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A controlled 6-month clinical trial to study the effects of a stannous fluoride dentifrice on gingivitis

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Abstract

Objectives: This study was conducted to assess anti-plaque and anti-gingivitis benefits of a stabilized stannous fluoride (SnF_2)/sodium hexametaphosphate (SHMP) dentifrice *versus* a negative control.

Material and Methods: This was a randomized, 6-month, stratified, single-centre, double-blind, parallel group, clinical study conducted in harmony with the guidelines for evaluating chemotherapeutic products for the control of gingivitis outlined by the American Dental Association. A stabilized 0.454% SnF_2/SHMP dentifrice was tested against a commercially available negative control dentifrice. Following baseline measurements, subjects received a dental prophylaxis. Subjects were instructed to brush twice daily for 60 s using their assigned product. Efficacy measurements were obtained at baseline, 3 and 6 months post treatment using the Modified Gingival Index, Gingival Bleeding Index and the Turesky Modified Quigley-Hein Plaque Index. Oral tissue examinations were performed at all visits.

Results: A total of 140 subjects were enroled and 128 completed the study. Results after 6 months showed the SnF_2 dentifrice delivered a 16.9% reduction in gingivitis ($p < 0.001$), a 40.8% reduction ($p < 0.001$) in gingival bleeding, and an 8.5% reduction in plaque ($p = 0.001$) *versus* the negative control. Both treatments were well tolerated.

Conclusions: Twice daily use of the SnF_2/SHMP dentifrice over 6 months provided statistically significant anti-plaque and anti-gingivitis benefits relative to a negative control.

Key words: clinical trial; dentifrice; gingivitis; sodium hexametaphosphate; stannous fluoride

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Plaque-induced gingivitis is one of the most common forms of periodontal disease (Oliver et al. 1998, Sheiham & Netuveli 2002). One of the primary causative factors in the development of gingivitis is inadequately controlled supragingival plaque (Kinane & Hodge 2001). Plaque-induced gingivitis can be prevented with good oral hygiene (Brook 2003, Ower 2003). This includes regular toothbrushing and flossing of teeth and periodic professional cleaning to prevent buildup of plaque and calculus.

Toothbrushing with dentifrice is the most widely used method of home dental care for prevention of periodontal diseases (Sheen et al. 2001). A typical dentifrice is composed of many different ingredients, each having a very special function. The therapeutic components are the various fluorides, desensitizing and anti-bacterial agents. The cosmetic agents include anti-calculus and whitening ingredients. Anti-microbial agents such as stannous fluoride (SnF_2) have been incorporated into dentifrice formulations and have been shown to be effective in the prevention of dental caries (Stookey et al. 2004), reduction of plaque formation (Mankodi et al. 2005, White et al. 2006), control of gingivitis (White 1995, Archila et al. 2004, Mankodi et al. 2005, Paraskevas & van der Weijden 2006) and suppression of breath malodor (Gerlach et al. 1998). Moreover, SnF_2 has also been shown to be effective against dentinal hypersensitivity (Schiff et al. 2000, 2005, 2006).

Recently a SnF_2/sodium hexametaphosphate (SHMP) formulation has been

Conflict of interest and source of funding statement

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developed to maximize the chemotherapeutic benefits of SnF_2, while providing additional benefits of calculus protection and extrinsic whitening through the combination of SHMP along with a high cleaning silica abrasive system (Baig & He 2005).

The present study was conducted to assess the anti-plaque and anti-gingivitis benefits of a stabilized 0.454% SnF_2/SHMP formulation compared with a negative control dentifrice over a 6-month period following an oral prophylaxis.

Material and Methods

This study was a randomized, stratified, single-centre, double-blind, parallel group clinical trial conducted in West Palm Beach, Florida. Both the research protocol and written informed consent were reviewed and approved by an institutional review board before study initiation. Study subjects were generally healthy adult volunteers between 18 and 65 years of age. Subjects were required to have a minimum of 18 natural teeth, a baseline modified gingival index (MGI) score of at least 1.75 and not greater than 2.3, and a plaque index (PI) score of at least 1.5. Prospective subjects with any of the following conditions were ineligible for participation: requirement for antibiotic pre-medication before dental procedures; diabetes; pregnancy; rampant caries; advanced periodontal disease; or known allergy/sensitivity to SnF_2 or tartar-control dentifrices.

At the baseline visit, 140 subjects received MGI (Lobene et al. 1986), gingival bleeding index (GBI) (Saxton & van der Ouderaa 1989) and Turesky Modified Quigley–Hein PI (Fischman 1986) examinations. MGI scores, ranging from 0 (absence of inflammation) to 4 (severe inflammation), were taken on the buccal and lingual marginal gingivae and interdental papillae. GBI scores were recorded for buccal, mesial and lingual sites according to the following scale: 0 – absence of bleeding after 30 s; 1 – bleeding observed after 30 s; and 2 – immediate bleeding observed. Plaque was assessed on the mesial, distal and mid-surfaces of facial and lingual aspects following application of a disclosing solution using a 0 (no plaque) to 5 (plaque covering $>2/3$ of the surface) scale.

Oral hard and soft tissue exams were also conducted at the baseline visit. Assessment of the oral tissue was conducted via a visual examination of the oral cavity and perioral area.

Following the baseline examinations, subjects received an oral prophylaxis to remove supragingival plaque and calculus and were stratified by gender and smoking status. Subjects were then randomly assigned to one of the two treatment groups:

- Experimental 0.454% SnF_2/SHMP dentifrice (Crest Pro-Health dentifrice, Procter & Gamble, Cincinnati, OH, USA).
- Negative control dentifrice: Aquafresh® Triple Protection dentifrice (GlaxoSmithKline Consumer Healthcare, Pittsburgh, PA, USA) with sodium monofluorophosphate (0.15 w/v of fluoride ion); does not contain an anti-gingivitis/anti-plaque ingredient.

Products were packaged in sealed kits labelled by the code initial for each of the two products. The technician dispensing the products was blind to the randomization code. During the treatment phase, subjects were instructed to brush twice daily for 60 s with their assigned soft manual toothbrush, using the same method they normally employed. Subjects returned at 6 and 18 weeks post treatment for visual product compliance checks to ensure usage. To assure blinding, investigational products and kits were identical in their appearance except for a product identification code assigned based on randomization sequence. The randomization sequence and product distribution were performed by Dental Products Research.

At 3 and 6 months, post-baseline, subjects received MGI, GBI and PI exams to re-evaluate all baseline parameters, in addition to oral tissue exams.

Sample size was determined based on published clinical research involving dentifrices for the control of gingivitis (Mankodi et al. 2002, 2005). Statistical analysis was based on whole-mouth average MGI scores and whole-mouth total GBI scores. The effects on MGI scores and total bleeding scores, of the experimental SnF_2/SHMP dentifrice and the negative control dentifrice, were analysed for treatment group differences using analysis of covariance methods with the appropriate 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 $\leqslant 0.05$. Separate analyses were performed for 3- and 6-month data, with the 6-month data being of primary interest. In addition, the per cent reduction in scores for the SnF_2/SHMP dentifrice relative to the control dentifrice was calculated as 100% (control-adjusted mean $-$ SnF_2-adjusted mean/control-adjusted mean). As part of the analysis of covariance procedure, the covariate slopes were examined for consistency between treatment groups and models with separate slopes were applied if indicated. As an analysis model assumption, the tests for equal covariate slopes used a significance level of 0.10. If the covariate slopes were found to differ ($p \leqslant 0.10$), then the range of covariate values where the treatment groups did not differ significantly was estimated using the Johnson–Neyman procedure (Johnson & Neyman 1936). The same analysis methods were applied to whole-mouth average plaque scores (PI).

Results

Of the 140 subjects who were randomized to treatment, 132 were available for the 3-month examination with 128 subjects completing the entire 6-month study. Of the eight subjects not available for the 3-month examination, two were lost to follow-up and six voluntarily withdrew from the study. In addition to these eight subjects, four additional subjects were not available for the 6-month examinations because of voluntary withdrawal from the study before the 6-month examination. Demographic characteristics for 3- and 6-month results are shown in Table 1.

MGI

The 3-month MGI scores, analysed using an analysis of covariance with baseline MGI score as the covariate, were statistically significantly different ($p < 0.001$, Table 2) between the two groups. The 6-month MGI scores were analysed using the same analysis of covariance methods used for the 3-month MGI scores. In the analysis of covariance for this variable, the covariate slopes were found to differ ($p = 0.077$) between the treatment groups. The results in Table 2 are thus based on a model with separate

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Table 1. Demographic characteristics

Treatment	*N*	Age		Gender	
		mean ± SD	range	female	male
Subjects included in 3-month analysis					
Control dentifrice	67	37.5 ± 11.38	18–64	44	23
SnF_2/SHMP dentifrice	65	39 ± 11.96	18–65	40	25
Subjects included in 6-month analysis					
Control dentifrice	66	37.6 ± 11.41	18–65	43	23
SnF_2/SHMP dentifrice	62	38.4 ± 11.61	18–59	37	25

SnF_2, stannous fluoride; SHMP, sodium hexametaphosphate.

Table 2. Modified gingival index results

	Control dentifrice ($N = 67$)		SnF_2/SHMP dentifrice ($N = 65$)		*p*-value *versus* control	Percentage of reduction *versus* control[†]
	mean ± SD	adjusted mean ± SE[*]	mean ± SD	adjusted mean ± SE[*]		
Baseline	2.00 ± 0.13	–	2.00 ± 0.13	–	–	–
3 months	1.97 ± 0.15	1.97 ± 0.02	1.84 ± 0.17	1.84 ± 0.02	<0.001	6.8
6 months[‡]	1.90 ± 0.21	1.90 ± 0.03	1.58 ± 0.31	1.58 ± 0.03	<0.001	16.9

[*]Adjusted means and SE from analysis of covariance with baseline score as the covariate.
[†]Percent reduction = 100% × (control adjusted mean–experimental adjusted mean)/control adjusted mean.
[‡]Control dentifrice $N = 66$ and SnF_2/SHMP dentifrice $N = 62$ at 6 months.
SnF_2, stannous fluoride; SHMP, sodium hexametaphosphate.

Table 3. Gingival bleeding index results

	Control dentifrice ($N = 67$)		SnF_2/SHMP dentifrice ($N = 65$)		*p*-value *versus* control	Percentage of reduction *versus* control[†]
	mean ± SD	adjusted mean ± SE[*]	mean ± SD	adjusted mean ± SE[*]		
Baseline	10.90 ± 3.92	–	10.86 ± 4.93	–	–	–
3 months	8.51 ± 4.77	8.50 ± 0.383	5.62 ± 4.23	5.63 ± 0.389	<0.001	33.8
6 months[‡]	8.53 ± 4.48	8.55 ± 0.460	5.08 ± 4.89	5.06 ± 0.474	<0.001	40.8

[*]Adjusted means and SE from analysis of covariance with baseline score as the covariate.
[†]Percent reduction = 100% × (control adjusted mean – experimental adjusted mean)/control adjusted mean.
[‡]Control dentifrice $N = 66$ and SnF_2/SHMP dentifrice $N = 62$ at 6 months.
SnF_2, stannous fluoride; SHMP, sodium hexametaphosphate.

covariate slopes for the two treatment groups. A statistically significant difference between the treatment groups ($p < 0.001$) was detected at the average covariate score. The adjusted mean for the experimental dentifrice group was 16.9% lower than the adjusted mean for the negative control group. According to the Johnson–Neyman procedure, no statistically significant difference between the treatment groups could be detected for baseline MGI scores above 2.49. No subjects had baseline MGI scores in this region of ''no statistically significant difference'' between the treatment groups (the highest baseline score was 2.32).

Gingival bleeding

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. The analyses of covariance used the total bleeding scores at baseline as the covariate. The adjusted mean bleeding scores for the SnF_2/SHMP dentifrice were 33.8% lower at 3 months and 40.8% lower at 6 months than the adjusted mean bleeding scores for the negative control dentifrice ($p < 0.001$).

Plaque

The analyses of covariance used the baseline plaque scores as the covariate. The adjusted mean 3-month plaque scores were statistically significantly different ($p = 0.009$) between the groups. The adjusted mean 6-month plaque scores were 2.17 for the SnF_2/SHMP group and 2.37 for the negative control group. The difference between the groups was statistically significant ($p = 0.001$) and the adjusted mean for the SnF_2/SHMP dentifrice group was 8.5% lower than the adjusted mean for the negative control group (Table 4).

Safety results

There was one adverse event reported during the study. One subject in the control dentifrice group reported right-arm cellulitis. This event was determined by the investigator to be not related to treatment. Examinations of the oral tissues during the study revealed two subjects with abnormal oral soft tissue findings that were not present at baseline. One subject in the experimental dentifrice group had a healing herpetic lesion, and one subject in the control dentifrice group had a healing apthous ulcer. Overall, study subjects were well

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Table 4. Plaque index results

	Control dentifrice ($N = 67$)		SnF_2/SHMP dentifrice ($N = 65$)		*p*-value *versus* control	Percentage of reduction *versus* control[†]
	mean ± SD	adjusted mean ± SE[*]	mean ± SD	adjusted mean ± SE[*]		
Baseline	2.79 ± 0.42	–	2.88 ± 0.34	–	–	–
3 months	2.25 ± 0.51	2.28 ± 0.04	2.16 ± 0.41	2.12 ± 0.04	0.009	7.2
6 months[‡]	2.34 ± 0.49	2.37 ± 0.04	2.20 ± 0.40	2.17 ± 0.04	0.001	8.5

[*]Adjusted means and SE from analysis of covariance with baseline score as the covariate.
[†]Percent reduction = 100% × (control adjusted mean − experimental adjusted mean)/control adjusted mean.
[‡]Control dentifrice $N = 66$ and SnF_2/SHMP dentifrice $N = 62$ at 6 months.
SnF_2, stannous fluoride; SHMP, sodium hexametaphosphate.

tolerated with both test dentifrices over a 6-month period of time.

Discussion

This double-blind, controlled clinical study evaluated the anti-gingivitis efficacy of a stabilized 0.454% SnF_2/SHMP dentifrice *versus* a negative control dentifrice when used as part of a daily oral hygiene regimen following a professional prophylaxis. The study was conducted among a population of mild-to-moderate gingivitis sufferers, representing a population likely to use an over-the-counter anti-gingivitis dentifrice. Results of the study support the long-term anti-plaque and anti-gingivitis benefits of a stabilized 0.454% SnF_2/SHMP dentifrice, further adding to the published evidence of efficacy of this therapeutic dentifrice (Archila et al. 2004, Mankodi et al. 2005). In this study, the stabilized 0.454% SnF_2/SHMP dentifrice delivered a 16.9% reduction in gingivitis ($p < 0.001$), a 40.8% reduction ($p < 0.001$) in gingival bleeding and 8.5% reduction in plaque ($p = 0.001$) relative to negative control after a 6-month usage. The results demonstrated that the SnF_2/SHMP dentifrice was effective in the control of plaque and gingivitis.

For completeness, an-intent-to treat analysis of the 6-month data was performed with the 3-month values carried forward for the four subjects who withdrew between 3 and 6 months. The results were virtually identical to the primary results, with the stabilized 0.454% SnF_2/SHMP dentifrice delivering reductions of 16.9% in gingivitis, 41.2% in gingival inflammation and 9.3% in plaque relative to the negative control.

Reports of clinical studies in the literature have consistently demonstrated that 0.454% SnF_2 dentifrice is effective in reducing gingivitis and plaque when compared with either negative control dentifrice or positive control dentifrice as well as with essential oils rinse. These studies, encompassing a range of duration, a variety of clinical populations and the use of different dosage forms, have shown significant reductions in plaque and gingivitis for SnF_2 dentifrice (Beiswanger et al. 1995, 1997, Perlich et al. 1995, Mankodi et al. 1997, 2005, Williams et al. 1997, Archila et al. 2004).

Mankodi et al. (2005) demonstrated that the use of the stabilized 0.454% SnF_2/SHMP dentifrice over a 6-month period provided statistically significant reductions in gingivitis, gingival bleeding and plaque when compared with a negative control dentifrice. Moreover, Beiswanger et al. (1995) have shown that using a 0.454% SnF_2 dentifrice stabilized with 2.08% sodium gluconate twice daily for 6 months resulted in a statistically significant reduction in gingivitis of 18.8% compared with a negative control. Similar beneficial effects of a stabilized SnF_2 dentifrice on gingival health were also reported by Williams et al. (1997), where a 23% reduction in plaque and a 22% reduction in gingivitis were observed *versus* a negative control.

When compared with a positive control, a 6-month randomized clinical study reported that a stabilized 0.454% SnF_2/SHMP dentifrice had statistically significantly less gingivitis (25.8%) and statistically significantly less bleeding site (27.4%) on average compared with a triclosan/copolymer dentifrice (Archila et al. 2004). When compared with essential oils rinse, a 6-month double-blind clinical study reported that a stabilized 0.454% SnF_2 dentifrice produced statistically significant reductions in both gingivitis (10.8%) and gingival bleeding (23.0%) relative to the combination of sodium fluoride dentifrice and essential oil mouthrinse (Beiswanger et al. 1997). These results support the superior activity of stabilized SnF_2 dentifrice as compared with a combination of sodium fluoride negative control dentifrice, triclosan/copolymer positive control dentifrice and essential oil mouthrinse for the control of gingivitis and gingival bleeding.

It has been reported that molar teeth are most frequently affected by periodontitis (Brown et al. 1989) and that molars are at a greater risk of early attachment loss than are single-rooted teeth (Lindhe et al. 1989). In order to further investigate the effects of the SnF_2/SHMP dentifrice and the negative control dentifrice on gingivitis, supplemental statistical analyses were conducted with the dentition divided according to tooth type: anterior teeth, pre-molars and molars. The analysis was applied by gingival bleeding. Gingival bleeding represents the very early sign of gingivitis (Carter & Barnes 1974, Greenstein et al. 1981, Caton et al. 1989). Moreover, gingival bleeding has been shown to correlate well with the traditional Löe & Silness Gingival Index, which measures both visual signs of gingival inflammation and gingival bleeding (Charles et al. 2004). The average total bleeding score per tooth for subjects examined at 6 months are presented in Table 5 for each of these tooth types. Baseline bleeding scores were consistently low for the anterior dentition and within-treatment group scores ranged from 0.33 to 0.36 in this region. Pre-molars had within-treatment group scores that ranged from 0.61 to 0.65 and the highest baseline bleeding scores occurred for molars (within-treatment group scores of 1.57–1.62). The finding is consistent with our previous observation and with the reports in the literature (Archila et al. 2004).

The supplemental statistical analysis results (Table 5) showed that the treatment groups differed with respect to the

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Table 5. 6-Month gingival bleeding index results by tooth type*

Treatment	*N*	Baseline score (mean ± SD)	Adjusted mean† ± SE	Precentage of reduction *versus* control‡
Anterior teeth				
Control dentifrice	66	0.33 ± 0.31	0.25 ± 0.04	–
SnF_2/SHMP dentifrice	62	0.36 ± 0.42	0.13 ± 0.04	47.8
			Treatment difference $p = 0.029$	
Pre-molars				
Control dentifrice	66	0.65 ± 0.47	0.46 ± 0.05	–
SnF_2/SHMP dentifrice	62	0.61 ± 0.49	0.27 ± 0.05	41.7
			Treatment difference $p = 0.004$	
Molars				
Control dentifrice	66	1.62 ± 0.80	1.31 ± 0.08	–
SnF_2/SHMP dentifrice	62	1.57 ± 0.78	0.81 ± 0.08	38.2
			Treatment difference $p < 0.001$	

*Average bleeding index scores per tooth are shown due to the differing numbers of teeth in the various tooth categories.
†Adjusted means and SE from analysis of covariance with baseline score as the covariate.
‡Percent reduction = 100% × (control mean–experimental mean)/control mean.
SnF_2, stannous fluoride; SHMP, sodium hexametaphosphate.

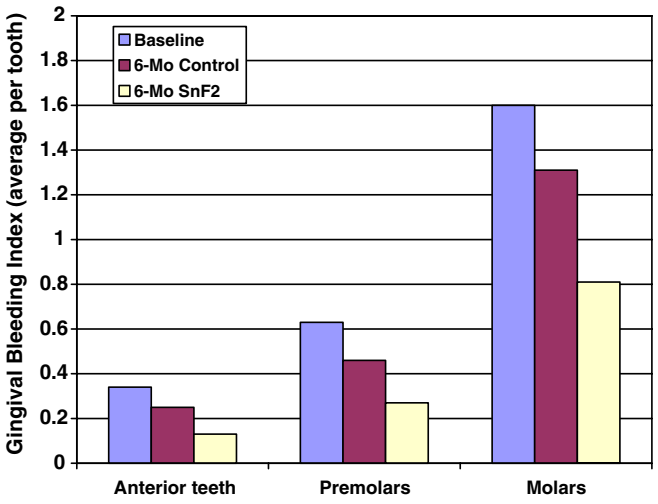

Fig. 1. Gingival Bleeding Index scores by tooth type.

bleeding scores for anterior teeth, pre-molars and molars ($p \leqslant 0.029$). The baseline and the 6-month post-treatment bleeding index scores for each of the tooth categories are displayed in Fig. 1. It is evident that the same pattern of treatment response exists for anterior teeth, pre-molars and molars. The benefit of the SnF_2/SHMP dentifrice over the negative control dentifrice on gingival bleeding is present throughout the dentition.

The present study results, in conjunction with earlier long-term studies reporting on the SnF_2 dentifrice, clearly establish the anti-gingivitis therapeutic benefit of this agent. In conclusion, the results of the present clinical study demonstrate that use of the experimental 0.454% stabilized SnF_2/SHMP dentifrice over a 6-month period provides a statistically significant benefit in the prevention and control of gingivitis and plaque when used in combination with regular personal oral hygiene procedures and professional care.

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Clinical Relevance

Scientific rationale for the study: Stannous fluoride has a long history of use for anti-plaque and anti-gingivitis benefits. A novel dentifrice technology system was recently developed combining stannous fluoride with sodium hexametaphosphate, a cosmetic agent. This study was conducted to evaluate the anti-gingivitis benefits of this unique system relative to a negative control dentifrice over 6 months.

Principal findings: The study showed that novel stannous fluoride and sodium hexametaphosphate dentifrice provided significant long-term reductions in gingival bleeding and gingival inflammation relative to a negative control.

Practical implications: The stabilized stannous fluoride and sodium hexametaphosphate dentifrice can provide significant gingival health benefits beyond a standard fluoride dentifrice when incorporated in patients' daily oral hygiene routine.

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