71)	0.362 (0.180)	0.089 (0.109)*	−0.273◇
	Placebo post-brushing		0.364 (0.196)	0.269 (0.158)	−0.095◇
Gingival index					
II	0.75% CPC post-brushing	Löe & Silness (70)	0.792 (0.177)◇	0.526 (0.15)◇,*	−0.266*
	0.10% CPC post-brushing rinse		0.800 (0.182)◇	0.548 (0.15)◇,*	−0.252◇
	Placebo rinse		0.814 (0.201)◇	0.683 (0.148)◇	−0.131◇
III	0.07% CPC post-brushing	Modified Gingival Index, Lobene & Mankodi	2.01 (0.097)◇	1.59 (0.299)◇,*	−0.42◇
	Placebo post-brushing		2.02 (0.110)◇	1.88 (0.299)◇	−0.14◇
IV	0.05% CPC post-brushing	Löe & Silness, modified by Talbott *et al.* (71)	1.37 (0.19)	0.92 (0.23)*	−0.45◇
	Placebo post-brushing		1.38 (0.21)	1.21 (0.15)	−0.17◇
V	0.05% CPC post-brushing	Löe & Silness (70)	1.25 (0.3)	1.22 (0.03)‡	−0.03◇
	Placebo prebrushing		1.33 (0.07)	1.28 (0.05)‡	−0.05◇
VI	0.1% CPC prebrushing	Löe & Silness (70)	1.29 (0.13)	1.10 (0.22)•	−0.19◇
	Placebo prebrushing		1.33 (0.16)	1.12 (0.27)•	−0.21◇

◇Calculated by the authors.
*Significant difference compared with the control or placebo group.
‡Standard error.
•Significant difference compared with baseline.

(#VII). In the other studies in which gingival bleeding was assessed (#I, II, III and IV), a significant difference was reported, indicating that the outcome of using a CPC was better than that of either toothbrushing only (#I) or toothbrushing followed by rinsing with a placebo (#II, III and IV) (Tables 4b and 5).

Table 5. **Summary of whether there is a significant difference in favour of the CPC mouth rinse compared with the toothbrushing alone or toothbrushing followed by a placebo rinse groups**

Author(s) #	Plaque	Bleeding	Gingival index	Comparison
I	**+***	**+**	□	Brushing only
VII	**+**	**0***	**0**	Brushing only
II (a)	**+**	**+**	**+**	Brushing and placebo
II (b)	**+**	**+**	**+**	Brushing and placebo
III	**+**	**+**	**+**	Brushing and placebo
IV	**+**	**+**	**+**	Brushing and placebo
V	**+**	□	**0**	Brushing and placebo
VI	**0**	□	**0**	Brushing and placebo
VIII	**+**	□	□	Brushing and placebo

+ = Significant difference, **0** = no difference, □ = no data available, * = 2 indices.
a: 0.075%, b: 0.10%.

Gingival index

Three out of six studies that measured the GI (#II, III and IV) reported a significant difference, indicating that the outcome of using a CPC mouth rinse was better than that of toothbrushing followed by rinsing with a placebo. In two studies, no significant difference was found between CPC mouth rinsing and toothbrushing only (#VII) or toothbrushing followed by a placebo rinse (#V), nor was there a significant effect of a CPC-containing prebrushing mouth rinse compared to a prebrushing placebo rinse followed by toothbrushing (#VI) (Tables 4c and 5).

Meta-analysis

A MA was performed to compare the effect of CPC mouth rinses to that of toothbrushing in conjunction with a placebo mouth rinse or toothbrushing only. The MA was performed four times: the plaque parameter for studies ≥4 weeks (A), the gingival health parameter for studies ≥4 weeks (B), the plaque parameter for studies <6 months (C) and the plaque parameter for studies ≥6 months (D). Some studies could not be included in the MA because they used different indices (#I, III and VII) or lacked baseline and end SD (#VII). Study #V was excluded from the MA because of it did not report the number of subjects for each test group. Data from study #II were used twice for the separate results for 0.075% CPC and 0.10% CPC mouth rinses.

Table 6 shows a summary of the MA outcome. In all cases, baseline scores were not statistically different. The end scores showed a significant effect for the Quigley and Hein PI (67) in favour of the CPC group compared to those of toothbrushing only or toothbrushing followed by a placebo rinse [weighted mean difference (WMD): −0.50, $P < 0.00001$; test for heterogeneity $P = 0.002$, $I^2 = 71.6\%$]. The heterogeneity was greater for intermediate-length studies ($I^2 = 68.1\%$) than long-term studies ($I^2 = 58.8\%$). One could deduce from these outcomes that a greater effect is observed in long-term studies than in intermediate-length studies. The end scores also displayed a significant effect for the Löe and Silness GI (70) in favour of the CPC group compared to those of the toothbrushing only or toothbrushing followed by a control rinse group (WMD: −0.25, $P < 0.00003$; test for heterogeneity $P = 0.0001$, $I^2 = 87.0\%$).

Discussion

Today, many studies on the efficacy of CPC have been published, and a range of over-the-counter and prescription formulations containing this agent are available. This additional therapeutic action requires patients to devote extra time for dental hygiene, to occasionally tolerate less than desirable side effects and to invest more money (6, 76). Consequently, before any preventative measure can be universally recommended, a decision must be made about its potential benefits and drawbacks (76). In particular, evidence-based practices and systematic reviews provide a strong scientific basis to identify effective therapeutic formulations.

Systematic reviews differ from traditional reviews in that they are usually confined to a single focussed question which servers as the basis for systematic searches, selection and clinical evaluation of the relevant research (77). Based on the present systematic review, the use of CPC-containing mouth rinses in addition to toothbrushing seems to be effective in controlling dental plaque and gingivitis in long term as well as in intermediate-length trials. Some important considerations concerning this outcome are discussed below.

Table 6. **Meta-analyses**

Time	Index	Studies			WMD (random)	Test for overall effect	95% CI	Test for heterogeneity
≥4 weeks	Quigley and Hein (1962) PI	I II* IIIIV VI VIII	Base End	−0.01 −0.35	$P = 0.71$ $P \leq 0.00001$	[−0.06; 0.04] [−0.47; −0.24]	$P = 0.80$ $P = 0.002$	$I^2 = 0\%$ $I^2 = 71.6\%$
≥4 weeks	Löe & Silness (70) GI	II* IV VI	Base End	−0.02 −0.15	$P = 0.15$ $P = 0.0003$	[−0.05, 0.01] [−0.23, −0.07]	$P = 0.87$ $P < 0.0001$	$I^2 = 0\%$ $I^2 = 87\%$
≥4 weeks - < 6months	Quigley & Hein (1962) PI	I VIII VI	Base End	−0.06 −0.25	$P = 0.22$ $P = 0.02$	[−0.16, 0.04] [−0.47, −0.03]	$P = 0.075$ $P = 0.04$	$I^2 = 0\%$ $I^2 = 68.1\%$
≥6months	Quigley & Hein (67) PI	II* III IV	Base End	0.01 −0.42	$P = 0.75$ $P < 0.00001$	[−0.05, 0.07] [−0.53, −0.31]	$P = 0.79$ $P = 0.06$	$I^2 = 0\%$ $I^2 = 58.8\%$

WMD, Weighted Mean Difference; CI, Confidence Interval.
*Used twice, once each for 0.075% and 0.10% CPC.

Evaluation period

In 2006, a systematic review of 6-month-long clinical trials described the plaque- and gingivitis-inhibiting effect of CPC-containing mouth rinses compared with that of other active agents (13). According to Gunsolley (13), short-term studies (4 days to 2 weeks) can be used to investigate anti-plaque effects. Intermediate-length trials (2 weeks to 2 months) have limitations in that they do not reflect the patients' actual long-term use of the product (13). The ADA requirements for a seal of acceptance demand a study period of 6 months with an intermediate evaluation at 3 months to evaluate both efficacy and safety of chemical agents as well as patients' compliance (12). Given that mouth rinses are also used and prescribed for short periods, their efficacy over shorter periods is also of interest (78). Therefore, studies with a minimum evaluation period of 4 weeks were also included in this review. This concurs with the ADA demands concerning adjunctive devices for controlling plaque and gingivitis (17). Furthermore, only formulations that met the ADA's safety criteria of CPC concentrations (between 0.045% and 0.10%) were included.

Clinical activity

The formulation of an active agent in a mouth rinse is extremely important to maintain its bioavailability, biofilm penetrability and substantivity as well as clinical activity (6, 10, 13, 79). In addition, the Food and Drug Administration (FDA) Subcommittee states that CPC bioavailability is indicative of a product's performance as 'it readily defines the amount of drug available for deposition at the site of action' (FDA, 2003: 5–6). Consequently, the FDA subcommittee recommends a bioavailability of CPC ranging from 72% to 77%. Two out of three trials (#V, VII) that reported no effect on the GI tested mouth rinses containing 0.05% CPC. The formulation used (Cepacol®) in these studies has a CPC bioavailability of 54%. In contrast, study #IV reported statistically significant plaque and gingivitis reduction by the use of 0.05% CPC. However, the bioavailability of CPC in the tested rinse was not mentioned. One possible explanation for this discrepancy is the low bioavailability of CPC in studies #V and VII. Moreover, different formulations with similar concentrations of an active agent may not necessarily have equivalent clinical efficacy.

Side effects and substantivity

Side effects such as staining of teeth and tongue are not considered to be severe from a medical viewpoint, but they may be regarded as an aesthetic detriment, possibly leading to reduced compliance (#I). Various groups have reported several objective side effects such as staining and ulcerations (33, 36) and subjective side effects such as burning sensations (29, 51) induced by CPC. Despite the known potential of CPC in inducing side effects, only five out of eight trials (#I, II, III, IV and VI) investigated in the present review assessed this aspect. Only one of these studies (#I) reported staining of tongue and teeth as significantly relevant. Staining caused by CPC has a similar dietary aetiology as that induced by chlorhexidine (CHX)

solutions, but it appears to be less severe (53). This phenomenon reflects the lower substantivity of CPC, which may also explain its lower efficacy compared with CHX. Despite its higher initial retention, CPC is cleared from the oral cavity more rapidly (9–11). As demonstrated by Roberts and Addy (53), the duration of the therapeutic effect as measured by residual salivary antibacterial activity is present up to 90 min for CPC when compared with 7 h for CHX. Its less prominent side effects, however, support the idea that CPC could have longer adjunctive use for oral hygiene even with its apparently lower potency compared with that of CHX. Additionally, one should be aware of an increase in staining propensity in situations where the enhancement of CPC formulations results in the increase of the retention and desorption rates of CPC (80).

Counteracting ingredients

Cationic antiseptics such as CPC have been shown to be inactivated when preceded by dentifrice ingredients such as sodium monofluorophosphate and sodium lauryl sulphate (SLS) (24, 81–83). In contrast to these findings, the potency of CPC appeared not to be diminished despite the use of dentifrice in studies included in this review. Two main factors may have led to these conflicting results: (i) in some trials (#I, II, III and IV), subjects were required to use a dentifrice as opposed to a dentifrice slurry used in the studies conducted by Sheen *et al.* (24). As most daily oral hygiene regimens include toothbrushing with a dentifrice, it is assumed that dentifrices were also used in studies where participants were instructed to maintain their usual oral hygiene (#VIII, VII), (ii) participants were also instructed to perform rinsing with water immediately after toothbrushing (#I, II and III). Rinsing with water helps to get rid of the SLS residual in the oral cavity (84) and to enhance CPC activity (19). The lower intra-oral SLS concentration and a short contact time with SLS do not seem to reduce the effect on CPC.

Evidence-based advice

Only products that have proven clinical activity using generally accepted safety and effectiveness criteria should be recommended to patients according to their needs (6). Consequently, it is important to determine what types of patients are likely to benefit from the additional use of CPC-containing mouth rinses. It has been suggested that chemical agents such as CPC-containing mouth rinses could be important adjuncts in patients with a high susceptibility of periodontal diseases or who lack the dexterity to effectively clean their teeth with mechanical methods alone (6, 84–86). It has also been suggested that patients who maintain good mechanical plaque control will benefit more from additional chemical agents as opposed to patients with poor mechanical plaque control (45, 87, 88, 89).

Improvement in gingival health is more apparent if a high level of inflammation is present at the baseline (GI < 1 represents a relatively healthy state) (90). The baseline GI of the investigated populations mostly varied between 0.7 and 2.02 (#II, III, IV, V and VII). Furthermore, some trials (#I, II, III and IV) involved a baseline prophylaxis, a variable for which the magnitude cannot be assessed in the outcome of plaque and gingivitis studies (24). The conclusions drawn in this systematic review are, therefore, applicable only to subjects in good general health and with good to moderate gingival health. As a result, more evidence-based research is needed to establish whether CPC-containing mouth rinses have additional efficacy in patients already suffering from periodontitis.

Outcome

Although the MA is now well established as a method of reviewing evidence, one common problem are sources of heterogeneity, in particular clinical differences between studies included. Heterogeneity should be investigated to increase the clinical relevance of the conclusions drawn (91). It was attempted to explore some of the possible causes of heterogeneity which could related to quality of trial design, accuracy of the outcome measures, population and length of follow-up. Considerable clinical heterogeneity was observed among the selected studies (Table 3). The strategy considered was to use the 'random effects model' in the calculation of the pooled estimator (92). In addition a subgroup MA were performed taking study duration into account. Heterogeneity may be caused by publication bias. For instance industry tends to discourage the publication of negative studies that it has funded. In this review six studies either had authors from industry or were industry sponsored. Last but not the least, heterogeneity may also be due to chance.

A MA helps detect whether the outcomes are in favour of the study product. However, in case the testing for heterogeneity is significant the reader should take caution in using the WMD as the exact measure for the effect.

Statistical heterogeneity is not a poor attribute in a MA, but it shows that the studies are not all estimating the same quantity. This does not necessarily suggest that the true intervention

effect varies (92). At baseline no heterogeneity for gingivitis was observed implicating that at the start of the studies the test and control groups included were comparable. Therefore the heterogeneity observed in the MA of the data at the end of the study reflects different behaviours of the study populations to the study product, differences in study designs and all other factors that may influence the outcomes. Because the test for heterogeneity was significant, the WMD value should be interpreted with caution and should not be quoted to demonstrate the magnitude of the effect. Although a degree of heterogeneity was observed the overall conclusions are supported by the results of the individual studies as presented in Table 5.

Conclusion

When used as an adjunct to either supervised or unsupervised oral hygiene, CPC-containing mouth rinses provide a small but significant additional benefit when compared with toothbrushing only or toothbrushing followed by a placebo rinse in that they reduce plaque and gingival inflammation.

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