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well-documented negatives, *i.e.*, tooth staining and poor taste.[36] Both strontium and stannous are believed to work by precipitating insoluble metal compounds on dentin surfaces to occlude, or partially occlude, open dentin tubules.[36]

In a review published in 2007, Markowitz and Pashley suggested that new technologies should target the underlying causes, as well as the symptoms of dentin hypersensitivity. Specifically, they proposed that increasing the surface mineral density of exposed dentin, while plugging and sealing open tubules with a calcium-rich dentin-like material, could increase its resistance to wear and erosive attack by blocking diffusion through open tubules into the dentin sub-surface. Further, they suggested that the ideal dentin hypersensitivity treatment would accelerate and enhance nature's own desensitizing process of occlusion of open dentin tubules.[47] This has now been accomplished with the development and validation of a novel technology based upon 8.0% arginine and calcium carbonate.

The Development and Validation of a Novel Technology, Based Upon 8.0% Arginine and Calcium Carbonate, for Relief of Dentin Hypersensitivity Associated with Professional Prophylaxis Procedures

Several decades of research into the mechanisms underpinning the natural process of dentin occlusion and the role of saliva in transporting calcium and phosphate into dentin tubules, by Kleinberg and coworkers, have resulted in the development and validation of a new in-office treatment for dentin hypersensitivity. This treatment, a desensitizing prophylaxis paste (ProClude®, Ortek Therapeutics, Roslyn Heights, NY, USA) based upon 8.0% arginine, an amino acid naturally present in saliva, bicarbonate, a pH buffer, and calcium carbonate, a source of calcium, has been marketed in the United States for the management of dentin hypersensitivity during professionally administered prophylaxis procedures.[48] Clinical studies have shown that this treatment is effective in providing instant sensitivity relief, when burnished onto sensitive teeth following professional dental prophylaxis, and that sensitivity relief lasts for at least 28 days following a single in-office treatment. The authors reported a 71.7% reduction in sensitivity measured by air blast, and an 84.2% reduction by the "scratch" test immediately following product application. In addition, *in vitro* studies have demonstrated that this product works by effectively occluding open dentin tubules.[49]

The Colgate-Palmolive Company acquired this technology in 2007, re-launched the product as an in-office desensitizing polishing paste in 2009 under the brand name Colgate® Sensitive Pro-Relief™ (Colgate-Palmolive Company, New York, NY, USA), and conducted additional clinical studies. A Special Issue publication of the *American Journal of Dentistry* summarizes the data from two clinical studies. In both studies, the arginine-calcium carbonate desensitizing paste was compared to a pumice-based prophylaxis paste as a control.[50,51] The dental professional uses the arginine-calcium carbonate desensitizing paste by applying the product to the teeth exhibiting sensitivity using a prophylaxis cup on a prophy angle. The product is applied using low speed and a moderate amount of pressure, in essence burnishing the material into the exposed tubules.[52]

In one study, the test products were applied, following scaling, as the final polishing step of the dental prophylaxis. Immediately following product application and four weeks later, subjects receiving the arginine-calcium carbonate treatment exhibited statistically significant improvements from baseline with respect to baseline-adjusted mean air blast (44.1% and 45.9%, respectively) and mean tactile hypersensitivity scores (156.2% and 170.3%, respectively). At the same time points, subjects receiving the control treatment exhibited statistically significant improvements from baseline with respect to baseline-adjusted mean air blast (15.1% and 8.9%, respectively) and mean tactile hypersensitivity scores (43.1% and 8.3%, respectively). Importantly, immediately following application and four weeks later, the arginine-calcium carbonate treatment provided statistically significant reductions in dentin hypersensitivity with respect to baseline-adjusted mean air blast (34.1% and 40.6%, respectively) and mean tactile hypersensitivity scores (79.0% and 149.6%, respectively) compared to the control treatment.[51]

In the other study, the products were applied prior to a professional dental cleaning procedure, and sensitivity measurements were made immediately thereafter. Subjects who received the arginine-calcium carbonate treatment exhibited statistically significant improvements from baseline with respect to baseline-adjusted mean tactile (132.1%) and air blast hypersensitivity scores (48.6%). Subjects who received the control treatment exhibited a statistically significant hypersensitivity improvement from baseline with respect to baseline-adjusted mean air blast hypersensitivity scores (13.9%). The hypersensitivity improvement from baseline for the control treatment, for mean tactile hypersensitivity scores (21.7%), was not statistically significant. Importantly, statistically significant differences were indicated between the arginine-calcium carbonate treatment and the control treatment with respect to baseline-adjusted mean tactile (110.0%) and air blast hypersensitivity scores (41.9%).[52]

Several state-of-the art imaging methods have been used to elucidate the mechanism of action of the arginine-calcium carbonate technology *in vitro*. Confocal laser scanning microscopy (CLSM) studies have shown that the arginine-calcium carbonate desensitizing paste is highly effective in occluding open dentin tubules. No dentin occlusion was observed with a paste containing calcium carbonate alone, or with a paste containing arginine with an alternative calcium abrasive, dicalcium phosphate dihydrate (Dical). Further, CLSM studies have shown that the occlusion achieved is resistant to acid challenge.[53]

High resolution scanning electron microscopy (SEM) images have verified that the arginine-calcium carbonate desensitizing paste provides complete occlusion of open dentin tubules, and freeze-fracture images have demonstrated that the plug reaches a depth of two microns into the tubule. Energy dispersive x-ray (EDX), used to chemically map the occluded surfaces, has shown that the material on the dentin surface and occluded within the dentin tubules primarily consists of calcium and phosphate. Electron spectroscopy for chemical analysis (ESCA) has provided quantitative data which have verified these observations and, in addition, have identified the presence of carbonate.[53]

Atomic force microscopy (AFM) has further substantiated the blocking mechanism. Untreated specimens showed the helical fine structure of the inter-tubular dentin, as well as tubules that were completely open. Specimens treated with the desensitizing prophylaxis paste showed that the helical structure on the dentin surface was no longer visible as a result of surface coating, and the tubules were sealed shut.[53]

Together, these clinical and mechanism of action studies have clearly demonstrated that the arginine-calcium carbonate desensitizing paste reduces dentin hypersensitivity by sealing and plugging dentin tubules.[36,50-53]

The Development and Validation of a Novel Dentifrice Containing 8.0% Arginine, Calcium Carbonate, and 1450 ppm Fluoride for Everyday Relief of Dentin Hypersensitivity

The Colgate-Palmolive Company has further developed and evaluated this innovative technology as a daily-use dentin hypersensitivity dentifrice with superior efficacy. In addition to 8.0% arginine and calcium carbonate, the dentifrice contains 1450 ppm fluoride, as sodium monofluorophosphate (MFP), for cavity protection.[36] Two eight-week dentin hypersensitivity clinical studies were conducted comparing this novel dentifrice to a benchmark commercial desensitizing toothpaste containing 2% potassium ion as the active ingredient.[54,55] A Special Issue publication of *The Journal of Clinical Dentistry* summarized the data from these clinical studies, together with the *in vitro* data from the mechanism of action studies.[36,53-55]

Both studies demonstrated that the dentifrice containing 8.0% arginine, calcium carbonate, and 1450 ppm fluoride provides superior sensitivity relief compared to a market-leading dentifrice containing 2% potassium ion, as 3.75% potassium chloride, and 1450 ppm fluoride, as sodium fluoride (NaF). In an eight-week study in Canada, the 8.0% arginine toothpaste provided statistically significant reductions in dentin hypersensitivity in response to tactile (16.2%, 22.4%, and 21.4%) and air blast (16.2%, 29.2%, and 63.4%) measures compared to the benchmark commercial desensitizing toothpaste at two, four, and eight weeks, respectively.[54] Likewise, in an eight-week study in Italy, the 8.0% arginine toothpaste provided statistically significant reductions in dentin hypersensitivity in response to tactile (37.0%, 30.0%, and 12.2%) and air blast (23.9%, 32.0%, and 29.3%) measures compared to the benchmark commercial desensitizing toothpaste at two, four, and eight weeks, respectively.[55]

A third study has now been conducted to further validate the superior dentin hypersensitivity relief obtained from regular twice-daily brushing with this new toothpaste containing 8.0% arginine, calcium carbonate, and 1450 ppm fluoride. In this new study, the 8.0% arginine toothpaste was compared to a benchmark commercial desensitizing toothpaste containing 2% potassium ion, as 5% potassium nitrate. The fourth paper in this Special Issue, by Docimo, *et al.*, reports the results of this study.[56]

This new clinical study confirms that regular brushing with the toothpaste containing 8.0% arginine, calcium carbonate, and 1450 ppm fluoride, as MFP, provides a significant reduction in dentin hypersensitivity. The study also verifies that the new 8.0% arginine toothpaste provides significantly greater reductions ($p < 0.05$) in dentin hypersensitivity in response to tactile (38.9%, 28.8%, and 11.6%) and air blast (16.8%, 26.4%, and 33.8%) stimuli compared to the benchmark commercial desensitizing toothpaste containing 2% potassium ion, as 5% potassium nitrate, and 1450 ppm fluoride, as NaF, in a silica base, after two weeks, four weeks, and eight weeks of product use, respectively.[56] The results of this study are consistent with the results of the two previously published studies, and demonstrate the superiority of the 8.0% arginine toothpaste in reducing dentin hypersensitivity versus potassium-based toothpaste technologies when used twice daily for two to eight weeks.[54,55]

Validation of a Novel Dentifrice Containing 8.0% Arginine, Calcium Carbonate, and 1450 ppm Fluoride in Delivering Instant Dentin Hypersensitivity Relief After a Single Direct Topical Application of the Product

Before publication of this Special Issue, twice-daily brushing was the only clinically proven method of application reported for desensitizing toothpastes. This Special Issue presents the first published evidence of significant sensitivity relief from the direct topical application of a desensitizing toothpaste. The first three papers in this Special Issue report the results of three important new clinical studies which clearly demonstrate that a single direct application of a novel dentifrice containing 8.0% arginine, calcium carbonate, and 1450 ppm fluoride to sensitive teeth provides statistically significant instant relief of dentin hypersensitivity.[57-59] In addition, two of these studies demonstrate that control products, one containing 2% potassium ion and 1450 ppm fluoride, and the other containing 1450 ppm fluoride alone, do not provide significant instant relief of dentin hypersensitivity.[57,58] Further, the third study demonstrates that direct application using a fingertip and a cotton swab are equally effective in providing instant relief of dentin hypersensitivity.[59]

The first paper in this Special Issue, by Ayad, *et al*., reports the results of a study conducted among 120 subjects in Canada. The first phase of the study consisted of a single topical application in which subjects applied a pea-size amount of their assigned toothpaste directly onto the hypersensitive surface of each of the two baseline-designated hypersensitive teeth, and massaged each surface for one minute. The second phase of the study consisted of twice-daily at-home brushing with the assigned toothpaste for three days. Relative to the desensitizing and the fluoride toothpaste control groups, the 8.0% arginine toothpaste group exhibited statistically significant ($p < 0.05$) reductions in dentin hypersensitivity on both tactile and air blast measures immediately after direct application. Reductions in sensitivity for the 8.0% arginine toothpaste compared to the desensitizing toothpaste and the fluoride toothpaste controls were 130.7% and 139.5% (tactile), and 43.8% and 49.6% (air blast), respectively. Relative to the desensitizing and the fluoride toothpaste control groups, the 8.0% arginine toothpaste group also exhibited statistically significant ($p < 0.05$) reductions in sensitivity, after completion of

the brushing phase of the study, of 104.9% and 136.1% (tactile) and 44.5% and 53.2% (air blast), respectively. There was no loss of the instant relief effect in the 8.0% arginine group after the brushing period.[57]

The second paper in this Special Issue, by Nathoo, *et al*., reports the results of a study conducted among 125 subjects in New Jersey, USA; this replicates the Ayad study. This study confirmed that, relative to the desensitizing and the fluoride toothpaste control groups, the 8.0% arginine toothpaste group exhibited statistically significant ($p < 0.05$) reductions in dentin hypersensitivity on both tactile and air blast hypersensitivity scores immediately after direct application. Reductions in sensitivity for the 8.0% arginine toothpaste compared to the desensitizing and the fluoride toothpaste controls were 161.2% and 180.2% (tactile), and 59.8% and 58.0% (air blast), respectively. This study also confirmed that, relative to the desensitizing and the fluoride toothpaste control groups, the 8.0% arginine toothpaste group exhibited statistically significant ($p < 0.05$) reductions in sensitivity after the subsequent three days of twice-daily regular tooth brushing of 147.1% and 181.2% (tactile), and 70.1% and 70.9% (air blast), respectively. The study verifies that a single fingertip topical self-application of a new 8.0% arginine-calcium carbonate toothpaste directly onto the hypersensitive surfaces of teeth provides significant immediate relief of dentin hypersensitivity relative to an identical application of a control toothpaste and a potassium-based desensitizing toothpaste. Significant improvements in dentin hypersensitivity were also demonstrated after three days of brushing with the 8.0% arginine-calcium carbonate toothpaste, subsequent to the single topical self-application of the product, relative to an identical application of the control toothpaste and the potassium-based desensitizing toothpaste. The improvement demonstrated by the 8.0% arginine toothpaste after direct application was maintained after three days of twice-daily brushing.[58]

The third paper in this Special Issue, by Schiff, *et al.*, reports the results of a study conducted among 84 subjects in California, USA, in which relief of dentin hypersensitivity through direct application of the 8.0% arginine-calcium carbonate toothpaste was compared using a fingertip versus a cotton swab. Immediately after direct topical application, the fingertip test teeth and the swab test teeth exhibited statistically significant ($p < 0.05$) improvements from baseline with respect to mean tactile hypersensitivity scores (191.7% and 182.1% respectively), and mean air blast hypersensitivity scores (58.1% and 56.3%, respectively). After one week of subsequent brushing with the product, the fingertip test teeth and the swab test teeth exhibited statistically significant ($p < 0.05$) improvements from baseline with respect to mean tactile hypersensitivity scores (191.7% and 190.5% respectively) and mean air blast hypersensitivity scores (57.4% and 58.2%, respectively). No statistically significant differences were indicated between the fingertip test teeth and the swab test teeth with respect to mean tactile hypersensitivity scores or mean air blast hypersensitivity scores immediately after topical application (3.4%, 4.4%, respectively), or after one week of twice-daily brushing with the product (0.41% and -1.90%, respectively). The results of this clinical study support that 1) both the fingertip and the cotton swab methods of application provided significant reductions in dentin hypersensitivity immediately after a single direct topical application of the 8.0% arginine-calcium carbonate dentifrice, 2) when topical application was followed by a one-week period of twice-daily brushing with the dentifrice, the sensitivity relief obtained instantly after topical application was maintained, and 3) after topical application and the seven-day brushing period, neither method of topical application provided a level of control of dentin hypersensitivity that differed significantly from the other.[59]

In conclusion, the clinical research presented in this Special Issue provides scientific evidence that a new dentifrice containing 8.0% arginine, calcium carbonate, and 1450 ppm fluoride provides instant relief of dentin hypersensitivity when applied directly to sensitive teeth using a fingertip or a cotton swab. The clinical research also shows that neither a desensitizing toothpaste containing 2% potassium ion and 1450 ppm fluoride, nor a control toothpaste containing 1450 ppm fluoride alone provides instant relief of dentin hypersensitivity when applied directly to sensitive teeth using a fingertip. The research further provides supportive scientific evidence that this new dentifrice delivers superior relief of dentin hypersensitivity when used regularly, twice-daily, for two to eight weeks, as compared to a benchmark commercial desensitizing toothpaste containing potassium ion.

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Comparing the efficacy in providing instant relief of dentin hypersensitivity of a new toothpaste containing 8.0% arginine, calcium carbonate, and 1450 ppm fluoride to a benchmark desensitizing toothpaste containing 2% potassium ion and 1450 ppm fluoride, and to a control toothpaste with 1450 ppm fluoride: A three-day clinical study in Mississauga, Canada. *J Clin Dent* 20:115–122, 2009.

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Comparing the Efficacy in Providing Instant Relief of Dentin Hypersensitivity of a New Toothpaste Containing 8.0% Arginine, Calcium Carbonate, and 1450 ppm Fluoride to a Benchmark Desensitizing Toothpaste Containing 2% Potassium Ion and 1450 ppm Fluoride, and to a Control Toothpaste with 1450 ppm Fluoride: A Three-Day Clinical Study in Mississauga, Canada

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Abstract

- **Objective:** The objective of this double-blind, randomized, parallel-design clinical study was to compare the efficacy in reducing dentin hypersensitivity of a novel toothpaste containing 8.0% arginine, calcium carbonate, and 1450 ppm fluoride to a benchmark desensitizing toothpaste containing 2% potassium ion and 1450 ppm fluoride, and to a control toothpaste containing 1450 ppm fluoride, instantly after a single direct topical self-application using a fingertip, and after subsequent brushing twice daily for three days.
- **Methods:** Qualifying subjects from the Mississauga, Canada area who presented two hypersensitive teeth with a tactile hypersensitivity score (Yeaple Probe) between 10 and 50 grams of force, and an air blast hypersensitivity score of 2 or 3 (Schiff Sensitivity Scale) participated in this study. The first phase of the study consisted of a single topical application of the assigned product directly onto the hypersensitive surface of each of the two baseline-designated hypersensitive teeth. Study subjects applied a pea-size amount of their assigned toothpaste onto the hypersensitive surface of each tooth, and massaged each surface for one minute. The second phase of the study consisted of twice-daily at-home brushing with the assigned toothpaste for three days. Dentin hypersensitivity assessments, as well as examinations of oral hard and soft tissues, were conducted at baseline, immediately after direct topical application, and after three days of product use.
- **Results:** One-hundred and twenty subjects complied with the protocol and completed the study. Relative to the desensitizing toothpaste and the control toothpaste groups, the 8.0% arginine toothpaste group exhibited statistically significant ($p < 0.05$) reductions in dentin hypersensitivity on both tactile and air blast measures immediately after completion of the first phase of the study. Reductions in sensitivity for the 8.0% arginine toothpaste, compared to the benchmark desensitizing toothpaste and the control toothpaste, were 130.7% and 139.5% (tactile), and 43.8.0% and 49.6% (air blast), respectively. Relative to the benchmark desensitizing toothpaste and control toothpaste groups, the 8.0% arginine group also exhibited statistically significantly ($p < 0.05$) reductions in sensitivity after completion of the second phase of the study, of 104.9% and 136.1% (tactile), and 44.5% and 53.2% (air blast), respectively. There was no loss of the instant relief effects in the 8.0% arginine group after the brushing period.
- **Conclusion:** A single fingertip topical self-application of the 8.0% arginine-calcium carbonate toothpaste directly onto the hypersensitive surface of teeth provides significant immediate improvements in dentin hypersensitivity relative to an identical application of the control toothpaste and to the benchmark potassium-based desensitizing toothpaste. Significant improvements in dentin hypersensitivity were also demonstrated after three days of brushing with the 8.0% arginine-calcium carbonate toothpaste, subsequent to the single topical self-application of the product, relative to an identical application of the control toothpaste and to the benchmark potassium-based desensitizing toothpaste. The improvement demonstrated by the 8.0% arginine toothpaste after direct application was maintained after three days of twice-daily brushing.

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Introduction

Dentin hypersensitivity is defined as pain arising from exposed dentin, typically in response to external stimuli, such as thermal, tactile, osmotic or chemical, that cannot be explained by any other form of dental defect or pathology.[1] Up to 57% of patients have been reported to be affected by this potential quality-of-life-altering condition.[1-4] As the incidence of dentin hypersensitivity is expected to rise as a result of changing diets,

longer life expectancy, and longer retention of the dentition, there is imminent need for effective management strategies that deliver rapid action and represent realistic and practical alternatives for most sufferers of this condition.[4,5]

Tactile, thermal, and osmotic-chemical triggers of dentin hypersensitivity are frequently present during appointments with oral care professionals, as well as during the conduct of the normal activities of daily living, such as eating, drinking, rinsing, tooth brushing, and even breathing.[6] The overall dental health impact of dentin hypersensitivity on a particular individual may ultimately correlate with the degree of discomfort experienced.[7] In the absence of effective pain relief strategies, individuals who experience hypersensitive responses to otherwise harmless stimuli may understandably elect to modify specific behavior and re-establish their oral care priorities, leading to poor compliance with routine oral hygiene maintenance regimens and decreased acceptance of treatment recommendations from their oral care providers. Sufferers may present inadequate levels of plaque control, putting themselves at increased risk for caries and periodontal complications.[6,8]

Gingival recession is considered the major predisposing factor for dentin hypersensitivity[1,9,10] Dentin hypersensitivity occurs more frequently on exposed root surfaces of canines, incisors, and premolars, sharing a similar predilection distribution for gingival recession.[11] When gingival tissue recedes, dentin can be instantly exposed in up to 18% of teeth (25% of anterior teeth) where cementum does not reach the cemento-enamel junction.[12] Cementum is otherwise easily removed following gingival recession by chemical and/or physical forces, such as instrumentation of root surfaces during scaling procedures and aggressive tooth brushing, leading to the exposure of the underlying dentin. The consumption of erosive dietary foods and drinks, common in today's diet, is also believed to contribute to the process of lesion localization (dentin exposure) via the loss of enamel.[13,14]

For dentin hypersensitivity to occur, exposed dentin must demonstrate at least two hyperconductive properties. These are open tubule orifices on its surface and patent tubules leading to a vital pulp.[11,15] Brännström's hydrodynamic theory is considered by most researchers as central to the problem of dentin hypersensitivity. This theory suggests that external stimuli provoke movement of the dentin fluid in the tubules, resulting in a pressure change across dentin which stimulates intra-dental nerve responses, signals that are ultimately interpreted by the brain as pain.[16] Product-based therapies for the management of dentin hypersensitivity aim at blocking the mechanism of pain transmission (preventing pain signals from being triggered) by either sealing the dentin tubules, or by increasing the pain threshold of sensory nerves.

Published consensus and expert opinion statements recommend the use of at-home desensitizing products as the first-line of treatment for this condition, along with management strategies to reduce etiologic and predisposing factors for dentin hypersensitivity.[2,17] Desensitizing toothpastes for daily use are often recommended for this indication, as these represent non-invasive treatments that have been proven to provide relief for most individuals when used over time.[3,4,18-20] Slow onset of action and difficulty to deliver the desensitizing agent to specific hypersensitive sites have been considered disadvantages of desensitizing toothpastes.[21] Most desensitizing toothpastes contain one of a number of potassium salts. Potassium-based toothpastes are thought to decrease the excitability of intradental nerves as a result of gradual penetration of the potassium ion into dentin tubules,[18,22-25] although this has never been confirmed in intact human teeth.[17] In clinical trials, potassium-based toothpastes have been shown to take at least two weeks of twice-daily use to show measurable reductions in hypersensitivity, and longer periods, generally eight weeks or more, to demonstrate maximum effectiveness.[3,4]

A recent review of biological approaches to therapy proposed that the ideal dentin hypersensitivity treatment should mimic natural desensitizing processes leading to spontaneous occlusion of open dentin tubules.[26] Kleinberg and coworkers have developed a dentin hypersensitivity treatment consisting of 8.0% arginine, an amino acid found in saliva, bicarbonate, and calcium carbonate. This desensitizing technology mimics saliva's natural process of plugging and sealing open dentin tubules.[27] When applied to exposed dentin, open dentin tubules are sealed with a plug that reduces dentin hypersensitivity.[4] This novel technology has been introduced as a desensitizing prophylaxis paste, with 8.0% arginine and calcium carbonate, for professional application. Results from clinical studies have demonstrated the efficacy of this professional product in providing instant and lasting (28 days) dentin hypersensitivity relief after a single in-office application of the product.[28,29] In view of the impressive results observed with the professional product, a new desensitizing toothpaste containing 8.0% arginine, calcium carbonate, and 1450 ppm fluoride, as sodium monofluorophosphate (MFP), was developed for regular, twice-daily brushing. Three eight-week, double-blind, randomized clinical trials have demonstrated the superior clinical efficacy in reducing dentin hypersensitivity of this dentifrice relative to market-leading potassium-based toothpastes when used twice daily during regular tooth brushing.[30-32]

Before the publication of this Special Issue, twice-daily brushing was the only clinically proven method of application reported for desensitizing toothpastes. There was no published evidence to support that direct topical application could accelerate the delivery of sensitivity relief and, thereby, enhance the effectiveness of desensitizing toothpastes.[2]

The objective of this double-blind, randomized clinical trial was to compare the efficacy in reducing dentin hypersensitivity of a toothpaste containing 8.0% arginine, calcium carbonate, and 1450 ppm fluoride, to that of a benchmark desensitizing toothpaste containing 2% potassium ion and 1450 ppm fluoride, and a control toothpaste containing 1450 ppm fluoride, instantly after a single direct topical self-application of the assigned toothpaste using a fingertip, and after subsequent unsupervised brushing twice daily for three days.

Materials and Methods

This three-day, parallel-group, double-blind, stratified, and randomized clinical study was conducted in the Canadian Clinical Research Center in Mississauga, Canada. One-hundred and twenty adult subjects (47 males and 73 females with mean age

of 32.65 ± 12.2 years) were enrolled in the study based upon the following criteria:

(i) Subjects had to be between the ages of 18 and 70 (inclusive), in generally good health, with no history of allergies or idiosyncrasies to dentifrice ingredients.

(ii) Subjects were required to possess a minimum of two hypersensitive teeth which were anterior to the molars and demonstrated cervical erosion/abrasion or gingival recession, and for which a tactile hypersensitivity stimuli score of 10 to 50 grams of force (Yeaple Probe), and an air blast stimuli score of 2 or 3 on a sensitivity scale were present at the baseline examination.

(iii) Subjects were required to be available for the three-day duration of the study, and to sign an informed consent form.

(iv) Subjects were excluded from the study if they had gross oral pathology, chronic disease, advanced periodontal disease, treatment for periodontal disease (within the previous 12 months), or hypersensitive teeth with a mobility greater than one. Subjects with teeth that had extensive/defective restorations (including prosthetic crowns), suspected pulpitis, caries, cracked enamel, or that were used as abutments for removable partial dentures were also excluded from the study.

(v) Subjects were also excluded from the study if they were current users of anticonvulsants, antihistamines, antidepressants, sedatives, tranquilizers, anti-inflammatory drugs, or daily analgesics.

(vi) Pregnant or lactating women, individuals who were participating in any other clinical study or who had participated in a desensitizing study, or who used any desensitizing agents within the previous three months were not allowed to participate in the study.

Qualifying subjects reported to the clinical facility having refrained from all oral hygiene procedures and from chewing gum for eight hours, and from eating and drinking for four hours prior to the conduct of the baseline examinations. Two hypersensitive teeth per study subject that satisfied the tactile and air blast sensitivity enrolment criteria were identified for evaluation throughout the study. Subjects were stratified according to mean baseline tactile and air blast hypersensitivity scores, and were randomly assigned within strata to one of the following study treatments: test toothpaste with 8.0% arginine, calcium carbonate, and 1450 ppm MFP (Colgate-Palmolive Co., New York, NY, USA; 8.0% arginine group), desensitizing toothpaste with 5% potassium nitrate and 1450 ppm NaF (Colgate-Palmolive Co., New York, NY, USA; 5% KNO_3 group); or control toothpaste with 1450 ppm MFP (Colgate-Palmolive Co., New York, NY, USA; Control group). All three toothpastes were provided in white over-wrapped tubes to ensure the double-blind design.

The first phase of the study consisted of applying the assigned toothpaste with a fingertip directly onto the buccal-cervical area of exposed dentin on each of the two baseline-designated hypersensitive teeth per subject. During a supervised session at the clinical site, subjects self-applied a pea size amount (approximately 0.3 grams) of their assigned product directly onto the hypersensitive surface of the study teeth and massaged each tooth for one minute. For the second phase of the study, subjects took their assigned product home and were provided with a soft-bristled toothbrush for unsupervised tooth brushing for a total of three days. At-home brushing instructions to study subjects consisted of brushing their teeth for one minute, twice daily, using only the toothpaste and toothbrush provided, and to refrain from any other oral hygiene procedures throughout the duration of the study. There were no restrictions regarding diet or smoking habits during the course of the study.

Oral soft and hard tissue assessments, as well as tactile and air blast hypersensitivity follow-up evaluations of baseline-designated study teeth were conducted immediately after fingertip topical application of the assigned product, and after three days of product use. Subjects were requested to return to the clinical facility for the three-day follow-up visit, having refrained from all oral hygiene procedures and chewing gum for eight hours, and from eating and drinking for four hours prior to their scheduled visit. All examinations were performed by the same dental examiner, using the same procedures as employed at baseline.

Tactile Hypersensitivity Assessment[33,34]

Hypersensitivity assessment in response to tactile stimuli was done using an Electronic Force Sensing Probe (Yeaple Probe Model 200A, Xinix Research Inc., Portsmouth, NH, USA) that was calibrated daily by the study examiner. Scores were recorded in terms of a quantified, reproducible force (grams) applied by use of an attached #19 explorer tip. After presetting the probe to 10 grams, the probe tip was stroked over the exposed dentin perpendicular to the examined surface of the hypersensitive teeth. Subsequent passes were made, each time with the applied force increased by 10 grams until the subject indicated that he/she was experiencing discomfort, or until the maximum force of 50 grams had been reached. A force of 50 grams was considered the cut-off point. Higher scores on this index correspond to lower levels of dentin hypersensitivity.

Air Blast Hypersensitivity Assessment

Teeth were evaluated for air blast hypersensitivity in the following manner:

1) The hypersensitive tooth was isolated from the adjacent teeth (mesial and distal) by the placement of the examiner's fingers over the adjacent teeth.
2) Air was delivered from a standard dental unit air syringe at 60 psi (± 5 psi) and 70˚F (± 3˚F). The air was directed at the exposed buccal surface of the hypersensitive tooth for one second from a distance of approximately 1 cm.
3) The Schiff Cold Air Sensitivity Scale[35] was used to assess subject response to this stimulus. This scale is scored as follows:
   - 0 = Subject does not respond to air stimulus;
   - 1 = Subject responds to air stimulus, but does not request discontinuation of stimulus;
   - 2 = Subject responds to air stimulus and requests discontinuation or moves from stimulus; and
   - 3 = Subject responds to air stimulus, considers stimulus to be painful, and requests discontinuation of the stimulus.

Only teeth scoring 2 or 3 were selected as study teeth at the baseline evaluation.

Statistical Methods

Dentin hypersensitivity scores for all subjects who completed all the scheduled examinations were included in the statistical analyses. Statistical analyses were performed separately for the tactile hypersensitivity assessments and air blast hypersensitivity assessments. Subject-wise scores were calculated at each hypersensitivity assessment by averaging the values measured on the two baseline-designated study teeth. Comparisons of the treatment groups with respect to baseline tactile scores and air blast scores were performed using analyses of variance (ANOVA). Within-treatment comparisons of the baseline versus follow-up tactile hypersensitivity and air blast hypersensitivity scores were performed using paired t-tests. Comparisons of the treatment groups with respect to baseline-adjusted mean tactile hypersensitivity and air blast hypersensitivity scores at the follow-up examinations were performed using analyses of covariance (ANCOVA). All pair-wise comparisons between the treatment groups *post hoc* were performed using Tukey's multiple comparison test. All statistical tests of hypotheses were two-sided, and employed a level of significance of $\alpha = 0.05$.

Results

One-hundred and twenty subjects complied with the protocol and completed the three-day clinical study. A summary of gender and age of the study population is presented in Table I. The treatment groups did not differ significantly with respect to either of these characteristics. Throughout the study, there were no adverse effects on the soft or hard tissues of the oral cavity which were observed by the examiner, or reported by the subjects when questioned.

Table I
Summary of Age and Gender for
Subjects Who Completed the Clinical Study

	Number of Subjects			Age	
Treatment	Male	Female	Total	Mean	Range
8.0% arginine-calcium carbonate[1]	15	26	41	32.2	18–66
5% KNO_3[2]	17	23	40	33.6	18–59
Control[3]	15	24	39	32.1	18–62

[1] Toothpaste containing 8.0% arginine, calcium carbonate, and 1450 ppm MFP.
[2] Toothpaste containing 5% potassium nitrate (KNO_3) and 1450 ppm NaF.
[3] Control toothpaste with 1450 ppm MFP.

Baseline Data

Table II presents a summary of the mean tactile and air blast scores measured at the baseline examination. For tactile-induced hypersensitivity, the mean baseline scores were 11.46 for the 8.0% arginine group, 10.88 for the 5% KNO_3 group, and 10.90 for the Control group. For air blast-induced hypersensitivity, the mean baseline scores were 2.90 for the 8.0% arginine group, 2.93 for the 5% KNO_3 group, and 2.95 for the Control group. No statistically significant differences were indicated among the treatment groups with respect to either baseline mean hypersensitivity score.

Immediately After Topical Application Data

Tactile Hypersensitivity. Table III presents a summary of the mean tactile hypersensitivity scores measured immediately after fingertip topical self-application of the assigned product.

Table II
Summary of the Baseline Mean Tactile Hypersensitivity
and Air Blast Hypersensitivity Scores for Subjects
Who Completed the Three-Day Clinical Study

Parameter	Treatment	n	Baseline Summary (Mean ± SD)[4]
Tactile Hypersensitivity	8.0% arginine-calcium carbonate[1]	41	11.46 ± 2.79
	5% KNO_3[2]	40	10.88 ± 1.92
	Control[3]	39	10.90 ± 2.26
Air Blast Hypersensitivity	8.0% arginine-calcium carbonate[1]	41	2.90 ± 0.20
	5% KNO_3[2]	40	2.93 ± 0.18
	Control[3]	39	2.95 ± 0.15

[1] Toothpaste containing 8.0% arginine, calcium carbonate, and 1450 ppm MFP.
[2] Toothpaste containing 5% potassium nitrate (KNO_3) and 1450 ppm NaF.
[3] Control toothpaste with 1450 ppm MFP.
[4] No statistically significant difference was indicated between the three treatment groups at baseline with respect to either tactile hypersensitivity or air blast hypersensitivity scores.

The mean tactile hypersensitivity scores recorded immediately after topical product application were 33.17 for the 8.0% arginine group, 14.38 for the 5% KNO_3 group, and 13.85 for the Control group. The percent changes from baseline were 189.4% for the 8.0% arginine group, 32.2% for the 5% KNO_3 group, and 27.1% for the Control group, all of which were statistically significant.

Relative to the 5% KNO_3 and the Control groups, the 8.0% arginine group exhibited statistically significant improvements in mean tactile hypersensitivity scores immediately after topical product application (130.7% and 139.5%, respectively). Relative to the Control group, the 5% KNO_3 group did not exhibit a statistically significant improvement in mean tactile hypersensitivity scores immediately after topical application of the product (3.8%).

Air Blast Hypersensitivity. Table IV presents a summary of the mean air blast hypersensitivity scores measured immediately after fingertip topical self-application of the assigned product. The mean air blast hypersensitivity scores recorded immediately after topical application of the product were 1.26 for the 8.0% arginine group, 2.24 for the 5% KNO_3 group, and 2.50 for the Control group. The mean percent reductions from baseline were 56.6% for the 8.0% arginine group, 23.5% for the 5% KNO_3 group, and 15.3% for the Control group, all of which were statistically significant.

Relative to the 5% KNO_3 group and the Control group, the 8.0% arginine group exhibited statistically significant reductions in mean air blast hypersensitivity scores immediately after topical application of the product (43.8% and 49.6%, respectively). Relative to the Control group, the 5% KNO_3 group did not exhibit a statistically significant reduction in mean air blast hypersensitivity scores immediately after topical application of the product (10.4%).

Three-Day Data

Tactile Hypersensitivity. Table V presents a summary of the mean tactile hypersensitivity scores measured after three days of at-home brushing with the assigned product, subsequent to the

Table III
Summary of the Immediately After Topical Application Mean Tactile Hypersensitivity Scores for Subjects Who Completed the Three-Day Clinical Study

Treatment	n	Immediately After Topical Application Summary (Mean ± SD)	Within-Treatment Analysis		Between-Treatment Comparison			
					vs. 5% KNO_3		vs. Control	
			Percent Change[4]	Sig.[5]	Percent Difference[6]	Sig.[8]	Percent Difference[7]	Sig.[8]
8.0% arginine-calcium carbonate[1]	41	33.17 ± 14.86	189.4%	$p < 0.05$	130.7%	$p < 0.05$	139.5%	$p < 0.05$
5% KNO_3[2]	40	14.38 ± 4.11	32.2%	$p < 0.05$	—	—	3.8%	NS
Control[3]	39	13.85 ± 3.53	27.1%	$p < 0.05$	—	—	—	—

[1] Toothpaste containing 8.0% arginine, calcium carbonate, and 1450 ppm MFP.
[2] Toothpaste containing 5% potassium nitrate (KNO_3) and 1450 ppm NaF.
[3] Control toothpaste with 1450 ppm MFP.
[4] Percent change exhibited immediately after topical application relative to the baseline mean. A positive value indicates an improvement in mean tactile hypersensitivity at the immediately after topical application examination.
[5] Significance of paired t-test comparing the baseline and the immediately after topical application examinations.
[6] Difference between the immediately after topical application means expressed as a percentage of the immediately after topical application mean for the toothpaste containing 5% potassium nitrate (KNO_3). A positive value indicates an improvement in mean tactile hypersensitivity scores relative to the toothpaste containing 5% potassium nitrate (KNO_3).
[7] Difference between the immediately after topical application means expressed as a percentage of the immediately after topical application mean for the control toothpaste. A positive value indicates an improvement in mean tactile hypersensitivity scores relative to the control toothpaste.
[8] Significance of ANCOVA comparison of baseline-adjusted means.

Table IV
Summary of the Immediately After Topical Application Mean Air Blast Hypersensitivity Scores for Subjects Who Completed the Three-Day Clinical Study

Treatment	n	Immediately After Topical Application Summary (Mean ± SD)	Within-Treatment Analysis		Between-Treatment Comparison			
					vs. 5% KNO_3		vs. Control	
			Percent Change[4]	Sig.[5]	Percent Difference[6]	Sig.[8]	Percent Difference[7]	Sig.[8]
8.0% arginine-calcium carbonate[1]	41	1.26 ± 0.75	56.6%	$p < 0.05$	43.8.0%	$p < 0.05$	49.6%	$p < 0.05$
5% KNO_3[2]	40	2.24 ± 0.49	23.5%	$p < 0.05$	—	—	10.4%	NS
Control[3]	39	2.50 ± 0.46	15.3%	$p < 0.05$	—	—	—	—

[1] Toothpaste containing 8.0% arginine, calcium carbonate, and 1450 ppm MFP.
[2] Toothpaste containing 5% potassium nitrate (KNO_3) and 1450 ppm NaF.
[3] Control toothpaste with 1450 ppm MFP.
[4] Percent change exhibited immediately after topical application relative to the baseline mean. A positive value indicates an improvement in mean air blast hypersensitivity at the immediately after topical application examination.
[5] Significance of paired t-test comparing the baseline and the immediately after topical application examinations.
[6] Difference between the immediately after topical application means expressed as a percentage of the immediately after topical application mean for the toothpaste containing 5% potassium nitrate (KNO_3). A positive value indicates a reduction in mean air blast hypersensitivity scores relative to the toothpaste containing 5% potassium nitrate (KNO_3).
[7] Difference between the immediately after topical application means expressed as a percentage of the immediately after topical application mean for the control toothpaste. A positive value indicates a reduction in mean air blast hypersensitivity scores relative to the control toothpaste.
[8] Significance of ANCOVA comparison of baseline-adjusted means.

single fingertip topical self-application performed at the beginning of the study. The mean three-day tactile hypersensitivity scores were 33.29 for the 8.0% arginine group, 16.25 for the 5% KNO_3 group, and 14.10 for the Control group. The percent changes from baseline were 190.4% for the 8.0% arginine group, 49.4% for the 5% KNO_3 group, and 29.4% for the Control group, all of which were statistically significant.

Relative to the 5% KNO_3 and Control groups, the 8.0% arginine group exhibited statistically significant improvements in mean tactile hypersensitivity scores after three days of product use (104.9% and 136.1%, respectively). Relative to the Control group, the 5% KNO_3 group did not exhibit a statistically significant improvement in mean tactile sensitivity scores after three days of product use (15.2%).

Air Blast Hypersensitivity. Table VI presents a summary of the mean air blast hypersensitivity scores measured after three days of at-home brushing with the assigned product, subsequent to the single fingertip topical self-application performed at the beginning of the study. The mean three-day air blast hypersensitivity scores were 1.17 for the 8.0% arginine group, 2.11 for the 5% KNO_3 group, and 2.50 for the Control group. The mean percent reductions from baseline were 59.7% for the 8.0% arginine group, 28.4% for the 5% KNO_3 group, and 15.5% for the Control group, all of which were statistically significant.

Relative to the 5% KNO_3 and Control groups, the 8.0% arginine toothpaste group exhibited statistically significant reductions in mean air blast hypersensitivity scores after three days of product use (44.5% and 53.2%, respectively). Relative to the Control

Table V
Summary of the Three-Day Mean Tactile Hypersensitivity Scores
for Subjects Who Completed the Three-Day Clinical Study

Treatment	n	Three-Day Summary (Mean ± SD)	Within-Treatment Analysis		Between-Treatment Comparison			
					vs. 5% KNO_3		vs. Control	
			Percent Change[4]	Sig.[5]	Percent Difference[6]	Sig.[8]	Percent Difference[7]	Sig.[8]
8.0% arginine-calcium carbonate[1]	41	33.29 ± 14.69	190.4%	$p < 0.05$	104.9%	$p < 0.05$	136.1%	$p < 0.05$
5% KNO_3[2]	40	16.25 ± 4.77	49.4%	$p < 0.05$	—	—	15.2%	NS
Control[3]	39	14.10 ± 4.27	29.4%	$p < 0.05$	—	—	—	—

[1] Toothpaste containing 8.0% arginine, calcium carbonate, and 1450 ppm MFP.
[2] Toothpaste containing 5% potassium nitrate (KNO_3) and 1450 ppm NaF.
[3] Control toothpaste with 1450 ppm MFP.
[4] Percent change exhibited by the three-day mean relative to the baseline mean. A positive value indicates an improvement in mean tactile hypersensitivity at the three-day examination.
[5] Significance of paired t-test comparing the baseline and three-day examinations.
[6] Difference between three-day means expressed as a percentage of the three-day mean for the toothpaste containing 5% potassium nitrate (KNO_3). A positive value indicates an improvement in mean tactile hypersensitivity scores relative to the toothpaste containing 5% potassium nitrate (KNO_3).
[7] Difference between three-day means expressed as a percentage of the three-day mean for the control toothpaste. A positive value indicates an improvement in mean tactile hypersensitivity scores relative to the control toothpaste.
[8] Significance of ANCOVA comparison of baseline-adjusted means.

Table VI
Summary of the Three-Day Mean Air Blast Hypersensitivity Scores
for Subjects Who Completed the Three-Day Clinical Study

Treatment	n	Three-Day Summary (Mean ± SD)	Within-Treatment Analysis		Between-Treatment Comparison			
					vs. 5% KNO_3		vs. Control	
			Percent Change[4]	Sig.[5]	Percent Difference[6]	Sig.[8]	Percent Difference[7]	Sig.[8]
8.0% arginine-calcium carbonate[1]	41	1.17 ± 0.68	59.7%	$p < 0.05$	44.5%	$p < 0.05$	53.2%	$p < 0.05$
5% KNO_3[2]	40	2.11 ± 0.47	28.4%	$p < 0.05$	—	—	15.6%	$p < 0.05$
Control[3]	39	2.50 ± 0.46	15.5%	$p < 0.05$	—	—	—	—

[1] Toothpaste containing 8.0% arginine, calcium carbonate, and 1450 ppm MFP.
[2] Toothpaste containing 5% potassium nitrate (KNO_3) and 1450 ppm NaF.
[3] Control toothpaste with 1450 ppm MFP.
[4] Percent change exhibited by the three-day mean relative to the baseline mean. A positive value indicates a reduction in mean air blast hypersensitivity at the three-day examination.
[5] Significance of paired t-test comparing the baseline and three-day examinations.
[6] Difference between three-day means expressed as a percentage of the three-day mean for the toothpaste containing 5% potassium nitrate (KNO_3). A positive value indicates a reduction in mean air blast hypersensitivity scores relative to the toothpaste containing 5% potassium nitrate (KNO_3).
[7] Difference between three-day means expressed as a percentage of the three-day mean for the control toothpaste. A positive value indicates a reduction in mean air blast hypersensitivity scores relative to the control toothpaste.
[8] Significance of ANCOVA comparison of baseline-adjusted means.

group, the 5% KNO_3 group exhibited a statistically significant reduction in mean air blast hypersensitivity scores after three days of product use (15.6%).

Discussion

Saliva is known to naturally reduce dentin hypersensitivity by carrying calcium and phosphate ions into open dentin tubules to gradually bring about tubule blocking, and by forming a surface protective layer consisting of precipitable aggregates of salivary glycoproteins with calcium phosphate.[27] The toothpaste tested in this study contains 8.0% arginine and calcium carbonate to mimic saliva's natural process of plugging and sealing open dentin tubules.[4,27] The mechanism of action of this technology has been established using a range of state-of-the-art measurement techniques: confocal laser scanning microscopy (CLSM) studies have demonstrated its effectiveness in occluding open dentin tubules, and shown that this occlusion is resistant to acid challenge; high resolution scanning electron microscopy (SEM) and atomic force microscopy (AFM) studies have confirmed tubule occlusion; electron spectroscopy for chemical analysis (ESCA) and energy dispersive x-ray (EDX) studies have shown that the occluded mineral contains calcium, phosphate, and carbonate; and hydraulic conductance experiments have shown that this occlusion blocks fluid movement to inhibit the hydrodynamic mechanism.[4,36]

Demands for the management of dentin hypersensitivity are expected to increase as the adult population lives longer and retains its teeth later in life, and as populations of all age groups engage in lifestyles and behaviors that promote dentin exposure through gingival recession or erosion of protective tooth surfaces. At-home use of desensitizing products has been considered a realistic and practical means of treating most patients.[37] Given

that they are widely available, cost-effective, non-invasive, and simple to use, desensitizing toothpastes are, consequently, recommended as the first line of treatment for the control of dentin hypersensitivity. Among the reported disadvantages of desensitizing toothpastes are that they have a relatively slow onset of action, and that they do not directly deliver their desensitizing agents to specific hypersensitive sites.[20] The tested regimen of use for the desensitizing toothpaste containing 8.0% arginine, calcium carbonate, and 1450 ppm fluoride offers the prospect of a desensitizing treatment alternative that can be used daily and provides significant instant hypersensitivity relief following fingertip application of the product directly onto the hypersensitive area of teeth.

An adult population with a history of dentin hypersensitivity was enrolled for participation in this study. Before product application, hypersensitivity symptoms were successfully stimulated in all the teeth included in the trial, and tactile and air blast scores were recorded as baseline hypersensitivity values. Dentin hypersensitivity was re-evaluated immediately after topical paste application, and after three days of twice-daily brushing with the product. The clinical results of this study confirm the results from a similar study conducted in New Jersey, also reported in this Special Issue.[38] To the authors' knowledge, prior to this Special Issue there was no published evidence that demonstrated significant reductions in dentin hypersensitivity after topical self-application of a desensitizing toothpaste. Prior to the studies reported in this publication, statistically significant reductions in dentin hypersensitivity had only been achieved via brushing with a desensitizing toothpaste at least twice daily on a regular basis for a time period ranging from 2–12 weeks.[2-4,19-21]

It could, perhaps, be speculated that the dramatic dentin hypersensitivity relief observed after massaging the 8.0% arginine toothpaste directly onto hypersensitive dentin results, at least in part, from the massaging process itself. The results for the Control group, however, show that massaging with toothpaste *per se* provides only minor relief. Likewise, the results for the KNO_3 group support this conclusion and reinforce the view that potassium-based toothpastes are relatively slow acting. The results of this study, which demonstrate that the 8.0% arginine toothpaste provides instant sensitivity relief when applied directly to hypersensitive teeth, are consistent with the findings of the *in vitro* mechanism of action studies that show effective deposition of a calcium-rich dentin plug and complete occlusion of open dentin tubules.[36] Subsequent twice-daily brushing with the 8.0% arginine toothpaste helps maintain the instant plugging effect achieved by direct application.

The results of a third study, also published in this Special Issue, provide users of the 8.0% arginine toothpaste with a proven alternative method of direct application. The study demonstrated that using a cotton swab instead of a fingertip for application of the product provided equivalent instant hypersensitivity relief efficacy.[39] The prospect of using either a fingertip or a cotton swab applicator for direct topical self-application of the desensitizing toothpaste with 8.0% arginine, followed by maintenance of the afforded instant relief through regular twice-daily brushing with the product, represents a treatment strategy that is non-invasive, cost effective, and compatible with the simplest at-home oral care regimens.

The results of this double-blind clinical study support the conclusions that: 1) a single fingertip topical self-application of a toothpaste containing 8.0% arginine, calcium carbonate, and 1450 ppm MFP, directly onto the hypersensitive surface of teeth, provides significant immediate improvements in dentin hypersensitivity relative to identical application of a control toothpaste with 1450 ppm MFP, and to a desensitizing toothpaste containing 5% potassium nitrate and 1450 ppm NaF; 2) three days of brushing with the 8.0% arginine toothpaste, subsequent to the single topical self-application of the product, provides significant improvements in dentin hypersensitivity relative to the identical application of the control toothpaste and to the desensitizing toothpaste with 5% potassium nitrate; and 3) the instant sensitivity relief benefit afforded by direct topical self-application of the 8.0% arginine toothpaste is maintained by subsequent regular twice-daily brushing for at least a period of three days.

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Comparing the Efficacy in Providing Instant Relief of Dentin Hypersensitivity of a New Toothpaste Containing 8.0% Arginine, Calcium Carbonate, and 1450 ppm Fluoride Relative to a Benchmark Desensitizing Toothpaste Containing 2% Potassium Ion and 1450 ppm Fluoride, and to a Control Toothpaste with 1450 ppm Fluoride: A Three-Day Clinical Study in New Jersey, USA

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Abstract

- **Objective:** The objective of this double-blind, randomized, parallel-design clinical study was to compare the efficacy in reducing dentin hypersensitivity of a novel toothpaste containing 8.0% arginine, calcium carbonate, and 1450 ppm fluoride to a benchmark desensitizing toothpaste containing 2% potassium ion and 1450 ppm fluoride, and to a control toothpaste containing 1450 ppm fluoride, instantly after a single direct topical self-application using a fingertip, and after subsequent brushing twice daily for three days.
- **Methods:** Qualifying subjects from the Piscataway, New Jersey, USA area who presented two hypersensitive teeth with a tactile hypersensitivity score (Yeaple Probe) between 10 and 50 grams of force, and an air blast hypersensitivity score of 2 or 3 (Schiff Sensitivity Scale), participated in this study. The first phase of the study consisted of a single topical application of the assigned product directly onto the hypersensitive surface of each of the two baseline-designated hypersensitive teeth. Study subjects applied a pea-size amount of their assigned toothpaste onto the hypersensitive surface of each tooth and massaged each surface for one minute. The second phase of the study consisted of twice-daily at-home brushing with the assigned toothpaste for three days. Dentin hypersensitivity assessments, as well as examinations of oral hard and soft tissues, were conducted at baseline, immediately after direct topical application, and after three days of product use.
- **Results:** One-hundred and twenty-five subjects complied with the study protocol and completed the study. Relative to the benchmark desensitizing toothpaste and the control toothpaste groups, the 8.0% arginine toothpaste group exhibited statistically significant ($p < 0.05$) reductions in dentin hypersensitivity on both tactile and air blast hypersensitivity scores immediately after direct application. Reductions in sensitivity for the 8.0% arginine toothpaste compared to the benchmark desensitizing toothpaste and control toothpaste were 161.2% and 180.2% (tactile), and 59.8% and 58.0% (air blast), respectively. Relative to the benchmark desensitizing toothpaste and control toothpaste groups, the 8.0% arginine group exhibited statistically significant ($p < 0.05$) reductions in sensitivity after the subsequent three days of twice-daily regular tooth brushing of 147.1% and 181.2% (tactile), and 70.1% and 70.9% (air blast), respectively.
- **Conclusion:** A single fingertip topical self-application of a new 8.0% arginine-calcium carbonate toothpaste directly onto the hypersensitive surface of teeth provides significant immediate improvement in dentin hypersensitivity relative to an identical application of a control toothpaste and to a benchmark potassium-based desensitizing toothpaste. Significant improvements in dentin hypersensitivity were also demonstrated after three days of brushing with the 8.0% arginine-calcium carbonate toothpaste, subsequent to the single topical self-application of the product, relative to an identical application of the control toothpaste and to the potassium-based desensitizing toothpaste. The improvement demonstrated by the 8.0% arginine toothpaste after direct application was maintained after three days of twice-daily brushing.

(J Clin Dent 20 (Spec Iss):123–130, 2009)

Introduction

Dentin hypersensitivity has been described in the past as an enigma because it is frequently encountered and yet poorly understood.[1] There is also a lack of consensus in the literature concerning the terminology used to describe the condition. The terms "dentin hypersensitivity" and "tooth hypersensitivity" have been questioned because dentin itself cannot be sensitive; stimuli, when applied to dentin, evoke a response from the pulp.[2] The terms "cervical dentin sensitivity" and "cervical tooth sensitivity" have also been used as location-based descriptors to differentiate it from other types of dental pain.[3,4]

A definition of dentin hypersensitivity was first suggested in 1983 and agreed to by an international workshop on design and conduct of clinical trials for the treatment of this condition.[5] The definition states, "Dentin hypersensitivity is characterized by short, sharp pain arising from exposed dentine in response to stimuli, typically thermal, evaporative, tactile, osmotic, and chemical which cannot be ascribed to any other form of dental defect or pathology." The term "pathology" was then replaced with "disease" by the Canadian Advisory Board on Dentin Hypersensitivity in 2002.[6] The definition provides a description of the condition, and identifies dentin hypersensitivity as a distinct clinical entity which enables the clinician to differentially diagnose the condition.[2,5,6]

As with any disease, understanding the etiology and mechanisms of dentin hypersensitivity is helpful in developing treatments to alleviate the pain. A prerequisite for the development of hypersensitivity is gingival recession and subsequent exposure of the dentin or overlying cementum. The causes of gingival recession include incorrect tooth brushing habits, normal aging, chronic periodontal disease, abnormal tooth position in the dental arch, periodontal surgery, and certain restorative procedures. Reasons for cementum and enamel loss are often difficult to determine; however, exposed root surfaces are prone to abrasion from aggressive tooth brushing and erosion from contact with acidic food substances.[7]

Several theories have been put forward to explain dentin hypersensitivity. In the mid-19th century, a Philadelphia dentist proposed that dentin tubules were filled with a fluid secreted by the pulp, and the pressure on the fluid within the tubules affected the pulp.[8,9] For a long time, it was unclear how the stimulus was transmitted to the pulp and recognized as pain by the nociceptive system. It was not until the 1960s that Brännström developed a theory, known as the hydrodynamic theory, to explain dentin hypersensitivity. The theory suggests that a stimulus causes the fluid within the dentin tubules to flow inward or outward, causing a mechanical disturbance or cellular perturbation. Thus, the movement excites the nerves in the tooth and transmits a signal to the pulp, where the sensation of pain is registered by depolarization of the neurons.[10]

If the hydrodynamic theory is correct, then experimental evidence would show that dentin tubules are open and connected directly or indirectly to the pulp, thereby acting as portals through which stimuli can be transmitted to the pulp. Evidence has, indeed, shown this. Scanning electron microscopy studies and dye penetration studies have shown that sensitive dentin has a greater number of tubules and the tubules are wider than those in non-sensitive dentin.[11-13] The evidence has also shown that the diameter of the tubules increases from the outer dentin to the pulp,[12,13] which may explain why loss of dentin through natural processes, such as disease, iatrogenic, and para-functional habits, may give rise to dentin hypersensitivity.[7,14]

Dentin hypersensitivity can be alleviated either by interfering with the neural transmission or by sealing the dentin tubules.[2] One of the most common ingredients used to treat dentin hypersensitivity is potassium nitrate. The potassium ions are thought to increase the nerve depolarization threshold and reduce the sensation of pain.[15,16] Clinical studies have shown that potassium nitrate is effective in reducing dentin hypersensitivity, but it takes from four to eight weeks to achieve maximum efficacy.[17]

Treatments which physically seal and plug open dentin tubules have the potential to be more effective than potassium-based treatments. An in-office product, sold under the brand name Gluma® (Heraeus Kulzer, Inc, South Bend, IN, USA), containing protein denaturants, has been shown to be an effective option to treat hypersensitivity by causing amino acids and proteins to coagulate in dentin tubules.[18] However, this procedure requires a visit to the dental office and, because some of the ingredients are water soluble, the treatment gradually loses its effect.[18,19] Other treatments to occlude the tubules include high fluoride gels and pastes. High levels of fluoride interact with calcium in the saliva or on the tooth surface precipitating calcium fluoride within the tubules to occlude them.[2] More recently, a new multi-benefit toothpaste has been introduced which contains a specially designed grade of silicon dioxide to penetrate tubules and occlude them.[20]

In a hospital-based study, the prevalence of dentin hypersensitivity was found to be about 53%. Of those with dentin hypersensitivity, about 25% used dentifrices for the alleviation of the condition, about 17% sought professional treatment, and about 11% modified their behavior and avoided normal oral hygiene procedures.[21,22] The reasons for the changes in behavior are not clear, but they are likely related to an attempt to manage pain by avoidance. The avoidance of oral care procedures is particularly significant, because the lack of appropriate oral care may exacerbate the condition, cause additional problems, and possibly have systemic manifestations.

In the past, the modification of behavior has been said to be of paramount importance in the management of hypersensitivity.[7,23] However, the success of a therapeutic regimen has also been directly related to the length of a therapy and the frequency of dosage.[24] Further, in the case of hypersensitivity, it has been reported that the pain is not easily reversed and sometimes requires professional or surgical intervention.[18,19] Thus, there is a need to develop a product that is easy to use, does not require dental office visits, is cost effective, and delivers immediate relief.

A recently introduced technology for the management of dentin hypersensitivity has been shown to provide effective pain relief. This technology, which is based upon arginine, an amino acid naturally present in saliva, and calcium carbonate, has been shown to physically block and seal open dentin tubules.[25-27] Clinical trials have demonstrated that a toothpaste containing 8.0% arginine, calcium carbonate and 1450 ppm fluoride as sodium

monofluorophosphate (MFP) is more efficacious in reducing dentin hypersensitivity during regular twice-daily brushing than leading potassium-based commercial desensitizing toothpastes with similar fluoride content.[28-30] Most importantly, three new studies reported in this Special Issue demonstrate that immediate pain relief from hypersensitive teeth can be obtained from a single patient-applied topical application of this novel product directly onto the hypersensitive surfaces of teeth.[31,32]

The objective of this double-blind, randomized clinical trial was to compare the efficacy in reducing dentin hypersensitivity of a toothpaste containing 8.0% arginine, calcium carbonate, and 1450 ppm fluoride to a desensitizing toothpaste containing 2% potassium ion and 1450 ppm fluoride, and to a control toothpaste containing 1450 ppm fluoride, instantly after a single direct topical self-application of the assigned toothpaste using a fingertip, and after subsequent unsupervised brushing twice daily for three days. This study is essentially a duplicate of the study preceding it in this publication.[32]

Materials and Methods

This three-day, parallel-group, double-blind, stratified, and randomized clinical trial tested the efficacy in reducing dentin hypersensitivity of three dentifrices using the hypersensitivity assessment methods described below.

One-hundred and twenty-five adult subjects (52 males and 73 females with mean age of 40.8 ± 12.7 years) participated in the trial. All clinical evaluations were conducted at the Oral Health Clinical Services LLC in Piscataway, New Jersey, USA. Qualifying subjects were enrolled into the study based on the following criteria:

(i) Subjects had to be between the ages of 18 and 70 (inclusive), in generally good health, with no history of allergies or idiosyncrasies to dentifrice ingredients.

(ii) Subjects were required to possess a minimum of two hypersensitive teeth which were anterior to the molars and demonstrated cervical erosion/abrasion or gingival recession, and for which a tactile hypersensitivity stimulus score of 10 to 50 grams of force (Yeaple Probe) and an air blast stimulus score of 2 or 3 (Schiff Cold Air Sensitivity Scale[33]) were presented at the baseline examination.

(iii) Subjects were required to be available for the three-day duration of the study, and to sign an informed consent form.

(iv) Subjects were excluded from the study if they had gross oral pathology, chronic disease, advanced periodontal disease, treatment for periodontal disease (within the previous 12 months), or hypersensitive teeth with a mobility greater than one. Subjects with teeth that had extensive/defective restorations (including prosthetic crowns), suspected pulpitis, caries, cracked enamel, or that were used as abutments for removable partial dentures, were also excluded from the study.

(v) Subjects were also excluded from the study if they were current users of anticonvulsants, antihistamines, antidepressants, sedatives, tranquilizers, anti-inflammatory drugs, or daily analgesics.

(vi) Pregnant or lactating women, individuals who were participating in any other clinical study or who had participated in a desensitizing study, or who used any desensitizing agents within the previous three months were not allowed to participate in the study.

Qualifying subjects reported to the clinical facility having refrained from all oral hygiene procedures and from chewing gum for eight hours, and from eating and drinking for four hours prior to the conduct of the baseline and subsequent examinations. The tactile-stimulated hypersensitivity measurements were performed first, followed by the air blast stimulated measurements. The two most hypersensitive teeth, based upon the inclusion criteria, were selected for evaluation throughout the study. Subjects were stratified according to mean baseline tactile and air blast hypersensitivity scores, and were randomly assigned within strata to one of the following study treatments: test toothpaste with 8.0% arginine, calcium carbonate, and 1450 ppm MFP (Colgate-Palmolive Co., New York, NY, USA; 8.0% arginine group); desensitizing toothpaste with 5% potassium nitrate and 1450 ppm NaF (Colgate-Palmolive Co., New York, NY, USA; 5% KNO_3 group); and control toothpaste with 1450 ppm MFP (Colgate-Palmolive Co., New York, NY, USA; Control group). All three toothpastes were provided in white over-wrapped tubes to ensure the double-blind design.

The initial phase of the study consisted of applying the assigned toothpaste with a fingertip directly onto the buccal-cervical area of exposed dentin on each of the two baseline-designated hypersensitive teeth per subject. During a supervised session, participants were provided with a facial mirror, and 0.3g or a "pea size" sample of their assigned product, and were instructed to gently massage each sensitive tooth at the cemento-enamel junction with their finger tip for a period of one minute for each tooth. For the second phase of the study, subjects took their assigned product home, and were provided with a soft-bristled toothbrush for unsupervised tooth brushing for a total of three days. At-home brushing instructions to study subjects consisted of brushing their teeth for one minute, twice daily, using only the toothpaste and toothbrush provided, and to refrain from any other oral hygiene procedures throughout the duration of the study. There were no restrictions regarding diet or smoking habits during the course of the study.

Oral soft and hard tissue assessments, as well as tactile and air blast hypersensitivity evaluations of baseline-designated study teeth, were conducted immediately after fingertip topical application of the assigned product and after three days of product use. Subjects were requested to return to the clinical facility for the three-day follow-up visit, having refrained from all oral hygiene procedures and chewing gum for eight hours, and from eating and drinking for four hours prior to their scheduled visit. All examinations were performed by the same dental examiner, using the same procedures as employed at baseline.

Tactile Hypersensitivity Assessment

Hypersensitivity assessment in response to tactile stimuli was done using an Electronic Force Sensing Probe (Yeaple Probe Model 200A, Xinix Research Inc., Portsmouth, NH, USA). Daily calibration of the probe consisted of establishing correlations of the probe meter readings in D-C microamperes, and the gram weight readings using an analytical balance (Model FX-400,

A&D Electronic Company, Japan). Scores were recorded in terms of a quantified, reproducible force (grams) applied by use of an attached #19 explorer tip. After presetting the probe to 10 grams, the probe tip was stroked over the exposed dentin, perpendicular to the examined surface of the hypersensitive teeth. Subsequent passes were made, each time with the applied force increased by 10 grams, until the subject indicated that he/she was experiencing discomfort, or until the maximum force of 50 grams had been reached.[33-35] A force of 50 grams was considered the cut-off point. Higher scores on this index correspond to lower levels of dentin hypersensitivity.

Air Blast Hypersensitivity Assessment

Teeth were evaluated for air blast hypersensitivity by applying cold air from a dental unit at 60 psi (± 5 psi) and a temperature of 70°F (± 3°F) directed perpendicular to the hypersensitive cervical area after isolating the test tooth by covering the two adjacent teeth. The hypersensitive tooth was stimulated for one second at a distance of one centimeter from the cervical area. The Schiff Sensitivity Scale was used to assess subject response to this stimulus. This scale is scored as follows:

0—Subject does not respond to air stimulus;
1—Subject responds to air stimulus, but does not request discontinuation of stimulus;
2—Subject responds to air stimulus and requests discontinuation or moves from stimulus;
3—Subject responds to air stimulus, considers stimulus to be painful, and requests discontinuation of the stimulus.

Only teeth scoring 2 or 3 were selected as study teeth at the baseline evaluation.

Statistical Methods

Dentin hypersensitivity scores for all subjects who completed all the scheduled examinations were included in the statistical analyses. Statistical analyses were performed separately for the tactile hypersensitivity assessments and air blast hypersensitivity assessments. Subject-wise scores were calculated at each hypersensitivity assessment by averaging the values measured on the two baseline-designated study teeth. Comparisons of the treatment groups with respect to baseline tactile scores and air blast scores were performed using analyses of variance (ANOVA). Within-treatment comparisons of the baseline versus follow-up tactile hypersensitivity and air blast hypersensitivity scores were performed using paired t-tests. Comparisons of the treatment groups with respect to baseline-adjusted mean tactile hypersensitivity and air blast hypersensitivity scores at the follow-up examinations were performed using analyses of covariance (ANCOVA). All pair-wise comparisons between the treatment groups *post hoc* were performed using a Tukey's multiple comparison test. All statistical tests of hypotheses were two-sided, and employed a level of significance of $\alpha = 0.05$.

Results

One-hundred and twenty-five subjects complied with the protocol and completed the three-day clinical study. A summary of the gender and age of the study population is presented in Table I. The treatment groups did not differ significantly with respect to either of these characteristics. Throughout the study, there were no adverse effects on the soft or hard tissues of the oral cavity which were observed by the examiner or reported by the subjects when questioned.

Table I
Summary of Age and Gender for Subjects Who Completed the Clinical Study

	Number of Subjects			Age	
Treatment	Male	Female	Total	Mean	Range
8.0% arginine-calcium carbonate[1]	15	27	42	40.8	18–61
5% KNO_3[2]	18	23	41	42.1	18–74
Control[3]	19	23	42	39.5	18–65

[1] Toothpaste containing 8.0% arginine, calcium carbonate, and 1450 ppm MFP.
[2] Toothpaste containing 5% potassium nitrate (KNO_3) and 1450 ppm NaF.
[3] Control toothpaste with 1450 ppm MFP.

Baseline Data

Table II presents a summary of the mean tactile and air blast hypersensitivity scores measured at the baseline examination for those subjects who completed the clinical study. For tactile-induced hypersensitivity, the mean baseline scores were 12.38 for the 8.0% arginine group, 11.95 for the 5% KNO_3 group, and 12.38 for the Control group. For air blast-induced hypersensitivity, the mean baseline scores were 2.33 for the 8.0% arginine group, 2.43 for the 5% KNO_3 group, and 2.23 for the Control group. No statistically significant differences were indicated among the treatment groups with respect to either baseline mean hypersensitivity score.

Table II
Summary of the Baseline Mean Tactile Hypersensitivity and Air Blast Hypersensitivity Scores for Subjects Who Completed the Three-Day Clinical Study

Parameter	Treatment	n	Baseline Summary (Mean ± SD)[4]
Tactile Hypersensitivity	8.0% arginine-calcium carbonate[1]	42	12.38 ± 3.86
	5% KNO_3[2]	41	11.95 ± 3.51
	Control[3]	42	12.38 ± 3.70
Air Blast Hypersensitivity	8.0% arginine-calcium carbonate[1]	42	2.33 ± 0.41
	5% KNO_3[2]	41	2.43 ± 0.44
	Control[3]	42	2.23 ± 0.35

[1] Toothpaste containing 8.0% arginine, calcium carbonate, and 1450 ppm MFP.
[2] Toothpaste containing 5% potassium nitrate (KNO_3) and 1450 ppm NaF.
[3] Control toothpaste with 1450 ppm MFP.
[4] No statistically significant difference was indicated between the three treatment groups at baseline with respect to either tactile hypersensitivity or air blast hypersensitivity scores.

Immediately After Topical Application Data

Tactile Hypersensitivity. Table III presents a summary of the mean tactile hypersensitivity scores measured immediately after fingertip topical self-application of the assigned product. The mean tactile hypersensitivity scores recorded immediately after topical product application were 35.36 for the 8.0% arginine

Table III
Summary of the Immediately After Topical Application Mean Tactile Hypersensitivity Scores for Subjects Who Completed the Three-Day Clinical Study

Treatment	n	Immediately After Topical Application Summary (Mean ± SD)	Within-Treatment Analysis		Between-Treatment Comparison			
					vs. 5% KNO_3		vs. Control	
			Percent Change[4]	Sig.[5]	Percent Difference[6]	Sig.[8]	Percent Difference[7]	Sig.[8]
8.0% arginine-calcium carbonate[1]	42	35.36 ± 8.07	185.6%	$p < 0.05$	161.2%	$p < 0.05$	180.2%	$p < 0.05$
5% KNO_3[2]	41	13.54 ± 4.37	13.3%	$p < 0.05$	—	—	7.3%	NS
Control[3]	42	12.62 ± 3.70	1.9%	NS	—	—	—	—

[1] Toothpaste containing 8.0% arginine, calcium carbonate, and 1450 ppm MFP.
[2] Toothpaste containing 5% potassium nitrate (KNO_3) and 1450 ppm NaF.
[3] Control toothpaste with 1450 ppm MFP.
[4] Percent change exhibited immediately after topical application relative to the baseline mean. A positive value indicates an improvement in mean tactile hypersensitivity immediately after topical application examination.
[5] Significance of paired t-test comparing the baseline and the immediately after topical application examinations.
[6] Difference between the immediately after topical application means expressed as a percentage of the immediately after topical application mean for the toothpaste containing 5% potassium nitrate (KNO_3). A positive value indicates an improvement in mean tactile hypersensitivity scores relative to the toothpaste containing 5% potassium nitrate (KNO_3).
[7] Difference between the immediately after topical application means expressed as a percentage of the immediately after topical application mean for the control toothpaste. A positive value indicates an improvement in mean tactile hypersensitivity scores relative to the Control toothpaste.
[8] Significance of ANCOVA comparison of baseline-adjusted means.

group, 13.54 for the 5% KNO_3 group, and 12.62 for the Control group. The percent changes from baseline were 185.6% for the 8.0% arginine group, 13.3% for the 5% KNO_3 group, and 1.9% for the Control group, of which the 8.0% arginine group and the 5% KNO_3 group were statistically significant.

Relative to the 5% KNO_3 and the Control groups, the 8.0% arginine group exhibited statistically significant improvements in mean tactile hypersensitivity scores immediately after topical product application (161.2% and 180.2%, respectively). Relative to the Control group, the 5% KNO_3 group did not exhibit a statistically significant improvement in mean tactile hypersensitivity scores immediately after topical application of the product (7.3%).

Air Blast Hypersensitivity. Table IV presents a summary of the mean air blast hypersensitivity scores measured immediately after fingertip topical self-application of the assigned product. The mean air blast hypersensitivity scores recorded immediately after topical application of the product were 0.92 for the 8.0% arginine group, 2.29 for the 5% KNO_3 group, and 2.19 for the Control group. The mean percent reductions from baseline were 60.5% for the 8.0% arginine group, 5.8% for the 5% KNO_3 group, and 1.8% for the Control group, of which the 8.0% arginine group and the 5% KNO_3 group were statistically significant.

Relative to the 5% KNO_3 group and the Control group, the 8.0% arginine group exhibited statistically significant reductions in mean air blast hypersensitivity scores immediately after topical application of the product (59.8% and 58.0%, respectively). Relative to the Control group, the 5% KNO_3 group did not exhibit a statistically significant reduction in mean air blast hypersensitivity scores immediately after topical application of the product (–4.6%).

Table IV
Summary of the Immediately After Topical Application Mean Air Blast Hypersensitivity Scores for Subjects Who Completed the Three-Day Clinical Study

Treatment	n	Immediately After Topical Application Summary (Mean ± SD)	Within-Treatment Analysis		Between-Treatment Comparison			
					vs. 5% KNO_3		vs. Control	
			Percent Change[4]	Sig.[5]	Percent Difference[6]	Sig.[8]	Percent Difference[7]	Sig.[8]
8.0% arginine-calcium carbonate[1]	42	0.92 ± 0.57	60.5%	$p < 0.05$	59.8%	$p < 0.05$	58.0%	$p < 0.05$
5% KNO_3[2]	41	2.29 ± 0.49	5.8%	$p < 0.05$	—	—	–4.6%	NS
Control[3]	42	2.19 ± 0.43	1.8%	NS	—	—	—	—

[1] Toothpaste containing 8.0% arginine, calcium carbonate, and 1450 ppm MFP.
[2] Toothpaste containing 5% potassium nitrate (KNO_3) and 1450 ppm NaF.
[3] Control toothpaste with 1450 ppm MFP.
[4] Percent change exhibited immediately after topical application relative to the baseline mean. A positive value indicates an improvement in mean air blast hypersensitivity at the immediately after topical application examination.
[5] Significance of paired t-test comparing the baseline and immediately after topical application examinations.
[6] Difference between the immediately after topical application means expressed as a percentage of the immediately after topical application mean for the toothpaste containing 5% potassium nitrate (KNO_3). A positive value indicates a reduction in mean air blast hypersensitivity scores relative to the toothpaste containing 5% potassium nitrate (KNO_3).
[7] Difference between the immediately after topical application means expressed as a percentage of the immediately after topical application mean for the Control toothpaste. A positive value indicates a reduction in mean air blast hypersensitivity scores relative to the Control toothpaste.
[8] Significance of ANCOVA comparison of baseline-adjusted means.

Three-Day Data

Tactile Hypersensitivity. Table V presents a summary of the mean tactile hypersensitivity scores measured after three days of at-home brushing with the assigned product, subsequent to the single fingertip topical self-application performed at the beginning of the study. The mean three-day tactile hypersensitivity scores were 39.17 for the 8.0% arginine group, 15.85 for the 5% KNO_3 group, and 13.93 for the Control group. The percent changes from baseline were 216.4% for the 8.0% arginine group, 32.6% for the 5% KNO_3 group, and 12.5% for the Control group, of which the 8.0% arginine group and the 5% KNO_3 group were statistically significant.

Relative to the 5% KNO_3 and Control groups, the 8.0% arginine group exhibited statistically significant improvements in mean tactile hypersensitivity scores after three days of product use (147.1% and 181.2%, respectively). Relative to the Control group, the 5% KNO_3 group did not exhibit a statistically significant improvement in mean tactile sensitivity scores after three days of product use (13.8%).

Air Blast Hypersensitivity. Table VI presents a summary of the mean air blast hypersensitivity scores measured after three days of at-home brushing with the assigned product, subsequent to the single fingertip topical self-application performed at the beginning of the study. The mean three-day air blast hypersensitivity scores were 0.60 for the 8.0% arginine group, 2.01 for the 5% KNO_3 group, and 2.06 for the Control group. The mean percent reductions from baseline were 74.2% for the 8.0% arginine group, 17.3% for the 5% KNO_3 group, and 7.6% for the Control group, all of which were statistically significant.

Relative to the 5% KNO_3 and Control groups, the 8.0% arginine toothpaste group exhibited statistically significant reductions in mean air blast hypersensitivity scores after three days of prod-

Table V
Summary of the Three-Day Mean Tactile Hypersensitivity Scores
for Subjects Who Completed the Three-Day Clinical Study

			Within-Treatment Analysis		Between-Treatment Comparison			
					vs. 5% KNO_3		vs. Control	
Treatment	n	Three-Day Summary (Mean ± SD)	Percent Change[4]	Sig.[5]	Percent Difference[6]	Sig.[8]	Percent Difference[7]	Sig.[8]
8.0% arginine-calcium carbonate[1]	42	39.17 ± 7.72	216.4%	$p < 0.05$	147.1%	$p < 0.05$	181.2%	$p < 0.05$
5% KNO_3[2]	41	15.85 ± 5.47	32.6%	$p < 0.05$	—	—	13.8%	NS
Control[3]	42	13.93 ± 6.30	12.5%	NS	—	—	—	—

[1] Toothpaste containing 8.0% arginine, calcium carbonate, and 1450 ppm MFP.
[2] Toothpaste containing 5% potassium nitrate (KNO_3) and 1450 ppm NaF.
[3] Control toothpaste with 1450 ppm MFP.
[4] Percent change exhibited by the three-day mean relative to the baseline mean. A positive value indicates an improvement in mean tactile hypersensitivity at the three-day examination.
[5] Significance of paired t-test comparing the baseline and three-day examinations.
[6] Difference between three-day means expressed as a percentage of the three-day mean for the toothpaste containing 5% potassium nitrate (KNO_3). A positive value indicates an improvement in mean tactile hypersensitivity scores relative to the toothpaste containing 5% potassium nitrate (KNO_3).
[7] Difference between three-day means expressed as a percentage of the three-day mean for the Control toothpaste. A positive value indicates an improvement in mean tactile hypersensitivity scores relative to the Control toothpaste.
[8] Significance of ANCOVA comparison of baseline-adjusted means.

Table VI
Summary of the Three-Day Mean Air Blast Hypersensitivity Scores
for Subjects Who Completed the Three-Day Clinical Study

			Within-Treatment Analysis		Between-Treatment Comparison			
					vs. 5% KNO_3		vs. Control	
Treatment	n	Three-Day Summary (Mean ± SD)	Percent Change[4]	Sig.[5]	Percent Difference[6]	Sig.[8]	Percent Difference[7]	Sig.[8]
8.0% arginine-calcium carbonate[1]	42	0.60 ± 0.47	74.2%	$p < 0.05$	70.1%	$p < 0.05$	70.9%	$p < 0.05$
5% KNO_3[2]	41	2.01 ± 0.71	17.3%	$p < 0.05$	—	—	2.5%	NS
Control[3]	42	2.06 ± 0.43	7.6%	$p < 0.05$	—	—	—	—

[1] Toothpaste containing 8.0% arginine, calcium carbonate, and 1450 ppm MFP.
[2] Toothpaste containing 5% potassium nitrate (KNO_3) and 1450 ppm NaF.
[3] Control toothpaste with 1450 ppm MFP.
[4] Percent change exhibited by the three-day mean relative to the baseline mean. A positive value indicates a reduction in mean air blast hypersensitivity at the three-day examination.
[5] Significance of paired t-test comparing the baseline and three-day examinations.
[6] Difference between three-day means expressed as a percentage of the three-day mean for the toothpaste containing 5% potassium nitrate (KNO_3). A positive value indicates a reduction in mean air blast hypersensitivity scores relative to the toothpaste containing 5% potassium nitrate (KNO_3).
[7] Difference between three-day means expressed as a percentage of the three-day mean for the Control toothpaste. A positive value indicates a reduction in mean air blast hypersensitivity scores relative to the Control toothpaste.
[8] Significance of ANCOVA comparison of baseline-adjusted means.

uct use (70.1% and 70.9%, respectively). Relative to the Control group, the 5% KNO_3 group did not exhibit a statistically significant reduction in mean air blast hypersensitivity scores after three days of product use (2.5%).

Discussion

The objective of this parallel, double-blind, placebo-controlled clinical trial was to evaluate the short-term efficacy of a novel dentin hypersensitivity prevention and control product containing 8.0% arginine, calcium carbonate, and 1450 ppm MFP.

One-hundred and twenty-five subjects with at least two hypersensitive teeth qualified for the study. Participants were assigned to use one of the three tested dentifrices. The baseline-designated study teeth were evaluated before treatment, immediately after a single direct topical self-application of the assigned product, and after three days of twice-daily brushing, using standard tactile and air blast tests.

Desensitizing toothpastes are typically used to help alleviate pain from dentin hypersensitivity by brushing the entire dentition at least twice daily. In contrast, in-office products target application directly onto the affected area. In this study, targeted self-application of a new desensitizing toothpaste was performed by the participants, *i.e.*, the two most sensitive teeth were identified and the participants were instructed to gently massage each sensitive tooth with approximately 0.3 grams of their assigned product using their finger tip for a period of one minute.

Some degree of dentin hypersensitivity relief, as in most pain studies, is expected to come from the placebo effect.[2,8,36,37] It is, therefore, recommended to base conclusions about the efficacy of new products, beyond statistical significance, on hypersensitivity improvements relative to the performance of a negative or positive control.[38] The results of this study showed that the arginine-calcium carbonate toothpaste provided large, and statistically significant reductions in tactile- and air blast-induced dentin hypersensitivity compared to baseline scores of the same study subjects, and compared to the performance of the positive control, potassium-based desensitizing toothpaste, and to the negative control fluoride toothpaste. These dramatic effects were demonstrated at both time points evaluated, *i.e.*, immediately after topical product application and after three days of subsequent brushing with the product. The hypersensitivity relief recorded in the study for the potassium nitrate toothpaste was minimal and did not reach statistical significance compared to the negative control fluoride toothpaste.

The results of this study confirm the outcome of a recently conducted study of identical design.[32] Together, these two studies provide clinical confirmation of the findings of mechanism of action studies. State-of-the-art methods have shown that products containing 8.0% arginine and calcium carbonate seal and plug dentin tubules, thereby preventing fluid flow and the resultant hydrodynamic forces responsible for the perception of pain.[25-27] The mechanism of action study results support the clinical findings that instant relief can be obtained by sealing the dentin tubules through a single direct topical patient-performed application of the product. The clinical study results also show that the instantly afforded efficacy in reducing dentin hypersensitivity is maintained after three days of twice-daily brushing with the product. It has been proposed that the efficacy of potassium salts is due to action on the nerve endings, and is dependent on the concentration gradient.[39] Thus, the onset of relief is dependent on the time it takes to develop and maintain high levels of potassium at the nerve endings.[19,39] This important time factor may explain the lack of efficacy of the potassium-based toothpaste immediately after direct application, and after three days of subsequent twice-daily brushing with the product.

From the clinical perspective, it is generally accepted that dentin hypersensitivity management should be based upon identifying factors that cause dentin hypersensitivity.[2,4,7,14,23] For a therapy to be effective, it is also important to identify and eliminate the predisposing factors.[2,4,23] In terms of dentin hypersensitivity, management has been further complicated because patients modify their behaviors and may neglect oral care to avoid dental pain. Such neglect may lead to increased plaque accumulation and periodontal problems, eventually leading to additional pain and finally tooth loss.[23,41] From the perspective of the afflicted individual, it is important to gain immediate pain relief. Thus, an ideal product is one that provides instant and lasting relief, and is safe, well tolerated, and easy to use. The results of this and two similar clinical trials show that the new toothpaste with 8.0% arginine, calcium carbonate, and 1450 ppm MFP meets these requirements. The results of these studies also indicate that the product is well tolerated, as no adverse effects were noted by any of the clinical investigators or reported by the participants of the studies. The ease of use was demonstrated by the fact that the individuals were able to self-apply the product directly to the affected teeth to relieve pain.[31,32]

The results of the three clinical studies, performed to assess the efficacy of direct topical self-application of a new toothpaste containing 8.0% arginine, calcium carbonate, and 1450 ppm fluoride show that instant and meaningful relief of dentin hypersensitivity can be obtained from use of this novel desensitizing toothpaste. The results also show that this product is easy to use, can be targeted to a specific painful area, and is well tolerated.[31,32]

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The Clinical Effect of a Single Direct Topical Application of a Dentifrice Containing 8.0% Arginine, Calcium Carbonate, and 1450 ppm Fluoride on Dentin Hypersensitivity: The Use of a Cotton Swab Applicator Versus the Use of a Fingertip

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Abstract

- **Objective:** The primary objective of this examiner-blind, randomized clinical study was to compare the effect of a toothpaste containing 8.0% arginine, calcium carbonate, and 1450 ppm fluoride, as sodium monofluorophosphate (MFP), in providing instant relief of dentin hypersensitivity when delivered as a single direct topical application using a cotton swab applicator versus using a fingertip. A secondary objective was to evaluate the effect on dentin hypersensitivity of the dentifrice after seven days of twice-daily at-home brushing, subsequent to the single direct topical application performed at the beginning of the study.
- **Methods:** Qualifying subjects possessed two baseline-designated hypersensitive teeth with a tactile hypersensitivity score of 10 to 50 grams of force (Yeaple Probe), and an air blast hypersensitivity score of 2 or 3 (Schiff Cold Air Sensitivity Scale). In the first phase of the study, subjects topically self-applied the test product using a fingertip, a previously validated method, for one of the hypersensitive teeth (fingertip test teeth), and a cotton swab applicator for the second hypersensitive tooth (swab test teeth). In the second phase of the study, subjects brushed with the test dentifrice twice daily for seven days. Dentin hypersensitivity assessments, as well as examinations of oral hard and soft tissues, were conducted immediately after direct topical product application, and after the subsequent seven-day brushing period.
- **Results:** Eighty-four subjects complied with the study protocol and completed the study. Immediately after direct topical application, the fingertip test teeth and the swab test teeth exhibited statistically significant ($p < 0.05$) improvements from baseline in mean tactile hypersensitivity scores (191.7% and 182.1%, respectively), and mean air blast hypersensitivity scores (58.1% and 56.3%, respectively). After the seven-day brushing period, the fingertip test teeth and the swab test teeth continued to exhibit statistically significant ($p < 0.05$) improvements from baseline in mean tactile hypersensitivity scores (191.7% and 190.5%, respectively) and mean air blast hypersensitivity scores (57.4% and 58.2%, respectively). No statistically significant ($p > 0.05$) differences were indicated between the fingertip test teeth and the swab test teeth with respect to mean tactile hypersensitivity scores or mean air blast hypersensitivity scores immediately after topical application (3.4% and 4.4%, respectively), or after seven days of twice-daily brushing with the product (0.41% and –1.90%, respectively).
- **Conclusion:** The results of this examiner-blind clinical study support the conclusions that 1) both fingertip and cotton swab methods of application provide significant reductions in dentin hypersensitivity immediately after a single direct topical application of the 8.0% arginine-calcium carbonate dentifrice, 2) when topical application is followed by seven days of twice-daily brushing with the dentifrice, the sensitivity relief obtained instantly after topical application is maintained, and 3) after topical application and after seven days of brushing, neither method of topical application provided a level of control of dentin hypersensitivity that differed significantly from the other.

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Introduction

Dentin hypersensitivity has been described as an exaggerated response to non-noxious stimuli and a condition that can be considered as a true pain syndrome.[1] The discomfort experienced with dentin hypersensitivity is a sharp pain of rapid onset. Dentin hypersensitivity can pose a threat to the quality of life for sufferers of the condition. It can affect eating, drinking, and breathing habits,[2] as individuals modify their behavior to avoid dentin stimulation instead of making the decision to seek treatment. Modification of oral care habits as a pain management strategy may include the discontinuation of adequate oral hygiene regimens or failure to comply with specific home care recommendations, leading to additional dental complications.

Certain criteria have been recognized as requirements for the ideal dentin hypersensitivity therapy. These include rapid action, permanently effective, non-irritating to the pulp, non-discoloring to tooth structure, ease of use, and painless upon application.[3] Dentin hypersensitivity sufferers would also benefit from additional desensitizing product attributes like compatibility with fluoride, good taste, cost effectiveness, and wide availability.

The engineering behind available treatment methods for dentin hypersensitivity has been based on the understanding of the hydrodynamic theory, as proposed by Brännström, and on the knowledge of the distinctive histological features of hypersensitive dentin. The hydrodynamic theory explains that the application of stimuli to exposed dentin elicits shifts in fluids within dentin tubules that can lead to the excitation of nerve endings at the pulp-dentin border or within the dentin tubules, triggering a sensation of pain.[4] External stimuli, such as thermal, evaporative, tactile, osmotic, or chemical, usually cause immediate and transient discomfort which subsides shortly after the stimulus is withdrawn. From a clinical perspective, it is evident that not all exposed dentin acts as hyper-conductive dentin, as not all surfaces of exposed dentin are found to be hypersensitive. Scanning electron microscope evaluations of dentin samples have revealed that hypersensitive teeth have exposed dentin tubules that are either completely open or only partially occluded,[5,6] and that the number of tubules per unit area, as well as the diameter of the tubules is greater than in non-hypersensitive teeth.[7] Therapeutic approaches to reduction or elimination of the ability of a stimulus to elicit discomfort have been either to physically modify the fluid flow within the dentin tubules through tubule occlusion, or to chemically interfere with the transmission of nerve impulses.

Desensitizing toothpastes, based upon either the principle of reduction of nerve excitability or reduction of dentin fluid flow, are often recommended as the first-line of treatment for dentin hypersensitivity. As desensitizing toothpastes are typically used to brush the entire dentition, slow onset of action and the lack of targeted delivery to specific hypersensitive sites have been considered product disadvantages.[8] According to published reviews of the literature, consensus statements and expert opinion papers, desensitizing dentifrices for home use are not expected to provide instant relief of dentin hypersensitivity. Most dentifrices for the treatment of dentin hypersensitivity contain potassium salts that work by reducing the excitability of pulpal nerves, rather than blocking open dentin tubules. Typically, significant relief is experienced after four to eight weeks of brushing, although some potassium-based toothpastes have recently been shown to provide significant relief after two to four weeks of twice-daily brushing.[9-14]

Based on their work with salivary components, Kleinberg and colleagues developed a new dentin hypersensitivity treatment, containing arginine bicarbonate and calcium carbonate, which mimics saliva's natural process of plugging and sealing open dentin tubules. This technology has recently been further developed by the Colgate-Palmolive Company, and a dentifrice containing 8.0% arginine, calcium carbonate, and 1450 ppm fluoride, as sodium monofluorophosphate (MFP), has been validated for routine daily use.[10] Two published randomized, double-blind clinical trials have demonstrated that this product provides superior relief of dentin hypersensitivity compared to commercially available desensitizing toothpaste products containing 2% potassium ion, when used twice daily for a period of eight weeks.[16,17] Further, extensive state-of-the art visualization methods have been used successfully to demonstrate the mode of action of this technology, and to show the plug which forms and occludes the tubules is resistant to acid challenge and effectively reduces hypersensitivity by reducing dentin fluid flow to inhibit the hydrodynamic mechanism.[10,18]

Prior to publication of this Special Issue, there was no published evidence to suggest that the use of direct topical application could accelerate the delivery of sensitivity relief and, thereby, enhance the effectiveness of desensitizing toothpastes. Twice-daily brushing was the only clinically supported method of application for desensitizing toothpastes.[11]

This Special Issue reports the results of three clinical studies in which the ability of a new dentifrice containing 8.0% arginine, calcium carbonate, and 1450 ppm fluoride to provide instant relief of dentin hypersensitivity following topical self-application directly to hypersensitive teeth was evaluated.

Two independent double-blind, randomized, controlled clinical studies have demonstrated the efficacy in providing instant sensitivity relief of the new dentifrice as compared to a benchmark desensitizing toothpaste containing 2% potassium ion, dosed as potassium nitrate, and to a 1450 ppm MFP control toothpaste.[19,20] In both of these studies, the products were first topically self-applied directly onto hypersensitive dentin using a fingertip, then the products were used during routine twice-daily tooth brushing for three days. Each of the two studies showed that 1) a single fingertip topical self-application of the 8.0% arginine-calcium carbonate toothpaste directly onto the hypersensitive surface of teeth provides significant immediate improvements in dentin hypersensitivity relative to an identical application of the control toothpaste and to the benchmark potassium-based desensitizing toothpaste, 2) three days of brushing with the 8.0% arginine-calcium carbonate toothpaste, subsequent to the single topical self-application of the product, provides significant improvements in dentin hypersensitivity relative to an identical application of the control toothpaste and to the benchmark potassium-based desensitizing toothpaste, and 3) the immediate improvements in dentin hypersensitivity provided by the 8.0% arginine-calcium carbonate toothpaste after direct topical self-application are maintained after three days of twice-daily brushing.[19,20]

This paper reports the results of the third study, which provides supplementary clinical evidence that topical self-application of the 8.0% arginine-calcium carbonate toothpaste directly onto the hypersensitive surface of teeth affords significant immediate improvements in dentin hypersensitivity. It also demonstrates that seven days of brushing with the 8.0% arginine-calcium carbonate toothpaste, subsequent to the single topical self-application of the product, maintains the significant improvements in dentin hypersensitivity provided by direct topical self-application.

The primary objective of the present study was to assess the ability of the new dentifrice containing 8.0% arginine, calcium carbonate, and 1450 ppm fluoride to provide effective

relief of dentin hypersensitivity immediately after a single direct topical application using a cotton swab applicator, as compared to the previously validated method of using a fingertip. The secondary objective was to compare the sensitivity relief obtained by the two modes of direct topical application dentifrice after seven days of subsequent at-home brushing with the dentifrice.

Materials and Methods

This seven-day clinical study employed an examiner-blind, stratified, two-treatment, single-product design. Eighty-four adult subjects (35 males and 49 females with mean age of 32.45 ± 11.1 years) from the San Francisco, California area were enrolled in the study based upon the following criteria:

(i) Subjects had to be between the ages of 18 and 70 (inclusive), in generally good health, with no history of allergies or idiosyncrasies to dentifrice ingredients.

(ii) Subjects were required to possess a minimum of two hypersensitive teeth, which were anterior to the molars and demonstrated cervical erosion/abrasion or gingival recession, and for which a tactile hypersensitivity stimuli score of 10 to 50 grams of force (Yeaple Probe) and an air blast stimuli score of 2 or 3 (Sensitivity Scale) were presented at the baseline examination.

(iii) Subjects were required to be available for the seven-day duration of the study and to sign an informed consent form.

(iv) Subjects were excluded from the study if they had gross oral pathology, chronic disease, advanced periodontal disease, treatment for periodontal disease (within the previous 12 months), or hypersensitive teeth with a mobility greater than one. Subjects with teeth that had extensive/defective restorations (including prosthetic crowns), suspected pulpitis, caries, cracked enamel, or that were used as abutments for removable partial dentures were also excluded from the study.

(v) Subjects were also excluded from the study if they were current users of anticonvulsants, antihistamines, antidepressants, sedatives, tranquilizers, anti-inflammatory drugs, or daily analgesics.

(vi) Pregnant or lactating women, individuals who were participating in any other clinical study, or who had participated in a desensitizing study, or who used any desensitizing agents within the previous three months were not allowed to participate in the study.

Qualifying subjects reported to the clinical facility having refrained from all oral hygiene procedures, from chewing gum for eight hours, and from eating and drinking for four hours prior to the conduct of baseline examinations. Two hypersensitive teeth per study subject that satisfied the tactile and air blast hypersensitivity enrollment criteria were identified for evaluation throughout the study.

The first phase of the study consisted of each subject directly applying the test product onto the buccal-cervical area of exposed dentin of each of the two baseline-designated hypersensitive teeth. Treatment consisted of two methods of self-application of the test product: 1) topical application using the subject's fingertip, the method previously clinically validated;[19,20] or 2) topical application using a cotton swab applicator. Using a fingertip, subjects self-applied the test product directly onto the surface of one of the hypersensitive teeth and massaged the tooth for sixty seconds. Subjects also used a cotton swab applicator to duplicate the massaging procedure for treatment of the second hypersensitive tooth. Thus, the two treatment groups consisted of baseline-designated study teeth that had the product topically applied with the use of a cotton swab (swab test teeth), and baseline-designated study teeth that had the product topically applied with the use of the subject's fingertip (fingertip test teeth). A randomization list was used to determine, on a per-subject basis, which tooth was to be treated first and by which mode of topical self-application.

The second phase of the study consisted of at-home brushing with the test dentifrice for a total of seven days, using an adult soft-bristled toothbrush which was also provided. At-home brushing instructions required study subjects to brush their teeth for one minute, twice daily, using only the dentifrice and toothbrush provided, and to refrain from any other oral hygiene procedures throughout the duration of the study. There were no restrictions regarding diet or smoking habits during the course of the study.

In addition to baseline evaluations, all subjects were re-evaluated immediately after topical product application and after the seven days of brushing with the product. At each time point, all subjects received a thorough oral evaluation of their oral hard and soft tissues, followed by a careful evaluation of their dentin hypersensitivity using tactile and air blast measures. All examinations were performed by the same investigator throughout the study.

Tactile Hypersensitivity Assessment

Teeth were evaluated for tactile sensitivity using an Electronic Force Sensing Probe (Yeaple Probe Model 200A, Xinix Research Inc., Portsmouth, NH, USA) that was calibrated daily by the study examiner.[21,22] Scores were recorded in terms of a quantified, reproducible force (grams) applied by use of an attached #19 explorer tip. After presetting the probe to 10 grams, the probe tip was stroked over the exposed dentin perpendicular to the examined surface of the hypersensitive teeth. Subsequent passes were made, each time with the applied force increased by 10 grams, until the subject indicated that he/she was experiencing discomfort, or until the maximum force of 50 grams had been reached. A force of 50 grams was considered the cut-off point; higher scores on this index correspond with lower levels of dentin hypersensitivity.

Air Blast Hypersensitivity Assessment

Teeth were evaluated for air blast hypersensitivity in the following manner:

1) The hypersensitive tooth was isolated from the adjacent teeth (mesial and distal) by the placement of the examiner's fingers over the adjacent teeth.
2) Air was delivered from a standard dental unit air syringe at 60 psi (± 5 psi) and 70°F (± 3°F). The air was directed at the exposed buccal surface of the hypersensitive tooth for one second from a distance of approximately 1 cm.

3) The Schiff Cold Air Sensitivity Scale[23] was used to assess subject response to this stimulus. This scale is scored as follows:
   0 = Subject does not respond to air stimulus.
   1 = Subject responds to air stimulus, but does not request discontinuation of stimulus.
   2 = Subject responds to air stimulus and requests discontinuation or moves from stimulus.
   3 = Subject responds to air stimulus, considers stimulus to be painful, and requests discontinuation of the stimulus.

Only teeth scoring 2 or 3 were selected as study teeth at the baseline evaluation.

Statistical Methods

Dentin hypersensitivity scores for all subjects who completed all the scheduled examinations were included in the statistical analyses. Statistical analyses were performed separately for the tactile hypersensitivity assessments and air blast hypersensitivity assessments. Scores for each of the treatment groups, the cotton swab group and the fingertip group, were calculated for each sensitivity assessment by averaging the hypersensitivity scores measured on the respective baseline-designated teeth. Comparisons of the treatment groups with respect to baseline tactile scores and air blast scores were performed using analyses of variance (ANOVA). Within-treatment comparisons of the baseline versus follow-up tactile hypersensitivity and air blast sensitivity scores were performed using paired t-tests. Comparisons of the treatment groups with respect to baseline-adjusted mean tactile hypersensitivity and air blast hypersensitivity scores at the follow-up examinations were performed using analyses of covariance (ANCOVA). All statistical tests of hypotheses were two-sided and employed a level of significance of $\alpha = 0.05$.

Results

All of the 84 subjects initially enrolled at baseline complied with the protocol and completed the seven-day clinical study.

There was no statistically significant ($p > 0.05$) difference between the recorded mean baseline dentin hypersensitivity, tactile or air blast, for teeth assigned to the cotton swab application method (swab test teeth) and teeth assigned to the fingertip application method (fingertip test teeth).

Tactile Hypersensitivity

Table I presents a summary of the mean tactile hypersensitivity scores for each set of test teeth as measured at baseline, immediately after direct topical self-application of the 8.0% arginine-calcium carbonate toothpaste, and after the treatment sequence of topical product application followed by seven days of at-home twice-daily brushing with the product.

Immediately after topical self-application of the test toothpaste, the mean tactile hypersensitivity scores were 29.17 for the fingertip test teeth and 28.21 for the swab test teeth, representing statistically significant ($p < 0.05$) improvements from mean baseline scores of 191.7% and 182.1%, respectively. After seven days of brushing with the test toothpaste, subsequent to topical self-application of the product, the mean tactile hypersensitivity scores were 29.17 for the fingertip test teeth and 29.05 for the swab test teeth, representing statistically significant ($p < 0.05$) improvements from mean baseline scores of 191.7% and 190.5%, respectively.

Table I
Summary of Mean Tactile Hypersensitivity Scores
(Grams of Force with Yeaple Probe)

Treatment	N	Baseline Mean ± SD	Immediately After Topical Application Mean ± SD	After Topical Application and 7 Days of Brushing Mean ± SD
Fingertip Test Teeth	84	10.00 ± 0.00	29.17 ± 2.78*	29.17 ± 2.78*
Swab Test Teeth	84	10.00 ± 0.00	28.21 ± 3.85*	29.05 ± 2.95*

*Mean tactile hypersensitivity score is statistically significantly different from the respective mean baseline score (paired t-test, $p < 0.05$).

There were no statistically significant ($p > 0.05$) differences indicated between the test groups regarding the mean tactile hypersensitivity improvements immediately after topical self-application of the product, or after subsequent brushing with the product for seven days.

Air Blast Hypersensitivity

Table II presents a summary of the mean air blast hypersensitivity scores for each set of test teeth as measured at baseline, immediately after direct topical self-application of the test dentifrice, and after the treatment sequence of topical product application followed by seven days of at-home twice-daily brushing with the test product.

Table II
Summary of Mean Air Blast Hypersensitivity Scores
(Schiff Scale)

Treatment	N	Baseline Mean ± SD	Immediately After Topical Application Mean ± SD	After Topical Application and 7 Days of Brushing Mean ± SD
Fingertip Test Teeth	84	2.55 ± 0.50	1.08 ± 0.28*	1.10 ± 0.30*
Swab Test Teeth	84	2.62 ± 0.49	1.13 ± 0.34*	1.08 ± 0.28*

*Mean air blast hypersensitivity score is statistically significantly different from its respective mean baseline score (paired t-test, $p < 0.05$).

Immediately after topical self-application of the test toothpaste, the mean air blast hypersensitivity scores were 1.08 for the fingertip test teeth and 1.13 for the swab test teeth, representing statistically significant improvements from mean baseline scores of 58.1% and 56.3%, respectively. After seven days of brushing with the test toothpaste, subsequent to topical self-application of the product, the mean air blast hypersensitivity scores were 1.10 for the fingertip test teeth and 1.08 for the swab test teeth, representing statistically significant improvements from mean baseline scores of 57.4% and 58.2%, respectively.

There were no statistically significant differences indicated between the test groups regarding the noted air blast hypersensitivity improvements immediately after topical self-application of the product, or after subsequent brushing with the product for seven days.

Discussion

Dentin hypersensitivity may be one of the most common painful conditions of the oral cavity, yet it is also one of the least

satisfactorily treated.[11] A recent epidemiological study has indicated that this condition affects one out of five adult patients.[24] However, higher prevalence rates, of up to 57%, have been summarized in a recent review.[10] As life expectancy and tooth retention increase, it is anticipated that there will be increased exposure to the multiple etiological and predisposing influences that have been linked to dentin hypersensitivity.[3]

Desensitizing toothpastes are the first-line treatment option that oral care professionals are likely to recommend, as well as the first "remedy" that dentin hypersensitivity sufferers are likely to "self-prescribe." Desensitizing toothpaste represents a treatment option that, given regimen compliance, may be efficacious for most individuals, and is simple to use, cost effective, and widely available.[8,13] However, the slow, gradual build-up of the effects of current commercially available desensitizing toothpastes may discourage sufferers of this distressing condition from achieving compliance to regular and sustained product use. Instead, they may modify their behaviors to avoid inducing pain, and in ways that can further jeopardize their oral health and quality of life. Product characteristics which may increase product compliance include instant onset of desensitizing action, lasting relief, ease of application, and product efficacy.[8]

Two independent double-blind, randomized, controlled clinical studies have demonstrated the superior efficacy in providing instant sensitivity relief of the new dentifrice with 8.0% arginine, calcium carbonate, and 1450 ppm fluoride as compared to a benchmark desensitizing toothpaste containing 2% potassium ion, dosed as potassium nitrate, and to a 1450 ppm MFP control toothpaste.[19,20] In both of these studies, the products were first topically self-applied directly onto hypersensitive dentin using a fingertip, then the products were used during routine twice-daily tooth brushing for three days. Each of the two studies showed that 1) a single fingertip topical self-application of the 8.0% arginine-calcium carbonate toothpaste directly onto the hypersensitive surface of teeth provides significant immediate improvement in dentin hypersensitivity relative to an identical application of the control toothpaste and to the benchmark potassium-based desensitizing toothpaste, 2) three days of brushing with the 8.0% arginine-calcium carbonate toothpaste, subsequent to the single topical self-application of the product, provides significant improvement in dentin hypersensitivity relative to an identical application of the control toothpaste and to the benchmark potassium-based desensitizing toothpaste, and 3) the immediate improvement in dentin hypersensitivity provided by the 8.0% arginine-calcium carbonate toothpaste after direct topical self-application is maintained after three days of twice-daily brushing.[19,20]

The current study confirms the findings of these two studies, and provides supplementary clinical evidence that topical self-application of the 8.0% arginine-calcium carbonate toothpaste directly onto the hypersensitive surface of teeth affords significant immediate improvements in dentin hypersensitivity. The current study also demonstrates that seven days of twice-daily brushing with the 8.0% arginine-calcium carbonate toothpaste, subsequent to the single topical self-application of the product, maintains the significant improvements in dentin hypersensitivity provided by direct topical self-application. Comparison of the results of this study, for the finger test teeth at baseline, immediately after topical application, and after the subsequent brushing periods, with the results of the previous two studies, for the arginine-calcium carbonate "test" group at the same time points, shows a remarkable consistency of study outcomes.[19,20]

The results of the study presented in this paper offer the alternative of using a cotton swab or a fingertip for effective topical application of the arginine-calcium carbonate desensitizing toothpaste to provide instant hypersensitivity relief. Treatment protocols using either method of topical self-application of this desensitizing toothpaste to deliver instant relief, followed by maintenance of the afforded relief through regular twice-daily brushing with the product, are non-invasive, cost effective, and compatible with the simplest at-home oral care regimen.

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Comparing the Efficacy in Reducing Dentin Hypersensitivity of a New Toothpaste Containing 8.0% Arginine, Calcium Carbonate, and 1450 ppm Fluoride to a Benchmark Commercial Desensitizing Toothpaste Containing 2% Potassium Ion: An Eight-Week Clinical Study in Rome, Italy

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Abstract

- **Objective:** The objective of this double-blind dentin hypersensitivity clinical study was to investigate the effectiveness of a new desensitizing toothpaste containing 8.0% arginine, calcium carbonate, and 1450 ppm fluoride as sodium monofluorophosphate (MFP), compared to that of a benchmark commercially available desensitizing toothpaste containing 2% potassium ion, dosed as 5.0% potassium nitrate, and 1450 ppm fluoride as sodium fluoride (NaF).
- **Methods:** A total of 80 subjects were entered into the study, and stratified into two balanced groups according to their baseline mean tactile and mean air blast sensitivity scores. The two groups were randomly assigned to use either the new arginine toothpaste or the benchmark commercially available desensitizing toothpaste containing 2% potassium ion. Subjects were instructed to brush their teeth twice daily (morning and evening) for one minute with their assigned toothpaste and a commercially available soft-bristled toothbrush. Dentin hypersensitivity examinations, which included tactile and air blast sensitivity measures, were conducted at baseline, one week, two weeks, four weeks, and eight weeks. Subject examinations were conducted by the same dental examiner at each examination period.
- **Results:** This clinical study demonstrated that the new toothpaste, containing 8.0% arginine and 1450 ppm fluoride as MFP in a calcium carbonate base, provided a significant reduction in dentin hypersensitivity when used over a period of eight weeks. The study also showed that the new arginine toothpaste provided significantly greater reductions ($p < 0.05$) in dentin hypersensitivity in response to tactile (38.9%, 28.8%, and 11.6%) and air blast (16.8%, 26.4%, and 33.8%) stimuli than the benchmark commercial desensitizing toothpaste containing 2% potassium ion and 1450 ppm fluoride as NaF in a silica base, after two weeks, four weeks, and eight weeks of product use, respectively.
- **Conclusion:** A new toothpaste containing 8.0% arginine, calcium carbonate, and 1450 ppm fluoride as MFP provides significantly increased hypersensitivity relief ($p < 0.05$) as compared to a benchmark commercial desensitizing toothpaste containing 2% potassium ion, dosed as potassium nitrate, after two weeks, four weeks, and eight weeks of product use.

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Introduction

Dentin hypersensitivity, as typically encountered clinically, can be characterized as a sharp pain which arises from exposed dentin in response to an external stimulus, and cannot be explained by any other form of dental pathology. The responsible trigger for such discomfort is usually a thermal (cold temperature), tactile (toothbrush or dental instrument), osmotic (sweet), or dehydrating (air blast) stimulus.[1] In addition, the use of in-home or in-office bleaching kits for cosmetic tooth whitening may trigger or exacerbate dentin hypersensitivity.[2] Dentin hypersensitivity is

typically experienced when the root of the tooth has been exposed to the oral environment as a result of gingival recession. Gingival recession may occur naturally, compounded by poor oral hygiene habits, especially over-zealous tooth brushing, or it may result from surgical or non-surgical periodontal treatment. The prevalence of dentin hypersensitivity is between 60 and 98 percent in patients with periodontitis.[3-5]

Despite the high prevalence of dentin hypersensitivity, some authors have reported that the majority of patients do not seek treatment to desensitize their teeth because they do not perceive dentin hypersensitivity to be a severe oral health problem.[6] Dentin hypersensitivity is most prevalent in the cervical area of the roots, where the cementum is very thin. Periodontal procedures, such as scaling and root planing, may entirely remove this thin cementum layer and induce hypersensitivity or, more correctly, root hypersensitivity. While dentin hypersensitivity most frequently occurs in patients between 20 and 50 years of age, and peaks between 30 and 40 years of age,[7] it may affect patients of any age. It affects women more often than men, though the sex difference rarely is statistically significant. The condition may affect any tooth, but it most often affects canines and premolars;[8,9] the affected teeth tend to vary among studies and populations, and different distribution patterns have been described.[10] As people live longer lives and maintain their dentitions, it is anticipated that there will be an increased demand on dental professionals to manage the sensitivity of cervically exposed dentin, as well as any secondary issues that may arise from the discomfort associated with dentin hypersensitivity. In particular, dentin hypersensitivity may render tooth brushing more difficult in some individuals, with the result that persistent and continued accumulation of dental plaque may increase the incidence of caries, gingivitis, and more serious periodontal problems.[11]

Several theories have been proposed to explain the mechanism of dentin hypersensitivity, which include the odontoblast transducer theory, the dentin receptor theory, and the hydrodynamic theory.[12,13] Scientific evidence supports the hydrodynamic theory and it is generally favored by the dental community to explain hypersensitivity. The hydrodynamic theory[14] (modified by Brännström[15] in 1963) ascribes fluid movement within the dentin tubules as the basis for the transmission of painful sensations. Specifically, it proposes that non-noxious stimuli at the tooth surface cause fluid movement within the dentin tubules, and this affects the pulpal mechanoreceptors and results in the sensation of pain. In 1994, Nähri, *et al.*[16] provided an addendum to the hydrodynamic theory, suggesting that the perception and sensation of pain were directly related to the stimulation of the nerves within the pulp via electrical current. Regardless of the etiology, the problem of dentin hypersensitivity needs to be addressed in order to provide sufferers with improved oral comfort and quality of life. To this end, a number of agents have been proposed to help control dentin hypersensitivity and relieve discomfort. Some have been incorporated into treatments, such as desensitizing toothpastes which can be used by the patient at home. Others have been incorporated into in-office treatments, such as topically applied varnishes which must be applied in the dental office by a dentist or dental hygienist. One approach by which control of dentin sensitivity can be achieved is to reduce the diameter of open dentin tubules in order to limit the displacement of fluids within them (decreased hydrodynamic flow), thereby blocking neurotransmission and decreasing the response to painful stimuli. According to Trowbridge and Silver,[17] this could be achieved by forming an occluding layer on the exposed dentin by use of topical agents that form insoluble precipitates within the tubules, or by blocking the entrance to tubules with plastic resins. This approach has been most extensively applied in professionally administered products. The most common products used by patients to relieve pain from dentin hypersensitivity are desensitizing dentifrices, especially toothpastes containing potassium salts. Potassium salts (*i.e.*, potassium nitrate, potassium citrate, and potassium chloride) have been used extensively as desensitizing agents, based upon a second approach to relief of discomfort. In effect, the potassium ion has a depolarizing effect on electrical nerve conduction causing nerve fibers to be less excitable to the stimuli[18] and this, in turn, reduces the patient's sensation of pain.

Arginine, an amino acid, has been identified as an active ingredient with potential oral health benefits. Kleinberg showed that the application to exposed dentin surfaces of a new technology, comprising arginine bicarbonate and calcium carbonate, physically blocks and seals open dentin tubules.[19] This concept has recently been further evaluated by the Colgate-Palmolive Company, and a novel toothpaste has been developed containing arginine in a calcium carbonate base with 1450 ppm fluoride as sodium monofluorophosphate (MFP). Clinical studies have demonstrated that this toothpaste is highly effective in reducing dentin hypersensitivity, and *in vitro* mechanism of action studies have shown that this novel technology works by robustly occluding dentin tubules.[20-23]

The objective of this eight-week clinical trial was to compare the efficacy in reducing dentin hypersensitivity of a new toothpaste containing 8.0% arginine and 1450 ppm fluoride as MFP in a calcium carbonate base (Colgate-Palmolive Co., New York, NY, USA) to a benchmark commercial desensitizing toothpaste, Sensodyne® Total Care Gentle Whitening, containing 2% potassium ion (as 5.0% potassium nitrate) and 1450 ppm fluoride as NaF in a silica base (GlaxoSmithKline, Weybridge, UK) over an eight-week period. This study essentially replicates two independent eight-week studies conducted in Canada and Italy, respectively, which were previously reported.[21,22]

Materials and Methods

This eight-week, single-center, parallel group, double-blind, stratified, randomized clinical study was conducted in a private practice setting in Rome, Italy. Subjects were recruited from the patient population in a nearby hospital, as well as by advertisement. Eighty subjects, 24 males and 56 females, with a mean age of 39.91 (± 11.2) years, were selected based on the following criteria:

(i) Subjects had to be between 18 and 70 years of age, in generally good health, with no history of allergies or idiosyncrasies to dentifrice ingredients.

(ii) Subjects were required to possess a minimum of two hypersensitive teeth which were anterior to the molars

and demonstrated cervical erosion/abrasion or gingival recession, and for which a tactile hypersensitivity stimuli score of 10 to 50 grams of force (Yeaple Probe) and an air blast stimuli score of 2 or 3 (Cold Air Sensitivity Scale) were presented at the baseline examination.

(iii) Subjects needed to be available for the duration of the study, and to sign an informed consent form.

(iv) Teeth that were abutments for partial dentures and teeth exhibiting extensive or defective restorations, caries, fractures, excessive mobility, or suspected pulpal pathology were not included in the study.

(v) Subjects that had orthodontic appliances, more than one incisor with a prosthetic crown or veneer, tumors of the soft or hard oral tissues, moderate or advanced periodontal disease, or more than one carious lesion were excluded from the study.

(vi) Subjects were also excluded from the study if they were concurrently using medications including analgesics with a potential to mask pain sensation, or if they had used commercially available desensitizing agents within the three-month time frame prior to the study.

(vii) Pregnant women and individuals who were participating in another clinical trial were also excluded.

Qualifying subjects were stratified according to baseline tactile and air blast sensitivity scores, and were randomly assigned within strata to one of the following two study treatments: the new toothpaste containing 8.0% arginine (Test Dentifrice) or Sensodyne Total Care Gentle Whitening Toothpaste (Control Dentifrice). Both toothpastes were provided in original tubes, over-wrapped with opaque white paper to ensure the double-blind design. Subjects were also given a soft-bristle toothbrush and instructed to brush their teeth twice a day (morning and evening) for one minute each time. A log of the dispensed products was kept, and all clinical supplies were refurbished as needed.

After the baseline evaluation, subjects were re-evaluated at one, two, four, and eight weeks. At each time point, they received a thorough oral examination of their hard and soft tissues, followed by a careful evaluation of their dentin hypersensitivity using the Yeaple probe and the air/water syringe. All examinations were performed by the same investigator throughout the study.

Tactile Sensitivity Assessment

Tactile sensitivity was assessed using a calibrated Model 200A Yeaple Electronic Pressure Sensitive Probe (Yeaple Research, Pittsford, NY, USA). Scores were recorded in terms of a quantified, reproducible force (grams).[24-26] After presetting the force to 10 grams, the probe tip was passed over the exposed dentin on the buccal surface of the selected teeth, apical to the cemento-enamel junction. Subsequent passes were made, each time with the applied force increased by 10 grams until the subject indicated that he/she was experiencing discomfort, or until the maximum force of 50 grams had been reached. A force of 50 grams was considered the cut-off point. Higher scores on this index correspond to lower levels of dentin hypersensitivity.

Air Blast Sensitivity Assessment

Air blast sensitivity was assessed by directing a one-second blast of air onto the exposed buccal root surface of the sensitive tooth, from a distance of one centimeter, using the air component of a dental air/water syringe. After shielding the adjacent proximal teeth from the air blast through the placement of two fingers, the air blast was applied with a pressure of 60 p.s.i. (± 5 p.s.i) and a temperature of 70˚F (± 3˚F) for one second. Sensitivity was recorded in accordance with the air sensitivity scale as described by Schiff, *et al.*[26] as follows:

0 = Tooth/Subject does not respond to air stimulus.

1 = Tooth/Subject responds to air stimulus, but does not request discontinuation of stimulus.

2 = Tooth/Subject responds to air stimulus, and requests discontinuation or moves from stimulus.

3 = Tooth/Subject responds to air stimulus, considers the stimulus to be painful, and requests discontinuation of the stimulus.

Only teeth with a score of 2 or 3 were selected at the baseline examination. Higher scores correspond to higher sensitivity.

Statistical Methods

Subject-wise scores in tactile and air blast were calculated by averaging the values measured on the two baseline-designated study teeth. Statistical analyses were performed separately for the tactile sensitivity assessments and air blast sensitivity assessments. Comparisons of the treatment groups with respect to baseline tactile scores and air blast scores were performed using an independent t-test. Within-treatment comparisons of the baseline versus follow-up tactile sensitivity and air blast sensitivity scores were performed using paired t-tests. Comparisons of the treatment groups with respect to baseline-adjusted tactile sensitivity and air blast sensitivity scores at the follow-up examinations were performed using analyses of covariance (ANCOVA). All statistical tests of hypotheses were two-sided, and employed a level of significance of $\alpha = 0.05$.

Results

All eighty (80) subjects complied with the protocol and completed the eight-week clinical study. A summary of the demographics of the study population is presented in Table I. The treatment groups did not differ significantly with respect to age characteristics.

Throughout the study, there were no adverse events on the soft or hard tissues of the oral cavity which were observed by the examiner, or reported by the subjects when questioned.

Baseline Data

Table II presents a summary of the mean tactile and air blast scores measured at the baseline examination for those subjects who completed the clinical study. For tactile sensitivity, the mean baseline scores were 11.75 for the Test Dentifrice group and 11.50 for the Control Dentifrice group. For air blast sensitivity, the mean baseline scores were 2.49 for the Test Dentifrice group and 2.39 for the Control Dentifrice group. No statistically significant difference was indicated between the treatment groups with respect to either sensitivity score at baseline.

Table I
Summary of Age and Gender for
Subjects Who Completed the Clinical Study

Treatment	Number of Subjects			Age	
	Male	Female	Total	Mean	Range
Test Denifrice[1]	11	29	40	39.10	19–63
Control Dentrifice[2]	13	27	40	40.72	19–70

[1] Colgate toothpaste containing 8.0% arginine and 1450 ppm fluoride as MFP in a calcium carbonate base.
[2] Sensodyne Total Care Gentle Whitening Toothpaste containing 2% potassium ion as 5% potassium nitrate and 1450 ppm fluoride as NaF in a silica base.

Table II
Summary of the Baseline Mean Tactile and
Air Blast Hypersensitivity Scores for Subjects
Who Completed the Eight-Week Clinical Study

Parameter	Treatment	n	Baseline Scores (Mean ± SD)[3]
Tactile Sensitivity	Test Dentifrice[1]	40	11.75 ± 3.11
	Control Dentifrice[2]	40	11.50 ± 3.24
Air Blast Sensitivity	Test Dentifrice[1]	40	2.49 ± 0.42
	Control Dentifrice[2]	40	2.39 ± 0.33

[1] Colgate toothpaste containing 8.0% arginine and 1450 ppm MFP fluoride in a calcium carbonate base.
[2] Sensodyne Total Care Gentle Whitening Toothpaste containing 2% potassium ion as 5% potassium nitrate and 1450 ppm fluoride as NaF in a silica base.
[3] No statistically significant difference was indicated between the two treatment groups at baseline with respect to either mean tactile sensitivity or mean air blast sensitivity scores.

One-Week Data

Tactile Sensitivity. Table III presents a summary of the mean tactile sensitivity scores measured after one week of product use. The one-week mean tactile sensitivity scores were 17.25 for the Test Dentifrice group and 13.38 for the Control Dentifrice group. Compared to baseline, the percent changes were 46.8% for the Test Dentifrice group and 16.3% for the Control Dentifrice group, both of which were statistically significantly different from baseline. Relative to the Control Dentifrice group, the Test Dentifrice group exhibited a statistically significant 28.9% improvement in mean tactile sensitivity scores after one week of product use.

Table III
Summary of the One-Week Mean Tactile Sensitivity Scores
for Subjects Who Completed the Eight-Week Clinical Study

Treatment	n	One-Week Tactile Sensitivity Scores (Mean ± SD)	Within-Treatment Analysis		Between-Treatment Comparison	
			Percent Change[3]	Sig.[4]	Percent Difference[5]	Sig.[6]
Test Dentifrice[1]	40	17.25 ± 8.08	46.8%	$p < 0.05$	28.9%	$p < 0.05$
Control Dentifrice[2]	40	13.38 ± 4.44	16.3%	$p < 0.05$		

[1] Colgate toothpaste containing 8.0% arginine and 1450 ppm fluoride as MFP in a calcium carbonate base.
[2] Sensodyne Total Care Gentle Whitening Toothpaste containing 2% potassium ion as 5% potassium nitrate and 1450 ppm fluoride as NaF in a silica base.
[3] Percent change exhibited by the one-week mean relative to the baseline mean. A positive value indicates an improvement in tactile sensitivity at the one-week examination.
[4] Significance of paired t-test comparing the baseline and one-week examinations.
[5] Difference between one-week means expressed as a percentage of the one-week mean for the Control Dentifrice. A positive value indicates an improvement in tactile sensitivity for the Test Dentifrice containing 8.0% arginine relative to the Control Dentifrice.
[6] Significance of ANCOVA comparison of baseline-adjusted means.

Air Blast Sensitivity. Table IV presents a summary of the mean air blast sensitivity scores measured after one week of product use. The one-week mean air blast sensitivity scores were 1.98 for the Test Dentifrice group and 2.05 for the Control Dentifrice group. The mean percent reductions from baseline were 20.5% for the Test Dentifrice group and 14.2% for the Control Dentifrice group, both of which were statistically significantly different from baseline. There was no statistically significant difference indicated between the treatment groups with respect to mean air blast sensitivity scores after one week of product use.

Table IV
Summary of the One-Week Mean Air Blast Sensitivity Scores
for Subjects Who Completed the Eight-Week Clinical Study

Treatment	n	One-Week Air Blast Sensitivity Scores (Mean ± SD)	Within-Treatment Analysis		Between-Treatment Comparison	
			Percent Change[3]	Sig.[4]	Percent Difference[5]	Sig.[6]
Test Dentifrice[1]	40	1.98 ± 0.63	20.5%	$p < 0.05$	3.4%	NS
Control Dentifrice[2]	40	2.05 ± 0.39	14.2%	$p < 0.05$		

[1] Colgate toothpaste containing 8.0% arginine and 1450 ppm fluoride as MFP in a calcium carbonate base.
[2] Sensodyne Total Care Gentle Whitening Toothpaste containing 2% potassium ion as 5% potassium nitrate and 1450 ppm fluoride as NaF in a silica base.
[3] Percent change exhibited by the one-week mean relative to the baseline mean. A positive value indicates an improvement in air blast sensitivity at the one-week examination.
[4] Significance of paired t-test comparing the baseline and one-week examinations.
[5] Difference between one-week means expressed as a percentage of the one-week mean for the Control Dentifrice. A positive value indicates an improvement in air blast sensitivity for the Test Dentifrice containing 8.0% arginine relative to the Control Dentifrice.
[6] Significance of ANCOVA comparison of baseline-adjusted means.

Two-Week Data

Tactile Sensitivity. Table V presents a summary of the mean tactile sensitivity scores measured after two weeks of product use. The two-week mean tactile sensitivity scores were 25.87 for the Test Dentifrice group and 18.63 for the Control Dentifrice group. The percent changes from baseline were 120.2% for the Test Dentifrice group and 62.0% for the Control Dentifrice group, both of which were statistically significantly different from baseline. Relative to the Control Dentifrice group, the Test Dentifrice group exhibited a statistically significant 38.9% improvement in mean tactile sensitivity scores after two weeks of product use.

Air Blast Sensitivity. Table VI presents a summary of the mean air blast sensitivity scores measured after two weeks of product use. The two-week mean air blast sensitivity scores were 1.59 for the Test Dentifrice group and 1.91 for the Control Dentifrice group. The mean percent reductions from baseline were 36.1% for the Test Dentifrice group and 19.2% for the Control Dentifrice group, both of which were statistically significantly different from baseline. Relative to the Control Dentifrice group, the Test Dentifrice group exhibited a statistically

Table V
Summary of the Two-Week Mean Tactile Sensitivity Scores for Subjects Who Completed the Eight-Week Clinical Study

Treatment	n	Tactile Sensitivity Scores (Mean ± SD)	Within-Treatment Analysis: Percent Change[3]	Within-Treatment Analysis: Sig.[4]	Between-Treatment Comparison: Percent Difference[5]	Between-Treatment Comparison: Sig.[6]
Test Dentifrice[1]	40	25.87 ± 8.16	120.2%	p < 0.05	38.9%	p < 0.05
Control Dentifrice[2]	40	18.63 ± 4.67	62.0%	p < 0.05		

[1] Colgate toothpaste containing 8.0% arginine and 1450 ppm fluoride as MFP in a calcium carbonate base.
[2] Sensodyne Total Care Gentle Whitening Toothpaste containing 2% potassium ion as 5% potassium nitrate and 1450 ppm fluoride as NaF in a silica base.
[3] Percent change exhibited by the two-week mean relative to the baseline mean. A positive value indicates an improvement in tactile sensitivity at the two-week examination.
[4] Significance of paired t-test comparing the baseline and two-week examinations.
[5] Difference between two-week means expressed as a percentage of the two-week mean for the Control Dentifrice. A positive value indicates an improvement in tactile sensitivity for the Test Dentifrice containing 8.0% arginine relative to the Control Dentifrice.
[6] Significance of ANCOVA comparison of baseline-adjusted means.

Table VI
Summary of the Two-Week Mean Air Blast Sensitivity Scores for Subjects Who Completed the Eight-Week Clinical Study

Treatment	n	Air Blast Sensitivity Scores (Mean ± SD)	Within-Treatment Analysis: Percent Change[3]	Within-Treatment Analysis: Sig.[4]	Between-Treatment Comparison: Percent Difference[5]	Between-Treatment Comparison: Sig.[6]
Test Dentifrice[1]	40	1.59 ± 0.59	36.1%	p < 0.05	16.8%	p < 0.05
Control Dentifrice[2]	40	1.91 ± 0.36	19.2%	p < 0.05		

[1] Colgate toothpaste containing 8.0% arginine and 1450 ppm fluoride as MFP in a calcium carbonate base.
[2] Sensodyne Total Care Gentle Whitening Toothpaste containing 2% potassium ion as 5% potassium nitrate and 1450 ppm fluoride as NaF in a silica base.
[3] Percent change exhibited by the two-week mean relative to the baseline mean. A positive value indicates an improvement in air blast sensitivity at the two-week examination.
[4] Significance of paired t-test comparing the baseline and two-week examinations.
[5] Difference between two-week means expressed as a percentage of the two-week mean for the Control Dentifrice. A positive value indicates an improvement in air blast sensitivity for the Test Dentifrice containing 8.0% arginine relative to the Control Dentifrice.
[6] Significance of ANCOVA comparison of baseline-adjusted means.

significant 16.8% reduction in mean air blast sensitivity scores after two weeks of product use.

Four-Week Data

Tactile Sensitivity. Table VII presents a summary of the mean tactile sensitivity scores measured after four weeks of product use. The four-week mean tactile sensitivity scores were 40.75 for the Test Dentifrice group and 31.62 for the Control Dentifrice group. The percent changes from baseline were 246.8% for the Test Dentifrice group and 175.0% for the Control Dentifrice group, both of which were statistically significantly different from baseline. Relative to the Control Dentifrice group, the Test Dentifrice group exhibited a statistically significant 28.9% improvement in mean tactile sensitivity scores after four weeks of product use.

Air Blast Sensitivity. Table VIII presents a summary of the mean air blast sensitivity scores measured after four weeks of

Table VII
Summary of the Four-Week Mean Tactile Sensitivity Scores for Subjects Who Completed the Eight-Week Clinical Study

Treatment	n	Tactile Sensitivity Scores (Mean ± SD)	Within-Treatment Analysis: Percent Change[3]	Within-Treatment Analysis: Sig.[4]	Between-Treatment Comparison: Percent Difference[5]	Between-Treatment Comparison: Sig.[6]
Test Dentifrice[1]	40	40.75 ± 7.30	246.8%	p < 0.05	28.9%	p < 0.05
Control Dentifrice[2]	40	31.62 ± 8.04	175.0%	p < 0.05		

[1] Colgate toothpaste containing 8.0% arginine and 1450 ppm fluoride as MFP in a calcium carbonate base.
[2] Sensodyne Total Care Gentle Whitening Toothpaste containing 2% potassium ion as 5% potassium nitrate and 1450 ppm fluoride as NaF in a silica base.
[3] Percent change exhibited by the four-week mean relative to the baseline mean. A positive value indicates an improvement in tactile sensitivity at the four-week examination.
[4] Significance of paired t-test comparing the baseline and four-week examinations.
[5] Difference between four-week means expressed as a percentage of the four-week mean for the Control Dentifrice. A positive value indicates an improvement in tactile sensitivity for the Test Dentifrice containing 8.0% arginine relative to the Control Dentifrice.
[6] Significance of ANCOVA comparison of baseline-adjusted means.

Table VIII
Summary of the Four-Week Mean Air Blast Sensitivity Scores for Subjects Who Completed the Eight-Week Clinical Study

Treatment	n	Air Blast Sensitivity Scores (Mean ± SD)	Within-Treatment Analysis: Percent Change[3]	Within-Treatment Analysis: Sig.[4]	Between-Treatment Comparison: Percent Difference[5]	Between-Treatment Comparison: Sig.[6]
Test Dentifrice[1]	40	0.89 ± 0.82	64.3%	p < 0.05	26.4%	p < 0.05
Control Dentifrice[2]	40	1.21 ± 0.37	49.4%	p < 0.05		

[1] Colgate toothpaste containing 8.0% arginine and 1450 ppm fluoride as MFP in a calcium carbonate base.
[2] Sensodyne Total Care Gentle Whitening Toothpaste containing 2% potassium ion as 5% potassium nitrate and 1450 ppm fluoride as NaF in a silica base.
[3] Percent change exhibited by the four-week mean relative to the baseline mean. A positive value indicates an improvement in air blast sensitivity at the four-week examination.
[4] Significance of paired t-test comparing the baseline and four-week examinations.
[5] Difference between four-week means expressed as a percentage of the four-week mean for the Control Dentifrice. A positive value indicates an improvement in air blast sensitivity for the Test Dentifrice containing 8.0% arginine relative to the Control Dentifrice.
[6] Significance of ANCOVA comparison of baseline-adjusted means.

product use. The four-week mean air blast sensitivity scores were 0.89 for the Test Dentifrice group and 1.21 for the Control Dentifrice group. The mean percent reductions from baseline were 64.3% for the Test Dentifrice group and 49.4% for the Control Dentifrice group, both of which were statistically significantly different from baseline. Relative to the Control Dentifrice group, the Test Dentifrice group exhibited a statistically significant 26.4% reduction in mean air blast sensitivity scores after four weeks of product use.

Eight-Week Data

Tactile Sensitivity. Table IX presents a summary of the mean tactile sensitivity scores measured after eight weeks of product use. The eight-week mean tactile sensitivity scores were 45.63 for the Test Dentifrice group and 40.88 for the Control Dentifrice group. The percent changes from baseline were 288.3% for the

Table IX
Summary of the Eight-Week Mean Tactile Sensitivity Scores for Subjects Who Completed the Eight-Week Clinical Study

Treatment	n	Tactile Sensitivity Scores (Mean ± SD)	Within-Treatment Analysis: Percent Change[3]	Within-Treatment Analysis: Sig.[4]	Between-Treatment Comparison: Percent Difference[5]	Between-Treatment Comparison: Sig.[6]
Test Dentifrice[1]	40	45.63 ± 3.95	288.3%	$p < 0.05$	11.6%	$p < 0.05$
Control Dentifrice[2]	40	40.88 ± 5.18	255.5%	$p < 0.05$		

[1] Colgate toothpaste containing 8.0% arginine and 1450 ppm fluoride as MFP in a calcium carbonate base.
[2] Sensodyne Total Care Gentle Whitening Toothpaste containing 2% potassium ion as 5% potassium nitrate and 1450 ppm fluoride as NaF in a silica base.
[3] Percent change exhibited by the eight-week mean relative to the baseline mean. A positive value indicates an improvement in tactile sensitivity at the eight-week examination.
[4] Significance of paired t-test comparing the baseline and eight-week examinations.
[5] Difference between eight-week means expressed as a percentage of the eight-week mean for the Control Dentifrice. A positive value indicates an improvement in tactile sensitivity for the Test Dentifrice containing 8.0% arginine relative to the Control Dentifrice.
[6] Significance of ANCOVA comparison of baseline-adjusted means.

Test Dentifrice group and 255.5% for the Control Dentifrice group, both of which were statistically significantly different from baseline. Relative to the Control Dentifrice group, the Test Dentifrice group exhibited a statistically significant 11.6% improvement in mean tactile sensitivity scores after eight weeks of product use.

Air Blast Sensitivity. Table X presents a summary of the mean air blast sensitivity scores measured after eight weeks of product use. The eight-week mean air blast sensitivity scores were 0.45 for the Test Dentifrice group and 0.68 for the Control Dentifrice group. The mean percent reductions from baseline were 81.9% for the Test Dentifrice group and 71.5% for the Control Dentifrice group, both of which were statistically significantly different from baseline. Relative to the Control Dentifrice group, the Test Dentifrice group exhibited a statistically significant 33.8% reduction in mean air blast sensitivity scores after eight weeks of product use.

Table X
Summary of the Eight-Week Mean Air Blast Sensitivity Scores for Subjects Who Completed the Eight-Week Clinical Study

Treatment	n	Air Blast Sensitivity Scores (Mean ± SD)	Within-Treatment Analysis: Percent Change[3]	Within-Treatment Analysis: Sig.[4]	Between-Treatment Comparison: Percent Difference[5]	Between-Treatment Comparison: Sig.[6]
Test Dentifrice[1]	40	0.45 ± 0.34	81.9%	$p < 0.05$	33.8%	$p < 0.05$
Control Dentifrice[2]	40	0.68 ± 0.31	71.5%	$p < 0.05$		

[1] Colgate toothpaste containing 8.0% arginine and 1450 ppm fluoride as MFP in a calcium carbonate base.
[2] Sensodyne Total Care Gentle Whitening Toothpaste containing 2% potassium ion as 5% potassium nitrate and 1450 ppm fluoride as NaF in a silica base.
[3] Percent change exhibited by the eight-week mean relative to the baseline mean. A positive value indicates an improvement in air blast sensitivity at the eight-week examination.
[4] Significance of paired t-test comparing the baseline and eight-week examinations.
[5] Difference between eight-week means expressed as a percentage of the eight-week mean for the Control Dentifrice. A positive value indicates an improvement in air blast sensitivity for the Test Dentifrice containing 8.0% arginine relative to the Control Dentifrice.
[6] Significance of ANCOVA comparison of baseline-adjusted means.

Discussion

Although dentin hypersensitivity is a relatively common problem seen in daily clinical practice, it has been reported to be under-treated.[27] Several reasons have been identified, which include that dental professionals are not routinely trained in the science of dentin hypersensitivity, and so may lack understanding of the causes, diagnosis, and management of sensitivity.[27] The condition should be diagnosed only after excluding other possible causes of pain, such as pain arising from a chipped or fractured tooth, cracked cusps, carious lesions, or leaky restorations. Dentin hypersensitivity is characterized by a sharp transient pain evoked by thermal, mechanical, evaporative, osmotic, or chemical stimuli, and it may affect eating, drinking, brushing teeth, and breathing.[28] This condition affects nearly 40 million Americans,[2] approximately one in five adults, and can be seen in all age groups.[3] Patients who have received periodontal therapy are four times more at risk of developing hypersensitivity than the general population.[4] Epidemiological research suggests that prevalence peaks between 30 and 40 years of age, and that women experience a higher incidence of dentin hypersensitivity at a younger age than men.[3] As individuals retain their dentitions for longer periods, and as diets change, it is reasonable to expect that there will be a higher incidence of oral complaints related to dentin hypersensitivity, and with that an increase in requests for treatment. Thus, there is an increasing need for the dental team to understand the biology, etiology, as well as the modalities of treatment of dentin hypersensitivity.

Active management of dentin hypersensitivity usually involves a combination of at-home and in-office treatments. In practice, the regimen adopted will depend on the severity of the condition reported by the patient, as well as the number of teeth involved. Active treatment could begin with an at-home method, such as a desensitizing dentifrice. This alone may alleviate the condition; otherwise an in-office treatment will be used.[29] Dental practitioners should educate patients on how to use dentifrices properly, and should monitor their tooth brushing techniques.

Potassium salts have been added to dentifrices as sensitivity-reducing agents for many years. There is a body of clinical evidence demonstrating that potassium-based toothpastes are effective in reducing dentin hypersensitivity; however, some investigators have suggested that potassium-based toothpastes are no more effective than regular fluoride toothpaste in this regard.[20] In addition, the exact mechanism of action is not completely elucidated. It is believed that delivering and maintaining a high level of extra-cellular potassium ions deep in the dentin tubules and around the nerve endings causes depolarization of nerve fiber membranes and prevents repolarization.[18] A second route investigated by the dental research community is to occlude dentin tubules, or at least reduce their diameter, with a technology that coats the dentin surface and fills the openings of the tubules. This approach has primarily been used to manage sensitivity in the form of professional products applied by dental professionals, and has included using either a varnish or precipitates.[30] Such an approach impairs or limits the displacement of

fluids in the dentin tubule, *i.e.*, hydrodynamic flow, and results in the blockage of painful stimuli. While several *in vitro* studies have shown occlusion of dentin tubules with calcium phosphate,[30-33] there is a paucity of clinical data proving efficacy *in vivo.*

An essential amino acid, arginine was first isolated from a lupin seedling extract in 1886 by the Swiss chemist Ernst Schultze, and has been investigated as arginine bicarbonate together with calcium carbonate for its ability to occlude dentin tubules and reduce pain from dentin hypersensitivity.[19] This technology has recently been further developed by the Colgate-Palmolive Company, resulting in a highly effective toothpaste containing 8.0% arginine, calcium carbonate, and 1450 ppm fluoride as sodium monofluorophosphate.[20]

The results from the present clinical investigation clearly show that the new arginine toothpaste and the Sensodyne Total Care Gentle Whitening toothpaste, containing 2% potassium ion as potassium nitrate, were both effective in treating dentin hypersensitivity when used twice daily for a period of eight weeks. At all time points post-baseline, increases in tactile scores and decreases in air blast scores were observed, reflecting relief of dentin hypersensitivity. Importantly, this clinical study also demonstrates that the new arginine toothpaste provides a level of control of dentin hypersensitivity that is significantly better ($p < 0.05$) than Sensodyne Total Care Gentle Whitening toothpaste after two, four, and eight weeks of product use.

The results of this clinical study, together with the results of two similar studies conducted in Canada[21] and Italy,[22] confirm the superior efficacy of the new arginine-calcium carbonate toothpaste in treating dentin hypersensitivity as compared to benchmark commercial desensitizing toothpastes, containing 2% potassium ion as the anti-sensitivity agent, marketed under the Sensodyne brand name.

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