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Efficacy of two alcohol-free cetylpyridinium chloride mouthwashes – a randomized double-blind crossover study

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Abstract

Aim: (1) To determine the plaque inhibition properties of two formulations of alcohol-free mouthwash [0.1% w/w cetylpyridinium chloride (CPC) (B) and 0.05% w/w CPC (A)] *versus* a placebo mouthwash (C). (2) To compare the plaque-inhibiting activity between these two new CPC mouthwashes.

Material and Methods: A double-blind, crossover study with three 1-week periods was used. Subjects were randomly assigned to one of the following groups. Group 1 ($n = 10$) received the mouthwashes A, C and B in the periods 1, 2 and 3, respectively, group 2 ($n = 11$) received the mouthwashes in the order B, A, C, while group 3 ($n = 11$) received the mouthwashes in the order C, B, A.

Mean plaque areas and Quigley & Hein plaque index scores were analysed using ANOVA (analysis of variance). Measurements were made at the start of each period (baseline) and at 16, 24 and 40 h.

Results: Mean plaque scores were similar across the groups at baseline. At all time points thereafter, volunteers using mouthwash A or B had significantly lower plaque areas and plaque index scores than those using mouthwash C ($p < 0.05$), but there were no significant differences between the test formulations. At 16 h, the reduction in plaque area relative to mouthwash C was 22% for mouthwash A and 18% for mouthwash B; at 24 h, 11% for mouthwash A and 15% for mouthwash B; and at 40 h, 15% for mouthwash A and 16% for mouthwash B.

Conclusions: The use of both CPC mouthwashes resulted in less plaque accumulation compared with the control. There was no statistically significant difference in plaque accumulation between the two CPC mouthwashes.

Key words: alcohol free; cetylpyridinium chloride; clinical trial; mouthwash

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Conflict of interest and source of funding statement

Professor Rawlinson, Miss Pollington, Professor Walsh and Dr. Lamb had full access to all the data in this study and take complete responsibility for the integrity of the data and the accuracy of the data analysis. None of these authors are associated with Boots PLC, Nottingham, UK. Mr. Marlow, Ms. Haywood and Mr. Wright of Boots PLC contributed their experience only to the study design and did not participate in the actual clinical study. The study was company initiated, with Boots PLC only supplying the materials and supporting the study financially. No other form of support was given. In addition, the study was not supported by any other party (other than ethics approval).

The daily removal of dental plaque is an important factor in the prevention of gingival inflammation and smooth surface enamel caries. It is also important for the healing to occur after periodontal therapy (Axelsson et al. 2002). Plaque control is largely accomplished by effective tooth brushing and inter-dental cleaning, but in some patients daily plaque control may be improved by the

adjunctive use of a mouthwash. Mouthwashes are frequently recommended where oral hygiene is compromised or difficult. A wide range of products containing a variety of active ingredients is available for patient selection. Two cationic antiseptics are particularly common as the active ingredients in these products, namely chlorhexidine and cetylpyridinium chloride (CPC). Their mode of action is by reducing both the amount of supragingival plaque formed and the virulence of the biofilms, which in turn leads to a reduced inflammatory response (White 2005).

In general, chlorhexidine has been considered the most effective of these active ingredients in reducing dental plaque formation (Addy & Moran 1997, Jones 1997). However, it suffers from the drawbacks of staining teeth and restorations, an unpleasant taste and alterations to taste sensation. CPC containing mouthwashes may also cause staining, although this seems to be less marked compared with chlorhexidine and has been shown in a number of clinical trials to reduce plaque formation (Allen et al. 1998, Mankodi et al. 2005).

Most mouthwashes contain an alcohol, especially ethanol, to dissolve other ingredients (Claffey 2003) and impart a ''mouth impact sensation''. Concern has been raised over the possible adverse effects in the mouth arising from the long-term use of alcohol in products used for daily oral health care although other lifestyle factors also have a confounding effect on these studies. These include possible increased risk of oral and oesophageal cancer (Elmore & Horwitz 1995) and effects on dental restorative materials (McKinney & Wu 1985, Penugonda et al. 1994). In addition, a fatal outcome was reported following the ingestion of a large volume of alcohol containing mouthwash (Soo Hoo et al. 2003). Consequently, there are many possible health benefits associated with alcohol-free mouthwash preparations in comparison with alcohol-containing preparations.

There is some evidence that alcohol-free mouthwashes containing amine fluoride/stannous fluoride or triclosan are effective in reducing plaque accumulation in comparison with a placebo solution (Arweiler et al. 2001). However, there is a need for further research on the efficacy of alcohol-free products in inhibiting dental plaque formation. Most CPC-containing products have a concentration of 0.05% CPC however, it may be necessary to increase the concentration to improve the plaque inhibitory properties of these mouthwashes.

The aims of this study were to (1) to determine the plaque-inhibiting properties of two new alcohol-free mouthwash formulations containing CPC compared with a placebo mouthwash and (2) to compare the plaque-inhibiting activity between these two new CPC mouthwashes.

Material and Methods

Patients

Ethical approval from the South Sheffield Research Ethics Committee was obtained and the study was undertaken using the Good Clinical Practice guidelines. Volunteers were recruited from staff and students of the University of Sheffield by use of the electronic network, and from patients attending the Charles Clifford Dental Hospital in response to advertisements displayed on notice boards in the Restorative Clinics. Thirty-two volunteers were recruited following screening in May 2004 over a 3-week period. The minimum sample size required was determined by power calculations based on previous studies undertaken in Sheffield and sample sizes used in published studies from UK Dental Schools. A review of key papers and previous work undertaken suggested that the study should be designed to enable the detection of a mean difference of 0.2 between the control and test groups for plaque scores. To detect a potential mean difference between control and test groups of 0.2 with 90% power, assuming a standard deviation of 0.31 for the difference between a subject's values on the Quigley & Hein plaque index, the estimated required sample size was 28 for each regime. In view of this, a sample size of 32 subjects were recruited to allow for subject loss during the trial. All volunteers were given verbal and written information about the study and gave their written consent to participate. The study directors informed volunteers of the following:

- The aim of the study and the procedures to be followed.
- How to use the test or control products.
- The possible advantages and disadvantages of the products.
- That they were free to withdraw/may be withdrawn from the study at any time, without prejudice, if continued participation may be detrimental to their well-being.
- That they should inform the organiser of any change in medical condition during the study.

A record of compliance was given to all subjects, and this was collected for analysis at the end of the study. Adverse effects were also monitored and recorded. All subjects were assigned a study code number and randomly allocated using computer-generated numbers to one of the study groups by the study directors and senior nurse manager. Group size was equalized by alternate random allocation. The trial was a three-stage crossover design so all groups were approximately equal ($n = 10$ for the group receiving treatments in the order ACB, $n = 11$ for the BAC group, $n = 11$ for the CBA group). A randomized list with equal time for the subjects was devised and subjects were allocated to their crossover sequence after being randomly allocated using randomized tables. Post-allocation analysis was used to confirm the equality of the groups in terms of age and gender.

The inclusion criteria for the study were as follows:

- Able to attend for the period of the trial.
- Able to form plaque to a Turesky et al. (1970) modification of the Quigley & Hein (1962) plaque index mean score of 2 or more after 18 h of abstinence from oral hygiene measures.
- At least 20 natural teeth, without restorations affecting buccal, lingual or inter-dental surfaces.
- Age over 18 years.

The exclusion criteria were as follows:

- Pregnant or lactating.
- Currently participating in any other trial/study involving the oral cavity.
- Participation in a clinical pharmacology trial during the last three months.
- Antibiotic or anti-inflammatory therapy in previous month.
- Any known serious systemic (e.g. hepatic renal, haematological or cardiovascular) or oral disease.

- Sufferers of heart disease or current or past sufferers of rheumatic fever.
- Known sensitivity/allergy or oral mucosal tissue reaction to dental products (oral hygiene products, mouthwashes, etc.) or ingredients.
- Dental treatment during the study period.
- Use of chewing gum during the study period.
- Presence of significant amounts of calculus.
- Presence of mouth ulcers or known susceptibility to frequent or severe occurrences of ulceration.
- Wearing any oral prosthesis.
- Any inadequate restoration or untreated dental caries.

Study design

The study was a double-blind (both assessors and volunteers) crossover design. The investigative areas were the buccal and lingual tooth surfaces of all premolar and anterior teeth. Molar teeth were excluded due to difficulties with access for accurate measurements. Volunteers recruited to the study following screening were randomly allocated to use the experimental or placebo product (flavoured water).

Assessments of plaque were made at the following intervals: (1) Baseline (0), (2) 16 h, (3) 24 h. (4) 40 h. Volunteers used a standard 1000 p.p.m. toothpaste (Boots PLC, Nottingham, UK) and brush (medium head, Boots PLC) for 5 days before baseline. On the morning of day 0, following breakfast, the volunteers brushed their teeth with water and checked their plaque control with a disclosing tablet (Plaque Check, Oral B, London, UK). They were instructed to brush a second time with water to remove disclosed and highlighted plaque.

At baseline, volunteers had their plaque levels scored using the Addy and Turesky indices, then rinsed with either 10 ml of experimental product or the coloured water placebo for 1 min. under supervision, ensuring good distribution around the mouth. They were instructed not to rinse with water, eat or drink for 1 h following this rinse. The subjects rinsed under supervision in the clinic twice a day, at 08:00 and 16:00 hours.

The study lasted for three consecutive week days – days 0, 1 and 2 in weeks 1, 2 and 3 and thus there was a 5-day wash-out period between treatments when subjects returned to their normal oral hygiene regime. Volunteers used the mouthwashes provided by the investigators during the period of the study.

Both experimental mouthwashes were provided by The Boots Company PLC and were delivered in labelled containers. The control product was made up each week on site.

The experimental or control mouthwash was used under supervision, and the use of accessory methods, interdental cleaning, oral rinses or other toothpaste products was not permitted.

Data collection

- Plaque re-growth on all buccal and lingual surfaces, of premolar and anterior teeth in both dental arches.
- All unwanted effects were noted using a questionnaire.

The Addy et al. (1983) plaque area index and the Turesky et al. (1970) modification of the Quigley & Hein (1962) plaque index were both used to assess plaque re-growth in the clinic. A plaque index for each subject was determined by dividing the total plaque score by the individual surfaces scored.

All examiners were trained and calibrated before the study.

Statistical analysis

The data were first averaged across scored tooth surfaces to give a single value for plaque area and plaque index at each time point (0, 16, 24 and 40 h) for each treatment and each volunteer. Analysis of plaque area and plaque index at 16, 24 and 40 h was undertaken by analysis of variance with volunteer, treatment and period as factors. This was followed by comparison of treatments (mouthwashes) in pairs. The statistical analysis took account of any possible differences between periods. Initial work also checked for any relevance of baseline values by analysis of covariance or any differences between treatment effects in the three periods. All statements of statistical significance was based on $\alpha = 0.05$, two-tailed tests.

Results

No subjects were lost from the trial and there were no reports of any significant adverse reactions. However, the following comments were made by subjects about the test mouthwash: two subjects did not like taste (C) and three subjects complained about a ''Burning'' sensation (A & B). A complete data set for all subjects was obtained at each evaluation. Table 1 presents a summary of the actual plaque area and interval. Differences between treatments and 95% confidence intervals for the differences are also given. At baseline, mean areas were similar across the three treatment groups. At each interval, however, the mean plaque area was greater for mouthwash C compared with mouthwashes A and B.

At all time points (16, 24 and 40 h), clear differences between the treatments were observed. Parameter estimates show significant reductions in plaque area for both mouthwash A (alcohol-free mouthwash 0.05% w/w CPC) and mouthwash B (alcohol-free mouthwash 0.1% w/w CPC) compared with mouthwash C (inactive placebo mouthwash), for all three time points ($p < 0.05$). The comparisons of mouthwash A with mouthwash B show no significant differences between these two treatments with respect to the mean plaque areas. Period effects were observed at 24 h

Table 1. Actual Plaque Area and changes from baseline for each interval

Interval/mouthwash	Mean (SD)			
	baseline	16 h plaque area	24 h plaque area	40 h plaque area
Actual plaque area				
Mouthwash A	5.0 (2.1)	6.5 (2.2)	7.9 (2.3)	9.0 (2.6)
Mouthwash B	5.1 (2.3)	6.9 (2.3)	7.5 (2.4)	9.0 (2.4)
Mouthwash C	4.5 (1.9)	8.4 (1.8)	8.6 (2.0)	10.6 (2.6)
Changes in plaque area from baseline				
Mouthwash A		1.5 (2.1)*	2.9 (2.6)*	4.0 (3.2)*
Mouthwash B		1.6 (2.9)*	2.2 (2.0)*	3.6 (2.3)*
Mouthwash C		3.9 (2.1)	4.4 (1.8)	6.1 (2.6)

*Statistically significant reduction compared with mouthwash C ($p < 0.05$).
Means given in millimetres with standard deviation in parentheses.

only, with larger plaque area means seen in period 2. The mean plaque area shows similar reduced efficacy for mouthwash C. Estimated differences between mouthwash A and C, and mouthwash B and C, were significant at all three time points ($p < 0.05$). Again, no clear differences between mouthwashes A and B were observed. At 16 h, the reduction in plaque area relative to mouthwash C was 22% for mouthwash A and 18% for mouthwash B; at 24 h, 11% for mouthwash A and 15% for mouthwash B; and at 40 h, 15% for mouthwash A and 16% for mouthwash B.

The actual mean Quigley & Hein plaque indices are presented in Table 2. The baseline plaque indices were similar in each group.

However, from and including 16 h, treatment effects were clear. Significantly lower Quigley & Hein plaque index scores were observed for both mouthwashes A and B compared with mouthwash C ($p < 0.05$). There was no clear evidence for a difference in efficacy between mouthwashes A and B with respect to the Quigley & Hein plaque index, although marginal evidence for superior efficacy of mouthwash B over mouthwash A was seen at 24 h ($p = 0.0649$).

The Quigley & Hein plaque index scores are also shown in Table 2. Clear treatment effects were seen at 16, 24 and 40 h, with estimated treatment differences showing reduced efficacy for mouthwash C. No differences were observed between mouthwashes A and B.

Discussion

The development of caries, gingivitis and periodontal diseases are associated with dental plaque formation. Mechanical removal by brushing and flossing alone is unlikely to be successful for complete plaque removal. Antimicrobial mouthwashes have become popular adjuncts, since rinsing with these products may lead to more surfaces of the oral cavity being reached. These act as vehicles for plaque inhibitory agents, allowing improved plaque control and gingival health. Chlorhexidine is considered the 'gold standard' of antimicrobial mouthwash due to its proven long-term efficacy and safety (Jones 1997). However, as a consequence of its known side effects and alcohol content, certain patient groups are unable to use chlorhexidine, and its usage can only be considered on a short-term basis. Consequently, there is a need to develop alternative alcohol-free preparations as alternatives for these and others who may wish not to use alcohol-containing mouthwashes. CPC mouthwashes may fulfil these criteria.

The results of this clinical trial show that the two mouthwashes containing 0.05% and 0.1% CPC, respectively, provided clinically and statistically significant improved plaque inhibition properties compared with the placebo. There was no significant difference in plaque inhibition properties between these two CPC mouthwashes. At 16 h, the reduction in plaque area relative to mouthwash C was 22% for mouthwash A and 18% for mouthwash B; at 24 h, 11% for mouthwash A and 15% for mouthwash B; and at 40 h, 15% for mouthwash A and 16% for mouthwash B. These results are consistent with other studies, that CPC mouthwashes have comparable plaque inhibitory properties as opposed to placebo when used as an adjunct to tooth brushing. Previous research has also proven that CPC mouthwashes provide a comparable plaque reduction with essential oil mouthwashes when used as an adjunct to toothbrushing (Witt et al. 2005). Clinically, this study demonstrated that the two CPC were superior to the placebo and, in addition, the level of plaque reduction was similar to clinical studies using chlorhexidine (Charles et al. 2004).

The effects of two CPC mouthwashes containing 0.075% and 0.1% CPC, respectively, were evaluated on the development of gingivitis and plaque, compared with a control over a 6-month period. No statistically significant difference in efficacy was found between of the two CPC mouthwashes (Stookey et al. 2005, Witt et al. 2005). Witt et al. (2005) conducted a study evaluating the antiplaque effect of a 0.07% high bioavailable alcohol-free CPC rinse *versus* a positive control (essential oil) and a negative control (placebo CPC rinse). The authors found that both the essential oil and CPC mouthwash exhibited a statistically significant benefit compared with the placebo, indicating that the CPC mouthwash was as effective as the essential oil mouth rinse. In another study, CPC mouthwash reduced gingivitis and gingival bleeding by 15% and 33%, respectively, relative to the placebo after 6 months usage (Mankodi et al. 2005). Statistically significant plaque inhibitory effects were also observed. Allen et al. (1998) reported the effectiveness of 0.05% CPC mouthwash at 3 and 6 months. The CPC mouthwash exhibited statistically significantly less supragingival plaque and gingivitis than the control group. A 0.07% CPC rinse has also been demonstrated to have plaque inhibitory effects on interproximal sites, an area commonly missed by mechanical plaque removal alone (Gallitschke et al. 2006). Rane et al. (2006) investigated the change in plaque microflora over a 3-week period of rinsing with 0.07% CPC mouthwash and reported a change to a less-pathogenic plaque composition over that period. These studies confirm our findings that CPC mouthwashes have the efficacy for plaque inhibition.

CPC mouthwashes have therapeutic benefits due to their broad-spectrum antibacterial action. They belong to the quaternary ammonium compound of the cationic surface-active agents (Mandel 1988, Herrera et al. 2005). Their antimicrobial activity against many oral bacteria is by penetration of the cell membrane, causing cell leakage

Table 2. Actual plaque indices and changes in plaque index from baseline at each interval

Interval/mouthwash	Mean (SD)			
	baseline	16 h plaque index	24 h plaque index	40 h plaque index
Actual plaque index				
Mouthwash A	1.1 (0.3)	1.4 (0.4)	1.5 (0.3)	1.7 (0.3)
Mouthwash B	1.1 (0.3)	1.4 (0.4)	1.4 (0.4)	1.7 (0.4)
Mouthwash C	1.0 (0.4)	1.6 (0.3)	1.6 (0.3)	1.9 (0.4)
Changes in plaque index from baseline				
Mouthwash A		0.3 (0.4)*	0.4 (0.4)*	0.6 (0.4)*
Mouthwash B		0.3 (0.4)*	0.3 (0.3)*	0.6 (0.4)*
Mouthwash C		0.5 (0.4)	0.6 (0.3)	0.9 (0.4)

*Statistically significant difference to mouthwash C ($p < 0.05$).
Means given with standard deviation in parentheses.

and disruption of bacterial metabolism, and inhibiting cell growth, which ultimately leads to cell death (Scheie 1989).

CPC mouthwashes have fewer side effects compared with chlorhexidine mouthwashes, which can cause temporary taste alteration, staining and calculus formation. The most significant side effect of chlorhexidine is extrinsic staining of the teeth, oral mucosa, acrylic dentures and restorative (Sheen et al. 2003). With CPC mouthwashes, staining also occurs but to a lesser extent (Blenman et al. 2005). An alteration in taste, a bitter taste or burning sensation is sometimes reported with alcohol-based mouthwashes. However, alcohol contributes to the 'mouth impact' feeling, which could be influential to consumers. As CPC mouthwashes do not contain alcohol, there should be no burning sensation and improved taste, which could encourage a longer rinsing time (Blenman et al. 2005). However, three subjects complained about a ''burning'' sensation from the CPC mouthwash in this study. Supragingival calculus formation is most commonly reported with chlorhexidine, but rarely with the other mouthwashes (Hase et al. 1998).

Most over-the-counter mouthwashes contain between 5% and 25% alcohol. It is incorporated into mouthwash for several reasons. Alcohol itself is an antiseptic agent and can stabilize active ingredients in the mouthwash as well as acting as a solvent for other agents. It can also prolong the shelf life of the mouthwash and prevent contamination by microorganisms (Quirynen et al. 2005). Certain patient groups are excluded from using alcohol-based mouthwashes. These include children, pregnant and nursing women, diabetics, alcoholics, patients on metronidazole, patients with xerostomia and members of certain religious faiths (Mankodi et al. 2005, Van Strydonck et al. 2005, Witt et al. 2005). Similarly, patients with mucositis, patients undergoing head and neck irradiation and the immunocompromised are not advised to use alcohol-based mouthwashes (White 2005). Some mouthwashes with high-alcohol content could theoretically constitute an increased risk of oral cancer in regular users (Elmore & Horwitz 1995). Another problem reported with ethanol is surface softening and increased wear rates of dental resins and composite materials, which could contraindicate the use of these mouthwashes in certain patients (McKinney & Wu 1985, Penugonda et al. 1994). The absence of alcohol in the CPC formulations tested in this study means that these mouthwashes are suitable for a wider range of patients.

In conclusion, both alcohol-free cetylpyridinium mouthwashes tested in this study consistently lowered the amount of plaque present on the teeth when compared with an inactive placebo. This effect was significant at all time periods, and supports the use of an antibacterial alcohol-free mouthwash as an alternative to an alcohol-containing antibacterial mouthwash in the control of dental plaque.

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Clinical Relevance

Scientific rationale for the study: Mouthwashes can be a useful aid to oral hygiene in addition to mechanical methods and the use of dentifrices. Most commercially available mouthwashes contain alcohol. Concerns about the possible adverse effects on oral health of alcohol-containing mouthwashes has led to an interest in developing alcohol-free preparations.

Principal findings: Both mouthwashes A and B (0.05% and 0.1% w/w CPC) demonstrated superior performance compared with the control (inactive placebo) with regard to mean plaque areas and Quigley & Hein plaque index at all time intervals. There was no significant difference between these two concentrations of mouthwash.

Practical implications: CPC mouthwashes are effective plaque-inhibitory agents and are suitable alcohol-free alternatives to the alcohol-containing mouthwashes.