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Clinical efficacy of a chlorhexidine-delivering toothbrush

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Abstract

Objectives: Evaluate the efficacy and safety of an experimental toothbrush with a slow-release system of chlorhexidine (CHX) and determine its ability to inhibit plaque, bleeding, staining and oral tissue abnormalities during 6 weeks of use.

Material and Methods: One hundred and fifty healthy volunteers were randomly assigned to one of three groups: the Test Brush group with a template slow-delivery system of CHX (Ttb), the Control Brush group without CHX (Ctb) and the Control Brush group without CHX but rinsing post-brushing with a 0.2% CHX mouthrinse (Ctb+R). At baseline as well as at 3 and 6 weeks, all clinical parameters were assessed. Following the baseline assessment, a supragingival prophylaxis was provided.

Results: One hundred and forty subjects completed the study. The Ctb+R group had lower plaque and bleeding scores than the Ttb and the Ctb group and significantly ($p = 0.0001$) higher stain scores. There were no significant differences in plaque, bleeding and stain scores between the Ttb and the Ctb group. No differences were detected in oral tissue changes, except for discoloration of the tongue.

Conclusions: In the present study, no beneficial effect could be demonstrated for the experimental CHX-releasing toothbrush. The use of a 0.2% CHX mouthrinse (in combination with brushing) remains the gold standard for additional chemical plaque control.

Key words: bleeding; chlorhexidine; oral tissues; plaque; stain; toothbrush

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The importance of oral hygiene in the prevention of caries and periodontal disease has been demonstrated extensively (Löe et al. 1965, Axelsson et al. 1991). The most reliable methods currently used for plaque control are mechanical cleaning using a toothbrush (for a review, see Hancock 1996) and a range of interproximal devices. In order to achieve efficiency by mechanical methods only, individual motivation and high standards of skill are required, and in the interdental spaces, where the highest prevalence of marginal gingivitis occurs, efficient tooth brushing alone still has only a limited effect (Löe et al. 1965, Gjermo & Flötra 1970). Furthermore, meticulous dental cleaning is a time-consuming procedure.

Chemotherapeutic agents have the potential to inhibit plaque growth, reduce gingivitis and improve oral health beyond tooth brushing alone (Addy & Moran 1997). As an effective antibacterial agent, chlorhexidine (CHX) still remains the gold standard, unsurpassed by other agents (Gjermo et al. 1970, Addy 1986, Paraskevas 2005). The method of CHX application, however, seems to be important for its effect on the bacterial flora (Emilson & Fornell 1976, Bay 1978). Four methods of application with various CHX concentrations are available for the user: a fluid (0.2% and 0.12%), a gel (1% and 0.5%), a dentifrice (0.12%) and a spray (0.12%).

A new design of toothbrush was developed for the present study. This brush contains a template within the brush head, which releases CHX when brought into contact with oral fluids (Fig. 1). This delivery system may provide the benefits of reduced plaque and gingivitis beyond toothbrushing alone, while also diminishing the negative side effects of traditional CHX therapy, and

Conflict of interest and source of funding statement

The authors declare that they have no conflict of interests.
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additionally enhancing users' oral hygiene. The purpose of this study was to test whether a manual toothbrush with a slow-release system of CHX is safe and more effective in inhibiting plaque and gingival bleeding following 6 weeks of use.

A secondary objective was to assess the amount of stain on the teeth.

Material and Methods

Subjects

A total of 150 subjects ($n = 150$), between 18 and 65 years of age, were selected on the basis of good general health, and no medical or dental history or medication, which might interfere with the outcome or the progress of the study. The participants were non-dental students at the University of Amsterdam, the Netherlands. Subjects were eligible for the study if they had a minimum of 18 scorable natural teeth, excluding third molars or crowned teeth with porcelain or gold restorations. To be enrolled in the study, the subjects were required to have a minimum of 40% bleeding sites as determined by the Bleeding on Marginal Probing Index (BOMP, Van der Weijden et al. 1994).

Subjects were excluded if they had any physical limitations or restrictions, which might preclude normal toothbrushing skills. They were also excluded if they had used an oral CHX product or had taken a systemic antibiotic or anti-inflammatory drug for 3 consecutive days within the previous 3 months. Subjects with removable prostheses or orthodontic appliances were not allowed to participate.

All eligible subjects were given oral and written information about the products and the purpose of the study. After screening for suitability, they were requested to give their written informed consent to qualify for enrolment. The study was approved by the Medical Ethic Committee of the Amsterdam Medical Center (MEC 98/139).

Description of study materials

The toothbrushes for this clinical study had a straight handle and soft, rounded bristles. The toothbrushes were produced at Oral-B Laboratories using the same trim filament pattern as the commercially available Oral B Advantage 40 Soft brush. However, the brush head was slightly larger and hollow to accommodate the template of freeze-dried CHX. Three tufts of bristles in the middle brush section were excluded to allow capillary movement of CHX along the tufts of the bristles, thereby allowing a slow CHX release while brushing (Fig. 1). Study materials were maintained under secure, dry, room-temperature conditions until assigned to subjects.

The template toothbrush (Fig. 1a and b)

The total amount of CHX digluconate in each test toothbrush was approximately 124 mg.

In vitro testing (data on file) showed that the average release per brushing was 1.3 mg. The maximum release per brushing (60 s) was 5.04 mg CHX, which occurred after the second brushing. The release profile dropped below the average after 23 brushings and fell after 40 brushings to 0.19 mg. After 42 brushings, 45.3% of the CHX digluconate had been released from the template.

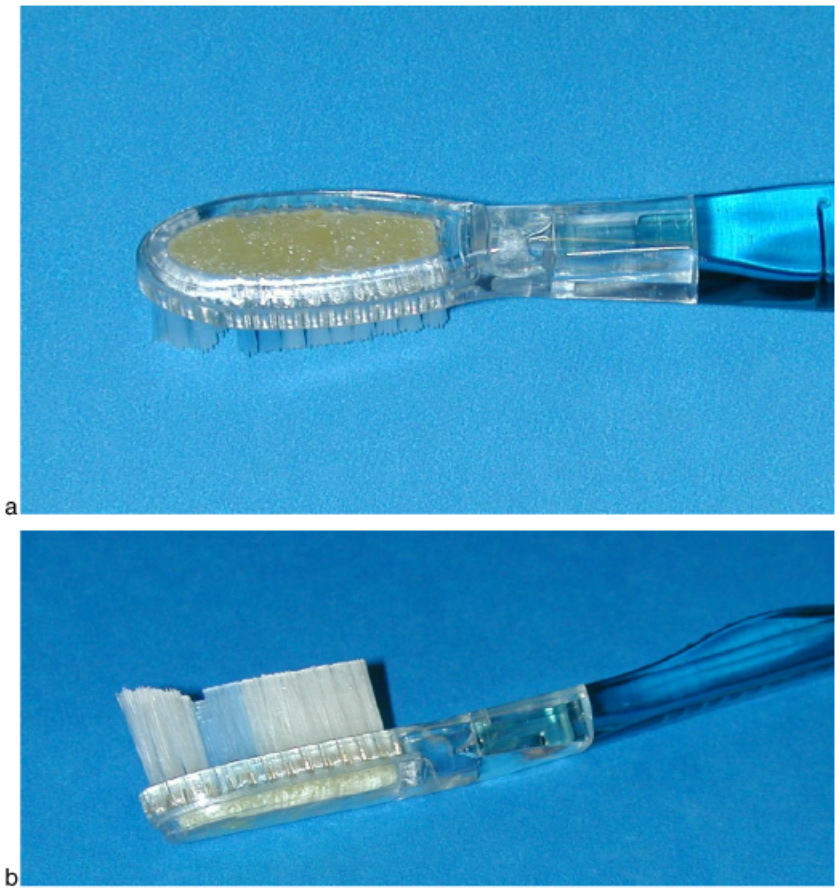

Fig. 1. The template toothbrush.

Procedure

This was a three-cell longitudinal, examiner-blind, randomized, controlled, parallel designed study of 6 weeks' duration. Randomization was performed using a computer-generated list of random numbers. Study products were coded and distributed to the subjects in a location away from the examiners to ensure and maintain blinding. The examiners were blind to treatment randomization and records of earlier examinations were not available at the time of re-examinations. The study coordinator was responsible for allocation concealment. One examiner assessed all plaque scores (Silness & Löe 1964, Danser et al. 2003) and performed all stain evaluations on the buccal surfaces of all scorable teeth using the Gründemann Modified Stain Index (GMSI, Gründemann et al. 2000). Another examiner assessed all bleeding scores using the BOMP (Saxton & Van der Ouderaa 1989, Van der Weijden et al. 1994) and all safety evaluations. Both examiners (M. P. and Y. I.) were well trained and had been involved in previous studies.

Baseline

At baseline, subjects received a supragingival prophylaxis to render them plaque and stain free. They were randomly assigned to one of the three following treatment groups:

- *Template Test Brush (Ttb)*: the manual experimental toothbrush with a template slow-releasing delivery system of 124 mg CHX digluconate (see Fig. 1).
- *Template Control Brush (Ctb)*: the same toothbrush as the template test brush (Ttb), without CHX digluconate,which was the negative control (see Fig. 1).
- *Template Control Brush+CHX rinse (Ctb+R)*: the template toothbrush without CHX digluconate plus twice daily rinsing with a commercially available 0.2% CHX digluconate mouthrinse,which was the positive control (Corsodyl® GlaxoSmithkline, Zeist, the Netherlands).

All subjects were provided with written instructions for their assigned products. Subjects in the Ttb and the Ctb group were instructed to brush twice daily without a dentifrice for 1 min. (in the morning and the evening), using only their assigned products. Subjects in the Ctb+R group were instructed to brush twice daily without a dentifrice, and to rinse afterwards for 60 s with 10 ml of 0.2% CHX digluconate mouthrinse (Corsodyl®). To monitor compliance, subjects were given a brushing diary and instructed to record each day the time of their toothbrushing and/or toothbrushing plus rinsing. In addition, all mouthrinse bottles were weighed before distribution. Throughout the duration of the study, subjects were asked to refrain from rinsing, eating or drinking for 30 min. after using their assigned product. They were asked to refrain from all forms of oral hygiene for 12–18 h before their baseline, interim (3 weeks) and final (6 weeks) visits and to bring their randomly assigned (test) toothbrush, mouthrinse (if applicable) and diary.

Interim examination

At study week 3, each subject was scheduled for an interim examination. During this visit, subjects were asked about changes in their medical and dental histories, and concomitant medications and adverse events were reviewed. Assessments of oral tissues, plaque and bleeding on marginal probing were performed. In addition, staining was assessed. Used toothbrushes were collected and replaced by fresh brushes. Returned mouthrinse bottles and fresh mouthrinse bottles (before distribution) were weighed. All brushing diaries were evaluated for compliance and returned to the subjects. The subjects were reminded to refrain from using assigned products for 12–18 h before their final examination and to bring with them their randomly assigned (test) toothbrush, mouthrinse (if applicable) and brushing diary.

Final examination

The outline of this last visit was identical to the interim examination. Upon completion, subjects returned the assigned products and ended the study.

Data analysis

Using variability estimates from a previous study (van der Weijden et al. 1994), power curves were examined to indicate the number of subjects needed to detect statistically significant treatment differences in the BOMP index. Based on these data, assuming a constant variability of $\sigma \approx 0.775$ and $\alpha = 0.05$, a sample size of 45 subjects per treatment group was needed to ensure an 80% (power $= 1 - \beta$) or greater chance of detecting differences of $\geqslant 0.11$ whole-mouth BOMP units.

Full-mouth mean plaque (MSLPI), bleeding (BOMP) and stain (GMSI) scores were calculated. Plaque and bleeding scores were considered to be the primary efficacy variables and stain (GMSI) as a secondary variable. p-value $\leqslant 0.05$ were considered to be statistically significant. Within each treatment group, a Wilcoxon's test was used to compare the means of each of the three scores at the interim and final timepoints in order to assess treatment effects across time. The Kruskal–Wallis test, with post-testing corrected for multiple comparisons, was used to analyse the differences in plaque, bleeding and staining between the three regimens.

Oral tissue data were summarized by tabulating the frequency and percentage of abnormal observations. Oral tissue observations within a treatment group were examined to assess the safety of treatments across time using McNemar's test. Differences between treatments were determined by comparing the distributions of abnormal findings in each treatment group utilizing the χ^2 test for homogeneity.

Results

A total of 150 subjects meeting the inclusion criteria were recruited and enrolled into the study. After having signed the informed consent, they were randomly divided into three groups of 50 subjects each. At the baseline assessment, 10 subjects disqualified due to personal reasons, such as vacation, or for medical reasons, such as the use of antibiotics or CHX. No data were obtained for these subjects and they were therefore not included in the data analysis. One hundred and forty subjects completed the study and were included in the ''Intention to treat analysis'' (Fig. 2). No adverse events were reported. Demographic data for the three treatment groups ($n = 140$) are shown in Table 1. Treatment group Ttb had a population size of 46 subjects, while treatment groups Ctb and Ctb+R had 47 subjects. There was no statistically significant difference in mean age detected among the groups (23, 22 and 21 years, respectively). At baseline, no significant differences were detected among the treatment groups with respect to mean whole-mouth plaque and gingival bleeding levels.

Plaque

The mean plaque score data are presented in Table 2. At both follow-up assessments (interim and final), the mean, whole-mouth plaque scores of the three groups were significantly lower than the baseline scores. Comparisons of plaque scores among treatment groups showed a statistically significant ($p < 0.0001$) difference. The CHX-Rinse group (Ctb+R) had lower plaque scores than the other two groups. There was no significant difference between the plaque scores of treatment groups Ttb and Ctb (see Table 5).

Bleeding

The mean bleeding score data are presented in Table 3. At the final examination, all treatment groups demonstrated significantly less whole-mouth bleeding as compared with the baseline scores. At both follow-up assessments (interim and final), comparison of bleeding reduction

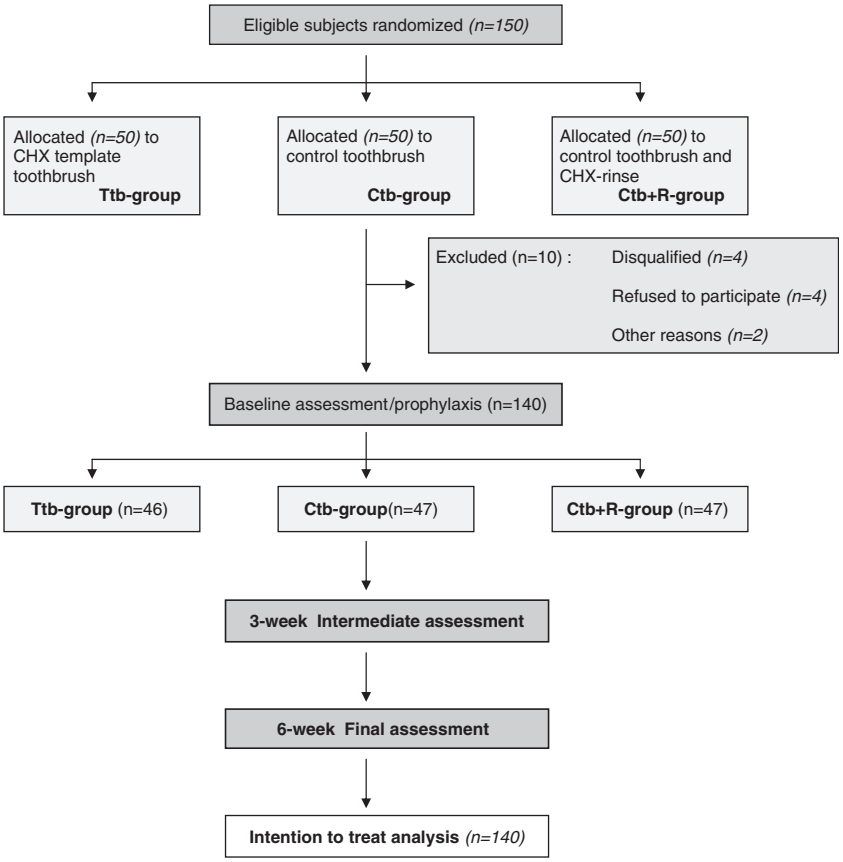

Fig. 2. Flowchart subject enrolment.

Table 1. Demographics ($n = 140$)

	Ttb group	Ctb group	Ctb+R group
Total number	46	47	47
% Female	63	74	79
% Male	37	26	21
Mean age	23	22	21

Ttb, Template Test Brush; Ctb, Template Control Brush; Ctb+R, Template Control Brush+CHX rinse.

Table 2. Mean overall plaque scores for each regimen; standard deviation in parenthesis ($n = 140$)

	Ttb group ($n = 46$)	Ctb group ($n = 47$)	Ctb+R group ($n = 47$)	p-value**
Baseline†	1.29 (0.30)*	1.26 (0.22)*	1.16 (0.37)*	
Interim	0.96 (0.35)*	0.90 (0.27) NS	0.21 (0.17) NS	$\leqslant 0.0001$**
Final	1.09 (0.36)	0.99 (0.32)	0.26 (0.29)	$\leqslant 0.0001$**

†At baseline all subjects were given a professional prophylaxis and were rendered free of plaque.
*Significant change from ''baseline to interim'' or form ''interim to final'' ($p \leqslant 0.05$, Wilcoxon).
**Significant difference among groups (Kruskal–Wallis H-test).
NS, not significant; Ttb, Template Test Brush; Ctb, Template Control Brush; Ctb+R, Template Control Brush+CHX rinse.

scores among treatment groups showed statistically significant ($p < 0.0001$) differences. The CHX-Rinse group (Ctb+R) had lower bleeding scores than the other two groups. No significant difference was detected between the bleeding scores of treatment Ttb and Ctb (see Table 5).

Stain

The GMSI was used to evaluate whole-mouth buccal stain and is presented in Table 4.

All subjects were rendered free of stain at baseline and so no scores are provided. There was a significant increase in staining during the course of the study for the three groups. At both follow-up assessments (interim and final), comparison of stain scores among treatment groups showed a statistically significant difference (see Table 4).

The mean stain scores for treatment Ctb+R were statistically greater ($p = 0.0001$) than for treatments Ttb and Ctb. There were no differences in stain scores between treatments Ttb and Ctb (see Table 5).

Oral tissues

No differences were detected in the proportion of oral tissue abnormalities among the groups, with the exception of the tongue. Changes noted were the presence of stain or discoloration on the tongue. Treatment Ctb+R yielded a statistically significantly ($p = 0.0001$) greater proportion of abnormal observations than treatments Ttb and Ctb.

Discussion

The present study evaluated whether the effect of toothbrushing could be enhanced by the use of CHX. The CHX digluconate was slowly released from the head of a newly designed experimental toothbrush when brought into contact with oral fluids. The Ttb (template test brush) and the Ctb (template control brush) were modified Oral B Advantage toothbrushes. CHX mouthrinse was used as a positive control in combination with the Ctb. A positive control compares and positions the efficacy of a test product and is frequently used in oral hygiene study protocols (Addy 1986, Addy 1995). Within the limitations of the present study, no beneficial effect could be demonstrated for this prototype product.

The outcome of the present study is not in agreement with earlier clinical studies, which have attempted to improve the effects of toothbrushing with the use of different CHX agents. Some have used a CHX gel for toothbrushing, while others have dipped the brushes in a CHX solution. Bassiouny and Grant (1975) used a 1% CHX gel

Table 3. Mean overall bleeding scores for each regimen; standard deviation in parenthesis ($n = 140$)

	Ttb group ($n = 46$)	Ctb group ($n = 47$)	Ctb+R group ($n = 47$)	p-value
Baseline[†]	1.26 (0.26) NS	1.22 (0.25)**	1.21 (0.24)*	
Interim	1.19 (0.30)*	1.12 (0.24)*	1.03 (0.27)*	0.0177**
Final	1.03 (0.34)	0.95 (0.31)	0.74 (0.31)	0.0001**

[†]At the start of the study all subjects were given a professional prophylaxis and were rendered free of plaque.
*Significant change from ''baseline to interim'' or form ''interim to final'' ($p \leqslant 0.05$, Wilcoxon).
**Significant difference among groups (Kruskal–Wallis H-test).
NS, not significant; Ttb, Template Test Brush; Ctb, Template Control Brush; Ctb+R, Template Control Brush+CHX rinse.

Table 4. Mean overall stain scores for each regimen, standard deviation in parenthesis

	Ttb group ($n = 46$)	Ctb group ($n = 47$)	Ctb+R group ($n = 47$)	p-value
Interim	0.16 (0.19)*	0.22 (0.21)*	0.57 (0.39)	0.0001**
Final	0.30 (0.24)	0.42 (0.26)	1.02 (0.48)	0.0001**

At baseline all subjects were given a professional prophylaxis and were rendered free of stain ($n = 140$).
*Significant change from ''interim to final'' ($p \leqslant 0.05$, Wilcoxon).
**Significant difference among groups (Kruskal–Wallis H-test).
Ttb, Template Test Brush; Ctb, Template Control Brush; Ctb+R, Template Control Brush+CHX rinse.

Table 5. Statistical comparison between groups (Intention to treat analysis, $n = 140$)

Regimen	Plaque		Bleeding		Stain	
	interim	final	interim	final	interim	final
Ttb *versus* Ctb	NS	NS	NS	NS	NS	NS
Ttb *versus* Ctb+R*	*	*	*	*	*	*
Ctb *versus* Ctb+R	*	*	NS	*	*	*

*p-value $\leqslant 0.05$.
Results of post-testing for plaque, gingivitis and stain using a Kruskal–Wallis H-test with post-testing corrected for multiple comparisons.
NS, not significant; Ttb, Template Test Brush; Ctb, Template Control Brush; Ctb+R, Template Control Brush+CHX rinse.

for toothbrushing twice daily for 6 weeks, which resulted in a statistically significant decline in plaque and gingivitis scores, as compared with the use of placebo gel. Bay (1978) showed that twice-daily brushing with a toothbrush that had been immersed in a CHX solution prevented plaque formation and the development of gingivitis, even with low CHX concentrations (0.15%, 0.10% and 0.05%). Flötra (1973) and Usher (1975) have reported that 1% CHX gel, when used by mentally and physically disabled people with a very low standard of mechanical cleaning, had a therapeutic effect on gingival conditions. Epstein et al. (1994) and Ransier et al. (1995) concluded that a foam brush, which is usually ineffective in controlling plaque levels and gingivitis (Addems et al. 1992), could improve the gingival conditions as effectively as a toothbrush when the foam brush is soaked in 0.2% CHX. In other studies, however, CHX active gel did not markedly influence plaque formation and gingival conditions (Hansen et al. 1975, Emilson & Fornell 1976, Saxen et al. 1976, Bain & Strahan 1978).

Contradictions in the existing literature may have their origins in several factors, such as the presence of a baseline prophylaxis, the level of plaque control, the concentration of CHX and the brushing frequency. In those studies where initial prophylaxis sessions and extensive instructions in oral hygiene were carried out, a positive effect of toothbrushing with CHX was noted (Bassiouny & Grant 1975, Bay 1978, Epstein et al. 1994, Ransier et al. 1995). However, if the participants were not free of plaque initially and no attempts were made to remove subgingival plaque or calculus intermittently, the adjunctive effect of CHX appeared to be minimal (Hansen et al. 1975, Emilson & Fornell 1976). In the present study, therefore, at baseline, prophylaxis and professional oral hygiene instructions were provided in order to obtain the optimal benefit from the active CHX agent. In this respect, it is surprising that no beneficial chemotherapeutic effect on the gingival conditions was found. The most likely explanation seems the dose release profile of the active agent from the brush head. In comparison, rinsing for 60 s with 10 ml of a 0.2% CHX digluconate solution provides a dose of 20 mg, which is able to inhibit plaque re-growth and to prevent inflammation of the gums (Löe & Schiött 1970). Concentrations of 0.12% CHX appeared to be effective as 0.2% if the volume of the rinse was increased from 10 to 15 ml, giving an 18 mg dose on each occasion (Keijser et al. 2003). Following Bassiouny and Grant (1975), even a lowered dose of 5 mg CHX in a 1% gel was found to be effective. Stoeken et al. (2007) reported that 3.2 mg of a 0.12% CHX spray has a plaque-reducing effect. In the present study, the maximum dose of CHX per brushing was 5.04 mg (after second brushing). With an average release per brushing of 1.3 mg, the test brush did not provide any beneficial effect in addition to mechanical plaque removal. Based on these findings, future developments could focus on an elevated amount of CHX per brushing and a more regular release pattern over time.

Although no benefit could be shown for the use of the CHX template toothbrush, the positive control group, which combined a 1-min. toothbrushing without a dentifrice and rinsing for 60 s twice daily with 10 ml of 0.2% CHX (20 mg dose), confirms the results of earlier studies (Gjermo et al. 1970, Löe & Schiött 1970, Bay 1978) and remains an effective treatment for the control of plaque and gingivitis. Thus, a CHX rinse in combination with toothbrushing can provide an adequate therapeutic effect where additional efficacy is needed to control plaque and gingivitis. It has been suggested in the past that

toothbrushing with an SLS-containing dentifrice may inhibit the effect of CHX (Barkvoll et al. 1989, Owens et al. 1997). Recent studies, however, have clearly shown that ordinary toothbrushing with an SLS-containing dentifrice before or after the use of CHX does not reduce the anti-plaque efficacy of the rinse (Van Strydonck et al. 2004a, b, Van Strydonck et al. 2006).

In the present study, there was statistically more dental staining in the three groups compared with baseline. For the groups using CHX, Ttb and Ctb+R, this is in agreement with the results of earlier studies (Flötra et al. 1971, Addy et al. 1991, Gründemann et al. 2000). However, as only the Ttb group used a toothbrush that released CHX, the small difference in staining between the Ttb group and the Ctb group (without CHX release) was rather unexpected. The higher staining score in the Ctb group may be explained by the fact that no dentifrice was used. Although a dentifrice does not primarily result in ''instant'' mechanical plaque removal (Paraskevas et al. 2006), brushing with a dentifrice is traditionally recommended for the prevention of staining (Lobene 1968, Forward 1991).

Conclusion

Within the limitations of the present study, no beneficial effect could be demonstrated for the prototype CHX releasing toothbrush. Whilst studies continue to search for the most convenient and clinically effective way of delivering additional chemical plaque control, the use of a 0.2% CHX mouthrinse (in combination with toothbrushing) remains the gold standard.

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Clinical Relevance

Scientific rationale for the study: An experimental manual toothbrush with a slow-release template system for CHX could safely and effectively inhibit plaque growth and bleeding on marginal probing, and prevent the development of stain formation.
Principal findings: No beneficial effect could be demonstrated for twice-daily brushing with this prototype product.
Practical implications: The use of a 0.2% CHX mouthrinse as an adjunct to toothbrushing is an effective chemotherapeutic approach to inhibit plaque growth and reduce gingival inflammation.