J Clin Periodontol 2005; 32: 75–80, doi: 10.1111/j.1600-051X.2004.00639.x

Journal of Clinical Periodontology

Anti-gingivitis efficacy of a stabilized 0.454% stannous fluoride/sodium hexametaphosphate dentifrice

A controlled 6-month clinical trial

Suru Mankodi[1], Robert D. Bartizek[2], J. Leslie Winston[2], Aaron R. Biesbrock[2], Stephen F. McClanahan[2] and Tao He[2]

[1]Dental Products Testing, Inc., West Palm Beach, FL, [2]Health Care Research Center, Procter & Gamble Company, Mason, OH, USA

Mankodi S, Bartizek RD, Winston JL, Biesbrock AR, McClanahan SF, He T: Anti-gingivitis efficacy of a stabilized 0.454% stannous fluoride/sodium hexametaphosphate dentifrice: a controlled six-month clinical trial. J Clin Peridontol 2005; 32: 75–80. doi: 10.1111/j.1600–051X.2004.00639.x. © Blackwell Munksgaard, 2004.

Abstract

Objective: Stannous fluoride is a broad-spectrum anti-microbial agent that has been used in dentistry as a chemical adjunct to prevent dental caries and gingivitis. The objective of this study was to assess the anti-gingivitis efficacy of a stabilized 0.454% stannous fluoride/sodium hexametaphosphate dentifrice relative to a negative control.

Methods: This was a randomized, 6-month, double-blind, parallel-group gingivitis study conducted according to the guidelines for evaluating chemotherapeutic products for the control of gingivitis outlined by the American Dental Association. A stabilized 0.454% stannous fluoride/sodium hexametaphosphate dentifrice was tested against a commercially available negative control dentifrice. Following baseline measurements, subjects received a dental prophylaxis. Subjects were then instructed to brush twice daily for 60 s using their assigned product. Oral soft-hard-tissue examinations and clinical examinations using the Modified Gingival Index, Gingival Bleeding Index, and the Turesky modification of the Quigley–Hein Plaque Index were performed at baseline, 3 and 6 months post-treatment.

Results: A total of 143 subjects were enrolled and 130 of them completed the 6-month study. After 6 months of product usage, the experimental group had 21.7% less gingivitis ($p < 0.001$), 57.1% less bleeding ($p < 0.001$), and 6.9% less plaque ($p = 0.01$) on average compared with the negative control group. No adverse oral soft-hard-tissue effects or extrinsic tooth staining was observed in the study.

Conclusion: The results demonstrate that use of the stabilized 0.454% stannous fluoride/sodium hexametaphosphate dentifrice over a 6-month period provided statistically significant reductions in gingivitis, gingival bleeding, and plaque when compared with a negative control dentifrice.

Key words: dental plaque; dentifrice; gingival bleeding; gingivitis; randomized clinical trial; stannous fluoride

Accepted for publication 22 April 2004

Periodontal diseases are chronic infectious diseases of periodontal tissues (Brown & Loe 1993, He et al. 1999, Page 2002). The latest classification has grouped periodontal diseases into the following entities: gingivitis, chronic periodontitis, aggressive periodontitis, and systemic disease forms of periodontitis (Kinane & Hodge 2001). Gingivitis is the earliest form of periodontal disease characterized by inflammation of the marginal and attached gingiva with clinical presentation of tissue redness, swelling, bleeding, etc. (Lindhe & Koch 1966, Page 1986). Bacterial plaque is the principal etiologic agent in the development of gingivitis (Page 1986, Siegrist & Kornman 1982, Kornman & Loe 1993). When inadequately controlled, plaque matures which in turn can lead to the development of gingivitis and/or more severe forms of periodontal diseases.

Considerable emphasis has been placed on the prevention of gingivitis and on the prevention of its progression to the more destructive forms of periodontitis. Approaches to the prevention and treatment of gingivitis have been essentially twofold: mechanical and

chemical plaque control (Hancock 1996, Sheiham 1997). Epidemiologic and clinical studies have suggested that combined use of both mechanical and chemical therapy is the most efficient way to achieve the desired level of sustained plaque control (Ainamo 1977, Hancock 1996, Drisko 2001, Hancock & Newell 2001).

Stannous fluoride is a broad-spectrum anti-microbial agent. The mechanism of action of this agent constitutes inhibition and reduction of bacterial plaque biomass, virulence, and metabolism (Tinanoff 1990). Numerous clinical studies of 6 months or longer duration suggest that stannous fluoride is clinically effective in the prevention and reduction of gingivitis (Wolff et al. 1989, Chikte et al. 1991, Boyd & Chun 1994, Perlich et al. 1995, Bacca et al. 1997, Beiswanger et al. 1997, McClanahan et al. 1997, Williams et al. 1997). Furthermore, a stabilized stannous fluoride dentifrice was granted the anti-caries and anti-gingivitis American Dental Association Seal of Acceptance by the Council on Scientific Affairs. However, formulation challenges, poor esthetics, and the potential for undesired tooth staining associated with extended use has historically limited the broad application of stannous fluoride in practice (Tinanoff 1995).

Recently a novel stannous fluoride formulation has been developed to maximize the chemotherapeutic benefits of stannous fluoride, while providing additional benefits of tartar protection and inhibition of extrinsic stain through the incorporation of hexametaphosphate. The dentifrice is stabilized in a low water formulation to prevent hydrolysis and oxidation of the ionic stannous fluoride. The literature has reported that the largest reductions in gingivitis were observed following the use of stabilized stannous fluoride in non-aqueous preparations (Tinanoff 1990). Moreover, sodium hexametaphosphate has been incorporated into the formulation to aid in the control of calculus and extrinsic tooth staining via inhibition of pellicle formation and mineralization (White & Gerlach 2000, White 2002, White et al. 2002). This molecule is a longer chain variant of pyrophosphate and thus has higher affinity to enamel pellicle proteins (Baig et al. 2002). Numerous clinical studies have suggested that sodium hexametaphosphate can provide marked benefits in the control of extrinsic tooth stain (Gerlach et al. 2002a, b, Liu et al. 2002).

The present study was conducted to investigate the long-term anti-gingivitis efficacy of a stabilized 0.454% stannous fluoride/sodium hexametaphosphate dentifrice when compared with a negative control dentifrice.

Material and Methods

Study design

This was a randomized, 6-month, double-blind, longitudinal, parallel-group, single-center gingivitis study conducted in accordance with the guidelines for evaluating chemotherapeutic products for the control of gingivitis outlined by the American Dental Association (Council of Dental Therapeutics 1986). The objective of the present study was to assess the anti-gingivitis efficacy of a new stabilized 0.454% stannous fluoride/sodium hexametaphosphate dentifrice (Procter & Gamble Co., Cincinnati, OH, USA) relative to a negative control dentifrice (Colgate Cavity Protection®, Colgate-Palmolive Co., New York, NY, USA) (0.76% sodium monofluorophosphate).

Subsequent to institutional review and approval of the protocol, subjects who met all entrance criteria and signed the informed consent were enrolled into the study. At the baseline visit, an oral hard-soft-tissue examination was performed followed by a gingivitis examination using Modified Gingival Index (MGI) (Lobene et al. 1986, Coelho et al. 2000), a gingival bleeding examination using the index as defined by Saxton & van der Ouderaa (1989), and a plaque examination using the Turesky modification of the Quigley–Hein Index (Turesky et al. 1970). Following the baseline examination, subjects received a dental prophylaxis. Subjects were stratified into two balanced groups based on sex and smoking status. The subjects were then randomly assigned either to the experimental or the control group. Subjects were instructed to brush twice daily (morning and evening) for 1 min using only their assigned dentifrice and manual soft toothbrushes for 6 months. Re-examinations of subjects for the efficacy and safety parameters listed above were conducted after 3 and 6 months of product usage.

In order to minimize potential bias, the clinical examiners performing safety and efficacy measurements were blinded to the identity of the two test dentifrices as well as to each subject's assigned treatment group. Subjects were similarly unaware of test product identity. Both test dentifrices were overtubed for blinding purposes.

Subject population

Study subjects were generally healthy adult volunteers aged from 18 to 65 years. To participate in the study, subjects were required to have a minimum of 18 natural teeth, a baseline MGI score of at least 1.75 and not greater than 2.3, and a Turesky Plaque score of at least 1.5. Prospective subjects with any of the following conditions were ineligible for participation: requirement for antibiotic pre-medication prior to dental procedures, diabetes, pregnancy, rampant caries, advanced periodontal disease, or known allergy/sensitivity to stannous fluoride or tartar control dentifrices.

Clinical assessment

Gingivitis, gingival bleeding, plaque, and oral hard-soft-tissue evaluations were performed on all subjects at the baseline, 3- and 6-month examinations to assess efficacy and safety of the test products. One examiner performed safety, MGI, and the bleeding examinations. A separate examiner was used for plaque measurements. The same clinician performed the same measurement throughout the trial.

Assessment of the oral soft tissue was conducted via a visual examination of the oral cavity and perioral area utilizing a standard dental light, dental mirror, and gauze. The structures examined include the gingiva (free and attached), hard and soft palate, oropharynx/uvula, buccal mucosa, tongue, floor of the mouth, labial mucosa, mucobuccal/mucolabial folds, lips, and perioral area. Assessment of the oral hard tissues was conducted via a visual and tactile examination of the dentition and restorations utilizing a standard dental light, dental mirror, and air syringe. All abnormal oral soft-hard-tissue findings noted after baseline or those that were present at baseline but worsened during investigational product usage were recorded as adverse events.

Gingivitis was scored at baseline, 3 months, and 6 months by the MGI on the buccal and lingual marginal gingivae and interdental papillae of all scorable teeth. MGI differs slightly from the Löe–Silness Gingival Index (GI) as no probing is used to elicit

bleeding and the scoring system for mild and moderate inflammation is redefined (Lobene et al. 1986). Previous studies comparing gingivitis indices have shown that MGI correlates significantly with GI (Lobene et al. 1989). MGI thus permits non-invasive evaluation of early and subtle visual changes in severity and extent of gingivitis.

Gingival bleeding was assessed at baseline, 3 months, and 6 months according to the Gingival Bleeding Index (Saxton & van der Ouderaa 1989). Each of three gingival areas, i.e., buccal, mesial, and lingual, of the teeth was probed waiting approximately 30 s before recording the number of gingival units which bleed, according to the following scale: 0, absence of bleeding after 30 s, 1, bleeding observed after 30 s, and 2, immediate bleeding observed. Plaque area was scored at baseline, 3 months, and 6 months by the Turesky modification of the Quigley–Hein Plaque Index, which emphasizes plaque in contact with the gingivae, on six surfaces (distobuccal, midbuccal, mesiobuccal, distolingual, midlingual, and mesiolingual) of all scorable teeth following application of disclosing solution (Turesky et al. 1970).

Statistical analysis

The effects on MGI scores, total bleeding scores, and plaque scores of the experimental stannous fluoride/sodium hexametaphosphate dentifrice relative to the negative control dentifrice were analyzed for treatment group differences using analysis of covariance methods with the baseline value as the covariate (Lehnhoff & Grainger 1974). All statistical tests were two sided and treatment comparison results were reported as statistically significant if the test p-value was less than or equal to 0.05. As an analysis model assumption, the tests for equal covariate slopes used a significance level of 0.10.

Results

Of the 143 subjects enrolled in the study, 133 were available for the 3-month examination and 130 subjects completed the entire 6-month study. Subjects who did not complete the study did so for reasons unrelated to the use of either of the two dentifrices. Demographic characteristics for 3- and 6-month results are shown in Table 1. Subjects in the experimental dentifrice and negative control groups were equally represented in terms of age and gender throughout the trial.

A summary of the MGI data for all subjects examined is reported in Table 2. For subjects examined at 3 months, the average baseline MGI scores were 2.03 for the experimental group and 2.04 for the negative control group. The 3-month MGI scores were analyzed using an analysis of covariance with baseline MGI score as the covariate. The adjusted mean 3-month MGI scores were 1.75 for the experimental dentifrice and 1.98 for the negative control dentifrice. The difference between groups was statistically significant ($p<0.001$).

For subjects with MGI scores at 6 months (also in Table 2), the average baseline MGI scores were 2.03 for the experimental group and 2.04 for the negative control group. The 6-month MGI scores were analyzed using the same analysis of covariance methods used for the 3-month MGI scores. The adjusted mean 6-month MGI scores were 1.57 for the experimental dentifrice and 2.01 for the negative control dentifrice. The difference between groups was statistically significant ($p<0.001$). The adjusted mean MGI scores for the experimental dentifrice were 11.5% lower at 3 months and 21.7% lower at 6 months than the adjusted mean MGI scores for the negative control dentifrice.

The same statistical methods were applied to the 3- and 6-month data on gingival bleeding scores and the results are presented in Table 3. For subjects examined at 3 months, the average number of gingival bleeding scores at baseline was 9.36 for the experimental group and 8.67 for the negative control group. The analyses of covariance used the number of bleeding scores at baseline as the covariate. The adjusted mean 3-month bleeding scores were 4.14 for the experimental dentifrice and 7.92 for the negative control dentifrice. The difference between groups was statistically significant ($p<0.001$).

For subjects who were examined at 6 months (also in Table 3), the average number of gingival bleeding scores at baseline was 9.39 for the experimental group and 8.68 for the negative control group. The adjusted mean 6-month bleeding scores were 3.81 for the experimental dentifrice and 8.88 for the negative control dentifrice and the difference between groups was again statistically significant ($p<0.001$). The adjusted mean bleeding scores for the experimental dentifrice were 47.7% lower at 3 months and 57.1% lower at 6 months than the adjusted mean bleeding scores for the negative control dentifrice.

The 3- and 6-month plaque results are presented in Table 4. For subjects examined at 3 months, the mean plaque score at baseline was 2.74 for the experimental group and 2.90 for the negative control group. The analyses of covariance used the baseline plaque scores as the covariate. The adjusted mean 3-month plaque scores were 2.24 for the experimental dentifrice and 2.38 for the negative control dentifrice and the difference approached statistical significance ($p=0.06$). For subjects examined at 6 months, the mean plaque score at baseline was 2.73 for the experimental group and 2.91 for the negative control group. The adjusted mean 6-month plaque scores were 2.14 for the experimental group and 2.30 for the negative control group and this difference was statistically significant ($p=0.01$).

No severe adverse reactions were reported in the study. One subject was diagnosed with spinal meningitis and dropped from the study. This serious adverse event was determined to be not product related. Examinations of the oral tissues after 3 and 6 months revealed no remarkable findings related to either of the test dentifrices. No extrinsic tooth staining was observed by

Table 1. Demographics

		Age		Gender	
Treatment	*N*	mean ± SD	range	female	male
Subjects included in 3-month analysis					
control dentifrice	67	38.3 ± 11.3	18–64	44 (65.7%)	23 (34.3%)
experimental dentifrice	66	37.1 ± 10.7	18–65	45 (68.2%)	21 (31.8%)
Subjects included in 6-month analysis					
control dentifrice	66	38.5 ± 11.3	18–64	43 (65.2%)	23 (34.8%)
experimental dentifrice	64	37.1 ± 10.9	18–65	44 (68.8%)	20 (31.2%)

Table 2. Modified Gingival Index results

Treatment	*N*	Baseline score (mean ± SD)	Adjusted mean* ± SE	% Reduction†
3-month analysis‡				
control dentifrice	67	2.04 ± 0.10	1.98 ± 0.02	–
experimental dentifrice	66	2.03 ± 0.10	1.75 ± 0.02	11.5%
6-month analysis§				
control dentifrice	66	2.04 ± 0.10	2.01 ± 0.03	–
experimental dentifrice	64	2.03 ± 0.10	1.57 ± 0.03	21.7%

*Adjusted means and standard errors from analysis of covariance with baseline score as the covariate.
†% Reduction = 100% × (control mean − experimental mean)/control mean.
‡The adjusted means were statistically significantly different ($p < 0.001$).
§The adjusted means were statistically significantly different ($p = 0.001$).

Table 3. Gingival Bleeding Index results

Treatment	*N*	Baseline score (mean ± SD)	Adjusted mean* ± SE	% Reduction†
3-month analysis‡				
control dentifrice	67	8.67 ± 3.38	7.92 ± 0.34	–
experimental dentifrice	66	9.36 ± 3.19	4.14 ± 0.34	47.7%
6-month analysis§				
control dentifrice	66	8.68 ± 3.40	8.88 ± 0.39	–
experimental dentifrice	64	9.39 ± 3.22	3.81 ± 0.40	57.1%

*Adjusted means and standard errors from analysis of covariance with baseline score as the covariate.
†% Reduction = 100% × (control mean − experimental mean)/control mean.
‡The adjusted means were statistically significantly different ($p < 0.001$).
§The adjusted means were statistically significantly different ($p < 0.001$).

Table 4. Plaque Index Results

Treatment	*N*	Baseline score (mean ± SD)	Adjusted mean* ± SE	% Reduction†
3-month analysis‡				
control dentifrice	67	2.90 ± 0.36	2.38 ± 0.05	–
experimental dentifrice	66	2.74 ± 0.41	2.24 ± 0.05	5.6%
6-month analysis§				
control dentifrice	66	2.91 ± 0.35	2.30 ± 0.05	–
experimental dentifrice	64	2.73 ± 0.41	2.14 ± 0.05	6.9%

*Adjusted means and standard errors from analysis of covariance with baseline score as the covariate.
†% Reduction = 100% × (control mean − experimental mean)/control mean.
‡The adjusted means were not statistically significantly different ($p = 0.06$).
§The adjusted means were statistically significantly different ($p < 0.05$).

the study examiner or reported by the subjects in the study.

Discussion

Gingivitis has been reported to have a high prevalence worldwide. More than 80% of US adolescents have gingivitis and signs of gingival bleeding, with similar or higher prevalence of gingivitis being reported in other parts of the world (Stamm 1986, Jeffcoat 1994, Albandar & Tinoco 2002, Albandar 2002). Chemotherapeutic agents have been incorporated into dentifrice formulations to prevent and reduce gingivitis (Ainamo 1977). The objective of this double-blind, controlled study was to evaluate the anti-gingivitis efficacy of a stabilized 0.454% stannous fluoride/sodium hexametaphosphate dentifrice versus a negative control dentifrice when used as a part of a daily oral hygiene regimen following a professional prophylaxis. After 6 months of usage, the stabilized 0.454% stannous fluoride/sodium hexametaphosphate dentifrice delivered a 21.7% reduction in gingivitis ($p < 0.001$), a 57.1% reduction ($p < 0.001$) in gingival bleeding, and a 6.9% reduction in plaque ($p = 0.01$) when compared with the negative control, demonstrating that the stannous fluoride/sodium hexametaphosphate dentifrice was effective in the prevention and reduction of plaque and gingivitis.

Previously, the effects of stannous fluoride at a concentration of 0.4–0.45% on gingivitis when used in a mouth rinse, brush-on gel, or dentifrice form have been described in numerous clinical trials (Wolff et al. 1989, Chikte et al. 1991, Boyd & Chun 1994, Perlich et al. 1995, Bacca et al. 1997, Beiswanger et al. 1997, McClanahan et al. 1997, Mankodi et al. 1997, Williams et al. 1997). Tinanoff et al. (1989) showed that subjects using a 0.4% stannous fluoride gel twice daily for 6 months had 48% less gingivitis than subjects using a 0.22% sodium fluoride gel. The difference was statistically significant at $p = 0.05$. Perlich et al. (1995) demonstrated that using a 0.454% stabilized stannous fluoride dentifrice twice daily for 6 months resulted in 20.5% less gingivitis ($p < 0.05$) and 33.4% less bleeding ($p < 0.05$) when compared with a negative control. Stannous fluoride has been suggested to possess anti-gingivitis efficacy through suppression of supragingival plaque mass (Mankodi et al. 1997, Williams et al. 1997), virulence and plaque bacterial composition (Bacca et al. 1997, Beiswanger et al. 1997, McClanahan et al. 1997). Williams et al. (1997) reported that subjects who have used a 0.454% stannous fluoride dentifrice twice daily for 6 months yielded a statistically significant plaque reduction when compared with a negative control dentifrice. In another 6-month plaque/gingivitis clinical trial conducted by Mankodi et al. (1997), a 0.454% stannous fluoride dentifrice again exhibited statistically significant plaque reduction versus a negative control. The magnitude of these percent reductions exceeded 20% for both studies. Collectively, the present study results in conjunction with previously reported long-term clinical studies clearly support the anti-plaque/anti-gingivitis therapeutic benefits and the underlying mechanism of action of this agent.

In the present study, one benefit of using the stabilized stannous fluoride/sodium hexametaphosphate dentifrice was manifested as fewer bleeding sites during the course of treatment ($p < 0.001$). When the percentage of

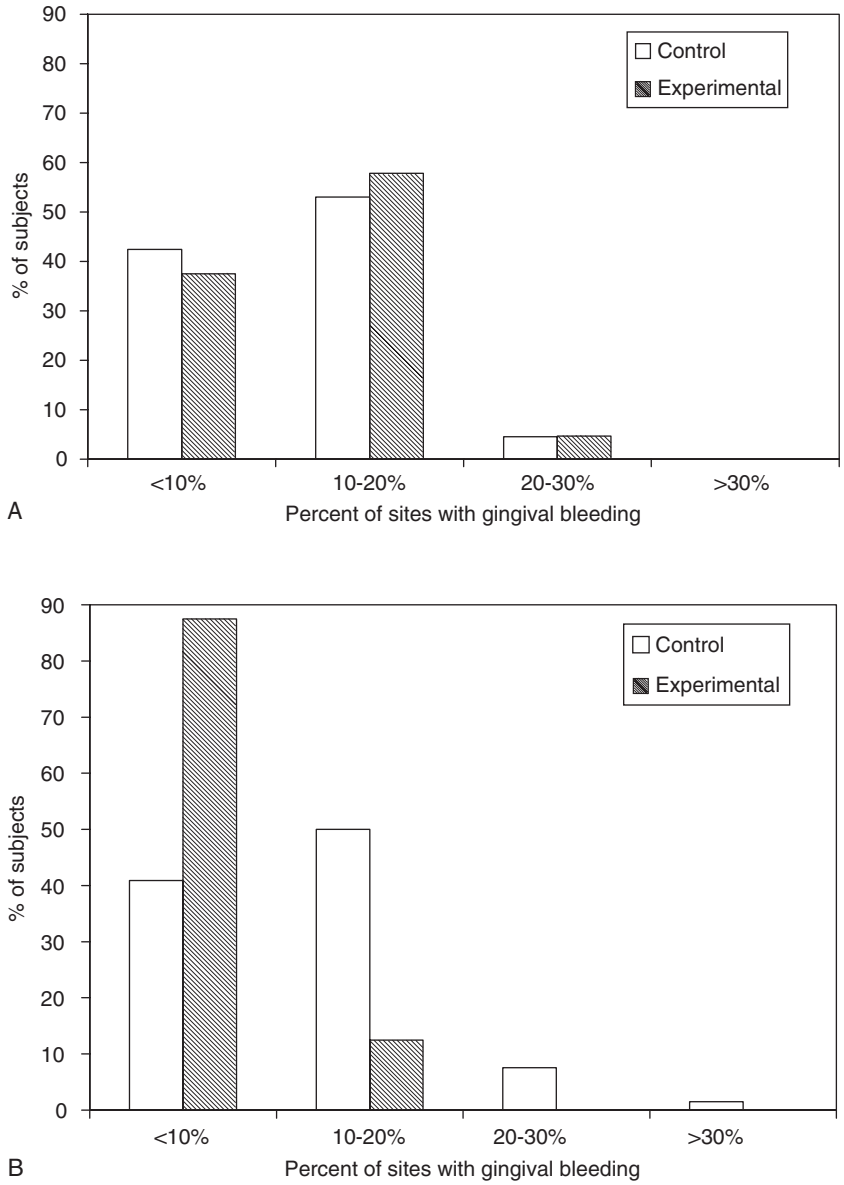

Fig. 1. (A) Bleeding categories at baseline. (B) Bleeding categories at 6 month.

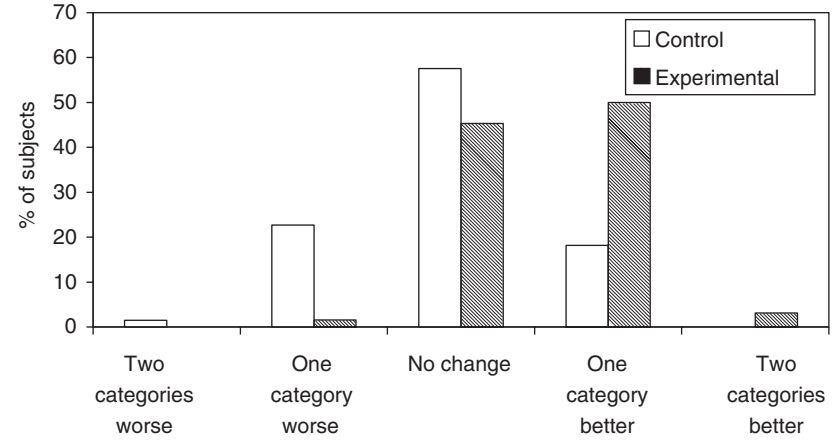

Fig. 2. Bleeding category – change from baseline to 6 month.

bleeding sites were categorized into four groups: $<10\%$, 10–20%, 20–30%, and $>30\%$, there was even distribution between the test and the control groups at baseline ($p = 0.87$) (Fig. 1A). At 6 months, 87.5% of subjects on the test product had less than 10% of sites bleeding compared with 40.9% of subjects in the negative control group ($p < 0.001$) (Fig. 1B). Interestingly, when the shift of the disease level from baseline to 6 months was monitored, 50% of the subjects in the test group moved at least one category from more bleeding sites to less bleeding sites while only 18.2% did so in the negative control group (Fig. 2). The conversion of bleeding sites to non-bleeding sites potentially represents a significant decrease in risk to future periodontal breakdown. Lang (1990) reported that sites that do not bleed do not progress, indicating the lack of gingival bleeding has high specificity in predicting a continuation of health.

In conclusion, the results of the present clinical study demonstrate that use of the stabilized 0.454% stannous fluoride/sodium hexametaphosphate dentifrice over a 6-month period provides a statistically significant and clinically relevant effect in the control and prevention of gingivitis as compared with a negative control dentifrice.

Acknowledgments

The authors acknowledge the contributions of Karen Bauroth (DPT) and Jeff Finkeldey, Marta Somogyi-Mann, Iain Hughes, Arif Baig and Lisa Prater (P&G). This research was supported by Procter & Gamble Company.

References

Ainamo, J. (1977) Control of plaque by chemical agents. *Journal of Clinical Periodontology* **4**, 23–35.

Albandar, J. M. (2002) Periodontal diseases in North America. *Periodontology 2000* **29**, 31–69.

Albandar, J. M. & Tinoco, E. M. (2002) Global epidemiology of periodontal diseases in children and young persons. *Periodontology 2000* **29**, 153–176.

Bacca, L. A., Leusch, M., Lanzalaco, A. C., Macksood, D., Bouwsma, O. J., Shaffer, J. B., Howard-Nordan, K. S., Knippenberg, S. H., Kreutzjans, M. K., Miller, J. M., Poore, C. L., Sunberg, R. J., Vastola, K. A., Becus, M., Bartizek, R. D., Block, R. P., Briner, W. W. & White, D. J. (1997) A comparison

of intraoral antimicrobial effects of stabilized stannous fluoride dentifrice, baking soda/peroxide dentifrice, conventional NaF dentifrice and essential oil mouthrinse. *Journal of Clinical Dentistry* **8**, 54–61.

Baig, A. A., Kozak, K. M., Cox, E. R., Zoladz, J. R., Mahony, L. & White, D. J. (2002) Laboratory studies on the chemical whitening effects of a sodium hexametaphosphate dentifrice. *Journal of Clinical Dentistry* **13**, 19–24.

Beiswanger, B. B., McClanahan, S. F., Bartizek, R. D., Lanzalaco, A. C., Bacca, L. A. & White, D. J. (1997) The comparative efficacy of stabilized stannous fluoride dentifrice, peroxide/baking soda dentifrice and essential oil mouthrinse for the prevention of gingivitis. *Journal of Clinical Dentistry* **8**, 46–53.

Boyd, R. L. & Chun, Y. S. (1994) Eighteen-month evaluation of the effects of a 0.4% stannous fluoride gel on gingivitis in orthodontic patients. *American Journal of Orthodontics Dentofacial Orthopedics* **105**, 35–41.

Brown, L. J. & Loe, H. (1993) Prevalence, extent, severity and progression of periodontal disease. *Periodontology 2000* **2**, 57–71.

Chikte, U. M., Pochee, E., Rudolph, M. J. & Reinach, S. G. (1991) Evaluation of stannous fluoride and chlorhexidine sprays on plaque and gingivitis in handicapped children. *Journal of Clinical Periodontology* **18**, 281–286.

Coelho, J., Kohut, B. E., Mankodi, S., Parikh, R. & Wu, M. M. (2000) Essential oils in an antiplaque and antigingivitis dentifrice: a 6-month study. *American Journal of Dentistry* **13**, 5C–10C.

Council of Dental Therapeutics (1986) Guidelines for the acceptance of chemotherapeutic products for the control of supragingival dental plaque and gingivitis. *Journal of American Dental Association* **112**, 529–532.

Drisko, C. H. (2001) Nonsurgical periodontal therapy. *Periodontology 2000* **25**, 77–88.

Gerlach, R. W., Liu, H., Prater, M. E., Ramsey, L. L. & White, D. J. (2002a) Removal of extrinsic stain using a 7.0% sodium hexametaphosphate dentifrice: a randomized clinical trial. *Journal of Clinical Dentistry* **13**, 6–9.

Gerlach, R. W., Ramsey, L. L. & White, D. J. (2002b) Extrinsic stain removal with a sodium hexametaphosphate-containing dentifrice: comparisons to marketed controls. *Journal of Clinical Dentistry* **13**, 10–14.

Hancock, E. B. (1996) Periodontal diseases: prevention. *Annals of Periodontolology* **1**, 223–249.

Hancock, E. B. & Newell, D. H. (2001) Preventive strategies and supportive treatment. *Periodontology 2000* **25**, 59–76.

He, T., Nishihara, T., Demuth, D. R. & Ishikawa, I. (1999) A novel insertion sequence increases the expression of leukotoxicity in *Actinobacillus actinomycetemcomitans* clinical isolates. *Journal of Periodontology* **70**, 1261–1268.

Jeffcoat, M. K. (1994) Prevention of periodontal diseases in adults: strategies for the future. *Preventive Medicine* **23**, 704–708.

Kinane, D. F. & Hodge, P. J. (2001) Periodontal disease in children and adolescents: introduction and classification. *Periodontology 2000* **26**, 7–15.

Kornman, K. S. & Loe, H. (1993) The role of local factors in the etiology of periodontal diseases. *Periodontology 2000* **2**, 83–97.

Lang, N. P. (1990) Epidemiology of periodontal disease. *Archives of Oral Biology* **35** (Suppl.), 9S–14S.

Lehnhoff, R. W. & Grainger, R. M. (1974) Use of analysis of covariance in periodontal clinical trials. *Journal of Periodontal Research* **14** (Suppl.), 143–159.

Lindhe, J. & Koch, G. (1966) The effect of supervised oral hygiene on the gingiva of children. Progression and inhibition of gingivitis. *Journal of Periodontal Research* **1**, 260–267.

Liu, H., Segreto, V. A., Baker, R. A., Vastola, K. A., Ramsey, L. L. & Gerlach, R. W. (2002) Anticalculus efficacy and safety of a novel whitening dentifrice containing sodium hexametaphosphate: a controlled six-month clinical trial. *Journal of Clinical Dentistry* **13**, 25–28.

Lobene, R. R., Mankodi, S. M., Ciancio, S. G., Lamm, R. A., Charles, C. H. & Ross, N. M. (1989) Correlations among gingival indices: a methodology study. *Journal of Periodontology* **60**, 159–162.

Lobene, R. R., Weatherford, T., Ross, N. M., Lamm, R. A. & Menaker, L. (1986) A modified gingival index for use in clinical trials. *Clinical Preventive Dentistry* **8**, 3–6.

Mankodi, S., Petrone, D. M., Battista, G., Petrone, M. E., Chaknis, P., DeVizio, W., Volpe, A. R. & Proskin, H. M. (1997) Clinical efficacy of an optimized stannous fluoride dentifrice, Part 2: a 6-month plaque/gingivitis clinical study, northeast USA. *Compendium of Continuing Education in Dentistry* **18** Special issue, 10–15.

McClanahan, S. F., Beiswanger, B. B., Bartizek, R. D., Lanzalaco, A. C., Bacca, L. & White, D. J. (1997) A comparison of stabilized stannous fluoride dentifrice and triclosan/copolymer dentifrice for efficacy in the reduction of gingivitis and gingival bleeding: six-month clinical results. *Journal of Clinical Dentistry* **8**, 39–45.

Page, R. C. (1986) Current understanding of the aetiology and progression of periodontal disease. *International Dental Journal* **36**, 153–161.

Page, R. C. (2002) The etiology and pathogenesis of periodontitis. *Compendium of Continuing Education in Dentistry* **23**, 11–14.

Perlich, M. A., Bacca, L. A., Bollmer, B. W., Lanzalaco, A. C., McClanahan, S. F., Sewak, L. K., Beiswanger, B. B., Eichold, W. A., Hull, J. R., Jackson, R. D. & Mau, M. S. (1995) The clinical effect of a stabilized stannous fluoride dentifrice on plaque formation, gingivitis and gingival bleeding: a six-month study. *Journal of Clinical Dentistry* **6** Special issue, 54–58.

Saxton, C. A. & van der Ouderaa, F. J. (1989) The effect of a dentifrice containing zinc citrate and triclosan on developing gingivitis. *Journal of Periodontal Research* **24**, 75–80.

Sheiham, A. (1997) Is the chemical prevention of gingivitis necessary to prevent severe periodontitis? *Periodontology 2000* **15**, 15–24.

Siegrist, B. & Kornman, K. S. (1982) The effect of supragingival plaque control on the composition of the subgingival microbial flora in ligature-induced periodontitis in the monkey. *Journal of Dental Research* **61**, 936–941.

Stamm, J. W. (1986) Epidemiology of gingivitis. *Journal of Clinical Periodontology* **13**, 360–370.

Tinanoff, N. (1990) Review of the antimicrobial action of stannous fluoride. *Journal of Clinical Dentistry* **2**, 22–27.

Tinanoff, N. (1995) Progress regarding the use of stannous fluoride in clinical dentistry. *Journal of Clinical Dentistry* **6** Special issue, 37–40.

Tinanoff, N., Manwell, M. A., Zameck, R. L. & Grasso, J. E. (1989) Clinical and microbiological effects of daily brushing with either NaF or SnF2 gels in subjects with fixed or removable dental prostheses. *Journal of Clinical Periodontology* **16**, 284–290.

Turesky, S., Gilmore, N. D. & Glickman, I. (1970) Reduced plaque formation by the chloromethyl analogue of victamine C. *Journal of Periodontology* **41**, 41–43.

White, D. J. (2002) A new and improved ''dual action'' whitening dentifrice technology – sodium hexametaphosphate. *Journal of Clinical Dentistry* **13**, 1–5.

White, D. J., Cox, E. R., Suszcynskymeister, E. M. & Baig, A. A. (2002) In vitro studies of the anticalculus efficacy of a sodium hexametaphosphate whitening dentifrice. *Journal of Clinical Dentistry* **13**, 33–37.

White, D. J. & Gerlach, R. W. (2000) Anticalculus effects of a novel, dual-phase polypyrophosphate dentifrice: chemical basis, mechanism, and clinical response. *Journal of Contemporary Dental Practice* **1**, 1–19.

Williams, C., McBride, S., Bolden, T. E., Mostler, K., Petrone, D. M., Petrone, M. E., Chaknis, P., DeVizio, W., Volpe, A. R. & Proskin, H. M. (1997) Clinical efficacy of an optimized stannous fluoride dentifrice, Part 3: a 6-month plaque/gingivitis clinical study, southeast USA. *Compendium of Continuing Education in Dentistry* **18** Special issue, 16–20.

Wolff, L. F., Pihlstrom, B. L., Bakdash, M. B., Aeppli, D. M. & Bandt, C. L. (1989) Effect of toothbrushing with 0.4% stannous fluoride and 0.22% sodium fluoride gel on gingivitis for 18 months. *Journal of American Dental Association* **119**, 283–289.

Address:
Tao He
Health Care Research Center
Procter & Gamble Company
8700 Mason-Montgomery Road
Mason, OH 45040
USA
Fax: +1 513 622 0560
E-mail: he.t@pg.com