Journal of Periodontology; Copyright 2010 DOI: 10.1902/jop.2010.100056

COMPARISON OF THE CLINICAL EFFICACY OF A DENTIFRICE CONTAINING CALCIUM SODIUM PHOSPHOSILICATE WITH A DENTIFRICE CONTAINING POTASSIUM NITRATE AND A PLACEBO ON DENTINAL HYPERSENSITIVITY: A RANDOMIZED CLINICAL TRIAL

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Background: A considerable number of various agents are apparently effective in the treatment of dentine hypersensitivity (DH). A randomized clinical trial of 6 weeks was designed to compare dentifrice containing calcium sodium phosphosilicate with potassium nitrate and a placebo.

Methods: Total of 110 subjects (58 males and 52 females) were entered into the study. The volunteers selected at baseline, had a history of dentin hypersensitivity due to gingival recession or cervical erosion. Patients were required to have at least two teeth with a Visual Analog Scale score (VAS) of at least 4 to be included into the study. After recording of sensitivity scores for controlled air stimulus (evaporative stimulus) and cold water (thermal stimulus) at baseline, subjects were given respective toothpaste randomly and sensitivty score again checked at 2 weeks and 6 weeks follow up.

Results: All the three groups showed reduction in sensitivity score at 2 weeks and 6 weeks for both the measures of sensitivity. But Calcium sodium phosphosilicate group was found to be significantly better in reducing VAS score compared to Potassium nitrate and placebo group at any point of time for both the measures of sensitivity.

Conclusions: Under the conditions of a clinical trial, subject group using Calcium sodium phosphosilicate toothpaste showed comparable reduction in the symptoms of DH.

Key words: Desensitizing agents, Biomaterial(s), Pain, Clinical trial(s).

Dentinal hypersensitivity (DH) has been defined as a short, sharp pain arising from exposed dentin as a result of various stimuli such as heat, cold, chemical or osmotic, and that cannot be ascribed to any other pathology.[1] DH is a painful clinical condition that affects 8% to 35% of the population.[2] The incidence of DH reportedly peaks during the third and fourth decade of life.[3]

There are many and varied etiological and predisposing factors related to dentin hypersensitivity. Removal of enamel, as a result of attrition, abrasion and erosion, or denudation of the root surface by loss of the overlying cementum and periodontal tissues is commonly cited.[4] As exposure of the root area may be multifactorial, chronic trauma from tooth brushing, tooth flexure due to abnormal occlusal loading forces, parafunctional habits, acute and chronic inflammatory gingival and periodontal diseases, acute trauma, periodontal surgery, and acidic

DOI: 10.1902/jop.2010.100056

dietary components, are commonly cited as major causes of cervical lesions and dentin hypersensitivity.[5]

Pain, due to DH, can be explained by the widely accepted "Hydrodynamic theory" proposed by Brannstrom and Astrom in 1964. According to this theory, the presence of lesions involving enamel and/or cementum loss in cervical area and the consequent opening of dentinal tubules to the oral environment, under certain stimuli, allows the movement of dentinal fluid inside the tubules, indirectly stimulating the extremities of the pulp nerves, causing the pain sensation.[6] It is also found that open dentinal tubules serve as pathways for diffusive transport of bacterial elements in the oral cavity to the pulp, which may cause a localized inflammatory pulpal response.[7] Histologically, under transmission electron microscope, sensitive tooth shows widened dentinal tubules, two times larger than tubules of normal dentin and in greater number per area in comparision with tooth without DH.[8] Though macroscopically the dentin of hypersensitive tooth does not differ from that of a normal tooth, the symptoms would suggest minor inflammation of pulp.[9]

Various treatment strategies have been implicated in the treatment of DH including lasers, ions and salts, fluoride iontophoresis, dentin sealers, periodontal soft tissue grafting and homeopathic medications.[10] But it is still not possible to reach a consensus about such techniques that represent the gold standard in the treatment of DH.

Nowadays, two main approaches are used in the treatment and prevention of DH: Tubular occlusion and blockage of nerve activity. In tubular occlusion approach, tooth is treated with a physical or chemical agent that forms a layer which mechanically occludes the dentinal tubules and prevents pulpal fluid flow thereby leading to reduction in DH.[11,12] Lasers, dentin sealers, periodontal soft tissue grafting and others work on the same principle. In blockage of nerve activity, potassium ion tends to concentrate in the interior of the dentinal tubules, causing a depolarization of the cellular membrane of the nerve terminal and a refractory period with decreased sensitivity.[13] Various clinical trials[14-17] have been performed to test the efficacy of such agents to reduce DH and most of these proved efficient but some failed to show such beneficial effects. Though both the ways are effective in reducing DH, DH usually reappears due to toothbrush abrasion, the presence of acid challenges in the mouth, and/or degradation of the coating material. There is a need to develop new desensitizing agents which permit the relief of the symptoms of DH from the beginning of their appearance.

Calcium sodium phosphosilicate, a bioactive glass, reacts when exposed to aqueous media and provides calcium and phosphate ions that form a hydroxy-carbonate apatite (HCA), a mineral that is chemically similar to the mineral in enamel and dentin.[18] The chemical reaction intiated by Calcium sodium phosphosilicate to promote the formation of an HCA layer for the treatment of DH may also be useful in treating demineralized tooth structure and/or preventing further deminralization.

The purpose of this study was to investigate the effect of a new toothpaste containing 5% Calcium sodium phosphosilicate on dentine hypersensitivity over a period of 6 weeks. The efficacy of the new toothpaste was compared with that of positive control toothpaste containing 5% potassium nitrate and a placebo.

 DOI: 10.1902/jop.2010.100056

MATERIALS AND METHODS

The study was a single-center, longitudinal, triple blinded (Investigators, subjects and statistician) randomized parallel arm design. The study duration was 6 weeks, in which sensitivity scores were measured at baseline, 2 weeks and 6 weeks. The research protocol was initially submitted to the Ethical Committee of the Government Dental College and Research Institute, Bangalore. After ethical approval, subjects were selected from out patient section of department of periodontics, Government Dental College and Research Institute, Bangalore. Duration of the study was from May 2009 to July 2009.

Three toothpastes taken into study were:

1) A commercially available nonaqueous toothpaste containing 5% Calcium sodium phosphosilicate with fused silica.†
2) Commercially available toothpaste containing 5% potassium nitrate as positive control.‡
3) Toothpaste containing same formulation as Calcium sodium phosphosilicate toothpaste except active ingredient (Calcium sodium phosphosilicate) as negative control.§

Investigators (ARP & AS) as well as patients were blinded to toothpaste content. The toothpastes were dispensed in the tubes namely A, B and C, the contents of which were disclosed to the investigators only after the completion of statistical analysis.

Sample size calculation were based on detecting a difference of 30% reduction in Visual Analog Scale score (VAS)[19] between test and control group using a two tailed significance level of 5% with a 90% power. 120 subjects were included in the study and categorized into three groups each containing 40 subjects. A total of 110 subjects (58 males and 52 females) were finally considered as 10 subjects failed to follow up or discontinued the treatment. Selected subject randomly assigned to one of three treatment groups by lottery method. Number of subjects in the groups was 36 in Calcium sodium phosphosilicate group, 37 in potassium nitrate group, and 37 in placebo group. Subjects participated in the study were of 20-60 years of age. The mean age of subjects was not statistically different between groups and ranged from 41.9 years for calcium sodium phosphosilicate group, 36.9 years for positive control group and 39.4 years for negative control. Subjects who were in good general health, could fulfill the scheduled appointment, and gave written informed consent to participate were recruited into 6 weeks trial. A flow chart of the study is provided in Fig. 1.

Inclusion/exclusion criteria

The volunteers selected at baseline, had a history of dentin hypersensitivity due to gingival recession or cervical erosion. Patients were required to have at least two teeth with a VAS score of at least 4 to be included in the study. Teeth included in the study had small or no occlusal restoration. Teeth with caries, defective restorations, and subjects with orthodontic appliances or bridge work that would interfere with evaluation were excluded. In addition subjects were also excluded if they were allergic to ingredients used in the study or exhibited any gross oral pathology, eating disorders, chronic disease or any disease requiring repeated or regular analgesia, antinflammatory drugs or antihistamins.

Sensitivity assessment

To assess tooth sensitivity, a controlled air stimulus (evaporative stimulus) and cold water (thermal stimulus) were used. Sensitivity was measured using a 10 centimeters VAS score, with

score '0' being pain free response and score '10' being excruciating pain/discomfort.Scoring of tooth sensitivity was done; first by using controlled air presure, from a standard dental syringe at 40-65 psi at ambient temperature, directed perpendicular and at a distance of 1-3 mm from exposed dentin surface while adjacent teeth were protected with gloved fingers to prevent false positive results. This was followed by scoring of tooth sensitivity using 10µl of iced cold water which was applied to exposed dentin surface while neighboring teeth were isolated during testing using the operator's fingers and cotton rolls. A period of at least 5 minutes was allowed between the two stimuli on each tooth. Types of teeth included in the study are shown in table 1.

After recording of sensitivity scores at baseline, subjects were given respective toothpastes randomly and advised to use the toothpaste with soft bristle tooth brush** twice a day.Subjects were also directed to refrain from any other dentrifrice or mouthrinse during the trial but allowed to continue normal oral hygiene practice.

Statistical Analysis

Mean VAS scores and standard errors of the mean were calculated from raw VAS score from all the subjects in a treatment group. Mean VAS scores were compared among groups at different time points (baseline, 2 weeks, 6 weeks) and between groups at each time point using one way ANOVA. Post-hoc pairwise multiple comparisons done using the Holm-Sidak method ($P < 0.05$), when significance was detected. Data were statistically analyzed using a software program.[††]

RESULTS

Mean VAS scores for air stimulus for.Calcium sodium phosphosilicate, potassium nitrate group and placebo group at baseline, 2 weeks and 6 weeks are shown in table 2.

VAS scores for air stimulus of all 3 groups were not statistically different from each other at baseline. Though all the three groups showed reduction in sensitivity score at 2 weeks and 6 weeks, Calcium sodium phosphosilicate group was found to be significantly better in reducing VAS score compared to potassium nitrate at 2 weeks and 6 weeks and placebo group at 6 weeks.

Mean VAS score for water stimulus for Calcium sodium phosphosilicate group, potassium nitrate group and placebo group at baseline, 2 weeks and 6 weeks are shown in table 3.

VAS score for water stimulus was not statistically different between the groups at baseline. There was greater reduction in mean sensitivity score for Calcium sodium phosphosilicate group compared to placebo and potassium nitrate group at 2 weeks and 6 weeks. Calcium sodium phosphosilicate group showed significant reduction at 6 weeks compared to other groups.

Percentage change in mean sensitivity score for all three groups at all time points for both measures are shown in table 4.

Percentage change in sensitivity score for Calcium sodium phosphosilicate group was 72.0% and 68.7% for air and water stimulus respectively at 6 weeks. This change in score was statistically significant compared to other groups. Negative value in all percentage change in sensitivity scores showed that there was reduction in sensitivity score from baseline to 2 weeks and 6 weeks.

Inter group comparison of percentage change in air and water sensitivity scores at all time points are shown in table 5 and table 6 respectively. Calcium sodium phosphosilicate group showed statistically significant difference in percentage change for both air and water sensitivity

to both potassium nitrate and placebo group at all time points but percentage change difference was greater for air stimulus at all time points.

DISCUSSION

Study compared Calcium sodium phosphosilicate paste with potassium nitrate and placebo. The trial was designed and reported in accordance with good clinical practice. The results of the present study demonstrated reduction in symptoms for all treatment groups from baseline to 2 weeks and 6 weeks for both the measures of sensitivity. There was a remarkable pattern toward reduction of DH with time for all the variables during the 6 weeks of active phase of the study independent of treatment groups. Calcium sodium phosphosilicate group showed higher degree of effectiveness at reducing DH than commercially avaliable potassium nitrate and a placebo for both sensitivity measures. Percentage reduction in sensitivity score was greater for air stimulus compared to water stimulus from baseline to 2 weeks and to 6 weeks except potassium nitrate group which showed greater percentage reduction for water stimulus compared to air stimulus with meager difference.

Researching the literature, one can find well designed clinical trials providing some evidence for the formulation containing all potential actives used in the study. Calcium sodium phosphosilicate, originally developed as a bone regenerative material, has been shown to be effective at physically occluding dentinal tubules through the development of a hydroxyapatite-like mineral layer.[18,20] Clinical evaluations of Calcium sodium phosphosilicate for the treatment of dentin hypersensitivity have shown statistically significant and clinically positive results.[21] The significant clinical treatment of hypersensitivity through the formation of crystalline apatite lead researchers to hypothesize that Calcium sodium phosphosilicate could be useful in remineralization and the prevention of demineralization of tooth structures, especially dentin. Moreover it has demonstrated strong anti-microbial behavior in vitro[22] which reduces symptoms of DH by preventing bacteria to induce pulpal response.

5% Potassium nitrate toothpaste was used as a positive control in our study as it has proven to be clinically efficient in the treatment of DH. Some studies have reported the effectiveness of 5% potassium nitrate gel as an active ingredient.[23-25] In our study potassium nitrate group showed significant percentage reduction in sensitivity scores for both the measures but reduction compared to Calcium sodium phosphosilicate group was less though reduction was equal or even better than placebo group. Difference in sensitivity reduction between potassium nitrate and Calcium sodium phosphosilicate can be explained by their mechanism of action. Potassium nitrate blocks intradental nerves by raising extracellular potassium ion. Evidence from experiments on nerve excitability indicates that potassium-induced effects are transient and reversible.[26] On the other hand Calcium sodium phosphosilicate directly blocks dentinal tubules and has better densensitizing effects than 5% potassium nitrate.

Though suitable duration for most of the previous clinical trials for evaluating the effectiveness of desensitizing toothpaste was considered 8 weeks, but some studies have stated that the optimum time course for different agents differ based on their action. Study duration of our study was 6 weeks with sensitivity measurement at baseline, 2 weeks and 6 weeks, based on previous clinical trial conducted for assessment of Calcium sodium phosphosilicate as desensitizing agent.[27] The duration of a trial may vary, depending on whether it is evaluating short-term or long- term effects of the product. The trial duration should be sufficient to allow

DOI: 10.1902/jop.2010.100056

expression of the maximum efficacy of the 'active' agent, while minimizing the magnitude of any 'placebo effects'.

Dentin sensitivity may be different for different stimuli[28] and it is recommended that at least 2 hydrodyoamic stimuli should be used in the clinical trial. We have used evaporative air stimulus and cold water stimuli in our study as these are both physiologic and controllable. Evaporative air stimulus was used first for sensitivity assessment followed by water stimuli in our study as the least severe stimulus should be applied first to prevent interpretation error. The interval of minimum 5 minutes was allowed between two stimuli to minimize interactions between stimuli.

In the present study, placebo group has also reported greater reduction in mean sensitivity score over the time. One probable factor must be the environment under which this study was performed. The patients were knowingly participating in a clinical trial to determine the efficacy of desensitizing products. Despite randomisation and stratification effects to homogenize sample characteristics, enrolled volunteers often try to please the investigators. Furthermore, positive emotional and motivational behavioral responses can activate the body's central pain inhibiting system, which can modulate painful stimuli from the periphery through the release of endorphins centrally.[29] Many investigators have described patients obtaining relief without any treatment because of placebo effect which varies from 20% to 60% in dentine hypersensitivity clinical trials.[30,31] Yet another possible phenomenon, which could cause such change, is the Hawthorne effect.The Hawthorne effect is a response to non-intervention procedures, such as improved oral hygiene or frequent examinations. Improved oral hygiene would decrease the pain as this may allow greater saliva access to patent dentinal tubules which in turn may enhance tubules obliteration through the deposition of salivary calcium, phosphate and proteins. The influence of the Hawthorne effect is difficult to calculate. No attempt was made to give oral hygiene instructions and the number of visits was kept to minimum.

With our present state of knowledge and technical skills, evaluation of compounds for the treatment of dentine hypersensitivity is based on clinical trials.[32] Till date no standard technology have been developed to test products designed for treatment of DH. To prevent the placebo effect which can mask any treatment effects, clinical trial designs for dentine hypersensitivity should be modified.

CONCLUSIONS

After the 6 weeks clinical evaluation, all treatment showed lower VAS sensitivity values compared with baseline, independently of their different modes of action. It can be concluded that under the conditions of a clinical trial, subject group using Calcium sodium phosphosilicate toothpaste showed comparable tremendous reduction in the symptoms of DH.

As Calcium sodium phosphosilicate showed greater reduction in sensitivity compared to highly efficacious potassium nitrate, it may provide a new direction for the treatment of DH. For the future prospects longer term studies with scanning electron microscope evaluation should be undertaken to ascertain the efficacy of Calcium sodium phosphosilicate.

ACKNOWLEDGMENTS

The authors express their gratitude to Mr. Pacheiyappan. R, Manager-Sales and Marketing, Group Pharmaceuticals Ltd. Bangalore office, India, and Group Pharmaceuticals, India for their support in providing SHY-NM (Calcium

sodium phosphosilicate), SHY (Potassium nitrate) and placebo pastes. The authors also express their thanks to Mr. Jagannatha P S, a Statistician, Rajajinagar, Bangalore, for carrying all required statistics. The authors report no conflicts of interest related to this study.

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Submitted January 30, 2010; accepted for publication March 16, 2010

Figure 1. STUDY FLOW CHART

Table 1: Types of teeth included in the study.

Type of teeth	Percentage of teeth selected by the investigators
Upper Central Incisors	**5.4%**
Upper Lateral Incisors	**6.2%**
Upper Canine	**13.1%**
Lower Central Incisors	**4.6%**
Lower Lateral Incisors	**3.4%**
Lower Canine	**12.4%**
Upper Premolars	**18.4%**
Lower Premolars	**14.3%**
Upper Molars	**11.8%**
Lower Molars	**10.4%**

 DOI: 10.1902/jop.2010.100056

Table 2: Sensitivity scores to air stimulus for all treatment groups at all time points.

Mean sensitivity score ± standard error			
Toothpaste groups	**Baseline**	**2 weeks**	**6 weeks**
Potassium nitrate	6.57±0.25	5.66±0.22	3.66±0.18
Calcium sodium phosphosilicate	7.17±0.25	4.71±0.23	1.97±0.14
Placebo	6.40±0.18	5.20±0.18	3.83±0.12

Table 3: Sensitivity scores to water stimulus for all treatment groups at all time points.

Mean sensitivity score ± standard error			
Toothpaste groups	**Baseline**	**2 weeks**	**6 weeks**
Potassium nitrate	7.66±0.25	6.51±0.25	3.94±0.21
Calcium sodium phosphosilicate	8.43±0.21	6.37±0.17	2.57±0.14
Placebo	6.91±0.21	6.00±0.18	4.31±0.18

Table 4: Anova Test: Percentage change in mean sensitivity score for all three groups at all time points for both measures.

			Percentage change in mean sensitivity score		
			Baseline to 2 weeks		**Baseline to 6**
weeks					
Air stimulus					
	Potassium nitrate		**−12.6%**		**−42.7%**
	Calcium sodium	**−34.6%**		**−72.0%**	
	phosphosilicate				
	Placebo		**−18.3%**		**−39.2%**
Water stimulus					
	Potassium nitrate		**−14.2%**		**−47.4%**
	Calcuim sodium	**−24.0%**		**−68.7%**	
	phosphosilicate				
	Placebo		**−12.7%**		**−36.8%**

Table 5: Holm-Sidak method for inter group comparison of percentage change in air sensitivity score.

Difference in percentage change (Mean ± Standard error)		
Groups compared	**Baseline to 2 weeks**	**Baseline to 6 weeks**
Potassium nitrate vs Calcium		
Sodium		
phosphosilicate	22.0±3.1*	29.3±3.6*
Calcium sodium		
phosphosilicate vs Placebo	−16.3±3.1*	−32.7±3.6*
Potassium nitrate vs Placebo	5.7±3.1	−3.4±3.6

*Statistically significant at p-value<0.05

Table 6: Holm-Sidak method for inter group comparison of percentage change in Water sensitivity score.

Difference in percentage change (Mean ± Standard error)		
Groups compared	**Baseline to 2 weeks**	**Baseline to 6 weeks**
Potassium nitrate vs Calcium		
Sodium		
phosphosilicate	9.8±2.8*	21.3±3.6*
Calcium sodium		
phosphosilicate vs Placebo	−11.2±2.8*	−31.9±3.6*
Potassium nitrate vs Placebo	−1.4±2.8	−10.6±3.6

*Statistically significant at p-value<0.05

DOI: 10.1902/jop.2010.100056

† SHY-NM, GROUP PHARMACEUTICALS LTD., Mumbai, India.

‡ SHY, GROUP PHARMACEUTICALS LTD., Mumbai, India.

§ GROUP PHARMACEUTICALS LTD., Mumbai, India.

** Colgate sensitive, Colgate-Palmolive (India) Ltd., India.

††SPSS statistical package (Version 17.5), SPSS, Chicago, IL.