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Randomized controlled trial to study plaque inhibition in calcium sodium phosphosilicate dentifrices

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Abstract

Objectives: To evaluate the effect of three calcium sodium phosphosilicate (CSPS)/sodium monofluorophosphate containing dentifrices, compared to positive and negative controls on plaque re-growth in a non-brushing model, after 4 days of twice daily use, as determined by plaque area and Turesky plaque index (TPI).

Methods: This was an exploratory, single-centre, examiner-blind, randomised, controlled, five treatment period, crossover, plaque re-growth study, with supervised use of study products. Twenty-three healthy adult volunteers were randomized to receive experimental 5% CSPS dentifrice; two marketed 5% CSPS dentifrices; active comparator mouthrinse and negative control dentifrice. At the start of each treatment period, zero plaque was established by dental prophylaxis and study products were dispensed as either dentifrice slurries or mouthrinse, twice daily for the next 4 days. No other forms of oral hygiene were permitted. After 96 hours, supra-gingival plaque was determined by plaque area (direct entry, planimetric method) and TPI. Changes from zero plaque were analysed.

Results: For both measures, plaque re-growth at 96 hours was significantly lower following treatment with active comparator mouthrinse and significantly higher following treatment with the experimental 5% CSPS dentifrice, compared to all other treatments. There were no statistically significant differences between the three other treatments, except between the marketed 5% CSPS dentifrices, for overall plaque area.

Conclusions: The comparator mouthwash was significantly more effective at preventing plaque accumulation than the dentifrice slurries. The three marketed dentifrices contained sodium lauryl sulphate and were more effective at reducing plaque re-growth than the experimental dentifrice formulated with a tegobetaine/adinol surfactant system.

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Clinical relevance

The CSPS containing dentifrices tested in this study showed no significant chemical-therapeutic anti-plaque benefits compared to a negative control dentifrice. However, sodium lauryl sulphate-containing dentifrices controlled plaque more effectively than a tegobetaine/adinol-containing CSPS dentifrice suggesting that the impact of surfactant selection on anti-plaque activity of formulations warrants further investigation.

NHS REC Reference: 12/SW/0294

Introduction

Dental plaque is a soft, sticky deposit of bacteria that collects on the teeth and along the gingival margin. Bacterial by-products from dental plaque can affect the health of the gingiva by causing inflammation of the gingival tissue (gingivitis). Whilst gingivitis is reversible, if untreated it can progress to periodontitis in susceptible individuals, which can result in bone loss and ultimately tooth loss [1]. Gingivitis and periodontal disease can develop when dental plaque accumulates above levels compatible with oral health[2-4], management of gingivitis therefore being both a primary prevention strategy for periodontitis and a secondary prevention strategy for recurrent periodontitis. The maintenance of gingival health and the prevention of gingivitis are predominantly determined by the control of dental plaque[5]. The mechanical action of tooth brushing alone is often insufficient for most individuals to achieve adequate plaque control[6-8]; in a recent systematic review it was demonstrated that an average of only 42% of plaque is removed in a single brushing[9]. As tooth-brushing with dentifrice is the most common oral hygiene regime, dentifrices are an obvious choice for the delivery of anti-plaque agents and many have been developed to chemically inhibit plaque deposition or augment its removal[3].

Active ingredients (such as metal salts, triclosan, cetylpyridinium chloride and chlorhexidine) have been incorporated into dentifrices for many years with a view to delivering plaque control and oral health benefits[10]. While some efficacy has been demonstrated for metal salts, a meta-analysis of stannous fluoride demonstrated significant heterogeneity in the findings of clinical studies[11]and most studies have shown zinc salts to be effective only when used in combination with other agents such as triclosan or chlorhexidine[10]. Triclosan has been shown to be effective against plaque and gingivitis in two systematic reviews[12-13]; however, a second systematic review with different inclusion/exclusion criteria failed to demonstrate

the same efficacy[11]. Furthermore, while triclosan is known to be safe for use in toothpaste formulations[14], its use in a wide range of healthcare products have resulted in an accumulation of it and its breakdown products in the environment[15]. Triclosan is not readily decontaminated, and concerns about its long term impact on health and bacterial resistance are now being raised[15]. To date, chlorhexidine is the most effective active ingredient tested. It has been shown to reduce plaque and improve gingival health[16]; however, the side effects of tooth-staining and altered taste sensation have resulted in the continued quest for other ingredients with similar efficacy.

Calcium sodium phosphosilicate (CSPS) (Novamin®; GSK Consumer Healthcare, Brentford, UK) is a particulate bioactive material that upon exposure to the aqueous oral environment undergoes degradation at the tooth surface, releasing calcium and phosphate ions. This reaction is accompanied by a localized rise in pH and results in the formation of a hydroxycarbonate apatite-like material[17-19]. Studies have shown that particles of CSPS and associated silicas within the dentifrice formulation can bind to the dentine surface and within the tubules to physically occlude the dentinal tubules *in vitro* [17,18,20] and *in situ*[21], giving rise to its use as an occlusion agent in desensitizing dentifrices[22].

In addition to its de-sensitizing effects, CSPS has been reported to act as an anti-bacterial agent *in vitro*[23] and, in two clinical studies, to reduce supra-gingival plaque and gingival bleeding compared to a placebo dentifrice[24-25]. It is postulated that the high rate of ionic exchange when bioglasses such as CSPS come into contact with water, the release of large quantities of calcium and the localized increases in pH described above, may affect the dental plaque and be responsible for these effects[24,26]. However, evidence for this is not conclusive and further studies to confirm the mode of action and clinical efficacy of CSPS as an anti-

plaque, anti-gingivitis agent are needed.

A number of plaque indices have been developed to assess the control of supra-gingival dental plaque. These can be objective (such as plaque weight) or subjective (such as plaque area). Subjective measures require a degree of examiner judgement during data collection[27]. The validity and credibility of subjective indices are increased by using more than one index to score plaque or by repeating the same subjective index, then assessing the variability of repeated measurements[27].

The Turesky modification of the Quigley Hein[28] plaque index (TPI[29]) is a subjective index commonly used to assess disclosed plaque. It focuses initially on plaque in contact with the gingival margin and gives an ordinal plaque score. By contrast, the assessment of plaque area by planimetric means, developed by Addy et al[30] as an adaptation of the Shaw and Murray[31] stain index, is based upon the subjective drawing of the outline of the area of disclosed plaque covering the entire scorable surface on a standard tooth chart. Planimetric data have been shown to be accurate[32] and provide an additional level of detail regarding plaque levels and distribution, but determining plaque areas from tooth charts on which they have been hand drawn is time consuming.

The objective of this study was to evaluate the effect of three 5.0% w/w CSPS/sodium-monofluorophosphate (SMFP) containing dentifrices, an active comparator mouthwash and a negative control dentifrice (with no CSPS) on plaque re-growth in a non-brushing model after four days of twice daily use, as measured by plaque area[30] and the TPI. The efficacy data generated by the study was used to evaluate and compare results from a new computer-based, direct data entry, planimetric methodology for recording and calculating plaque area, with the

data derived using the TPI.

Materials and methods

Study design and methodology

This study was an exploratory, single centre, examiner blind, randomized, controlled, five way crossover *in vivo* study to investigate the effect of CSPS-containing dentifrices on plaque re-growth over four days twice-daily treatment in the absence of tooth brushing. Ethical approval for the study was awarded by a UK research ethics committee (NHS Research Ethics Committee Reference 12/SW/0294) and the study was conducted to Good Clinical Practice guidelines[33]. Volunteer recruitment, screening, treatment and clinical assessments were carried out at the study site, a UK Dental School. Potential subjects who had expressed an interest in the study were invited to screening and allocated a unique screening number assigned in ascending numerical order as they gave written informed consent to take part in the study. Eligible subjects were aged 18 years or over, and in the investigator's opinion, based on medical history, in good general health. Volunteers who were pregnant or breast feeding, had known allergies or intolerances to study materials, or who were on (or had been on) antibiotic or antimicrobial treatment within 14 days of the first treatment visit were excluded. Volunteers with diabetes mellitus (Type 1 or 2) or other diseases that could impact study outcomes were also excluded. Following an oral examination, participants were included if they had at least 20 natural, uncrowned teeth with at least 40 facial/buccal and lingual/palatal surfaces gradable for plaque area and TPI. If caries, severe gingivitis or periodontal disease was detected participants were excluded. Similarly subjects with orthodontics bands or oral lesions that could impact the study outcome were not included. Any volunteer with a dental condition requiring immediate treatment or that could worsen as

a result of suspending normal oral hygiene procedures during the five treatment periods was also excluded.

Volunteers who satisfied the inclusion and exclusion criteria were randomized to the order in which they would receive each of the five treatments according to the randomization schedule provided by the sponsor. Randomization numbers were assigned by study staff at the study site in ascending numerical order as subjects were determined to be fully eligible to participate in the study. Following randomization subjects were given sub- and supra-gingival prophylaxis with flossing, followed by disclosure and removal of any residual plaque, to ensure all stain, calculus and plaque had been removed from the teeth. A second clinician confirmed that there was no visible plaque on the participants' teeth. All subjects were given a standard fluoride (washout) dentifrice (UK Colgate Cavity Protection; Colgate-Palmolive Ltd, Guildford, UK; 1000 ppm fluoride) and toothbrush to use twice daily for a minimum of 2 days prior to the start of each treatment period. In addition to using the washout dentifrice, participants were asked to adhere to a number of lifestyle restrictions for the duration of the trial including refraining from professional tooth cleaning or elective dental procedures, the use of dental products (other than those provided), chewing gum and interproximal cleaning devices, and tongue brushing. Study subjects were required to abstain from normal oral hygiene (i.e. twice daily tooth-brushing with washout toothpaste) for the duration of each 4-day treatment period.

There were five treatment periods, each of which took place over five consecutive days (Days 0–4) and followed the same schedule (two visits on Days 0–3 and one on Day 4), with a minimum of 2 days between treatment periods. Each subject evaluated one study treatment per treatment period, the order of testing being determined by the randomization schedule.

On the first visit of a treatment period (Day 0), subjects were given a full oral soft tissue (OST) examination and supra-gingival prophylaxis with flossing; zero visible plaque (plaque area = 0, TPI = 0) was confirmed by a second clinician. Following this, subjects were given the first slurry (1.5 g toothpaste in 10 ml of water) or rinse of their allocated treatment. Treatment was administered twice a day on days 0–3 with a minimum of 5 hours between treatments. Subjects were required to abstain from eating and drinking for at least 30 minutes after each treatment rinse.

On Day 4, subjects visited the study site (96 ± 2 hours from the time of first treatment on Day 0), having refrained from eating, drinking or smoking for at least 4 hours prior to the visit (volunteers were permitted to drink water up to 1 hour before plaque assessments). Subjects were given a full OST examination and supra-gingival plaque re-growth was assessed using plaque area and the TPI. Compliance with all study restrictions was checked at each visit to the study site.

Study treatment and mode of application

Study treatments and treatment preparation/administration are described in Table 1.

Clinical measurements of plaque re-growth

Supra-gingival plaque accumulation was evaluated (following disclosure using Gum Red Cote® disclosing solution; Sunstar Americas, Inc, Chicago, IL) after 4 days treatment using the plaque area index described by Addy et al[30] and the six-site modification of the TPI[29] . For both measures, only natural teeth in each 7-7 dental arch, where 50% of the tooth surface

was gradable (i.e. where restorative materials covered less than 50% of the tooth surface), were scored.

TPI was assessed for distal, body and mesial sites on each of the facial/buccal and lingual/palatal surfaces of each scorable tooth, according to the scoring system shown in Table 2. Plaque area index was determined by drawing the area of disclosed plaque present on the facial/buccal and lingual/palatal surfaces of each scorable tooth onto a standard tooth chart (Figure 1)[30-31]. Previously, plaque area outlines have been drawn on paper tooth charts which are then assessed using a pen driven digitizer to determine the area of plaque coverage. By contrast, in the present study an application (Cplaque app, Clinical Trials Unit, Periodontology, University of Bristol, UK) that allowed the examiner to draw the plaque area outline directly onto a tablet screen was used. Once the image was captured, it was locked as original source data with no possibility of further modification. The area of tooth surface covered by plaque was calculated automatically and expressed as a percentage of scorable area.

Examiner repeatability

Repeatability data were generated during the study for both computer-based planimetric plaque area and TPI from repeat examinations of selected subjects on Day 4. There was a minimum of 10 minutes between repeat assessments and, where possible, another subject was assessed between the repeat assessments.

Statistical analysis

As this was an exploratory study no formal sample size calculation was possible. However, differences that might be able to be detected together with the probability of finding that

these differences were statistically significant at the end of the study were calculated based on the data of He et al[34] regarding the distribution of differences in TPI between treatments.

With a reasonable (conservative) assumption on the covariance structure of the repeated measures ($\rho = 0.3$), an idea of detectable differences in this study was estimated using these published data (SE [differences] = 0.04). It was calculated that 20 subjects would provide moderate power (80%) of detecting a difference in TPI between two treatments of 0.17 with a two sided 5% paired t-test. This does not include any correction for multiplicity. Based on this, a sufficient number of subjects were screened to ensure that up to 25 were randomized and 20 completed the study.

For data analysis, the changes from zero-plaque following prophylaxis at baseline in 96 hour plaque area (mean percentage [%] area of the tooth surface covered by plaque, all surfaces and facial/buccal surfaces only) and TPI were analysed using analysis of variance (ANOVA). The mixed models had treatment and period as fixed effects. Participant was included as a random variable. Two-sided treatment comparison tests were performed at the 5% significance level. Treatment differences are presented with 95% confidence intervals. The assumptions of normality and homogeneity of variance were investigated and were not violated.

Repeatability was assessed using the intra-class correlation coefficient for the plaque area and the kappa statistic for the TPI. Data analysis was conducted using SPSS.

Results

Demographics and tolerance of treatments

Screening began on the 17th Jan 2013 and the clinical phase of the study completed on the 26th April 3013. Twenty three subjects were randomized (19 female and 4 male); all received treatment and formed the Safety and Intention to Treat (ITT) populations. Nineteen were White (82.6%) and four (17.4%) Asian (native of Asia or of Asian descent), none were Hispanic or Latino, with an average age of 38.6 years (range 21–63 years). Twenty one subjects completed the entire study; the remaining two participants completed either three or four of the five treatment periods.

A total of three subjects reported three treatment-emergent adverse events (TEAEs), none were considered to be treatment related or serious and all resolved. Of these, two (dental discomfort and nasopharyngitis) were mild and one (influenza) was severe. The single oral TEAE (dental discomfort) was reported for the experimental 5% CSPS treatment. There were no OST abnormalities or incidents.

Efficacy results

The efficacy results are based on the ITT population. There were no protocol deviations assessed as affecting efficacy and therefore a Per Protocol (PP) analysis was not performed.

Ninety-six hour plaque re-growth, as assessed by mean percentage plaque area, was significantly higher following 4 days treatment with the experimental 5% CSPS dentifrice with tegobetaine/adinol compared to all other treatments, and significantly lower following 4 days treatment with the active comparator mouthwash compared to all other treatments (Table 3 and Fig. 2A). The results were the same irrespective of whether mean percentage plaque area was calculated for all surfaces or just for the facial/buccal surfaces. There were no significant differences in plaque re-growth at 96 hours between the two marketed 5%

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CSPS containing dentifrices and the negative control. There was a very small, but statistically significant, difference between the two marketed 5% CSPS dentifrices, favouring marketed 5% CSPS dentifrice [2], when all surfaces were included in the plaque area calculation (2.82%, p=0.0386).

The findings of analysis of the TPI data (Table 3 and Fig. 2B) were similar to those for plaque area, with 96 hour plaque re-growth being significantly higher following treatment with the experimental 5% CSPS dentifrice containing tegobetaine/adinol, and significantly lower following treatment with the active comparator mouthwash compared to all other treatments. There were no statistically significant differences between the two marketed 5% CSPS containing dentifrices and the negative control.

Examiner repeatability results

Eleven subjects had repeat assessments of plaque area and TPI and contributed to the repeatability analyses. For plaque area the intra-class correlation was 0.974 (95% CI 0.97 to 0.98), calculated for all surfaces, and 0.969 (95% CI 0.96 to 0.98), calculated for the facial/buccal surfaces. For TPI the weighted kappa statistic was 0.94 (95% CI 0.93 to 0.95). These levels of agreement are considered excellent.

Discussion

The accumulation of plaque was first shown to play a causal role in the development of gingivitis in the original plaque re-growth study performed by Löe et al[35]. Plaque may be removed by mechanical means; however, it has been shown that most uninstructed individuals brush ineffectively and as a result only modest amounts of plaque are removed[36]. To improve the plaque control delivered during tooth-brushing, dentifrices are frequently

formulated with chemical ingredients that target the plaque bacteria[37] , with new formations continually being developed.

A small number of previous studies have reported that CSPS has antimicrobial properties *in vitro*[23] and can reduce plaque and improve gingival health, as compared to a control dentifrice, *in vivo*[24-25]. In the present study three dentifrice formulations containing 5% CSPS were tested for efficacy against plaque, as compared to an active comparator mouthwash (Listerine® Cool Mint Antibacterial Mouthwash) and a negative control dentifrice (Crest Decay Prevention). In this non-brushing model, the mouthwash treatment proved the most effective against plaque re-growth and was statistically significantly better than all dentifrices tested. The mouthwash included in this study (Listerine® Cool Mint Antibacterial Mouthwash) was chosen as a comparator as its efficacy has been previously demonstrated in a number of clinical studies, including recently a 4 day plaque re-growth study[38] and a 28 week clinical study[39]. Its efficacy has been further supported by a recent meta-analysis[40] . The efficacy reported in this study was therefore expected.

In the present study, no significant differences in plaque control were observed between any of the 5% w/w CSPS dentifrices and the negative control dentifrice. This finding does not support the anti-plaque activity reported for 5% CSPS dentifrices in two previously published clinical studies where the toothpaste was applied by toothbrushing[24-25]. The experimental 5% w/w CSPS dentifrice was the least plaque inhibitory of all the products tested.

The three CSPS-containing dentifrices differed in abrasivity; however, the main difference of relevance to a non-brushing study was considered to be the presence of tegobetaine/adinol as surfactant in the experimental formulation, compared to SLS in the marketed 5% CSPS

dentifrices. SLS was also present in the negative control dentifrice. SLS is an anionic surfactant primarily included in dentifrice formulations to enhance foaming and cleaning. In a previous *in vitro* study, dentifrice supernatants containing SLS were shown to detach bacteria from the surface of the salivary pellicle[41] and, *in vivo*, SLS-containing mouthwashes have been shown to decrease salivary bacterial counts for up to 7 hours[42]. It is possible, therefore, that SLS contributed a plaque inhibitory effect to both the marketed 5% w/w CSPS dentifrices and the negative control dentifrice in the present study.

The clinical evaluation of new methods and ingredients for plaque control typically begins with short-term screening studies[30] , which may vary in length from a matter of hours to days. Such studies provide an effective *in vivo* screen to assess the potential of novel technologies prior to the more extensive studies required for validation purposes[43] . The methodology employed in this study was considered appropriate to examine the potential chemo-therapeutic effect of CSPS delivered from a fully formulated dentifrice. The crossover design of the study minimised inter-subject variation.

The assessment of plaque area by planimetric means was developed by Addy et al[30] as an adaptation of the Shaw & Murray[31] stain index. Planimetry has been shown to have a high discriminating power[44] and to be recorded accurately with minimal variability between examiners[32] . In the present study a modification was made to the planimetry technique with the introduction of a tablet application that enabled the examiner to draw directly onto the tablet and then have the plaque area calculated. Previously, areas have been recorded by the examiner in the clinic on paper toothcharts, followed by calculation of plaque area using a pen-driven digitizer at a later date[45] , a time consuming process, the new method being able to calculate the plaque area immediately after recording at chairside. As planimetry is

subjective in nature, and a new method of electronically capturing the data was employed, it was interesting to compare the data from the modified method with that from another established measure of supra-gingival plaque accumulation, the TPI, and to assess repeatability of the method. Good agreement in treatment efficacy findings was obtained using both planimetric and TPI methods. Examiner repeatability for plaque area was excellent using the new planimetric method. Whilst the TPI method of recording plaque is simpler, planimetric data have been shown to provide an additional level of detail regarding plaque levels and distribution[32], which can add value in evaluating efficacy of agents, with the CPlaque app dramatically reducing the time taken to capture data by this method.

Conclusions

The aim of this exploratory study was to evaluate the effect of three 5.0% w/w CSPS dentifrices, a comparator mouthwash and a negative control dentifrice on plaque re-growth in a non-brushing model after 4 days of twice daily use. Overall, 4-day plaque re-growth was lowest for the active comparator (Listerine Cool Mint Antibacterial Mouthwash), which was significantly more effective in the inhibition of plaque re-growth than the dentifrice treatments investigated for the plaque measures employed. In this clinical study, SLS-containing dentifrices were shown to be more effective in reducing plaque re-growth than a dentifrice with an alternative tegobetaine/adinol surfactant system. The tablet application used to record and calculate plaque area had the virtue of direct data entry, automatic calculation of percentage plaque area and the ability to re-visit the source data for verification; it provided similar efficacy data in the present study to the TPI, a well-established tool for the assessment of supra-gingival plaque accumulation.

Table 1: Study treatments and mode of administration

Treatment name	Composition	Administration
Experimental 5% CSPS dentifrice	5% CSPS/927 ppm fluoride as SMFP* with tegobetaine/adinol (RDA**~160)	Dentifrices were administered as an aqueous slurry (1.5 g ± 0.1 g dentifrice, dispersed in 10 ml injection quality water using a bench top speed mixer). Slurries were administered within 5 minutes of preparation. Volunteers rinsed with slurry for 1 minute and were not permitted to rinse with water after expectorating.
Marketed 5% CSPS dentifrice [1] (UK Sensodyne® Repair & Protect Whitening; GSK Consumer Healthcare, Weybridge, UK)	5% CSPS/1450 ppm fluoride as SMFP* with SLS*** (RDA~140)	
Marketed 5% CSPS dentifrice [2] (UK Sensodyne® Repair & Protect; GSK Consumer Healthcare, Weybridge, UK)	% CSPS/1450 ppm fluoride as SMFP with SLS (RDA~100)	
Negative control dentifrice (UK Crest® Decay Prevention; Procter & Gamble UK, Weybridge, UK)	1450 ppm fluoride as NaF with SLS	
Active Comparator (Listerine® Cool Mint Antibacterial Mouthwash; Johnson & Johnson Ltd, Wokingham, UK)	Eucalyptol, menthol, methyl salicylate and thymol	Mouthwash (20 ml) was administered undiluted, according to the manufacturer's instructions. Volunteers rinsed for 30 seconds and were not permitted to rinse with water after expectorating.

*SMFP = sodium monofluorophosphate; **RDA= relative dentine abrasivity; ***SLS = sodium lauryl sulphate; NaF = sodium fluoride

Table 2: TPI scoring system

Score	Definition
0	No plaque
1	Slight flecks of plaque at the cervical margin of the tooth
2	Thin continuous band of plaque (1 mm or smaller) at the cervical margin of the tooth
3	Band of plaque wider than 1 mm but covering less that 1/3 of the area
4	Plaque covering at least 1/3 but less than 2/3 of the area
5	Plaque covering 2/3 or more of the crown of the tooth

Table 3 Analysis of mean plaque area (%) and TPI at 96 hours—ITT Population

Treatment comparison	Treatment difference (95% CI) p-value[1]		
	0–96 hour plaque area (all surfaces)	0–96 hour plaque area (facial/buccal surfaces)	0–96 hour TPI (all surfaces)
Experimental 5% CSPS dentifrice vs marketed 5% CSPS dentifrice [1]	4.85 (2.11, 7.59) p=0.0007	5.84 (2.13, 9.55) p=0.0024	0.18 (0.07, 0.28) p=0.0011
Experimental 5% CSPS dentifrice vs marketed 5% CSPS dentifrice [2]	7.66 (4.92, 10.41) p<0.0001	8.96 (5.24, 12.68) p<0.0001	0.27 (0.17, 0.38) p<0.0001
Experimental 5% CSPS dentifrice vs active comparator	15.52 (12.78, 18.26) p<0.0001	20.29 (16.58, 24.01) p<0.0001	0.60 (0.50, 0.71) p<0.0001
Experimental 5% CSPS dentifrice vs negative control	6.42 (3.62, 9.21) p<0.0001	8.48 (4.69, 12.27) p<0.0001	0.23 (0.12, 0.33) p<0.0001
Marketed 5% CSPS dentifrice [1] vs marketed 5% CSPS dentifrice [2]	2.82 (0.15, 5.48) p=0.0386	3.12 (−0.49, 6.73) p=0.0897	0.10 (0.00, 0.20) p=0.0619
Marketed 5% CSPS dentifrice [1] vs active comparator	10.67 (8.01, 13.34) p<0.0001	14.45 (10.85, 18.06) p<0.0001	0.43 (0.32, 0.53) p<0.0001
Marketed 5% CSPS dentifrice [1] vs negative control	1.57 (−1.14, 4.28) p=0.2524	2.64 (−1.03, 6.31) p=0.1564	0.05 (−0.06, 0.15) p=0.3636
Marketed 5% CSPS dentifrice [2] vs active comparator	7.85 (5.19, 10.52) p<0.0001	11.34 (7.72, 14.95) p<0.0001	0.33 (0.23, 0.43) p<0.0001
Marketed 5% CSPS dentifrice [2] vs negative control	−1.25 (−3.95, 1.45) p=0.3607	−0.48 (−4.14, 3.18) p=0.7953	−0.05 (−0.15, 0.05) p=0.3439
Active comparator vs negative control	−9.10 (−11.81, −6.40) p<0.0001	−11.81 (−15.48, −8.15) p<0.0001	−0.38 (−0.48, −0.28) p<0.0001

[1]Mean difference (95% CI) adjusted for other factors in the model
Marketed 5% CSPS dentifrice [1] = Sensodyne Repair and Protect Whitening
Marketed 5% CSPS dentifrice [2] = Sensodyne Repair and Protect
Active comparator = Listerine Cool Mint antibacterial mouth wash
Negative control = Crest Decay Prevention with SLS
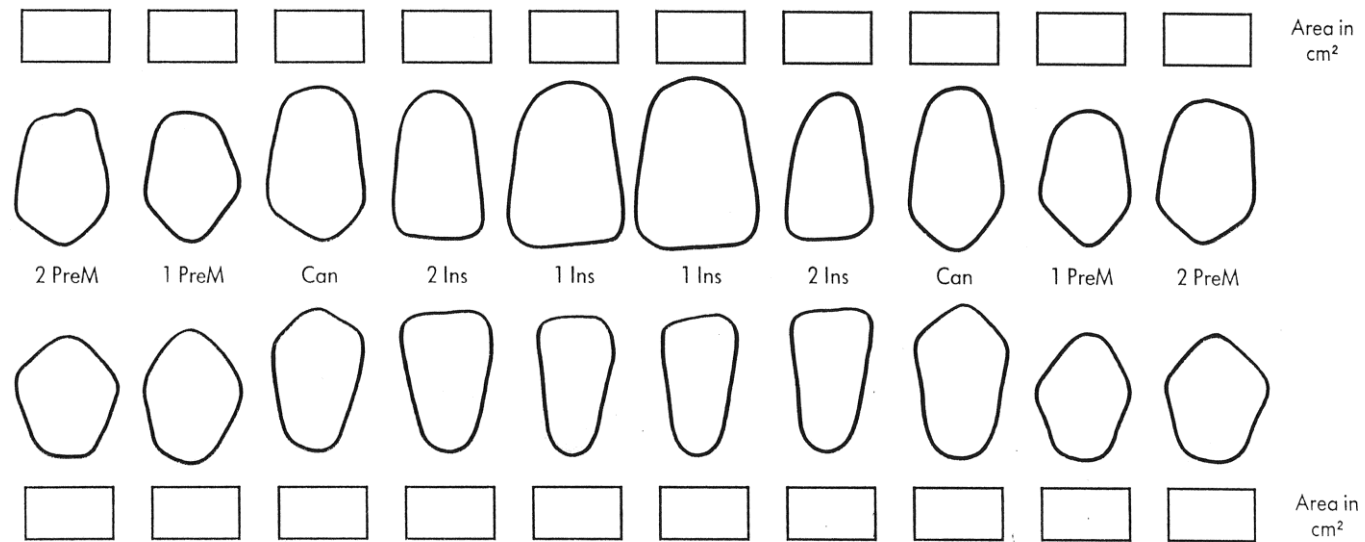Note: A negative value favours the first mentioned treatment.

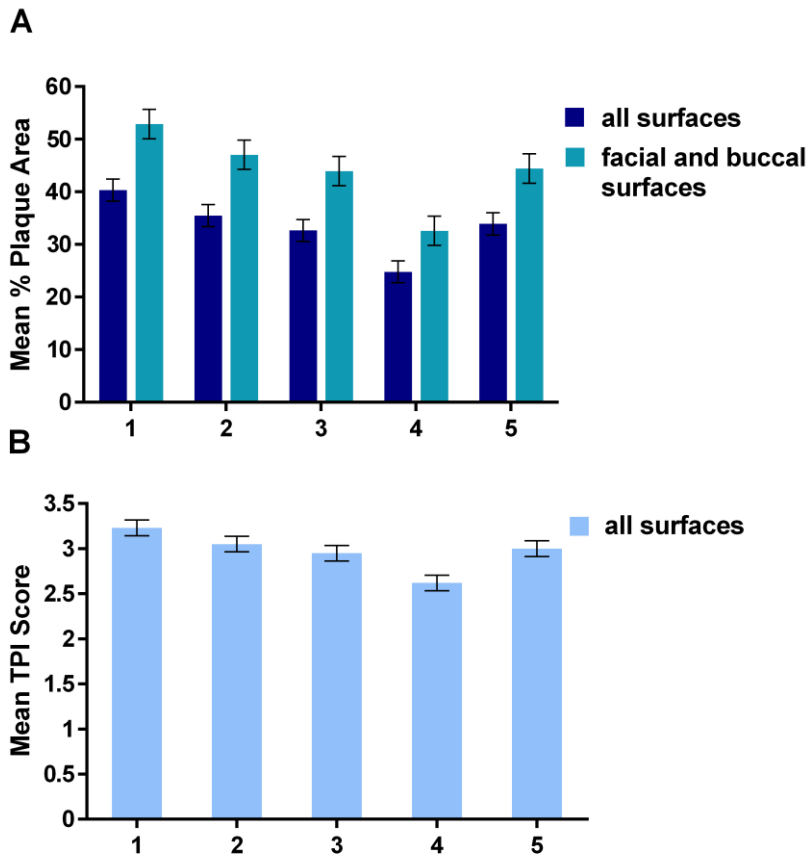*Fig. 1:* Standard Tooth Chart for recording plaque area.

Fig. 2: Plaque re-growth scores

(A) Plaque re-growth as measured as percentage plaque area, graph shows the mean percentage of plaque re-growth area ± SE as measured using the plaque application for all tooth surfaces and for facial/buccal surfaces

(B) Plaque re-growth as measured by TPI, graph shows the mean TPI score ± SE

Treatments are as follows:
[1] Experimental 5% CSPS dentifrice (with tegobetaine/adinol; n=21)
[2] Marketed 5% CSPS dentifrice [1] (with SLS; n=23),
[3] Marketed 5% CSPS dentifrice [2] (with SLS; n=23),
[4] Active comparator (n=23),
[5] Negative control (n=22)

References

1. Kinane D F. & Attström, R. Advances in the pathogenesis of periodontitis. Group B consensus report of the fifth European Workshop in Periodontology. Journal of Clinical Periodontology 2005; 32(Suppl. 6), 130–131.

2. Marsh PD. Microbiological aspects of the chemical control of plaque and gingivitis. *Journal of Dental Research* 1992; **71:** 1431–1438.

3. Davies RM. Dentifrice in the control of plaque/gingivitis and periodontitis. *Periodontology 2000* 2008; **48:** 23–30.

4. Trombelli L, Farina R. A review of factors influencing the incidence and severity of plaque-induced gingivitis. *Minerva Stomatolologica* 2013; **62**: 207–234.

5. Poklepovic T, Worthington HV, Johnson TM, Sambunjak D, Imai P, Clarkson JE et al. Interdental brushing for the prevention and control of periodontal diseases and dental caries in adults. *Cochrane Database of Systematic Reviews* 2013; **12:** CD009857.

6. MacGregor IDM, Rugg-Gunn AJ. A survey of tooth-brushing sequence in children and young adults. *Journal of Periodontal Research* 1978; **14**: 225–230.

7. Rugg-Gunn AJ, MacGregor IDM. A survey of tooth-brushing behaviour in children and young adults. *Journal of Periodontal Research* 1978; **13**: 382–388.

8. De la Rosa MR, Zacarias Guerra J, Johnston DA, Radike AW. Plaque growth and removal with daily tooth-brushing. *Journal of Periodontology* 1979; **50:** 661–664.

9. Chapple IL, Van der Weijden F, Doerfer C, Herrera D, Shapira L, Polak D, Madianos P et al. Primary prevention of periodontitis: managing gingivitis. *Journal of Clinical Periodontolology*. 2015; **42 Suppl 16:**S71–6.

10. Sanz M, Serrano J, Iniesta M, Cruz IS, Herrera D. Antiplaque and anitgingivitis dentifrices. *Monographs in Oral Science* 2013; **23**: 27–44.

11. Gunsolley JC. A meta-analysis of six-month studies of antiplaque and antigingivitis agents. *Journal of the American Dental Association* 2006; **137:** 1649–1657.

12. Hioe KPKJ, van der Weijden GA. The effectiveness of self-performed mechanical plaque control with triclosan containing dentifrices. *International Journal of Dental Hygiene* 2005; **3:** 192–204.

13. Riley P, Lamont T. Triclosan/copolymer containing toothpastes for oral health. *Cochrane Database of Systematic Reviews* 2013; **12:** CD010514

14. DeSalva SJ, Kong BM, Lin YJ. Triclosan: a safety profile. *American Journal of Dentistry*. 1989; **2 Spec**: 185-196

15. Dhillon GS, Kaur S, Pulicharla R, Brar SK, Cledón M, Verma M, Surampalli RY. Triclosan: current status, occurrence, environmental risks and bioaccumulation potential. *International Journal of Environmental Research and Public Health*. 2015; **12**: 5657-5684

16. Yates R, Jenkins S, Newcombe R, Wade W, Moran J, Addy M. A 6-month home usage trial of a 1% chlorhexidine dentifrice (1). Effects on plaque, gingivitis, calculus and toothstaining. *Journal of Clinical Periodontology* 1993; **20:** 130–138.

17. Greenspan DC. CSPS® and tooth sensitivity—an overview. *Journal of Clinical Dentistry* 2010; **21:** 61–65.

18. Earl JS, Leary RK, Muller KH, Langford RM, Greenspan DC. Physical and chemical characterization of dentin surface following treatment with CSPS® technology. *Journal of Clinical Dentistry* 2011a; **22:** 62–67.

19. Earl JS, Topping N, Elle J, Langford RM, Greenspan DC. Physical and chemical characterisation of the surface layers formed on dentin following treatment with a fluoridated toothpaste CSPS®. *Journal of Clinical Dentistry* 2011b; **22:** 68–73.

20. Parkinson CR, Willson RJ. A comparative *in vitro* study investigating the occlusion and mineralization properties of commercial dentifrices in a four-day dentin disc model, *in vitro*. *Journal of Clinical Dentistry* 2011; **22:** 68–73

21. West NX, Macdonald EL, Jones SB, Hughes N, North M, Claydon NCA. Clinical *in situ* study comparing the ability of two new desensitising dentifrice technologies to occlude patent dentine tubules. *Journal of Clinical Dentistry* 2011; **22:** 82–89.

22. Milleman JL, Milleman KR, Clark CE, Mongiello KA, Simonton TC, Proskin HM. NUPRO Sensodyne prophylaxis paste with CSPS for the treatment of dentin hypersensitivity: a 4-week clinical study. *American Journal of Dentistry* 2012; **25:** 262–268.

23. Greenspan DC, Clark A, LaTorre GP. In-vitro antimicrobial properties of a bioactive glass (CSPS®) containing dentifrice. *Journal of Dental Research* 2004; **83:** 1586.

24. Tai BJ, Bian Z, Jiang H, Greenspan DC, Zhong J, Clark AE, Du MQ. Anti-gingivitis effect of a dentifrice containing bioactive glass (CSPS®) particulate. *Journal of Clinical Periodontology* 2006; **33:** 86–91.

25. Aruna Devi M, Vijaylakshmi B, Radha, Pallavi, Kadanakuppe S, Nagashree SR. Antiplaque and antigingivitis effect of a dentifrice containing bioactive glass particulate—a randomized clinical trial. *International Journal of Clinical Dental Science* 2011; **2:** 46–49.

26. Allan I, Newman H, Wilson M. Antibacterial activity of particulate bioglass against supra- and subgingival bacteria. *Biomaterials* 2001; **22:** 1683–1687.

27. Claydon N, Yates R, Labello R, Hall C, Armstrong R, Addy M. A methodology using subjective and objective measures to compare plaque inhibition by toothpastes. *Journal of Clinical Periodontology* 2004; **31:** 1106–1109.

28. Quigley GA, Hein JW. Comparative cleansing efficacy of manual and power brushing. *Journal of the American Dental Association* 1962; **65:** 26–29

29. Turesky S, Gilmore ND, Glickman I. Reduced plaque formation by the chloromethyl analogue of victamine C. *Journal of Periodontology* 1970; **41:** 41–43.

30. Addy M, Willis L, Moran J. The effect of dentifrice and chlorhexidine rinses on plaque accumulation during a 4 day period. *Journal of Clinical Periodontology* 1983; **10:** 89–98.

31. Shaw L, Murray JJ. A new index for measuring extrinsic stains in clinical trials. *Community Dentistry and Oral Epidemiology* 1977; **5:** 116–120.

32. Shaloub A, Addy M. Evaluation of accuracy and variability of scoring-area-based plaque indices. A laboratory model. *Journal of Clinical Periodontology* 2000; **27**: 16–21.

33. ICH. Topic 6 Guidelines for Good Clinical Practice. *Committee for Proprietary Medicinal Products* 1996 17th July; International Conference on Harmonisation. 135 95.

34. He T, Sun L, Li S, Ji N. The anti-plaque efficacy of a novel stannous-containing sodium fluoride dentifrice: a randomized and controlled clinical trial. *American Journal of Dentistry* 2010; **23**, B11–B16.

35. Löe H, Theilade E, Jensen SB. Experimental gingivitis in man. *Journal of Periodontology* 1965; **36:** 177–187.

36. van der Weijden GA, Hioe KP. A systematic review of the effectiveness of self-performed mechanical plaque removal in adults with gingivitis using a manual toothbrush. *Journal of Clinical Periodontology* 2005; **32**: 214–228.

37. Cummins D, Creeth JE. Delivery of antiplaque agents from dentifrices, gels, and mouthwashes. *Journal of Dental Research.* 1992; **71**: 1439–1449.

38. Singh A, Daing A, Dixit J. The effect of herbal, essential oil and chlorhexidine mouthrinse on *de novo* plaque formation. *International Journal of Dental Hygiene* 2013; **11**: 48–52.

39. Goutham BS, Manchanda K, Sarkar AD, Prakash R, Jha K, Mohammed S. Efficacy of two commercially available oral rinses—chlorhexidine and Listerine on plaque and gingivitis—a comparative study. *Journal of International Oral Health* 2013; **5**: 56–61.

40. Van Leeuwen MP, Slot DE, Van der Weijden, GA. The effect of an essential-oils mouthrinse as compared to a vehicle solution on plaque and gingival inflammation: a systematic review and meta-analysis. *International Journal of Dental Hygiene.* 2014; **12:** 160–167.

41. Busscher HJ, White DJ, Atema-Smit J, van der Mei HC. Efficacy and mechanisms of non-antibacterial, chemical plaque control by dentifrices—an in vitro study. *Journal of Dentistry* 2007; **35**: 294–301.

42. Jenkins S, Addy M, Newcombe R. Triclosan and sodium lauryl sulphate mouthwashes (I). Effects on salivary bacterial counts. *Journal of Clinical Periodontology* 1991; **18**: 140–144

43. Lang NP, Brecx MC. Chlorhexidine digluconate—an agent for chemical plaque control and prevention of gingival inflammation. *Journal of Periodontal Research* 1986; **21**: 74–89.

44. Quirynen M, Dekeyser C, van Steenberge D. Discriminatory power of five plaque indices. *Journal of Periodontology* 1991; **62**: 100–105.

45. Claydon N, Addy M. The use of planimetry to record and score the modified Navy index and other area-based plaque indices. A comparative toothbrush study. *Journal of Clinical Periodontology* 1995; **22**: 670–673.