J Clin Periodontol 2006; 33: 561–567 doi: 10.1111/j.1600-051X.2006.00946.x

Journal of Clinical Periodontology

Effect of two new chlorhexidine mouthrinses on the development of dental plaque, gingivitis, and discolouration. A randomized, investigator-blind, placebo-controlled, 3-week experimental gingivitis study

K. Lorenz[1], G. Bruhn[1], C. Heumann[2], L. Netuschil[1], M. Brecx[3] and T. Hoffmann[1]

[1]Department of Conservative Dentistry Medical Faculty, Dresden University of Technology, Dresden, Germany; [2]Department of Statistics, University of Munich, Munich, Germany; [3]Private Practice, Brussels, Belgium

Lorenz K, Bruhn G, Heumann C, Netuschil L, Brecx M, Hoffmann T. Effect of two new chlorhexidine mouthrinses on the development of dental plaque, gingivitis, and discolouration. A randomized, investigator-blind, placebo-controlled, 3-week experimental gingivitis study. J Clin Periodontol 2006; 33: 561–567. doi: 10.1111/j.1600-051X.2006.00946.x.

Abstract

Objectives: The aim of this experimental gingivitis study was to assess the efficacy and safety of two new chlorhexidine (CHX) mouthrinses.

Materials and Methods: Ninety volunteers participated in this investigator-blind, randomized, clinical-controlled trial in parallel groups. During the treatment period, no oral hygiene measures except rinsing with non-alcoholic 0.2% CHX or 0.2% CHX/0.055% sodium fluoride mouthrinses, a positive control, or a negative control were permitted. The primary parameter was the gingival index; the secondary parameters were plaque index, discolouration index, and bleeding on probing. Clinical examinations were conducted 14 days before the start of the study, at baseline, and after 7, 14, and 21 days. The two sample *t*-test, ANOVA, and ANCOVA were used for the statistical analysis.

Results: No difference in efficacy was found between the two new CHX formulations and the positive control. On day 21, statistically significantly less gingival inflammation and plaque accumulation compared with placebo were observed. Besides discolouration and taste irritations, no adverse events were recorded.

Conclusion: The two new CHX mouthrinses were able to inhibit plaque re-growth and gingivitis. Neither the omission of alcohol nor the supplementation with sodium fluoride had weakened the clinical efficacy of CHX with respect to the analysed clinical parameters.

Key words: chlorhexidine mouthrinse; discolouration; fluoride mouthrinse; gingivitis; plaque

Accepted for publication 13 April 2006

Plaque control and prevention of gingivitis is the main goal of the prevention of periodontal diseases. Therefore, in addition to mechanical oral hygiene, the use of antiseptics is strongly recommended and performed (Baehni & Takeuchi 2003). Among a variety of antiseptic agents, chlorhexidine digluconate (CHX) has been used and tested for many years. The efficiency of CHX 0.2% in preventing plaque formation and development of gingivitis has been demonstrated in many publications (Fardal & Turnbull 1986, Addy & Moran 1997, Addy 2003). To date, it presents

the gold standard (Jones 1997) among the anti-plaque agents.

It is still an open question whether CHX mouthrinses have to contain ethanol or not (Brecx et al. 2003). While some preparations contain ethanol (as an example Corsodyl® and its German analogue Chlorhexamed forte®), some others do not (e.g. Curasept®, Paroex®). Unfortunately, very scarce data exist regarding the effect of ethanol. Very recent data are available about Curasept® (Addy et al. 2005) and another alcohol-free formulation tested by Quirynen et al. (2001).

It has also been well documented that CHX leads to staining of the dental biofilm (Brecx et al. 2003). Unfortunately, only a few investigations exist that correlate different concentrations of the drug to clinical efficacy and staining potential. In a recent investigation, the clinical action (reduction of plaque and gingivitis indices) of 0.06% and 0.10% CHX was compared with the concomitant staining (Hoffmann et al. 2001). While the 0.10% CHX led to clinical indices similar to the 0.06% CHX, 0.10% CHX showed a heavier staining at the 3- and 6-month intervals. The 0.10% CHX showed the highest reduction of the indices and also the highest amounts of staining. Some other studies (Brecx et al. 1993, Lang et al. 1998) compared the clinical effects of mouthrinses containing different active preparations with their staining potential. The higher percentage of CHX showed a stronger antibacterial effect and a higher level of staining. However, it is still an unsolved question as to whether this kind of side effect is actually an intrinsic consequence of the action (Brecx et al. 2003).

Additional to the established antiplaque effect of CHX, this compound also exerts an action against *Streptococcus mutans*, in this way leading to an anti-caries efficacy (Kidd 1991, Grönroos et al. 1995, Bowden 1996, van Rijkom et al. 1996). Also, the fluoride anion is well known and thoroughly documented to have an anti-caries effect (Petersson et al. 2002). It can be assumed that CHX and fluoride may act synergistically (Twetman & Petersson 1997). However, it is necessary to prove this potential synergistic action.

The aim of the present randomized, investigator-blind, placebo-controlled experimental gingivitis study was therefore to monitor the clinical efficacy of two newly developed ethanol-free CHX preparations, each containing 0.2% CHX digluconate, one without fluoride and one containing 250 mg/kg fluoride (i.e. 0.055% sodium fluoride), in comparison with a placebo mouthrinse and in comparison with the ''gold standard'', the 0.2% Corsodyl® (German brand: Chlorhexamed®). Especially, the relationship between positive clinical effects and the most prominent side effect, tooth staining, had to be considered.

Materials and Methods

This randomized, controlled, clinical study was conducted in a parallel group design and was performed according to GCP/ICH requirements. Ethical approval was obtained from the Ethics Committee of the Medical Faculty, University of Technology, Dresden, Germany. The experimental gingivitis model consisted of a 2-weeks recruitment phase, followed by a 21-day rinsing period during which all mechanical oral hygiene measures were suspended (Brecx et al. 1990).

Study population

For this study, healthy students of the dental school were recruited by means of advertisements throughout the building. The participants had to be aged between 18 and 50 years and had to have at least 20 teeth excluding the wisdom teeth. Their gingival index (GI; Löe 1967) at the screening examination was required to be $\leqslant 0.5$ to fulfil the inclusion criterion of a very high level of dental hygiene. Participants were not included in the study when one or more of the following criteria were present: (1) systemic diseases, (2) current periodontitis, (3) pathologic conditions of the tongue, mucosa, gingiva, (4) pregnancy or breast feeding, (5) untreated caries, (6) partial dentures or orthodontic appliances, (7) heavy smokers $\geqslant 30$ packyears, (8) treatment with CHX 2 weeks before and during recruitment, (9) treatment with antibiotics, steroidal and non-steroidal antiphlogistics, immunostimulants, immunosuppressive drugs, antimitotic drugs, drugs which influence salivary flow within 3 months before inclusion, and (10) topical medication that interferes with the study medication. Furthermore, current participation in another clinical trial or missing emergency contact numbers were reasons for exclusion in the trial. All investigations and data recordings were performed in the Department of Periodontitis, Dental School, University of Technology, Dresden, Germany. The enrolment of the participants was performed by the clinical investigators according to these inclusion and exclusion criteria.

General design

Ninety-six subjects had to be enrolled after signing an informed consent form. The treatment protocol requested five visits of each participant in the study centre.

At the Screening Visit, 14 days before the first administration of the study products, the subjects received a professional tooth cleaning and oral hygiene instructions, which were followed by a 2-week period during which the participants were asked to practice a high standard of plaque control at home. All subjects were supplied with the same toothpaste (Colgate Regular®, Colgate-Palmolive, Hamburg, Germany). At baseline (Visit 1), inclusion and exclusion criteria were recorded again. All study parameters were assessed, followed by a professional tooth cleaning. The use of the study product was explained to the subjects by an individual not involved in the clinical data recording. Subjects started with the use of the allocated study products on the same day. The first rinsing was performed under supervision in the study centre. The subsequent rinsings were performed by the subjects at home each morning and evening during the 21-day study period. During the experimental gingivitis period, the participants were examined at Visit 2 (after 7 days), at Visit 3 (after 14 days), and at Visit 4 (after 21 days).

Treatments and controls

The participants were randomized to four treatment groups including two test mouthrinses, a positive and a negative control (Table 1). The subjects rinsed with 10 ml for 1 min. twice a day regardless of the rinsing group they were allocated to.

The study products were blinded. All four mouthrinses were delivered in identical opaque white bottles. The bottles bore a label with the subject number that corresponded to the subject number in the case report form (CRF). The two test products and the placebo were light blue; the Corsodyl® had its typical light

Table 1. Composition of mouthrinses

Treatment	Composition
Test product 1	0.2% chlorhexidine digluconate, ethanol-free formulation, pH 5.5 (GABA International AG, Münchenstein, Switzerland, # 315307)
Test product 2	0.2% chlorhexidine digluconate, 0.055% sodium fluoride, ethanol-free formulation, pH 5.5 (GABA International AG, # 408309, meridol® chlorhexidine 0.2 % mouthrinse)
Positive control	0.2% chlorhexidine digluconate, 7% ethanol (Corsodyl®, GlaxoSmithKline Consumer Healthcare GmbH, Bühl, Germany, # 133F/A1784)
Negative control	Placebo, no active agent (ethanol and sodium fluoride free), pH 5.5 (GABA International AG, # 316307)

red colour. Each subject received two identical bottles of the study product. The first bottle was handed over to the subject during Visit 1, the second bottle during Visit 2. On the occasion of Visit 4, the subject returned both bottles to the study site. Both bottles were then weighed to estimate the subject's compliance. The study products were delivered and collected by the study nurse according to the randomization plan. The clinical investigators did not have an insight into this process at any time because the handling of the study products occurred at a separate site.

Investigated parameters

The following study parameters were assessed at each visit:

- PLI (Silness & Löe 1964).
- GI (Löe 1967).
- Discolouration index (DI, Brecx et al. 1993).
- Bleeding on probing (BOP, Ainamo & Bay 1975) was assessed only at the Screening Visit and Visit 4.

The parameters were assessed by two trained clinical investigators experienced with the index systems from various previous clinical trials. The GI and BOP were always assessed by one investigator, while the PLI and DI were assessed by the other investigator.

Safety and data monitoring

At each visit during the experimental gingivitis period, adverse events (AE) were reported. Subjects were not allowed to take any medications, especially antibiotics, which could influence the build-up of dental biofilm and/or the signs of gingival inflammation starting 8 weeks before the Screening Visit and lasting until the final Visit 4. In addition, any analogous concomitant medication was forbidden during the study. Any usage of additional products was reported to the clinical investigators and documented in CRFs. Moreover, the use of additional mouthrinse preparations, dentifrices, and mechanical tooth cleaning measures was not allowed.

This study was monitored and audited by the Coordination Centre for Clinical Trials of the Medical Faculty, University of Technology, Dresden, Germany.

Randomization, statistics, and analysis sets

The randomization list was generated by the Manager for Good Manufacturing Practice (GMP) of the sponsor according to the corresponding standard operation procedure of the sponsor. The randomization list as well as the emergency envelopes were created by means of a specifically designed software. The 96 subjects were distributed at random into four treatment arms of 24 subjects each. Three balanced blocks consisting of 32 subjects each were generated by the software. Subjects were assigned to consecutive participant numbers starting at 01 according to their chronological entry in the study. Each participant number corresponded to a randomly assigned study product according to the randomization plan.

Study participants, clinical investigators, and all personnel in the study centre were blinded. The GMP manager of the sponsor was the only person who had knowledge of the content of the mouthrinse bottles.

All data collected in the CRFs of this study were entered into the electronic study database using a double data-entry procedure. Any discrepancies or errors were clarified and corrected using signed data query forms. For PLI, GI, BOP, and DI summary measures were calculated. The sum of the recorded scores per subject and visit divided by the number of investigated sites per subject and visit gave the PLI, GI, DI, or BOP for the individual subject per visit, which was the unit of measurement for the statistical analysis. According to the pre-established statistical analysis plan, the comparability of the four treatment groups at the start of the study (Visit 1) after randomization was checked using ANOVA on the 5% error level α. Decisions about whether to use parametric or non-parametric analysis models were made based on the results of Kolmogorov–Smirnov tests for normal distribution. The primary efficacy variable in this clinical study was the GI at Visit 4. This GI test value for each test product was used to compare the treatment Test product 2 (CHX/sodium fluoride mouthrinse) and negative control (placebo mouthrinse) as well as the Test product 1 (CHX without ethanol) and the negative control. The secondary parameters of interest were PLI and DI.

For confirmative statistical testing of primary and secondary efficacy variables, the *t*-test for two independent groups was used. Additionally, PLI and DI were compared between all four treatment groups of the study at Visit 4 using ANOVA. ANCOVA with Bonferroni-adjusted confidence intervals was applied for GI and BOP with baseline as the covariate ($\alpha = 0.05$).

A beneficial effect on gingivitis development would be acknowledged when the differences in GI between the treatment arms with CHX rinses and placebo rinse are proven to be statistically significant and these differences are clinically relevant, i. e. differing $\geqslant 20\%$ from the placebo group GI.

Confirmative testing of the hypotheses of efficacy was performed using the full analysis (FA) set, which included all randomized subjects who had received at least one dose of the study product and from whom at least one measurement of postrandomization data was available. The FA also included subjects with protocol violations and premature termination (intention-to-treat principle). Results from the FA were compared with the results obtained from analysis of the per protocol analysis (PA) set, which included all randomized subjects who had not violated any inclusion or exclusion criteria, who had an assumed compliance of at least 75%, and who had not discontinued the study prematurely.

Table 2. Demographic characteristics of the subjects

	Placebo (negative control)	0.2% CHX/ethanol (positive control)	0.2% CHX (test 1)	0.2% CHX/NaF (test 2)	All groups
Sample size	22	23	24	21	90
Mean age	23.3	22.5	22.7	23.7	23.0
Male (*n*)	9	15	10	5	39
Female (*n*)	13	8	14	16	51
Non-smokers (*n*)	18	15	17	12	62
Smokers (*n*)	4	8	7	9	28

CHX, chlorhexidine; NaF, sodium fluoride.

Results

At the Screening Visit (D-14), 96 subjects were recruited for the study. Of these, six retracted their consent to the study before Visit 1 or did not appear at Visit 1. After unblinding, the remaining 90 participants appeared to be distributed as shown in Table 2. No participants dropped out during the time of experimental gingivitis, i.e. between Visits 1 and 4. The FA involved all 90 participants who were randomly assigned to one of the four treatment arms. It was only obvious after computer-aided calculation of the mean GI per subject and visit that 23 subjects showed values of GI between 0.5 and 0.8 at time point D-14. It was decided by the investigators to retain subjects with a GI $\leqslant 0.6$ in the per PA set because there is no clinically relevant difference between a GI of 0.5 and a GI of 0.6. Consequently, only four subjects were excluded from the PA because of a GI higher than 0.6. Seven subjects were excluded from the PA because it was not possible to assess their compliance; one subject was excluded from the PA because of non-reception of oral hygiene instructions at the beginning of the study. Consequently, the PA included 78 subjects. Subjects were recruited from April 19 to 30, 2004. During the treatment phase from May 3 to May 28, 2004, the subjects returned at 7-day intervals for data and AE recording. All emergency envelopes were returned unopened to the sponsor at the end of the study.

Primary Parameter: GI (Fig. 1)

No statistically significant differences were found between groups at Visit 1. However, at Visit 4, the statistical calculation showed a highly significant difference between placebo and test products 1 and 2 ($p < 0.001$). Additional calculations revealed no statistically significant differences at Visit 4 between the three groups with CHX mouthrinses, but all of them were different from the placebo mouthrinse with respect to GI. For the primary and secondary parameters, a summary of the results after 21 days of rinsing is given in Tables 3 and 4.

Secondary Parameters

PLI (Fig. 2)

No statistically significant differences were found between groups at Visit 1. At Visit 4, the statistical calculation showed a highly significant difference between the placebo and CHX/sodium fluoride as well as between the placebo and the CHX mouthrinse without ethanol ($p < 0.001$). Additional calculations revealed no statistically significant differences at Visit 4 between the three groups with CHX mouthrinses, but all of them were different from the placebo mouthrinse with respect to PlI.

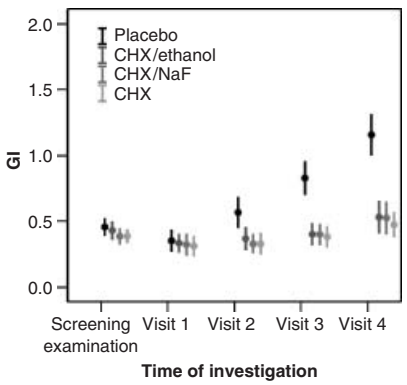

Fig. 1. GI scores for all mouthrinse groups and time points (mean; 95% CI).

DI (Fig. 3)

The DI was recorded throughout the study as depicted in Fig. 3. After professional tooth cleaning at the Screening Visit, the DI dropped to low values (0.18–0.22) at Visit 1, which were not statistically different in the four treatment groups. Because of the experimental gingivitis design, the DI values increased in all four groups from Visit 1 to 4. At the latter, the placebo group was proven to be statistically significantly different from all of the groups using CHX mouthrinses, while those revealed no statistically significant inter-group differences.

BOP

The analysis of BOP at Visit 4 revealed that the placebo group was statistically

Table 3. Primary and secondary endpoints at Visit 4 (D 21)

	Placebo negative control ($n = 22$)	0.2% CHX (Corsodyl®) ($n = 23$)	0.2% CHX test product 1 ($n = 24$)	0.2% CHX/NaF test product 2 ($n = 21$)
GI after 21 days				
Descriptive (mean ± SD)	1.16 ± 0.06	0.53 ± 0.06	0.47 ± 0.06	0.53 ± 0.06
Adjusted (mean ± SD)	1.13 ± 0.04	0.53 ± 0.04	0.49 ± 0.04	0.53 ± 0.04
PLI after 21 days				
Descriptive (mean ± SD)	1.88 ± 0.05	0.17 ± 0.05	0.20 ± 0.05	0.22 ± 0.05
BOP after 21 days				
Descriptive (mean ± SD)	0.31 ± 0.02	0.17 ± 0.02	0.15 ± 0.02	0.17 ± 0.02
Adjusted (mean ± SD)	0.30 ± 0.02	0.17 ± 0.02	0.16 ± 0.02	0.17 ± 0.02
DI after 21 days				
Descriptive (mean ± SD)	0.79 ± 0.09	1.40 ± 0.09	1.43 ± 0.08	1.48 ± 0.09

Descriptive means for all indices and adjusted means with baseline as the covariate for GI and BOP. CHX, chlorhexidine; NaF, sodium fluoride; BOP, bleeding on probing; PLI, plaque index; DI, discolouration index.

Table 4. Primary and secondary endpoints at Visit 4 (D 21)

	Difference placebo – (95% CI), *p* value		
	Corsodyl®	CHX	CHX/NaF
Primary endpoint			
GI after 21 days	0.60 (0.44; 0.77) $p<0.001$	0.64 (0.48; 0.80) $p<0.001$	0.60 (0.43; 0.77) $p<0.001$
Secondary endpoints			
PLI after 21 days	1.71 (1.52; 1.90) $p<0.001$	1.68 (1.49; 1.87) $p<0.001$	1.66 (1.47; 1.86) $p<0.001$
BOP after 21 days	0.14 (0.05; 0.22) $p<0.001$	0.15 (0.07; 0.23) $p<0.001$	0.13 (0.05; 0.22) $p<0.001$
DI after 21 days	− 0.61 (− 0.94; − 0.28) $p<0.001$	− 0.64 (− 0. 97; − 0.31) $p<0.001$	− 0.69 (− 1.03; − 0.35) $p<0.001$

Differences between placebo and active treatments following analysis of covariance for GI and BOP with baseline as the covariate and analysis of variance for PLI and DI; full analysis set.
CHX, chlorhexidine; NaF, sodium fluoride; BOP, bleeding on probing; PLI, plaque index; DI, discolouration index; GI, gingival index.

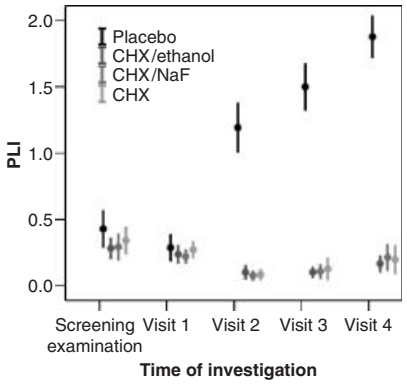

Fig. 2. PLI scores for all mouthrinse groups and time points (mean; 95% CI).

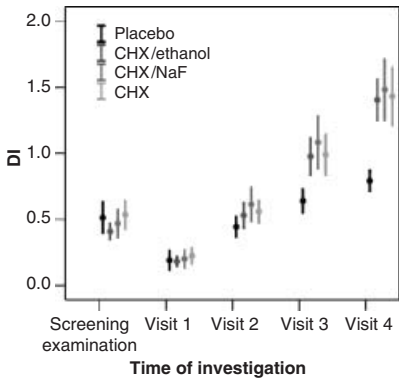

Fig. 3. DI scores for all mouthrinse groups and time points (mean; 95% CI).

significantly different from all of the groups using CHX mouthrinses, while the latter revealed no statistically significant inter-group differences.

FA set and Per PA set

Besides some marginal numerical differences, the results in the FA set and the Per PA set agreed. The conclusions from both data sets were consistent. A subanalysis, which excluded the smokers, did not reveal any changes in the outcome.

Treatment compliance

Seven subjects did not bring back one or both bottles and thus their compliance could not be assessed. In all other cases, the compliance (percentage of mouthwash used) was $\geqslant$78.5%, i.e. more than the 75%, which was defined as the borderline volume for compliance. No statistically significant differences were observed between groups.

When subjectively judged by the investigators, all subjects fulfilled the criteria of compliance in accordance with the volume assessments as described above and in accordance with the clinical parameters/results.

Safety

No serious adverse events (SAE) occurred during this experimental gingivitis study. Of the 68 participants who received one of the CHX products, 12 experienced taste disturbances and 40 showed discolouration of teeth and/or tongue. Three participants had prickling sensations in the tongue; three others reported dentin hypersensitivity. No other product-specific AE were recorded. No premature withdrawal during the active rinsing period of the study occurred.

Discussion

General aspects

The experimental gingivitis model (Löe et al. 1965) is acknowledged as the best design to prove both anti-plaque and anti-gingivitis effects of active components in mouthrinse preparations as shown in numerous clinical studies (Löe & Schiott 1970, Siegrist et al. 1986, Gusberti et al. 1988, Jenkins et al. 1989, Brecx et al. 1990, Richter et al. 2001). Therefore, the GI (Löe 1967) and the PLI (Silness & Löe 1964) were chosen as parameters to prove the anti-plaque properties of the test products. There are only very few clinical trials that could be compared directly with the present investigation. As examples, some authors examined 0.12% CHX (Siegrist et al. 1986, Gusberti et al. 1988, Eldridge et al. 1998), used other indices (Jenkins et al. 1989), or time scale (Quirynen et al. 2001). Only the study of Brecx et al. (1990) could be compared directly with the present study, showing similar plaque and gingival indices in the placebo and in the 0.2% CHX group at the start (day 0) as well as at the endpoint (day 21) of the clinical trial. As stated several times by Addy and co-workers (Addy & Wade 1995, Renton-Harper et al. 1995, Addy et al. 2005), the mere existence of CHX in a dentifrice does not automatically mean that this formulation may exert a beneficial clinical effect. Regarding our study, the data of the clinical effect of the different CHX preparations and brands were comparable. The statistical analysis revealed a clear-cut difference between the placebo group and all three CHX-containing mouth rinse preparations with respect to GI, PlI, DI, and BOP.

Ethanol content in mouthrinses

There is an ongoing debate on the relevance of alcohol in mouthrinse preparations (e.g. Arweiler et al. 2001, Brecx et al. 2003). Most mouthrinse products contain alcohol. In some cases, CHX products without ethanol have not been tested clinically in a sufficient manner. Therefore, it still remains an open question as to whether the omission of alcohol weakens the effect of CHX preparations and/or deteriorates their clinical effect. However, the results of the present controlled clinical study show a performance of the newly

developed non-alcoholic CHX preparation that are very comparable to the so-called ''gold standard'' (Jones 1997), the alcohol-containing 0.2% Corsodyl®.

Fluoride supplementation in CHX products

For decades, a view has circulated in the scientific (dental) society that CHX and fluoride would be chemically incompatible when used together. However, this seems to be an opinion only because no clear data existed until recently regarding this topic. The few former studies are hampered due to lack of appropriate controls (Joyston-Bechal & Hernaman 1993, Giertsen & Scheie 1995, Jenkins et al. 1993, Quirynen et al. 2001) or they dealt with toothpastes (Dolles & Gjermo 1980, Etemadzadeh et al. 1985). While one study suggests ''reduced chlorhexidine availability from the chlorhexidine fluoride product . . .'' (Mendieta et al. 1994, Quirynen et al. 2001), others showed equivalence of CHX/fluoride mixtures to CHX (Dolles & Gjermo 1980, Nuuja et al. 1992). In a previous, 6-month clinical investigation, a very similar clinical efficacy of two 0.06% CHX products, one ''traditional'' without sodium fluoride, the other containing 250 mg/kg of sodium fluoride, was proven (Hoffmann et al. 2001). These data support the idea that sodium fluoride and CHX may be added together without any incompatibility. In accordance therewith, the results of the present experimental gingivitis study demonstrated that the sodium fluoride-containing preparation, the corresponding test product without sodium fluoride, and the positive control 0.2% Corsodyl® without sodium fluoride did not show statistically significantly different efficacies.

Conclusion

The present controlled clinical trial used a classical, established design, appropriate controls (positive and negative), and was conducted under GCP and ICH standards. The results showed a clinically and statistically significant difference between placebo (no retardation of plaque re-growth and gingivitis development) and all three CHX-containing mouthrinses (strong inhibition of plaque re-growth and gingivitis). Neither the two non-alcohol-containing test products differed from the alcohol-containing positive control nor did the fluoride-containing preparation differ from the two mouthrinses without fluoride with respect to the analysed parameters. This shows that neither omission of alcohol nor the supplementation with sodium fluoride weakened the clinical efficacy of CHX in the test formulations. With the exception of discolouration (of teeth and tongue), which is a well-known and common side effect of CHX preparations, no product-specific AE were recorded.

Acknowledgements

This study was sponsored by GABA International AG, Münchenstein, Switzerland. The authors thank Dr. André Brunella for reviewing the manuscript.

References

Addy, M. (2003) The use of antiseptics in periodontal therapy. In: *Clinical Periodontology and Implant Dentistry*, (eds). Lindhe, J., Karring, T. & Lang, K. pp. 464–493. Copenhagen: Blackwell Munksgaard.

Addy, M. & Moran, J. M. (1997) Clinical indications for the use of chemical adjuncts to plaque control: chlorhexidine formulations. *Periodontology 2000* **15**, 52–54.

Addy, M. & Wade, W. (1995) An approach to efficacy screening of mouthrinses: studies on a group of French products. (I). Staining and antimicrobial properties in vitro. *Journal of Clinical Periodontology* **22**, 718–722.

Addy, M., Sharif, N. & Moran, J. (2005) A non-staining chlorhexidine mouthwash? Probably not: a study in vitro. *International Journal of Dental Hygiene* **3**, 59–63.

Ainamo, J. & Bay, I. (1975) Problems and proposals for recording gingivitis and plaque. *International Dental Journal* **25**, 229–235.

Arweiler, N. B., Netuschil, L. & Reich, E. (2001) Alcohol-free mouthrinse solutions to reduce supra-gingival plaque regrowth and vitality. A controlled clinical study. *Journal of Clinical Periodontology* **28**, 168–174.

Baehni, P. C. & Takeuchi, Y. (2003) Anti-plaque agents in the prevention of biofilm-associated oral diseases. *Oral Diseases* **9** (Suppl. I), 23–29.

Bowden, G. H. (1996) Mutans streptococci caries and chlorhexidine. *Journal of the Canadian Dental Association* **62**, 700–707.

Brecx, M., Netuschil, L., Reichert, B. & Schreil, G. (1990) Efficacy of Listerine, meridol and chlorhexidine mouthrinses on plaque, gingivitis and plaque bacteria vitality. *Journal of Clinical Periodontology* **17**, 292–297.

Brecx, M., MacDonald, L. L., Legary, K., Cheang, M. & Forgay, M. G. E. (1993) Long-term effects of meridol and chlorhexidine mouthrinses on plaque, gingivitis, staining, and bacterial vitality. *Journal of Dental Research* **72**, 1194–1197.

Brecx, M., Netuschil, L. & Hoffmann, T. (2003) How to select the right mouthrinses in periodontal prevention and therapy. Part II. Clinical use and recommendations. *International Journal of Dental Hygiene* **1**, 188–194.

Dolles, O. K. & Gjermo, P. (1980) Caries increment and gingival status during 2 years' use of chlorhexidine- and fluoride-containing dentifrices. *Scandinavian Journal of Dental Research* **88**, 22–27.

Eldridge, K. R., Finnie, S. F., Stephens, J. A., Mauad, A. M., Munoz, C. A. & Kettering, J. D. (1998) Efficacy of an alcohol-free chlorhexidine mouthrinse as an antimicrobial agent. *Journal of Prosthetic Dentistry* **80**, 685–690.

Etemadzadeh, H., Ainamo, J. & Murtomaa, H. (1985) Plaque growth-inhibiting effects of an abrasive fluoride-chlorhexidine toothpaste and a fluoride toothpaste containing oxidative enzymes. *Journal of Clinical Periodontology* **12**, 607–616.

Fardal, O. & Turnbull, R. S. (1986) A review of the literature on use of chlorhexidine in dentistry. *Journal of the American Dental Association* **112**, 863–869.

Giertsen, E. & Scheie, A. A. (1995) Effects of chlorhexidine–fluoride mouthrinses on viability, acidogenic potential, and glycolytic profile of established dental plaque. *Caries Research* **29**, 181–187.

Grönroos, L., Mättö, J., Saarela, M., Luoma, A. R., Luoma, H., Jousimies-Somer, H., Pyhälä, L., Asikainen, S. & Alaluusua, S. (1995) Chlorhexidine susceptibilities of mutans streptococcal serotypes and ribotypes. *Antimicrobial Agents and Chemotherapy* **39**, 894–898.

Gusberti, F. A., Sampathkumar, P., Siegrist, B. E. & Lang, N. P. (1988) Microbiological and clinical effects of chlorhexidine digluconate and hydrogen peroxide mouthrinses on developing plaque and gingivitis. *Journal of Clinical Periodontology* **15**, 60–67.

Hoffmann, T., Bruhn, G., Richter, S., Netuschil, L. & Brecx, M. (2001) Clinical controlled study on plaque and gingivitis reduction under long term use of low dose chlorhexidine solutions in a population exhibiting good oral hygiene. *Clinical Oral Investigations* **5**, 89–95.

Jenkins, S., Addy, M. & Newcombe, R. (1989) Comparison of two commercially available chlorhexidine mouthrinses: II. Effects on plaque reformation, gingivitis, and tooth staining. *Clinical Preventive Dentistry* **11**, 12–16.

Jenkins, S., Addy, M. & Newcombe, R. (1993) The effects of a chlorhexidine toothpaste on the development of plaque, gingivitis and tooth staining. *Journal of Clinical Periodontology* **20**, 59–62.

Jones, C. G. (1997) Chlorhexidine: is it still the gold standard? *Periodontology 2000* **15**, 55–62.

Joyston-Bechal, S. & Hernaman, N. (1993) The effect of a mouthrinse containing chlorhexidine and fluoride on plaque and gingival bleeding. *Journal of Clinical Periodontology* **20**, 49–53.

Kidd, E. A. M. (1991) Role of chlorhexidine in the management of dental caries. *International Dental Journal* **41**, 279–286.

Lang, N. P., Hase, J. C., Grassi, M., Hämmerle, C. H. F., Weigel, C., Kelty, E. & Frutig, F. (1998) Plaque formation and gingivitis after supervised mouthrinsing with 0.2% delmopinol hydrochloride, 0.2% chlorhexidine digluconate and placebo for 6 months. *Oral Diseases* **4**, 105–113.

Löe, H. (1967) The gingival index, the plaque index and the retention index systems. *Journal of Periodontology* **38**, 610–616.

Löe, H. & Schiott, C. R. (1970) The effect of mouthrinses and topical application of chlorhexidine on the development of dental plaque and gingivitis in man. *Journal of Periodontal Research* **5**, 79–83.

Löe, H., Theilade, E. & Jensen, S. B. (1965) Experimental gingivitis in man. *Journal of Periodontology* **36**, 177–187.

Mendieta, C., Vallcorba, N., Binney, A. & Addy, M. (1994) Comparison of 2 chlorhexidine mouthwashes on plaque regrowth in vivo and dietary staining in vitro. *Journal of Clinical Periodontology* **21**, 296–300.

Nuuja, T., Meurman, J. H., Murtomaa, H., Kortelainen, S. & Metteri, J. (1992) The effect of a combination of chlorhexidine diacetate, sodium fluoride and xylitol on plaque wet weight and periodontal index scores in military academy cadets refraining from mechanical tooth cleaning for 7-day experimental periods. *Journal of Clinical Periodontology* **19**, 73–76.

Petersson, L. G., Netuschil, L. & Brecx, M. (2002) Mouthrinses and dental caries. *International Dental Journal* **52**, 337–345.

Quirynen, M., Avontroodt, P., Peeters, W., Pauwels, M., Coucke, W. & Van Steenberghe, D. (2001) Effect of different chlorhexidine formulations in mouthrinses on de novo plaque formation. *Journal of Clinical Periodontology* **28**, 1127–1136.

Renton-Harper, P., Milsom, S., Wade, W., Addy, M., Moran, J. & Newcombe, R. G. (1995) An approach to efficacy screening of mouthrinses: studies on a group of French products. (II). Inhibition of salivary bacteria and plaque in vivo. *Journal of Clinical Periodontology* **22**, 723–727.

Richter, S., Bruhn, G., Netuschil, N., Brecx, M., Federlin-Ducani, M. & Hoffmann, T. (2001) Klinisch kontrollierte Studie zur Wirksamkeit einer 0.05%igen Chlorhexidin-Mundspüllösung. *Deutsche Zahnarztliche Zeitschrift* **56**, 193–196.

Siegrist, B. E., Gusberti, F. A., Brecx, M. C., Weber, H. P. & Lang, N. P. (1986) Efficacy of supervised rinsing with chlorhexidine digluconate in comparison to phenolic and plant alkaloid compounds. *Journal of Periodontal Research* **21**, 60–73.

Silness, J. & Löe, H. (1964) Periodontal disease in pregnancy. II. Correlation between oral hygiene and periodontal conditions. *Acta Odontologica Scandinavica* **22**, 121–135.

Twetman, S. & Petersson, L. G. (1997) Efficacy of a chlorhexidine and a chlorhexidine-fluoride varnish mixture to decrease interdental levels of mutans streptococci. *Caries Research* **31**, 361–365.

Van Rijkom, H. M., Truin, G. J. & vant't Hoff, M. A. (1996) A meta-analysis of clinical studies on the caries-inhibiting effect of chlorhexidine treatment. *Journal of Dental Research* **75**, 790–795.

Address:
Katrin Lorenz
Department of Conservative Dentistry
Medical Faculty
Dresden University of Technology
Fetscherstr. 74
01307 Dresden
Germany
E-mail: kl4@rcs.urz.tu-dresden.de

Clinical Relevance

Scientific rationale: The influence of ethanol and fluoride contained in CHX mouthrinses is still unclear in terms of the efficacy of the formulation. Therefore, the aim was to assess whether omission of ethanol and supplementation with fluoride in CHX mouthrinses influences the effect on plaque, gingivitis, and discolouration.

Principal findings: No differences were found between the CHX mouthrinses.

Practical implications: Taking the unsolved ethanol discussion into consideration as well as patients with special needs like immunosuppressant therapy, head and neck radiotherapy, and alcoholics, ethanol-free CHX mouthrinses supplemented with sodium fluoride are a true alternative to the ones containing ethanol.