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A Randomized Clinical Trial to Compare Plaque Inhibition of a Sodium Fluoride/Potassium Nitrate Dentifrice versus a Stabilized Stannous Fluoride/ Sodium Hexametaphosphate Dentifrice

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Abstract

Aim: To compare the plaque inhibition efficacy of a sodium fluoride/potassium nitrate (NaF/KNO_3 with 1450 ppm F) test dentifrice to a 0.454% stannous fluoride/sodium hexametaphosphate/sodium fluoride positive control dentifrice (SnF_2/SHMP with 1450 ppm F).

Methods and Materials: Twenty-five subjects were randomized to a two-period, two-treatment, double blind crossover sequence using NaF/KNO_3 (Sensodyne® ProNamel™ dentifrice) and SnF_2/SHMP (blend-a-med®* EXPERT GUMS PROTECTION dentifrice). Each treatment was conducted with a standard manual toothbrush (Oral-B® P35 Indicator). Digital plaque image analysis (DPIA) was used on three consecutive days to evaluate: (a) overnight plaque formation (A.M. pre-brushing); (b) following 40 seconds of brushing with the test product (A.M. post-brushing); and (c) mid-afternoon (P.M.). Images were analysed using an objective computer algorithm to calculate the total area of visible plaque. A four-day washout period was instituted for the crossover phase.

Results: All 25 subjects completed the study. The SnF_2/SHMP positive control dentifrice provided statistically significantly lower levels of plaque area coverage versus the NaF/KNO_3 test dentifrice at each timepoint. For the SnF_2/SHMP dentifrice, plaque coverage was 23.0% lower ($p<0.0001$) at A.M. pre-brushing, 17.3% ($p=0.0163$) lower at A.M. post-brushing, and 22.6% ($p= 0.0004$) lower at the P.M. measure relative to the NaF/KNO_3 dentifrice.

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Conclusion: The SnF_2/SHMP dentifrice (blend-a-med® EXPERT GUMS PROTECTION) inhibits plaque regrowth both overnight and during the day to a significantly greater degree than the NaF/KNO_3 dentifrice (Sensodyne® ProNamel™).

Clinical Significance: Dentists recommending an effective home use dentifrice for patients experiencing dentinal hypersensitivity and/or dental erosion may previously have needed to compromise on other key benefits, such as plaque control. blend-a-med® EXPERT GUMS PROTECTION is a dentifrice when integrated into an oral hygiene routine can provide a proven treatment for hypersensitivity, dental erosion, and a reduction in the regrowth of plaque.

Keywords: Plaque inhibition, stannous fluoride, SnF_2, sodium hexametaphosphate, SHMP, potassium nitrate, KNO_3, DPIA, plaque imaging, randomized clinical trial

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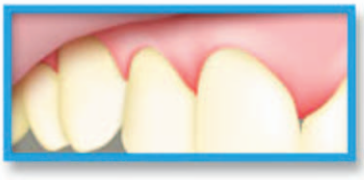
* Also branded Crest® and Ipana, depending on the country.

Introduction

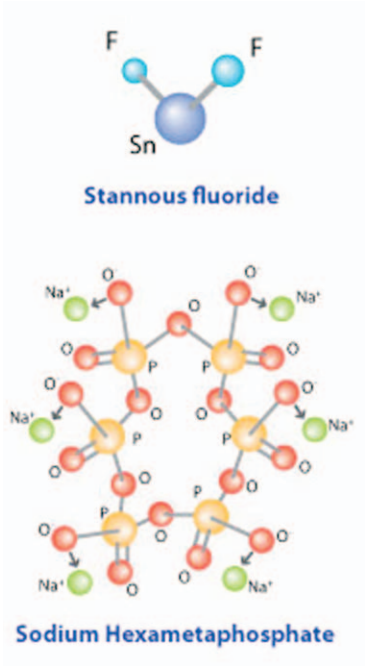


Gingivitis remains an ongoing public health issue in much of the western world, despite more than half a century of widespread availability of effective dental hygiene products (toothbrushes and toothpastes).[1] Dental plaque is universally accepted as the major contributing factor for poor gingival health, therefore, the suppression of plaque quantity and pathogenicity can be expected to provide a reduction in gingivitis.[2,3]

Effective plaque control can be attained through effective toothbrushing; in particular, rotating-oscillating electric toothbrushes have been shown to be particularly efficient.[4,5] Use of a quality manual toothbrush combined with a suitable brushing technique has also been shown to effectively reduce plaque and gingivitis.[6] Nevertheless, despite these findings, large proportions of the population continue to suffer from gingivitis.

Toothpaste, the most widely used brushing adjunct, provides an ideal vehicle for delivery of therapeutic agents to supplement tooth brushing in controlling plaque growth on a daily basis.[7] A number of active ingredients impacting the bacterial load on the oral surfaces have been utilized for this purpose over the years, including metal salts, quaternary ammonium compounds (e.g., CPC), essential oils, and triclosan.[8,9]

Dentifrices containing potassium nitrate (KNO_3) are primarily intended to mitigate the effects of dentinal hypersensitivity and have been marketed solely or mainly as such. These products, when correctly formulated, are broadly agreed to be effective at providing a simple home treatment for patients with hypersensitivity.[10] Recent marketing has expanded the benefits of a KNO_3/fluoride dentifrice beyond its historically singular limitation to now include the provision of prevention against dental erosion (a growing risk for a significant group of patients[11]) and the long-term replacement for regular fluoridated toothpaste.



Rarely does a practicing dentist encounter a patient with a single oral health issue.[12] More commonly, patients reporting issues such as hypersensitivity are also experiencing other health issues such as gingival recession caused by, among other things, inadequate plaque control over a number of years.[13]

This poses questions for the clinician as to whether a dentifrice with KNO_3/fluoride can provide the same level and breadth of benefits as other toothpaste products and whether it is suitable to be recommended to a broad population given the widely reported prevalence of other significant oral health problems such as gingival disease.[14] The role of a dentifrice in helping to reduce gingivitis and control plaque is considered to be an important attribute by a number of commentators.[7-9,15,16] A review of the literature reveals very little research on the ability of a KNO_3/fluoride dentifrice to provide this benefit to the large proportion of the population who experience gingival problems.

In a single recent 12-week study evaluating plaque and gingivitis by Wara-aswapati[17] a KNO_3/sodium monofluorophosphate (SMFP) dentifrice was found not to be statistically significantly different than a control dentifrice containing sodium monofluorophosphate (SMFP) as the only identified active ingredient. The KNO_3/SMFP product was shown to be effective at reducing hypersensitivity. Other agents are available to provide a hypersensitivity benefit. A review of the literature indicates dentifrices containing stabilized SnF_2[18] are effective at mitigating hypersensitivity[19] as well as providing a range of other benefits, including anti-plaque,[20] anti-gingivitis,[21] oral malodour alleviation,[22] and prevention against dental erosion.[23] Sodium hexametaphosphate (SHMP), when added to a stabilized SnF_2 dentifrice, provides the additional benefits of prevention of calculus formation, stain removal, and reduction of stain formation.[24] Therefore, a stabilized SnF_2/SHMP dentifrice was selected as a positive control in the subject study because it has previously been shown to provide both anti-plaque and hypersensitivity benefits.

This study evaluates the ability of a leading NaF/KNO_3 dentifrice to prevent daily plaque regrowth compared to a known positive control dentifrice (SnF_2/SHMP) over a 17-day period of treatment, using a randomized, double-blind crossover design.

Methods and Materials

Design Summary

The 25 subjects enrolled in this study were part of a panel at the London Innovation Centre (Procter & Gamble UK). All subjects had previously participated in plaque trials and, therefore, were accustomed to following direct oral hygiene instructions.

The study was a two-period, two-treatment double blind randomized crossover study which used digital plaque image analysis (DPIA) with fluorescein disclosure to evaluate plaque coverage on the anterior facial surfaces. Each treatment period was 17 days long, with a four-day washout period between the evaluation periods. The total study length, including a one week acclimatization period, was seven weeks. Plaque evaluations were conducted after an undisturbed 24 hour period of plaque growth on the measured surfaces (A.M. Pre-brushing) on the mornings of the last three days of each treatment period (days 15, 16, and 17), giving three repeat measures to improve statistical robustness. Plaque evaluations were also carried out post-brushing (A.M. Post brushing) and mid afternoon (P.M.) of the same three days.

Treatment Products

1. A sodium fluoride (1450 ppm F)/potassium nitrate (KNO_3) toothpaste widely marketed across Europe (Sensodyne® ProNamel™, GlaxoSmithKline, Turkey). Referred to as NaF/KNO_3 dentifrice (test product).
2. A 0.454% stannous fluoride (SnF_2)/sodium hexametaphosphate (SHMP)/0.078% sodium fluoride (NaF) formulation. In this product, the SnF_2 provides 1100 ppm of fluoride while the NaF provides 350 ppm of fluoride, giving a total fluoride level of 1450 ppm (blend-a-med® EXPERT GUMS PROTECTION toothpaste, Procter & Gamble, Germany). Referred to as SnF_2/SHMP dentifrice (positive control).

Detailed Study Design

All subjects, upon recruitment, were given an oral soft tissue (OST) examination, participated in a recorded confidential medical history and were assessed for inclusion/exclusion criteria. Selection criteria required subjects to be in good general health, to agree not to participate in any other clinical studies for the duration of the study, and to agree to use the study treatments as directed. Subjects were excluded if they were on medication (e.g., antibiotics), had poor dental health, or appliances (e.g., orthodontic appliances, dentures, etc.) which would interfere with study assessment. They were also excluded if they had undergone any dental treatment within one month of the start of the study (two weeks for dental prophylaxis) or were known to have any dye allergies or were pregnant or nursing. All subjects received an OST examination at the conclusion of the study and were asked to provide feedback on comfort levels while using the treatment products.

Prior to the treatment phase of the study, subjects underwent an acclimation phase of seven days, using a standard NaF toothpaste and manual brush (Crest® Decay Prevention 0.321% SnF and Oral-B® P35 Indicator medium hardness manual toothbrush, both manufactured by Procter & Gamble). Subjects were instructed to brush twice per day and to refrain from using any other oral hygiene aids. This standard product combination was also used during the four day washout phase at the treatment crossover.

On the first day of Period 1 (Monday) subjects were provided with their randomly assigned treatment product and a standard manual toothbrush (Oral-B® P35 Indicator medium). Products were supplied in white, unbranded (fully blinded) tubes. Subjects were instructed to brush their teeth twice a day as they would normally do but with a full brush-head of toothpaste (approximately 1g) for 17 days. However, on the evenings of Monday, Tuesday, and Wednesday of each week during the treatment periods, subjects were instructed to brush before 11:00 p.m. on only their lingual surfaces (untimed). This allowed plaque to accumulate on the facial surfaces of the upper and lower six anterior teeth. On the mornings of the last three days of the period (days 15, 16, and 17; Tuesday, Wednesday, and Thursday) subjects attended the imaging facility as early in the morning as possible, abstaining from brushing their teeth and refraining from eating or drinking (except water) that morning.

Subjects initiated their facility visit by disclosing their plaque (procedure described below) to have an immediate image captured on the DPIA system. Following this, they brushed with their assigned treatment product for a self-timed 40 seconds before re-disclosing for a re-imaging of their remaining plaque. The subjects were then free to leave the imaging facility and go about their normal daily activities until mid afternoon (2:00-4:00 p.m.). Subjects were allowed to resume eating and drinking until 30 minutes before the afternoon imaging session to avoid beverages and food debris from interfering with the imaging process. Upon their return to the imaging facility, they disclosed again and had their plaque imaged for a third time.

Once this procedure was completed on the afternoon of day 17, subjects were instructed to return to using the standard NaF paste and manual toothbrush for the four days prior to commencement of Period 2. Period 2 completed the study and consisted of the crossover product evaluated exactly the same as Period 1.

Plaque Disclosure and Imaging Procedure

The use of DPIA to evaluate plaque coverage and conduct product comparisons has been reported in the literature on a number of occasions. This study employed white light imaging of fluorescein disclosed plaque reported by Bellamy[25] with the application of the DPIA methodology for dentifrice research reviewed and approved by the Institutional Ethics Review Committee.

Immediately prior to every DPIA plaque evaluation, each subject performed a rinsing procedure using 5 ml of 1240 ppm solution of fluorescein diacetate disclosing dye in a phosphate buffer (pH 6). Fresh dye solutions were made daily. After disclosure, subjects performed three rinses for 10 seconds each with the phosphate buffer to stabilize the mouth pH and to rinse away any unattached dye. Images were captured using a standardized digital image analysis system fully described by Sagel.[26] The system was operated by an expert in image analysis who was blinded to the treatment.

Before analysis, captured images had a region of interest (ROI) determined where the ROI comprised the facial anterior surface of the clearly visible teeth (six maxillary, six mandibular: canine to canine). Following this, the computer batch analysed every pixel within the ROI according to a pre-determined analysis routine[25,26] and each pixel was assigned to one of four classes: tooth, gums, plaque, and background. The number of pixels in each class for every image was automatically reported to a Microsoft Excel spreadsheet. The results of the computer analysis were checked for consistency and accuracy by an expert in image analysis to exclude any poorly classified images from study results. No images needed to be excluded from this study for this reason.

Finally, to enable a valid comparison of data, the image analyst calculated the percentage of visible tooth area covered with plaque using the following equation:

% Plaque coverage = [plaque pixels/ (tooth pixels + plaque pixels)] *100

Statistical Methods

Percentage plaque area coverage measurements from each of three days were averaged for each subject and period separately for the A.M. pre-brushing, A.M. post-brushing, and P.M. timepoints. Analysis of variance for the crossover design (general linear mixed model) was used to compare the percent plaque area coverage between treatments using sequence (treatment use order AB or BA), period, and treatment dentifrice as fixed effects and subject as a random effect. All statistical comparisons were two-sided using a 0.05 significance level.

Results

All 25 subjects completed the study providing evaluable data. Subjects ranged in age from 25 to 57 with a mean of 35.3 years (standard deviation 8.6); 56% of subjects were female. No adverse events were recorded by the investigator. No product use discomfort was reported through the study by the subjects.

The mean percent plaque area for each sequence (AB or BA) was not statistically different ($p>0.60$) at each timepoint, indicating that subjects assigned to each sequence group (AB or BA) responded in a similar way. There was no statistically significant period effect as well ($p>0.52$) for any timepoint. The results are summarized in Table 1.

The adjusted mean for morning A.M. Pre-brush percent plaque area was 16.24 for NaF/KNO_3 and 12.50 for SnF_2/SHMP. These means represented an overnight plaque area coverage which was 23.0% lower favouring SnF_2/SHMP dentifrice relative to the NaF/KNO_3 dentifrice. This difference was highly statistically significant ($p<0.0001$).

For immediate post-brushing, adjusted mean percent plaque area was 6.52 for NaF/KNO_3 and 5.39 for SnF_2/SHMP. After brushing, mean percent plaque area when using SnF_2/SHMP was 17.3% lower than with NaF/KNO_3. This difference was statistically significant ($p=0.0163$).

At mid-afternoon (P.M. visit), adjusted mean percent plaque area was 12.22 for NaF/KNO3 and 9.46 for SnF_2/SHMP. Therefore, daytime plaque re-growth for SnF_2/SHMP was 22.6% lower than NaF/KNO_3. Again, this difference was statistically significant ($p=0.0004$).

Discussion

Product Comparison

Effective plaque control on a daily basis continues to be the primary means by which patients can control gingival conditions. Products claiming to

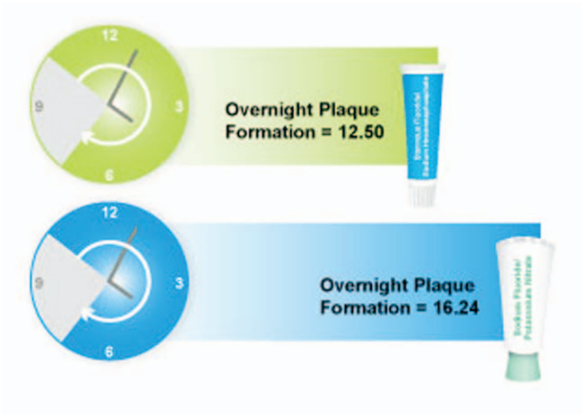
Table 1. Plaque coverage after two weeks product use; product comparison.

Timepoint/ Treatment	Mean plaque coverage % (SE*)	% difference between treatments	Treatment comparison 2-sided *p*-value**	Between Subject /Residual Variances
A.M. Pre-brush (N=25)				
SnF_2/SHMP	12.50 (1.63)	23.03	< 0.0001	61.889 / 3.625
NaF/KNO_3	16.24 (1.63)			
A.M Post-brush (N=25)				
SnF_2/SHMP	5.39 (0.89)	17.33	0.0163	17.606 / 1.892
NaF/KNO_3	6.52 (0.89)			
P.M. (N=25)				
SnF_2/SHMP	9.46 (1.26)	22.59	0.0004	34.681 / 4.341
NaF/KNO_3	12.22 (1.26)			

* SE = Standard Error
** Statistical method: Analysis of Variance for Crossover Designs (2 periods)

provide plaque control benefits are common, but comparative *in vivo* clinical testing of marketed products for their ability to reduce plaque is infrequent. This scarcity of data makes the job of the professional more complex as they seek to recommend the most effective products to their patients.

In this study the difference between the two tested products was clear (Table 1). The SnF_2/SHMP dentifrice (positive control) inhibited the plaque formation to a significantly greater degree than the NaF/KNO_3 dentifrice (test product). This was apparent at all evaluation points (early morning, after overnight regrowth and mid afternoon, after daytime regrowth). The overnight period was at least eight hours (11:00 p.m. to 7:30 a.m., the earliest for the pre-brushing A.M. image), while the daytime period was at least five hours (9:00 a.m. to 2:00 p.m.) and included a period when at least one meal was consumed (lunch).



Plaque coverage when using the SnF_2/SHMP dentifrice at the two timepoints of A.M. pre-brushing and P.M. were both 23% lower compared to when subjects used the NaF/KNO_3 dentifrice. Additionally, immediately after brushing with the SnF_2/SHMP dentifrice subjects had significantly less plaque (17%) than when brushing with the NaF/KNO_3 dentifrice. As the two toothbrushes were identical, the benefit immediately post-brushing was likely due to the fact subjects who had been using the SnF_2/SHMP product started with less plaque (due to reduced plaque regrowth in areas usually missed by the subject when brushing).

The design of this study employed an untimed lingual only brushing on the Monday, Tuesday, and Wednesday evenings of every week. This

method has previously been reported by White.[27] Using this design enabled delivery of the chemical actives in the dentifrice to the whole mouth, without the mechanical plaque removal from the toothbrush on the buccal surfaces. As a result, there were 24 hours of undisturbed plaque build up on these surfaces which enables a better demonstration of any chemical plaque inhibition effected by either treatment product.

The effectiveness of the SnF_2/SHMP dentifrice against plaque formation was consistent with studies published by White and others relative to both products that would be considered negative controls as well as dentifrices containing other actives. In two separate studies White reported a 17.4% and a 24.4% reduction in overnight plaque growth versus a standard 1100 ppm SnF paste (US Crest® Cavity Protection, Procter & Gamble) using DPIA.[27,28] The former study incorporated a 24 hour period of plaque accumulation on the facial surfaces; as in this study, the latter study only incorporated overnight plaque growth. When evaluated against a dentifrice containing the antimicrobial zinc citrate, Bellamy reported 25.3% less overnight plaque formation for a SnF_2/SHMP formulation also using DPIA.[25] In addition, stabilized SnF_2 dentifrice has been shown to reduce plaque vitality[29] and virulence.[30] This performance against plaque has also been shown to translate into a clinical gingival health benefit when compared to both negative controls[21,31] and to a product containing the antimicrobial triclosan in combination with a co-polymer.[32,33] In summary, the cited literature presents a comprehensive body of recent work supporting the clear, clinically meaningful benefit of SnF_2 when formulated in a bio-available way in combination with SHMP.

In contrast, a literature search for formulations containing KNO_3 and a source of fluoride as the only identified active ingredients provides no evidence of antimicrobial/antiplaque efficacy versus other toothpastes. Since the SnF_2/SHMP dentifrice also provides a hypersensitivity benefit in addition to its antiplaque benefit, dental professionals should consider recommending it to their patients who are experiencing hypersensitivity and who have sub-optimal plaque control.

Digital Plaque Image Analysis (DPIA)

DPIA used with crossover designs provides an efficient and objective *in vivo* method for comparative plaque inhibition testing. The ability to perform multiple repeat measures both before and after brushing, on consecutive days, in consecutive weeks, enables a great wealth of data to be collected rapidly. The whole process of disclosing plaque and then capturing a digital image takes approximately 120 seconds. Actual image capture itself can be less than 30 seconds by an experienced operator. All data for a 30 subject trial can easily be collected within a one hour window early in the morning.

Investigating the variability of plaque area coverage, the percent of variance due to between subject variability relative to the total variance was 94.5% at A.M. pre-brush, 90.3% at A.M. post-brush, and 88.9% at the P.M. visit, indicating a majority of the variability was due to differences between subjects. Since each subject used each treatment, the crossover design has greater efficiency to detect treatment differences than a comparable parallel group study using the same sample size, given that each subject was their own control. The repeated plaque measures on three consecutive days used in this study design helped to minimize the effects of outliers, which can increase variability in test designs where only a single datapoint was collected at each timepoint.

Conclusion

This *in vivo* study was conducted to compare the plaque inhibition benefit provided by a NaF/KNO_3 dentifrice (Sensodyne® ProNamel™) to a positive control SnF_2/SHMP dentifrice (blend-a-med® EXPERT GUMS PROTECTION), via a randomized, double-blind clinical study. The results showed there was a statistically significant difference in the magnitude of the plaque inhibition benefits provided by the two products. blend-a-med® EXPERT GUMS PROTECTION toothpaste provided a significantly greater degree of overnight and daytime plaque inhibition than Sensodyne® ProNamel™. Additionally, immediately after brushing, subjects had significantly lower plaque coverage when using blend-a-med® EXPERT GUMS PROTECTION compared to Sensodyne® ProNamel™.

Clinical Significance

Dentifrices containing KNO_3 and a source of fluoride (in this case Sensodyne ProNamel) are primarily intended as home use products for the treatment of hypersensitivity. New clinical data shows this active system to be significantly less effective than a positive control (in this case blend-a-med® EXPERT GUMS PROTECTION) at preventing plaque regrowth both during the day and overnight. This finding provides new clinical data to the dentist to help make more evidenced-based recommendations for the majority of their patients and communities requiring a multi-benefit dentifrice to meet today's oral challenges.

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