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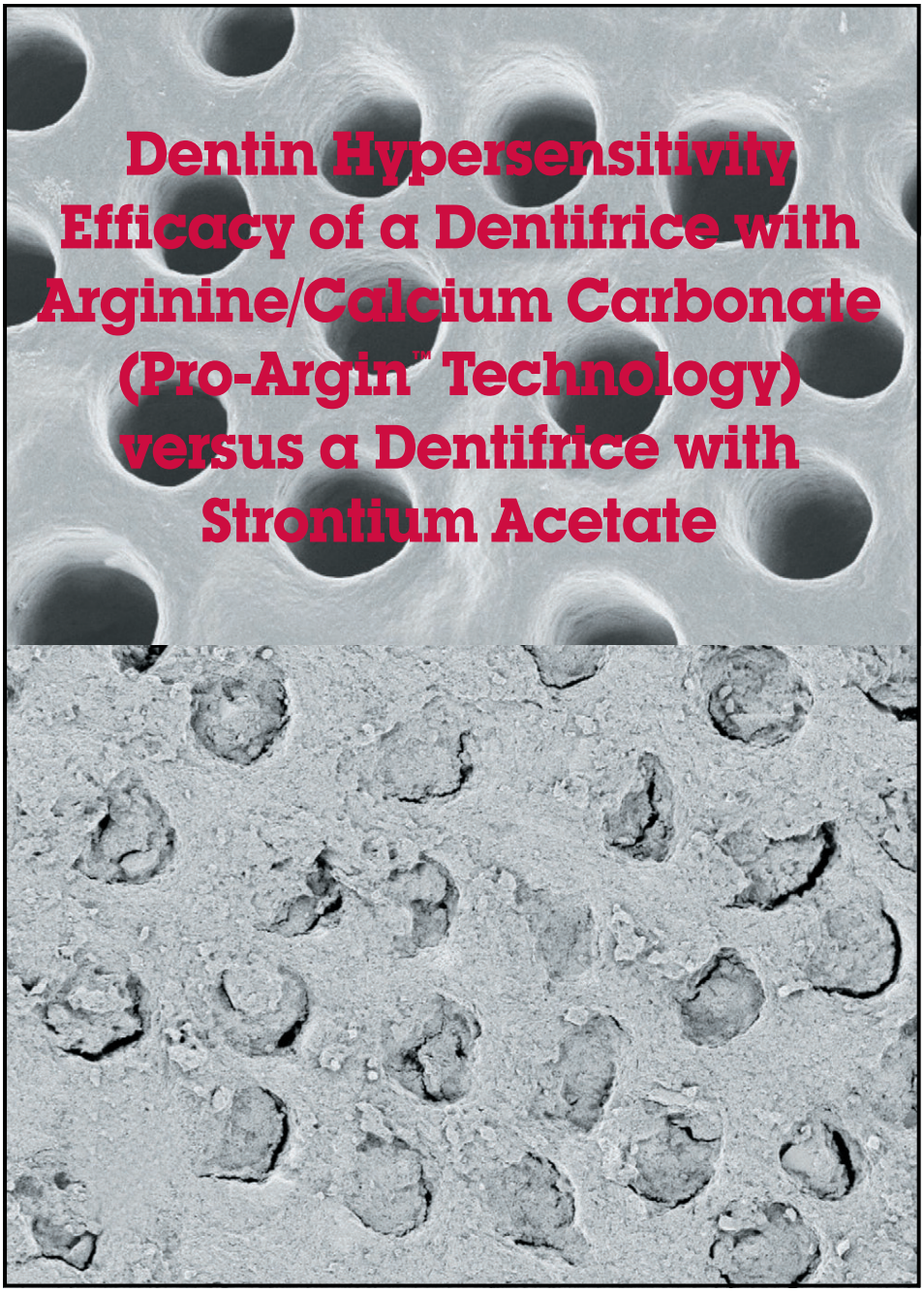
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On the cover, the top image is the surface of a dentin disk showing open tubules. The bottom image is the surface of a dentin disk treated with the arginine/calcium carbonate (Pro-Argin™ Technology) dentifrice. Complete occlusion of the tubules is evident from *in vitro* testing. The images were taken by a field emission Scanning Electron Microscope (SEM).

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# Contents

Clinical Evidence for the Superior Efficacy of a Dentifrice Containing 8.0% Arginine and Calcium Carbonate in Providing Instant and Lasting Relief of Dentin Hypersensitivity ..... 97
***D. Cummins***

Advances in the Clinical Management of Dentin Hypersensitivity: A Review of Recent Evidence for the Efficacy of Dentifrices in Providing Instant and Lasting Relief ..... 100
***D. Cummins***

Comparison of the Effects on Dentin Permeability of Two Commercially Available Sensitivity Relief Dentifrices ..... 108
***R. Patel, S. Chopra, M. Vandeven, D. Cummins***

Comparison of Clinical Efficacy of Three Toothpastes in Reducing Dentin Hypersensitivity ..... 113
***Yiming Li, Sean Lee, Yun Po Zhang, Evaristo Delgado, William DeVizio, Luis R. Mateo***

Comparative Evaluation of the Efficacy of Three Commercially Available Toothpastes on Dentin Hypersensitivity Reduction: An Eight-Week Clinical Study ..... 121
***Raffaella Docimo, Cesare Perugia, Martina Bartolino, Paolo Maturo, Luigi Montesani, Yun Po Zhang, William DeVizio, Luis R. Mateo, Serge Dibart***

Clinical Efficacy in Reducing Dentin Hypersensitivity of a Dentifrice Containing 8.0% Arginine, Calcium Carbonate, and 1450 ppm Fluoride Compared to a Dentifrice Containing 8% Strontium Acetate and 1040 ppm Fluoride Under Consumer Usage Conditions Before and After Switch-Over ..... 128
***T. Schiff, L.R. Mateo, E. Delgado, D. Cummins, Y.P. Zhang, W. DeVizio***

# Clinical Evidence for the Superior Efficacy of a Dentifrice Containing 8.0% Arginine and Calcium Carbonate in Providing Instant and Lasting Relief of Dentin Hypersensitivity

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**Overview**

This paper briefly discusses recent scientific and clinical research validating the effectiveness of a toothpaste containing 8.0% arginine and calcium carbonate, known as Pro-Argin™ technology, including clinical evidence for the superior efficacy of this toothpaste versus a potassium-based desensitizing toothpaste. It also introduces new clinical data which prove that a toothpaste containing 8.0% arginine and calcium carbonate delivers superior instant and lasting relief of dentin hypersensitivity compared to a toothpaste containing 8% strontium acetate.

**(J Clin Dent 2011;22[Spec Iss]:97–99)**

## Introduction

Recently, a breakthrough technology based on 8.0% arginine and calcium carbonate has been introduced that offers a step-change improvement in the treatment of dentin hypersensitivity.[1-3] Research has demonstrated that the technology provides rapid, complete, and robust occlusion of exposed and open dentin tubules.[4,5] Multiple independent clinical studies have proven that the technology delivers "immediate" relief of dentin hypersensitivity following a single direct topical application,[6-9] and lasting relief with twice-daily brushing.[10-13] In contrast, a potassium-based sensitive toothpaste does not provide "immediate" relief of dentin hypersensitivity;[6,7] it takes at least two weeks to provide significant pain relief.[1]

## The Studies

The first article in this Special Issue of *The Journal of Clinical Dentistry* is a review of advances in the clinical management of dentin hypersensitivity, with special focus on recent evidence for the efficacy of dentifrices in providing instant and lasting relief of dentin hypersensitivity.[14] The second article features a hydraulic conductance study comparing the ability of two commercial sensitivity relief dentifrices to occlude dentin tubules and, thereby, reduce dentin fluid flow.[15] This is followed by three articles describing new parallel, randomized, head-to-head clinical studies which directly compare the efficacy of these two desensitizing toothpastes which occlude dentin tubules.[16-18] The test toothpaste, which contains 8% strontium acetate—an ingredient with a long history in desensitizing toothpastes—and 1040 ppm fluoride as NaF in a silica base, is currently marketed as Sensodyne® Rapid Relief; the positive control toothpaste, which contains 8.0% arginine, calcium carbonate, and 1450 ppm fluoride as sodium monofluorophosphate, is marketed as Colgate® Sensitive Pro-Relief™ and elmex® Sensitive Professional™. In two of these clinical studies, Crest® Cavity Protection toothpaste with 1100 ppm fluoride as NaF in a silica base, was used as a negative control.

Study 1,[15] the hydraulic conductance study, compares the *in vitro* effects of these two commercial sensitivity relief toothpastes in occluding dentin tubules and reducing fluid flow. Hydraulic conductance measurements were made after each of three sequential treatment and measurement cycles, one direct finger tip application and two brushing applications; then the resistance of the overall occlusion to an acid challenge was determined. The results showed that the toothpaste containing 8.0% arginine, calcium carbonate, and 1450 ppm fluoride provided significantly higher percentage reductions in fluid flow after each product application compared to the toothpaste containing 8% strontium acetate and 1040 ppm fluoride, and these effects were maintained after the acid challenge. These study results are consistent with the results of the three new clinical studies published in this Special Issue, and invalidate the results previously presented by Parkinson, *et al*.[19,20]

The second study[16] is a direct application study which compares the efficacy of the three toothpastes immediately after direct topical application, and again after seven days of twice-daily brushing. Subjects self-applied their assigned toothpaste to their hypersensitive teeth using a fingertip, and massaged for one minute. They then brushed at home using the same toothpaste twice daily for seven days. Dentin hypersensitivity was evaluated at baseline, immediately after direct application, and after seven days. The positive control toothpaste containing 8.0% arginine, calcium carbonate, and 1450 ppm fluoride delivered statistically significant improvements in tactile (80.5% and 32.1%) and air blast (41.4% and 50.4%) sensitivity scores immediately after direct application and after seven days of twice-daily brushing, respectively, compared to the test toothpaste containing 8% strontium acetate and 1040 ppm fluoride. The positive control toothpaste also delivered statistically significant improvements in tactile (91.0% and 43.9%) and air blast (44.8% and 54.1%) sensitivity scores immediately after direct application and after seven days of twice-daily brushing, respectively, compared to the negative control toothpaste containing fluoride alone. In contrast, the test toothpaste containing 8% strontium acetate and 1040 ppm fluoride did not provide statistically significant improvements in tactile (5.8% and 8.9%) or air blast (5.7% and 7.5%) sensitivity scores immediately after direct application or after seven days' use, respectively, compared to the negative control toothpaste containing fluoride alone.[16]

The results from this study are highly consistent with those of previously published "instant" studies, showing statistically significant and clinically relevant reductions in dentin hypersensitivity immediately after direct application for the arginine-based toothpaste compared to the toothpaste with fluoride alone.[6,7,9] This validates the study design, as well as the results showing that the strontium-based toothpaste did not provide significant or meaningful reductions in sensitivity immediately after direct application.

Study 3[17] compares the efficacy of the three toothpastes during long-term use. Subjects brushed using their assigned toothpaste twice daily for eight weeks. Dentin hypersensitivity was evaluated at baseline, and after two, four, and eight weeks of product use. The positive control toothpaste containing 8.0% arginine, calcium carbonate, and 1450 ppm fluoride delivered statistically significant improvements in tactile (41.7%, 52.3%, and 28.4%) and air blast (24.9%, 58.3%, and 60.7%) sensitivity scores at two, four, and eight weeks, respectively, compared to the test toothpaste containing 8% strontium acetate and 1040 ppm fluoride. Additionally, the positive control toothpaste containing 8.0% arginine, calcium carbonate, and 1450 ppm fluoride delivered statistically significant improvements in tactile (66.9%, 140.1%, and 146.6%) and air blast (28.9%, 69.8%, and 81.8%) sensitivity scores at two, four, and eight weeks, respectively, compared to the negative control toothpaste containing fluoride alone. The test toothpaste containing 8% strontium acetate and 1040 ppm fluoride provided statistically significant improvements compared to the negative control toothpaste on both tactile (57.6% and 92.1%) and air blast (27.6% and 53.6%) measures after four and eight weeks' use, respectively. However, the 8% strontium acetate test toothpaste did not provide a statistically significant improvement in air blast score (5.4%) compared to the negative control toothpaste after two weeks' use.[17]

The results from this study are consistent with those of the previously published study showing statistically significant and clinically relevant reductions in dentin hypersensitivity for the arginine-based toothpaste compared to toothpaste with fluoride alone after two, four, and eight weeks of use.[13] This validates the study design and demonstrates the superiority of the arginine-based toothpaste as compared to the strontium-based toothpaste during routine twice-daily use. The results of this study, in addition, provide new evidence that the strontium-based toothpaste, if used for at least four weeks or longer, provides significant reductions in sensitivity compared to a toothpaste with fluoride alone.

The fourth study in this Special Issue[18] also compares the efficacy of the two commercial sensitive toothpastes during long-term use. The objective of this study was to mimic the consumer behavior in "real life" of switching from one sensitive toothpaste to another and, thus, to determine the effects of such a switch on sensitivity relief. To meet this objective, there was no wash-out period between the use of the two test products. In fact, introduction of a wash-out period between the use of the test products would have prevented the attainment of the study objective. Thus, in a two-phase study design, subjects brushed using their first assigned toothpaste twice daily for eight weeks. They then brushed using their second assigned toothpaste twice daily for a further eight weeks. Dentin hypersensitivity was evaluated at baseline, and after eight, ten, and sixteen weeks. After the first eight weeks, the toothpaste containing 8.0% arginine, calcium carbonate, and 1450 ppm fluoride provided statistically significant improvements in tactile (51.3%) and air blast (39.4%) hypersensitivity scores compared to the toothpaste containing 8% strontium acetate and 1040 ppm fluoride. After two weeks' use of the second assigned toothpaste, the group currently using the toothpaste containing 8.0% arginine, calcium carbonate, and 1450 ppm fluoride had improvements in tactile (38.4%) and air blast (22.8%) scores compared to those achieved previously using the toothpaste containing 8% strontium acetate and 1040 ppm fluoride. In contrast, the group using the toothpaste containing 8% strontium acetate and 1040 ppm fluoride experienced deteriorations in tactile (–10.7%) and air blast (–14.7%) sensitivity scores compared to the scores achieved previously using the toothpaste containing 8.0% arginine, calcium carbonate, and 1450 ppm fluoride. After eight weeks' use of the second assigned toothpaste, the group using the toothpaste containing 8.0% arginine, calcium carbonate, and 1450 ppm fluoride maintained their improved sensitivity scores (27.2% tactile and 22.8% air blast), while those using the toothpaste containing 8% strontium acetate and 1040 ppm fluoride toothpaste continued to experience increased sensitivity (-7.3% tactile and -5.9% air blast). At the end of the study, users of the toothpaste containing 8.0% arginine, calcium carbonate, and 1450 ppm fluoride during the second eight-week period had statistically significant improvements in tactile (10.3%) and air blast (16.3%) sensitivity scores compared to users of the toothpaste containing 8% strontium acetate and 1040 ppm fluoride during the same period.[18]

The results of this study, with an innovative design that reflects "real life" usage patterns, show that the toothpaste with the Pro-Argin™ technology provides superior sensitivity relief compared to the toothpaste with 8% strontium acetate.

## Conclusions

The results of the three new clinical studies clearly support the conclusions that: 1) a toothpaste containing 8.0% arginine, calcium carbonate, and 1450 ppm fluoride provides superior efficacy with respect to both immediate and lasting relief of dentin hypersensitivity compared to a toothpaste containing 8% strontium acetate and 1040 ppm fluoride; and 2) a toothpaste containing 8% strontium acetate is no more effective in providing immediate relief of dentin hypersensitivity than regular fluoride toothpaste.

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# Advances in the Clinical Management of Dentin Hypersensitivity: A Review of Recent Evidence for the Efficacy of Dentifrices in Providing Instant and Lasting Relief

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**Abstract**

This paper summarizes the current state of knowledge of the epidemiology, etiology, and clinical management of dentin hypersensitivity, with special emphasis on the evidence for the effectiveness of commonly available sensitivity relief toothpastes. It reviews the scientific and clinical research validating the effectiveness of a recently introduced toothpaste containing 8.0% arginine and calcium carbonate, known as Pro-Argin™ technology, including clinical evidence for the superior efficacy of this toothpaste versus potassium-based sensitivity relief toothpastes. It critiques recently published studies on a strontium-based sensitivity relief toothpaste. Finally, it summarizes new clinical data from three parallel, randomized, head-to-head studies comparing the efficacy of a toothpaste containing 8.0% arginine and calcium carbonate (positive control) to a strontium-based sensitivity relief toothpaste (test) in delivering superior instant and lasting sensitivity relief. The results of these new clinical studies clearly support the conclusions that 1) a toothpaste containing 8.0% arginine and calcium carbonate provides superior efficacy with respect to both immediate and lasting relief of dentin hypersensitivity compared to a toothpaste containing 8% strontium acetate, and 2) a toothpaste containing 8% strontium acetate is no more effective in providing immediate relief of dentin hypersensitivity than a regular fluoride toothpaste.

**(J Clin Dent 2011;22[Spec Iss]:100–107)**

## Introduction

Dentin hypersensitivity is a painful oral condition typically experienced by young to middle-aged adults, with peak incidence between 30 and 39 years. Studies have reported levels of 4–57% in general dental practice settings, whereas levels of 60–98% have been reported in patients following periodontal treatment.[1-3] Self-reported assessment versus professional clinical diagnosis, the population base and setting, and behavioral factors, such as oral hygiene habits and intake of acidic foods and drinks, appear to account for these wide variations in prevalence.[1,2,4,5] The buccal cervical regions of permanent teeth are most commonly affected, with canine, pre-molar, and incisor teeth being more frequently affected than molars. A slightly higher incidence has been observed in females, which may reflect oral hygiene and dietary practices.[1,2]

Dentin hypersensitivity is characterized by short, sharp pain arising from exposed dentin in response to external stimuli, such as tactile pressure during a professional dental cleaning, thermal shock from hot or cold beverages, and osmotic imbalance from sweet or sour foods, which cannot be ascribed to any other form of dental defect or disease.[1,6] Dentin hypersensitivity is most frequently characterized by a rapid onset, sharp burst of pain of short duration (seconds or minutes) associated with A-beta and A-delta nerve responses to stimuli.[1,7,8] Typically, dentin hypersensitivity occurs when the external stimulus contacts exposed dentin, triggers a rapid outflow of dentin fluid, and the resultant pressure change across the dentin activates intra-dental nerve fibers to cause immediate pain.[1,4,9] The hydrodynamic theory of dentin hypersensitivity, as this mechanism has become known, requires that dentin tubules are open at the dentin surface and patent to the pulp. Dentin tubules in clinically characterized "sensitive" exfoliated teeth are more numerous, larger in diameter, and are open, whereas tubules in "non-sensitive" teeth are fewer, smaller, and usually blocked.[10,11] Dentin fluid flow rate is proportional to the fourth power of the tubule radius, so the difference in tubule diameter between sensitive and non-sensitive teeth is, almost certainly, of clinical relevance to the treatment of dentin hypersensitivity.[1] As several oral conditions can give rise to dental pain, such as untreated caries, the correct attribution of dental pain to dentin hypersensitivity is essential to assess appropriate treatment options.[2,12]

Experts have concluded that gingival recession is the primary predisposing factor for dentin hypersensitivity, a secondary factor being cervical enamel loss.[1] Gingival recession and exposure of the underlying root dentin are caused by overzealous tooth brushing and improper tooth brushing technique, or by surgical and non-surgical treatment of periodontal disease.[1,3] Erosion from acidic foods and drinks, in combination with tooth brushing, can result in significant enamel loss, especially in the cervical area, and exposure of the underlying crown dentin.[1,5,13,14]

Scientific understanding of dentin hypersensitivity has progressed sufficiently for the dental professional to embrace a comprehensive six-step approach to the management of a patient's sensitivity:[1,6] 1) correct diagnosis of dentin hypersensitivity based upon history and clinical examination; 2) differential diagnosis to exclude other conditions giving rise to similar pain symptoms; 3) treatment of all secondary conditions with symptoms similar to dentin hypersensitivity; 4) identification of etiologic and predisposing factors, particularly dietary and oral hygiene habits, that predicate erosion and abrasion; 5) removal or minimization of etiologic and predisposing factors through dietary advice and oral hygiene instruction; and 6) recommendation or provision of treatment based upon individual needs.

Brushing routinely with a desensitizing toothpaste is often the first step to treatment because it can provide significant relief

for many individuals. If desensitizing toothpaste is insufficient, the dental professional may prescribe high fluoride products for home use, as these can offer patients the relief they are seeking. For those patients with additional treatment needs, a professionally applied in-office product may be appropriate.[6]

## Products to Treat and Prevent Reoccurrence of Dentin Hypersensitivity

There are two primary approaches to treat and prevent the reoccurrence of dentin hypersensitivity: 1) interruption of the neural response to pain stimuli; and 2) occlusion of exposed dentin tubules to block the hydrodynamic mechanism of pain stimulation.[15]

### *Potassium-based Toothpaste Interrupts the Neural Response to Pain Stimuli for Clinically Proven Sensitivity Relief*

The vast majority of desensitizing toothpastes contain 2% potassium ion to "numb" the pain of dentin hypersensitivity.[16,17] The reason for this is that potassium salts have been shown to interrupt the neural response to pain stimuli, and are clinically proven to provide relief from the pain of dentin hypersensitivity.[7,8,17] A review published in 2009 identified numerous published clinical studies that support that toothpaste formulations containing potassium nitrate, potassium chloride, and potassium citrate provide effective relief of dentin hypersensitivity, as compared to a regular fluoride toothpaste as a negative control, when used twice daily during routine brushing.[15] Nonetheless, others have suggested that the clinical evidence in support of the efficacy of potassium-based toothpastes is equivocal and that potassium-based toothpastes are no more effective than regular fluoride toothpaste.[15] Most potassium-based toothpastes contain other ingredients to provide additional benefits, such as fluoride for cavity protection, antibacterial ingredients for plaque and gingivitis control, and crystal inhibitors and high cleaning abrasives for tartar control and whitening, respectively. The addition of fluoride to potassium-based toothpaste does not negatively impact sensitivity relief efficacy. Likewise, the addition of other benefit agents to potassium-based toothpaste does not impact efficacy.[15] It is noteworthy that clinical studies have repeatedly shown that it takes at least two weeks of twice-daily use to show measurable reductions in sensitivity, and longer time periods, generally four to eight weeks, to demonstrate significant levels of pain relief for potassium-based toothpaste as compared to ordinary toothpaste with fluoride alone.[15] There are no published studies showing statistically significant and clinically meaningful levels of efficacy relative to a negative control over time periods shorter than two weeks,[15] or on different modes of product application, such as direct application.[18]

### *Occlusion of Exposed Dentin Tubules to Block the Hydrodynamic Mechanism of Pain Stimulation*

The principle of occluding dentin tubules is simple, yet there are many different ways in which agents and products could potentially act to occlude dentin tubules. A recent review provided an overview of several approaches to tubule occlusion and the evidence for clinical efficacy and mechanism of action of a range of products and technologies that fall into this category.[19]

There are two routes to tubule occlusion which are of particular relevance to the topic of this Special Issue. These are 1) deposition of a layer of fine particles, and 2) induction of natural mineral formation *in situ*. With respect to the first route, materials delivered directly from a dentifrice, such as fine abrasive particles, or formed as a precipitate *in situ*, such as strontium, stannous, and calcium phosphate particles, have been proposed to form a physical barrier on the exposed dentin surface and in the openings of the tubules.[19] With respect to the second route, new technologies, such as the Pro-Argin™ technology and NovaMin® bioactive glass, have been proposed to physically adhere to the exposed dentin surface and the openings of the dentin tubules to mediate formation of calcium- and phosphate-rich mineral.[19]

While these two approaches and several related technologies have potential to deliver effective sensitivity relief by occluding dentin tubules, it is important to note that all such potential approaches and technologies are theoretical until they are proven to be effective in well-designed and executed clinical studies.

### *Strontium-based Toothpaste Occludes Dentin Tubules, But is it Clinically Proven to Provide Sensitivity Relief?*

Strontium chloride was the first tubule blocking agent used in toothpaste, being introduced under the brand name Sensodyne® approximately fifty years ago.[20] Because of its incompatibility with fluoride, the product was fluoride-free. In the 1970s, strontium chloride was largely replaced by potassium nitrate which had been hailed as "a superior desensitizer."[16] However, upgrades were subsequently made to enable strontium-based toothpaste to play a continued role in the sensitivity toothpaste market. One was to replace the original abrasive with silica, and a second was to add fluoride and replace strontium chloride with strontium acetate, with which fluoride is compatible.

Despite the long history of availability of strontium-based toothpaste, a review published in 2010 identified a paucity of data demonstrating clinical efficacy of strontium-based toothpaste as compared to regular fluoride toothpaste as a negative control.[19] Several controlled clinical studies conducted in the 1980s and early 1990s showed monadic reductions (reductions versus baseline) in patients' symptoms of dentin hypersensitivity when used during routine brushing over four to twelve weeks. Importantly, however, they also demonstrated that strontium-based toothpaste did not provide significant sensitivity relief compared to regular fluoride toothpaste as a negative control.[19] For example, a study comparing toothpaste containing 8% strontium acetate and fluoride in a silica base to toothpaste containing 10% strontium chloride in a diatomous earth base, and to calcium-based fluoride toothpaste as a negative control showed all three groups experienced reduced sensitivity as compared to baseline, a result of the well-known "placebo" effect, but there were no significant differences between the two desensitizing toothpastes or between either of the desensitizing toothpastes and the control product over the twelve-week time period of the study.[21] This review also noted a hydraulic conductance study published by Pashley and coworkers which reported that strontium salts deposited on dentin to visually occlude dentin tubules, yet the occlusion observed did not result in a reduction in dentin permeability.[22] In summary, the

2010 review identified no conclusive evidence to support that toothpastes containing strontium salts have sufficient effectiveness to provide immediate relief of dentin hypersensitivity following direct application compared to control toothpastes, and that the clinical evidence regarding long-lasting relief during routine twice-daily brushing is equivocal.[19]

### *Tubule Occlusion by Induction of Natural Mineral Formation* In Situ

Advances in dentin hypersensitivity have triggered research into new treatments that will target its underlying causes. Increasing the mineral density of the dentin surface could improve resistance to tooth wear by acid erosion and abrasion, while plugging and sealing open tubules with a calcium- and phosphate-containing mineral could block diffusion through the tubules into the dentin sub-surface, increasing acid resistance.[7]

The principle of delivering calcium and phosphate ions to form calcium phosphate at the site of action is simple. However, the mouth is typically supersaturated with calcium and phosphate, so there is a considerable challenge to developing and validating a new material that is able to release and deliver additional calcium and phosphate to the mouth in a form that provides clinically proven efficacy during regular use. While several approaches to the deposition of amorphous calcium phosphate on the tooth surface are being investigated, published clinical data demonstrating effective sensitivity relief from products delivering amorphous calcium phosphate are currently limited.[19]

### *A New Technology, Pro-Argin, Based on Saliva's Role in the Natural Process of Tubule Occlusion: Clinical and Scientific Evidence for Instant and Lasting Relief of Sensitivity*

In nature, saliva forms a surface-protective layer of glycoprotein with calcium and phosphate that slowly induces dentin occlusion and tubule plugging, and results in sustained relief of dentin hypersensitivity over the long term. Based on pioneering research on this natural process by Kleinberg,[23] a new technology comprising 8.0% arginine and calcium carbonate, known as Pro-Argin, has been developed and validated as both an in-office desensitizing treatment, as well as a daily-use toothpaste.[15,18,19,24]

The in-office desensitizing paste with Pro-Argin technology has been clinically proven to provide instant sensitivity relief when applied with a prophy cup after professional cleaning procedures, and that the benefit of a single treatment lasts for at least 28 days.[25] Further, this desensitizing paste has been clinically proven to provide instant relief of dentin hypersensitivity when applied using the same procedure prior to dental prophylaxis.[26]

The desensitizing toothpaste combines the innovative Pro-Argin technology with fluoride to provide a significant advance in the everyday treatment of dentin hypersensitivity. Specifically, four eight-week clinical studies demonstrate that this daily-use toothpaste, containing 8.0% arginine and calcium carbonate with 1450 ppm fluoride as sodium monofluorophosphate, used twice daily during routine brushing, provides significantly better and significantly faster relief than the market-leading desensitizing toothpaste brand,[27-29] as well as regular fluoride toothpaste.[30] A summary of the results of these studies is provided in Table I. Three of these studies demonstrate that toothpaste containing 8.0% arginine and calcium carbonate provides superior relief of sensitivity compared to toothpastes containing 2% potassium ion as the active desensitizing agent (both as 3.75% KCl and as 5% $KNO_3$) after two, four, and eight weeks of twice-daily brushing.[27-29] The fourth study demonstrates that two toothpaste variants, each containing 8.0% arginine and calcium carbonate (one a whitening variant), both provide superior relief versus regular fluoride toothpaste after two, four, and eight weeks of twice-daily brushing.[30]

**Table I**

Summary of the Results of Four 8-Week Clinical Studies Assessing the Efficacy in Reducing Dentin Hypersensitivity of a New Toothpaste Containing 8.0% Arginine, Calcium Carbonate, and 1450 ppm Fluoride

| | | | Baseline-Adjusted Mean Tactile Sensitivity Scores | | | Baseline-Adjusted Mean Air Blast Sensitivity Scores | | |
|---|---|---|---|---|---|---|---|---|
| Reference | Products Tested | N | 2 Weeks | 4 Weeks | 8 Weeks | 2 Weeks | 4 Weeks | 8 Weeks |
| Ayad F, *et al*., 2009[27] | Test toothpaste[a] | 38 | 23.12* | 36.21* | 47.34* | 1.86* | 1.09* | 0.34* |
| | Positive Control[b] | 39 | 19.90 | 29.59 | 39.00 | 2.22 | 1.54 | 0.93 |
| Docimo R, *et al*., 2009[28] | Test Toothpaste[a] | 40 | 26.45* | 40.98* | 45.40* | 1.65* | 0.92* | 0.49* |
| | Positive Control[b] | 40 | 19.30 | 31.52 | 40.47 | 2.17 | 1.35 | 0.69 |
| Docimo R, *et al*., 2009[29] | Test Toothpaste[a] | 40 | 25.87* | 40.75* | 45.63* | 1.59* | 0.89* | 0.45* |
| | Positive Control[c] | 40 | 18.63 | 31.62 | 40.88 | 1.91 | 1.21 | 0.68 |
| Que K, *et al*., 2010[30] | Test Toothpaste[d] | 40 | 36.50** | 45.50** | 48.50** | 1.18** | 0.75** | 0.44** |
| | Positive Control[a] | 40 | 35.75** | 44.62** | 48.00** | 1.16** | 0.76** | 0.38** |
| | Negative Control[e] | 41 | 22.20 | 26.59 | 30.12 | 1.99 | 1.82 | 1.72 |

[a]Toothpaste containing 8.0% arginine and 1450 ppm fluoride, as sodium monofluorophosphate (MFP), in a calcium carbonate base (Colgate-Palmolive, New York, NY, USA).
[b]Sensodyne Total Care F toothpaste containing 2% potassium ion, as 3.75% potassium chloride, and 1450 ppm fluoride, as sodium fluoride (NaF), in a silica base (GlaxoSmithKline, Middlesex, UK).
[c]Sensodyne Total Care Gentle Whitening toothpaste containing 2% potassium ion, as 5% potassium nitrate, and 1450 ppm fluoride, as NaF, in a silica base (GlaxoSmithKline, Middlesex, UK).
[d]Toothpaste containing 8.0% arginine and 1450 ppm fluoride, as MFP, in a high cleaning calcium carbonate base (Colgate-Palmolive, New York, NY, USA).
[e]Colgate Cavity Protection toothpaste containing 1450 ppm fluoride, as MFP, in a calcium carbonate base (Colgate-Palmolive, New York, NY, USA).
*Statistically significant difference at $p < 0.05$ between test and control based on ANCOVA comparison of baseline-adjusted means.
**Statistically significant difference at $p < 0.05$ between test and negative control, and positive and negative controls, based on ANCOVA comparison of baseline-adjusted means; no significant difference at $p < 0.05$ between test and positive control based on ANCOVA comparison of baseline-adjusted means.

More important to the patient suffering from sensitivity is the fact that a toothpaste containing 8.0% arginine, calcium carbonate, and 1450 ppm fluoride has been clinically proven to provide immediate relief after a single direct topical application.[31-34] The ability to deliver immediate sensitivity relief in the treatment of dentin hypersensitivity requires a highly efficacious toothpaste and a new validated clinical study design. A summary of the results of four clinical studies on the effects of toothpaste containing 8.0% arginine, calcium carbonate, and 1450 ppm fluoride is given in Table II.

The results of the first two studies show that the toothpaste containing 8.0% arginine and calcium carbonate significantly reduces sensitivity immediately following direct application as compared to a toothpaste containing 2% potassium ion, as well as to regular fluoride toothpaste, and that relief is maintained with continued twice-daily brushing.[31,32] The results of these studies also show that the toothpaste containing 2% potassium ion does not provide immediate relief compared to regular fluoride toothpaste when directly applied in the same manner.[31,32] The third study shows that the toothpaste with 8.0% arginine and calcium carbonate is effective in providing immediate relief of dentin hypersensitivity when applied using a fingertip and when applied using a cotton swab.[33] The fourth study demonstrates that two toothpaste variants, each containing 8.0% arginine and calcium carbonate (one a whitening variant), both provide superior relief versus a regular fluoride toothpaste immediately after fingertip application.[34] These clinical findings are intriguing because this is the first time that any desensitizing toothpaste has been clinically proven to provide significant relief of sensitivity immediately following topical direct application. The fact that toothpaste containing 8.0% arginine and calcium carbonate provides instant relief, whereas the leading desensitizing toothpaste technology (2% potassium ion and 1450 ppm fluoride in a silica base) does not, is a real breakthrough for consumers suffering from this condition.

Several state-of-the art imaging methods have provided insight into the mechanism of action of the Pro-Argin technology, confirming that it effectively plugs and seals dentin tubules, and that the occlusion achieved is highly resistant to acid challenge. The arginine component triggers physical adherence of the calcium carbonate to the exposed dentin surface and to the inner surfaces of dentin tubules. This then induces deposition of a calcium- and phosphate-rich material on the dentin surface and occludes within the dentin tubules. Hydraulic conductance studies have shown that the occlusion achieved with toothpaste containing 8.0% arginine and calcium carbonate results in reduced dentin fluid flow and inhibition of the hydrodynamic mechanism. They have also confirmed that the dentin occlusion is robust, as reduced permeability was maintained after seven days of pulpal pressure and after treatment with strong acid.[35,36]

### *New Studies on Toothpaste Containing 8% Strontium Acetate*

Recently, a Special Issue publication of *The Journal of Clinical Dentistry* presented two new laboratory and two new clinical studies on a toothpaste containing 8% strontium acetate and 1040 ppm fluoride as sodium fluoride in a silica base, marketed as Sensodyne® Rapid Relief.[37-40]

One paper, by Earl, *et al*., describes a series of monadic *in vitro* studies using state-of-the-art sample preparation, imaging, and

**Table II**
Summary of Results of Clinical Studies Assessing the Immediate Effects on Dentin Hypersensitivity of Direct Application of a New Toothpaste Containing 8.0% Arginine, Calcium Carbonate, and Fluoride

| | | | Baseline and Baseline-Adjusted Mean Tactile Sensitivity Scores | | | Baseline and Baseline-Adjusted Mean Air Blast Sensitivity Scores | | |
|---|---|---|---|---|---|---|---|---|
| Reference | Products Tested | N | Baseline | Immediately | 3/7 Days | Baseline | Immediately | 3/7 Days |
| Ayad F, *et al*., 2009[31] | Test Toothpaste[a] | 41 | 11.46 | 33.17* | 33.29* | 2.90 | 1.26* | 1.17* |
| | Control[b] | 40 | 10.88 | 14.38 | 16.25 | 2.93 | 2.24 | 2.11 |
| | Negative Control[c] | 39 | 10.90 | 13.85 | 14.10 | 2.95 | 2.50 | 2.50 |
| Nathoo S, *et al*., 2009[32] | Test toothpaste[a] | 42 | 12.38 | 35.36* | 39.17* | 2.33 | 0.92* | 0.60* |
| | Control[b] | 41 | 11.95 | 13.54 | 15.85 | 2.43 | 2.29 | 2.01 |
| | Negative Control[c] | 42 | 12.38 | 12.62 | 13.93 | 2.23 | 2.19 | 2.06 |
| Schiff T, *et al*., 2009[33] | Fingertip[d] | 84 | 10.00 | 29.17** | 29.17** | 2.55 | 1.08** | 1.10** |
| | Cotton Swab[e] | 84 | 10.00 | 28.21** | 29.05** | 2.62 | 1.13** | 1.08** |
| Fu Y, *et al*., 2010[34] | Test toothpaste[f] | 41 | 14.88 | 28.90*** | 34.51*** | 2.11 | 1.21*** | 0.80*** |
| | Positive control[a] | 41 | 14.76 | 29.02*** | 33.41*** | 2.12 | 1.18*** | 0.83*** |
| | Negative control[c] | 40 | 14.38 | 15.88 | 16.00 | 2.15 | 2.06 | 1.93 |

[a]Toothpaste containing 8.0% arginine and 1450 ppm fluoride, as sodium monofluorophosphate (MFP), in a calcium carbonate base (Colgate-Palmolive, New York, NY, USA).
[b]Toothpaste containing 5% potassium nitrate and 1450 ppm fluoride, as sodium fluoride (NaF), in a silica base (Colgate-Palmolive, New York, NY, USA).
[c]Control toothpaste containing 1450 ppm fluoride, as MFP, in a calcium carbonate base (Colgate-Palmolive, New York, NY, USA).
[d]Direct topical application with a fingertip and massage for 1 minute.
[e]Direct topical application with a cotton swab and massage for 1 minute.
[f]Toothpaste containing 8.0% arginine and 1450 ppm fluoride, as MFP, in a high cleaning calcium carbonate base (Colgate-Palmolive, New York, NY, USA).
*Statistically significant difference at $p < 0.05$ between test and control and between test and negative control based on ANCOVA comparisons of baseline-adjusted means.
**Statistically significant difference at $p < 0.05$ from baseline based on paired t-test; no significant difference between application methods based on ANCOVA comparison of baseline-adjusted means.
***Statistically significant difference at $p < 0.05$ between test and negative control, and positive and negative controls, based on ANCOVA comparison of baseline-adjusted means; no significant difference at $p < 0.05$ between test and positive control based on ANCOVA comparison of baseline-adjusted means.

analysis techniques, and these showed that treatment of dentin samples with a toothpaste containing 8% strontium acetate resulted in occlusion of dentin tubules and deposition of strontium within the dentin tubules.[37] These results are consistent with previously published laboratory studies demonstrating that toothpaste containing strontium can visually occlude dentin tubules and may, therefore, serve a role in showing how this toothpaste containing 8% strontium acetate might work *in vivo*. However, these *in vitro* studies *per se* do not provide new evidence of the clinical efficacy of toothpaste containing 8% strontium acetate.

In a second paper, Parkinson, *et al*. presented an *in vitro* model which was developed to differentiate the acid resistance of occlusion following repeated cycles of brushing dentin disks with toothpaste containing 8% strontium acetate followed by immersion in acid as compared to similar cycles with toothpaste containing 8.0% arginine and calcium carbonate. The results suggested that, under laboratory conditions, the occlusion achieved with the strontium-based toothpaste might be more resistant to acid than the arginine-based toothpaste.[38] In a subsequent paper using the same *in vitro* model, Parkinson and Willson observed similar results following "dab on" application.[41] Once again, these *in vitro* studies do not provide new evidence of the clinical efficacy of toothpaste containing 8% strontium acetate.

It appears that the *in vitro* model developed by Parkinson, *et al*. may exaggerate the acid challenge experienced by sensitivity sufferers *in vivo*.[38,41] The results presented by Parkinson for the arginine-based toothpaste are in stark contrast to the results of the previously published mechanism of action studies, which showed that the occlusion resulting from treatment with the Pro-Argin technology is highly resistant to acid challenge.[35,36] More importantly, they are inconsistent with the results of the eight clinical studies, discussed above, which clearly show that the occlusion achieved with the arginine-based dentifrice is resistant to everyday acid challenges, being clinically proven effective in relieving dentin hypersensitivity under real life conditions in which patients maintained their normal diets without restrictions to their intake of acidic foods and beverages.[27-34]

A third paper by Mason, *et al.*, presented the results of a parallel, examiner-blind, randomized clinical study comparing the efficacy of 8% strontium acetate toothpaste to that of a control toothpaste containing 1450 ppm fluoride alone immediately following a single dab-on application, and after a subsequent period of brushing twice daily for three days. This is the first and only published study investigating the ability of a strontium-based toothpaste to deliver immediate sensitivity relief. The study did not include a positive control product.[39] For this reason, it is not possible to validate the study design by demonstrating significant and meaningful differences between positive and negative controls (upside and downside statistical sensitivity), nor is it possible to readily assess the clinical significance of the results for the 8% strontium acetate toothpaste. Notwithstanding this flaw, the results of the study, at face value, suggest that the strontium-based toothpaste may be more effective in relieving sensitivity immediately after direct topical application than the fluoride-only toothpaste. However, comparison of the data from this immediate relief study,[39] shown in Table III, with the data in Table II, reveals that the 8% strontium acetate toothpaste did not perform as effectively in this study as the arginine-based toothpaste performed in all of the previously published immediate relief clinical studies.[31-34] The results, therefore, beg the question of how effective the 8% strontium acetate toothpaste is compared to the arginine-based toothpaste.

A fourth paper by Hughes, *et al*. presented the results of a parallel, examiner-blind, randomized clinical study comparing the efficacy of an 8% strontium acetate toothpaste to that of the 8.0% arginine toothpaste after brushing twice daily for two, four, and eight weeks. At face value, the results of the study suggest that there is no significant difference in efficacy between the strontium acetate toothpaste and the arginine-based toothpaste.[40] However, the absence of a negative control in this study also precludes full assessment of the study results, including whether the study was sufficiently powered to demonstrate clinical equivalence of the two products.

### *Evidence for the Superior Efficacy of a Dentifrice with 8.0% Arginine and Calcium Carbonate as Compared to a Dentifrice with 8% Strontium Acetate in Providing Instant and Lasting Relief of Dentin Hypersensitivity*

A hydraulic conductance study has compared the *in vitro* effects of two commercial sensitive toothpastes in occluding dentin tubules and reducing fluid flow. The test toothpaste, marketed as Sensodyne Rapid Relief, contained 8% strontium and 1040 ppm fluoride; the positive control toothpaste, marketed as Colgate® Sensitive Pro-Relief™ and elmex® Sensitive Professional™, contained 8.0% arginine, calcium carbonate, and 1450 ppm fluoride. The results showed that the toothpaste containing 8.0% arginine, calcium carbonate, and 1450 ppm fluoride provided significantly higher percentage reductions in fluid flow

**Table III**
Summary of the Results of the Clinical Study Assessing the Immediate Effects on Dentin Hypersensitivity of Direct Application of a Toothpaste Containing 8% Strontium Acetate and 1040 ppm Fluoride

| | | | Baseline and Baseline-Adjusted Mean Tactile Sensitivity Scores | | | Baseline and Baseline-Adjusted Mean Air Blast Sensitivity Scores | | | Baseline and Baseline-Adjusted Mean VAS Sensitivity Scores | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Reference | Products Tested | N | Baseline | Immediate | 3 Days | Baseline | Immediate | 3 Days | Baseline | Immediate | 3 Days |
| Mason S, *et al*., 2010[39] | Test Toothpaste[a] | 40 | 15.5 | 26.7* | 27.5* | 2.8 | 1.5* | 1.2* | 40.5 | 22.4* | 16.6* |
| | Negative Control[b] | 39 | 14.9 | 16.4 | 20.7 | 2.8 | 2.1 | 1.7 | 46.0 | 36.7 | 32.0 |

[a]Toothpaste containing 8% strontium acetate and 1040 ppm fluoride, as NaF, in a silica base (Sensodyne Rapid Relief, GlaxoSmithKline Consumer Healthcare, Weybridge, Surrey, UK).
[b]Negative control toothpaste containing 1450 ppm fluoride, as NaF, in a silica base (GlaxoSmithKline Consumer Healthcare, Weybridge, Surrey, UK).
*Statistically significant difference at $p < 0.05$ between test and control based on ANCOVA comparison of baseline-adjusted means.

after each of three product applications compared with the toothpaste containing 8% strontium acetate and 1040 ppm fluoride, and these effects were maintained after an acid challenge.[42] These study results are consistent with the results of three new clinical studies, and invalidate the results previously presented by Parkinson.[38,41]

Three new parallel, randomized, head-to-head clinical studies have directly compared the efficacy of these two desensitizing toothpastes.[43-45] The test toothpaste was Sensodyne Rapid Relief; the positive control was Colgate Sensitive Pro-Relief, also marketed as elmex Sensitive Professional. In two of these studies, 1 and 2, Crest® Cavity Protection toothpaste with 1100 ppm fluoride, as NaF, in a silica base was used as a negative control.

Study 1 was a direct application study which compared the efficacy of the three toothpastes immediately after application and again after seven days of twice-daily brushing. The positive control toothpaste containing 8.0% arginine, calcium carbonate, and 1450 ppm fluoride delivered statistically significant improvements in tactile (80.5% and 32.1%) and air blast (41.4% and 50.4%) sensitivity scores immediately after direct application and after seven days of twice-daily brushing, respectively, compared to the test toothpaste containing 8% strontium acetate and 1040 ppm fluoride, as well as statistically significant improvements in tactile (91.0% and 43.9%) and air blast (44.8% and 54.1%) sensitivity scores immediately after direct application and after seven days of twice-daily brushing, respectively, compared to the negative control toothpaste containing fluoride alone. In contrast, the test toothpaste containing 8% strontium acetate and 1040 ppm fluoride did not provide statistically significant improvements in tactile (5.8% and 8.9%) or air blast (5.7% and 7.5%) sensitivity scores immediately after direct application or after seven days' use, respectively, compared to the negative control toothpaste containing fluoride alone.[43]

The results from this study are highly consistent with those of the previously published "instant" studies showing statistically significant and clinically relevant reductions in dentin hypersensitivity for the arginine-based toothpaste compared to toothpaste with fluoride alone, immediately after direct application.[31,32,34] This validates the study design as well as the results showing that the strontium-based toothpaste did not provide significant or meaningful reductions in sensitivity immediately after direct application to sensitive teeth.

Study 2 compared the efficacy of the three toothpastes during a period of twice-daily brushing for eight weeks. The positive control toothpaste, containing 8.0% arginine, calcium carbonate, and 1450 ppm fluoride, delivered statistically significant improvements in tactile (41.7%, 52.3%, and 28.4%) and air blast (24.9%, 58.3%, and 60.7%) sensitivity scores at two, four, and eight weeks, respectively, compared to the test toothpaste containing 8% strontium acetate and 1040 ppm fluoride. Additionally, the positive control toothpaste, containing 8.0% arginine, calcium carbonate, and 1450 ppm fluoride, delivered statistically significant improvements in tactile (66.9%, 140.1%, and 146.6%) and air blast (28.9%, 69.8%, and 81.8%) sensitivity scores at two, four, and eight weeks, respectively, compared to the negative control toothpaste containing fluoride alone. The test toothpaste containing 8% strontium acetate and 1040 ppm fluoride provided statistically significant improvements compared to the negative control toothpaste on both tactile (57.6% and 92.1%) and air blast (27.6% and 53.6%) measures after four and eight weeks' use, respectively. However, the 8% strontium acetate test toothpaste did not provide a statistically significant improvement in air blast score (5.4%) compared to the negative control toothpaste after two weeks' use.[44]

The results from this study are also consistent with those of the previously published study showing statistically significant and clinically relevant reductions in dentin hypersensitivity for the arginine-based toothpaste compared to toothpaste with fluoride alone after two, four, and eight weeks' use.[30] This validates the study design and demonstrates the superiority of the arginine-based toothpaste as compared to the strontium-based toothpaste during routine twice-daily use.

Study 3 also compared the efficacy of the two commercial sensitive toothpastes during long-term use. The objective of this study was to mimic "real life" consumer behavior of switching from one sensitive toothpaste to another and, thus, to determine the effects of switching toothpastes on sensitivity relief. There was no interim wash-out period, as introduction of a wash-out between use of the test products would have prevented the attainment of the study objective. After eight weeks' use of the first assigned product, the toothpaste containing 8.0% arginine, calcium carbonate, and 1450 ppm fluoride provided statistically significant improvements in tactile (51.3%) and air blast (39.4%) hypersensitivity scores compared to the toothpaste containing 8% strontium acetate and 1040 ppm fluoride. After the switch and two weeks' use of the second assigned toothpaste, the group currently using the toothpaste containing 8.0% arginine, calcium carbonate, and 1450 ppm fluoride had improvements in tactile (38.4%) and air blast (22.8%) scores compared to the scores achieved previously using the toothpaste containing 8% strontium acetate and 1040 ppm fluoride. In contrast, the group currently using the toothpaste containing 8% strontium acetate and 1040 ppm fluoride experienced deteriorations in tactile (–10.7%) and air blast (–14.7%) sensitivity scores compared to the scores achieved previously using the toothpaste containing 8.0% arginine, calcium carbonate, and 1450 ppm fluoride. After the switch and eight weeks' use of the second assigned toothpaste, the group using the toothpaste containing 8.0% arginine, calcium carbonate, and 1450 ppm fluoride maintained their improved sensitivity scores (27.2%, tactile and 22.8%, air blast), while those using the toothpaste containing 8% strontium acetate and 1040 ppm fluoride continued to experience increased sensitivity (–7.3%, tactile and –5.9%, air blast). At the end of the study, users of the toothpaste containing 8.0% arginine, calcium carbonate, and 1450 ppm fluoride during the second eight-week period had statistically significant improvements in tactile (10.3%) and air blast (16.3%) sensitivity scores compared to users of the toothpaste containing 8% strontium acetate and 1040 ppm fluoride during the same period.[45]

The results of this study, with an innovative design that reflects "real life" usage patterns, show that the toothpaste with the Pro-Argin technology provides superior sensitivity relief compared to the toothpaste with 8% strontium acetate.

## Conclusions

The results of three new clinical studies clearly support the conclusions that 1) a toothpaste containing 8.0% arginine, calcium carbonate, and 1450 ppm fluoride provides superior efficacy with respect to both immediate and lasting relief of dentin hypersensitivity compared to a toothpaste containing 8% strontium acetate and 1040 ppm fluoride, and 2) a toothpaste containing 8% strontium acetate is no more effective in providing immediate relief of dentin hypersensitivity than regular fluoride toothpaste.

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# Comparison of the Effects on Dentin Permeability of Two Commercially Available Sensitivity Relief Dentifrices

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**Abstract**

- **Objective:** The *in vitro* effects of two commercial sensitivity relief dentifrices, one containing 8.0% arginine, calcium carbonate, and 1450 ppm fluoride as sodium monofluorophosphate (MFP), and the other containing 8% strontium acetate and 1040 ppm fluoride as sodium fluoride, in occluding dentin tubules and reducing dentin fluid flow were compared in a blinded study using hydraulic conductance (Flodec).
- **Methods:** Human dentin segments were cut from extracted molars, mounted on acrylic blocks, etched, and connected to a Flodec to measure hydraulic conductance. Segments were divided into two groups (n = 6) and treated for one minute with either the arginine/calcium carbonate dentifrice or the strontium acetate dentifrice. The blocks were rinsed, connected to the Flodec, and the conductance was measured. Blocks were rinsed again and incubated in phosphate-buffered saline (PBS) for at least two hours before the next treatment. The cycle was repeated for a total of three treatments (one using a fingertip and the next two using a toothbrush). After the third treatment, the blocks were incubated in PBS overnight and conductance was re-measured. The two groups were further divided into three sets of two segments each, which were challenged for one minute with either 6% citric acid, orange juice, or grapefruit juice.
- **Results:** The hydraulic conductance study showed that the dentifrice containing 8.0% arginine, calcium carbonate, and 1450 ppm fluoride provided a significantly higher percentage reduction in fluid flow immediately after fingertip application, as well as after two brushing cycles, compared to the dentifrice containing 8% strontium acetate and 1040 ppm fluoride. After various acid challenges, the percentage reduction in fluid flow of dentin treated with the arginine/calcium carbonate dentifrice remained significantly higher than that of the strontium acetate dentifrice. These results are highly consistent with the results from an independent clinical study which showed that the arginine/calcium carbonate dentifrice provided dentin hypersensitivity relief immediately after direct topical application with a fingertip and massage for one minute per sensitive tooth, whereas the strontium acetate dentifrice did not.
- **Conclusion:** Based on this *in vitro* hydraulic conductance study, the dentifrice containing 8.0% arginine, calcium carbonate, and 1450 ppm fluoride was significantly more effective in reducing fluid flow through dentin tubules as a result of occlusion than the dentifrice containing 8% strontium acetate and 1040 ppm fluoride. Further, the superior occlusion obtained with the arginine/calcium carbonate dentifrice was resistant to acid challenge.

**(J Clin Dent 2011;22[Spec Iss]:108–112)**

## Introduction

Dentin hypersensitivity is a commonly experienced problem that is triggered by an external stimulus, such as hot and cold temperature changes, pressure from tooth brushing, and osmotic changes caused by sweet or sour foods and drinks. These cause displacement of the fluid in the dentin tubules, which activates the nerve endings at the pulp/dentin interface, resulting in sharp and sudden pain.[1]

There are two discrete technical approaches to help treat dentin hypersensitivity. The first is to interrupt the neural response to pain stimuli, and this can be accomplished by brushing with a dentifrice containing 2% potassium ion.[2,3] Potassium salts (nitrate, citrate, and chloride) work by permeating open exposed dentin tubules to build up to an effective level at the pulp/dentin interface, causing nerve fibers to be less excitable to external pain-producing stimuli, thereby reducing the sensation of pain.[2,3]

The second approach is to block the exposed dentin tubules, thus preventing external stimuli from triggering the displacement of dentin fluid and the consequent onset of pain.[2,4] Of particular interest to the current study are dentifrices containing a strontium salt; these are believed to have dentin occlusion properties and have been shown to provide reductions in dentin hypersensitivity when used twice daily for four weeks or longer.[2,5,6] Although strontium-based dentifrices have a long history of consumer use, a recent review identified a paucity of clinical data demonstrating significant reductions in sensitivity when a strontium-based dentifrice was compared to a regular fluoride dentifrice as a negative control.[5]

A breakthrough technology, based upon 8.0% arginine and calcium carbonate, has been introduced as an in-office professional treatment, Colgate® Sensitive Pro-Relief™ Desensitizing Paste, and as a daily-use fluoride-containing dentifrice, under the Colgate® Sensitive Pro-Relief™ and elmex® Sensitive Professional™ names (Colgate-Palmolive Company, New York, NY, USA), that offers a step-change improvement in the treatment of dentin hypersensitivity.[2,5,6] Laboratory research has demonstrated that the technology provides rapid and complete occlusion of exposed and open dentin tubules, and that the occlusion achieved is resistant to acid challenge.[7,8]

More than a dozen double-blind, randomized, controlled clinical studies have validated this mechanism of action, and have

verified that the occlusion achieved in practice, *i.e.*, when the professional in-office product or the daily-use dentifrice is used as directed, is highly effective in providing significant and meaningful dentin hypersensitivity relief and is robust to everyday challenges from dietary acids in foods and beverages. Specifically, clinical studies on the arginine/calcium carbonate-based in-office desensitizing paste have shown that a single professional application provides 1) immediate relief when applied after a professional dental cleaning that lasts for at least 28 days,[9] and 2) immediate relief when applied prior to a professional dental cleaning.[10] Likewise, multiple independent clinical studies have proven that the daily-use arginine/calcium carbonate dentifrice provides superior lasting relief of sensitivity as compared to marketed sensitive dentifrices containing potassium as the desensitizing agent, as well as to a regular fluoride dentifrice as a negative control.[11-14] More importantly, perhaps to the sensitivity sufferer, is the fact that for the first time ever for a dentifrice, multiple independent clinical studies have proven that this arginine/calcium carbonate dentifrice delivers statistically significant and clinically meaningful relief of dentin hypersensitivity immediately following direct topical application and one minute of massage per sensitive tooth.[15-18] In contrast, potassium-based sensitive dentifrices do not provide immediate relief of dentin hypersensitivity compared to regular fluoride dentifrice as a negative control when applied in the same manner;[15,16] rather, it takes at least two weeks, or even more, of regular twice-daily brushing to provide significant pain relief.

Recently, new laboratory and clinical studies were published on dentifrices containing 8% strontium acetate, marketed as Sensodyne® Rapid Relief (GlaxoSmithKline, Surrey, UK).[19-22] An *in vitro* study showed that treatment of dentin samples with a dentifrice containing 8% strontium acetate resulted in occlusion of dentin tubules and deposition of strontium within the dentin tubules.[19] A second *in vitro* study suggested that the strontium-based dentifrices might provide occlusion which is more acid resistant than a dentifrice containing 8.0% arginine and calcium carbonate.[20] These *in vitro* studies may support the proposed mechanism of action, but they do not *per se* provide new evidence of the clinical efficacy of a dentifrice containing 8% strontium acetate. A third paper presented the results of a clinical study comparing the efficacy of the 8% strontium acetate dentifrice to that of a control dentifrice containing 1450 ppm fluoride alone immediately following a single dab-on application, and after a subsequent period of brushing twice daily for three days. The results of the study suggest that the strontium-based dentifrice may provide some level of sensitivity relief immediately after direct topical application.[21] However, the effect was much lower in magnitude than the effects reproducibly demonstrated in clinical studies on the arginine/calcium carbonate dentifrice.[15-18] A fourth paper presented the results of a clinical study comparing the efficacy of the 8% strontium acetate dentifrice to that of the 8.0% arginine/calcium carbonate dentifrice after brushing twice daily for two, four, and eight weeks. The results of the study suggest that there is no significant difference in efficacy between the strontium acetate dentifrice and the arginine/calcium carbonate dentifrice.[22] However, the absence of a negative control in this study precludes full assessment of the study results, including whether the study was sufficiently powered to demonstrate true clinical equivalence of the two products. Importantly, the results of the clinical studies reported in the third and fourth papers are directly contradicted and refuted by the three clinical studies reported in this Special Issue.

The hydraulic conductance model, developed by Pashley, provides a useful *in vitro* method of assessing the effectiveness of products that work by tubule occlusion by measuring whether the occlusion achieved has a material effect on fluid flow through dentin specimens.[23] The objective of this hydraulic conductance study was to compare the effectiveness of occlusion achieved with two commercial sensitivity relief dentifrices, one containing 8.0% arginine, calcium carbonate, and 1450 ppm fluoride as sodium monofluorophosphate (MFP; marketed as Colgate Sensitive Pro-Relief and elmex Sensitive Professional) and the other containing 8% strontium acetate and 1040 ppm fluoride as sodium fluoride (marketed as Sensodyne Rapid Relief), and to assess the resistance of the occlusion to acid challenge under laboratory conditions. The study was designed to measure the sequential effects of 1) a single fingertip application, 2) two treatments with brushing, and 3) acid challenge. By providing mechanism of action information, this study is intended to complement the three clinical studies reported in this Special Issue which compare the efficacy of the two products under a range of different usage regimens.

## Materials and Methods

The products used in this study were a dentifrice containing 8.0% arginine, calcium carbonate, and 1450 ppm fluoride as sodium monofluorophosphate (Colgate Sensitive Pro-Relief and elmex Sensitive Professional), and a dentifrice containing 8% strontium acetate and 1040 ppm fluoride as sodium fluoride in a silica base (Sensodyne Rapid Relief).

The study was blinded since one person overwrapped the dentifrice samples and labeled them with a code number to hide the identity of the dentifrices, and another person conducted the treatments and conductance measurements. Thus, the person performing the study was unaware of the products being tested. Phosphate buffered saline (PBS) solution was prepared in the laboratory and was composed of 1.06 mM calcium chloride, 0.63 mM sodium phosphate monobasic, and 150 mM sodium chloride adjusted to pH 7 using sodium hydroxide.

Human molars were sectioned, mounted as dentin segments, etched (30 seconds, 34% phosphoric acid), and connected to a Flodec device (deMarco Engineering, Geneva, Switzerland) for hydraulic conductance measurements using the method of Pashley and coworkers.[24] The hydraulic conductance of each segment after etching was measured at 70 cm water pressure to give a baseline conductance value. Six segments (n = 6) were randomly assigned to each test product. Each segment was treated with a pea size amount of either the arginine/calcium carbonate dentifrice or the strontium acetate dentifrice on each of three treatment occasions. After each treatment, segments were gently rinsed with deionized water until all the dentifrice residue was removed, and incubated in PBS for at least two hours with agitation using a stir bar, then hydraulic conductance was measured. This process was carried out for a total of three one-

minute treatments in one day. The first of the three treatments was applied using a parafilm-covered fingertip. The following two treatments were applied using an Oral-B® Indicator® soft toothbrush (Procter & Gamble, Cincinnati, OH, USA). After the third treatment cycle, the blocks were incubated in PBS overnight with agitation using a stir bar, and hydraulic conductance was re-measured. The two groups were then divided into three sets of two segments; these were each challenged for one minute with either 6% citric acid, orange or grapefruit juice, then conductance was measured. In total, conductance was measured on each segment after each treatment, after overnight incubation and after acid challenge, and was reported as a percentage reduction relative to the baseline value for each segment.

### *Statistical Analysis*

The mean percentage reductions were calculated for each product at each time point. To compare the product means, two-sample t-tests were conducted at each time point. A p-value $< 0.05$ was used to indicate a statistically significant difference between the products. To assess the effect of acid type, the percentage reduction results after acid challenge were analyzed using a general linear model. The model included the main effects Product and Acid type, and the Product X Acid type interaction effect. An effect p-value $< 0.05$ was used to indicate statistical significance.

## Results

The results, expressed as % reduction, are shown graphically in Figure 1. Dentin treated with the arginine/calcium carbonate dentifrice provided a statistically significantly higher % reduction in fluid flow immediately after fingertip application, as well as after two brushing cycles compared to the strontium acetate dentifrice ($p < 0.05$ in all cases). In addition, after the series of acid challenges, the percentage reduction in fluid flow of dentin treated with the arginine/calcium carbonate dentifrice was higher than the percentage reduction with the strontium acetate dentifrice. The general linear model analysis indicated that the main effect for Product was significant, with the arginine/calcium carbonate dentifrice having a larger percentage reduction (consistent with the t-test results). The Acid type and Product X Acid type interactions were not statistically significant ($p = 0.36$ and 0.63, respectively), indicating that that there was no difference between the effects of the three types of acid.

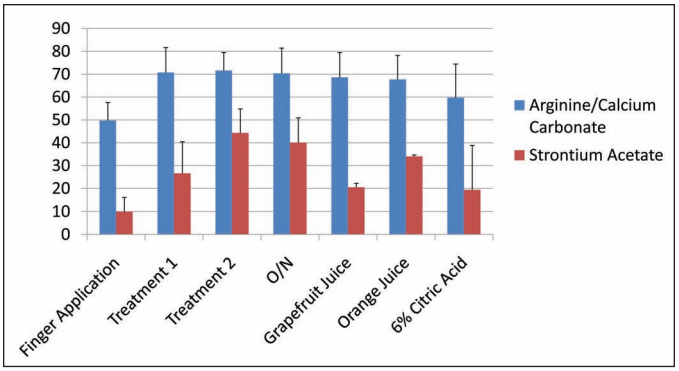



**Figure 1.** *Hydraulic conductance results after treatment and after exposure to acid challenge.*

## Discussion

The hydraulic conductance method provides quantitative data describing the ability of occluding deposits to retard the outward flow of fluid through dentin tubules, a key factor attributed to reducing hypersensitivity. The specific protocol and procedures used in this study have previously been repeatedly validated by comparing a dentifrice containing an established occluding agent to a control dentifrice without the occluding agent.

The hydraulic conductance experiments reported here demonstrated that the dentifrice containing 8.0% arginine, calcium carbonate, and 1450 ppm fluoride provided statistically significantly higher reductions in fluid flow as a result of occlusion than a dentifrice containing 8% strontium acetate and 1040 ppm fluoride. As the intent of the study was simply to provide a qualitative assessment of the ability of the two test dentifrices to occlude tubules, a negative control toothpaste was not included; the proof of efficacy and the quantification of sensitive relief benefits of the two test products relative to a negative control are assessed in the clinical studies summarized below. In addition, the results demonstrate that the arginine/calcium carbonate dentifrice produced an occlusion that is robust to acid challenge relative to the occlusion achieved with the strontium acetate dentifrice under the laboratory conditions utilized. These included a comparison of three different sources of acid challenge because previous *in vitro* studies on the effects of acid have typically selected a single fruit juice (usually orange or grapefruit) or a pure acid (usually citric acid).

Although the results of this study are contradictory to the results of the study recently published by Parkinson, *et al*. on the resistance of occlusion to acid challenge,[20] this is perhaps unsurprising as there is a wide range of laboratory conditions under which such laboratory studies can be conducted. Importantly, the results of the current study are highly consistent with the results of new hypersensitivity clinical studies which showed that the arginine/calcium carbonate dentifrice provided significant reductions in dentin hypersensitivity relative to the strontium acetate dentifrice, and that the arginine/calcium carbonate dentifrice was resistant to everyday acid challenges, as the superior level of sensitivity relief of the arginine/calcium carbonate dentifrice relative to the strontium acetate dentifrice was maintained throughout the study.[25-27]

Three new parallel, randomized, head-to-head clinical studies[25-27] have directly compared the efficacy of two desensitizing dentifrices which occlude dentin tubules: the test dentifrice contained 8% strontium acetate, an ingredient with a long history in a desensitizing dentifrice but equivocal efficacy, plus 1040 ppm fluoride, versus the positive control dentifrice containing 8.0% arginine, calcium carbonate, and 1450 ppm fluoride. In two of these studies, a commercial dentifrice with 1100 ppm fluoride was used as a negative control.

In the first study, subjects self-applied their assigned dentifrice to their hypersensitive teeth using a fingertip and massaged for one minute. They then brushed at home using the same dentifrice twice daily for seven days. Dentin hypersensitivity was evaluated at baseline, immediately after direct application, and after seven days. The dentifrice containing 8.0% arginine, calcium carbonate, and 1450 ppm fluoride delivered statistically significant

improvements in tactile and air blast sensitivity scores immediately after direct application and after seven days of twice-daily brushing compared to the dentifrice containing 8% strontium acetate and 1040 ppm fluoride, and to the regular fluoride dentifrice. In contrast, the 8% strontium acetate and 1040 ppm fluoride dentifrice did not provide statistically significant improvements immediately after direct application or after seven days' use compared to the regular fluoride dentifrice.[25]

In the second study, subjects brushed using their assigned dentifrice twice daily for eight weeks. Dentin hypersensitivity was evaluated at baseline, and after two, four, and eight weeks of product use. The dentifrice containing 8.0% arginine, calcium carbonate, and 1450 ppm fluoride delivered statistically significant improvements in tactile and air blast sensitivity scores compared to the dentifrice containing 8% strontium acetate and 1040 ppm fluoride. The dentifrice containing 8% strontium acetate and 1040 ppm fluoride provided statistically significant improvements compared to the regular fluoride dentifrice on both tactile and air blast measures after four and eight weeks' use. However, the 8% strontium acetate and 1040 ppm fluoride dentifrice did not provide a statistically significant improvement in air blast score compared to the regular fluoride dentifrice after two weeks' use.[26]

In the two-phase third study, subjects brushed using their first assigned dentifrice twice daily for eight weeks. They then brushed using their second assigned dentifrice twice daily for a further eight weeks to simulate typical consumer behavior in switching from one dentifrice brand to another, *i.e.*, without a wash-out period. Dentin hypersensitivity was evaluated at baseline and after eight, ten, and sixteen weeks. After eight weeks of using the first assigned dentifrice, the dentifrice containing 8.0% arginine, calcium carbonate, and 1450 ppm fluoride provided statistically significant improvements in tactile and air blast hypersensitivity scores compared to the dentifrice containing 8% strontium acetate and 1040 ppm fluoride. Two weeks after changing to the second assigned dentifrice, users of the dentifrice containing 8.0% arginine, calcium carbonate, and 1450 ppm fluoride experienced improvements in tactile and air blast scores compared to the scores achieved previously with the dentifrice containing 8% strontium acetate and 1040 ppm fluoride. In contrast, users of the dentifrice containing 8% strontium acetate and 1040 ppm fluoride were unable to maintain the tactile and air blast sensitivity scores compared to the scores achieved previously with the dentifrice containing 8.0% arginine, calcium carbonate, and 1450 ppm fluoride. After eight weeks' use of the second assigned dentifrice, users of the dentifrice containing 8.0% arginine, calcium carbonate, and 1450 ppm fluoride maintained the improvement in sensitivity seen in the first two weeks of use, while users of the dentifrice containing 8% strontium acetate and 1040 ppm fluoride continued not to maintain the improvement in sensitivity achieved when using the dentifrice containing 8.0% arginine, calcium carbonate, and 1450 ppm fluoride. At the end of the study, users of the dentifrice containing 8.0% arginine, calcium carbonate, and 1450 ppm fluoride during the second eight-week period had statistically significant improvements in tactile and air blast sensitivity scores compared to users of the dentifrice containing 8% strontium acetate and 1040 ppm fluoride during the same period.[27]

## Conclusion

The results of this hydraulic conductance study support the conclusion that a dentifrice containing 8.0% arginine, calcium carbonate, and 1450 ppm fluoride is more effective in occluding open dentin tubules and reducing dentin fluid flow than a dentifrice containing 8% strontium acetate and 1040 ppm fluoride, and that the occlusion achieved with the arginine/calcium carbonate dentifrice is resistant to acid challenge. The results provide the mechanistic rationale for the results of new clinical studies which demonstrate that a dentifrice containing 8.0% arginine, calcium carbonate, and 1450 ppm fluoride provides superior efficacy with respect to both immediate and lasting relief of dentin hypersensitivity compared to a dentifrice containing 8% strontium acetate and 1040 ppm fluoride, and that dentifrice containing 8% strontium acetate is no more effective in providing immediate relief of dentin hypersensitivity than a regular fluoride dentifrice.

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# Comparison of Clinical Efficacy of Three Toothpastes in Reducing Dentin Hypersensitivity

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**Abstract**

- **Objective:** The objective of the study was to compare the clinical efficacy in reducing dentin hypersensitivity of a test toothpaste containing 8% strontium acetate and 1040 ppm fluoride as sodium fluoride (NaF) in a silica base, to a positive control toothpaste containing 8.0% arginine and 1450 ppm fluoride as sodium monofluorophosphate (MFP) in a calcium carbonate base, and a negative control toothpaste containing 1100 ppm fluoride as NaF in a silica base.
- **Methods:** Subjects identified with two hypersensitive teeth using the tactile (Yeaple Probe) and air blast (Schiff's Scale) hypersensitivity methods were assigned to their treatment group. There were 50 subjects per group. Subjects then self-applied the assigned toothpaste to their hypersensitive teeth using a fingertip, then brushed their teeth at home using the same toothpaste twice daily for seven days. Dentin hypersensitivity and oral tissues were evaluated at baseline, immediately after the single application, and after seven days. A chi-square analysis was conducted to examine the effects with respect to gender between treatments. Comparisons of the age and baseline hypersensitivity data among groups were performed using the analysis of variance (ANOVA). Within-treatment effects were analyzed using the paired t-test, while the analysis of covariance (ANCOVA) was used to determine the between-treatment effects. The *post hoc* Tukey's test was performed for the pair-wise comparisons using a significance level of $\alpha = 0.05$.
- **Results:** All 150 subjects complied with the protocol and completed the study. The positive control toothpaste containing 8.0% arginine and 1450 ppm fluoride as MFP in a calcium carbonate base provided statistically significant improvements in mean tactile and air blast dentin hypersensitivity scores compared to the negative control toothpaste containing 1100 ppm fluoride as NaF in a silica base ($p < 0.05$). The toothpaste containing 8.0% arginine and 1450 ppm fluoride as MFP in a calcium carbonate base (positive control) also provided statistically significant improvements in mean tactile and air blast dentin hypersensitivity scores compared to the test toothpaste containing 8% strontium acetate and 1040 ppm fluoride as NaF in a silica base. The test toothpaste and the negative control toothpaste were not significantly different from each other.
- **Conclusion:** The test toothpaste containing 8% strontium acetate and 1040 ppm fluoride as NaF in a silica base, when used for a single topical application and twice-daily brushing for seven days, does not provide statistically significant relief of dentin hypersensitivity compared to a negative control toothpaste containing 1100 ppm fluoride as NaF in a silica base. In contrast, the positive control toothpaste containing 8.0% arginine and 1450 ppm fluoride as MFP in a calcium carbonate base provided significantly reduced dentin hypersensitivity compared to the negative control toothpaste, and was significantly more effective than the test toothpaste containing 8% strontium acetate and 1040 ppm fluoride as NaF in a silica base.

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## Introduction

Tooth brushing has been a primary method for maintaining daily oral hygiene. Traditionally, the major goal of tooth brushing is to remove dental plaque, a biofilm deposited on tooth surfaces that is composed of food debris, mucin, dead epithelial cells, and a complex community of coexisting and cohabitating bacteria.[1-3] The successful use of fluoride in toothpaste has added a therapeutic value to tooth brushing, and significantly enhanced the efficacy for combating dental caries. Continued advances in science and technology have helped the development of multi-functional toothpastes that prevent or treat caries and gingivitis, remove stains, improve oral odor, and reduce tooth sensitivity.

Tooth sensitivity, or more precisely "dentin hypersensitivity," is defined as short, sharp pain arising from exposed dentin in response to stimuli, typically thermal, evaporative, tactile, osmotic, or chemical, that cannot be ascribed to any other forms of dental defect or pathology.[4] It has become one of the most common complaints in dentistry, referred to as the "common cold of dentistry."[5] Studies have reported that dentin hypersensitivity affects up to 57% of dental patients of different lifestyles and cultures, and appears to peak between the ages of 20 and 40 years.[6-13]

Much research has focused on understanding the mechanisms involved in dentin hypersensitivity. A common key characteristic of dentin hypersensitivity is the exposed dentin that allows the

stimuli to affect the dentin tubular fluid and consequently to activate the pulpal nerves for the perception of pain by the patient. This hydrodynamic theory suggests that the pain sensation is caused by the activation of mechanoreceptors in intratubular nerves or in the superficial pulp due to changes in the flow and/or volume of fluid within dentinal tubules.[14,15] The findings that 60% to 98% of patients following periodontal treatment usually experience dentin hypersensitivity have provided supportive evidence for this theory; as such, procedures often result in dentin exposure.[6,15,16] Consequently, in addition to the use of potassium salts in toothpaste for nerve depolarization to disrupt the neural response to pain stimuli, efforts have been made to develop formulations that are capable of occluding the open dentin tubules to minimize or eliminate the flow of dentin fluids. A variety of agents and materials, including strontium acetate, strontium chloride, and stannous fluoride, have been used for a number of years as active ingredients in toothpaste for dentin hypersensitivity.[17,18]

More recently, a novel technology using 8.0% arginine, an amino acid naturally found in saliva, and calcium carbonate has been introduced to control dentin hypersensitivity.[19] This new desensitizing technology (Pro-Argin™) mimics saliva's natural process of plugging and sealing open dentin tubules. Its mechanism of action has been investigated using atomic force microscopy, confocal laser scanning microscopy, electron spectroscopy, and high resolution scanning electron microscopy; the results show that the formed sealing plugs are composed of arginine, calcium, phosphate, and carbonate.[20,21] Furthermore, hydraulic conductance studies have shown that the strength of these dentin plugs is adequate to withstand normal pulpal pressures and acid challenge, effectively reducing the dentin fluid flow[20,21] and, consequently, the sensation of tooth sensitivity.[22-24] Four double-blind, randomized clinical studies have validated the technology, demonstrating that toothpaste containing 8.0% arginine and 1450 ppm fluoride as MFP in a calcium carbonate base provides superior relief of dentin hypersensitivity compared to a leading potassium-based desensitizing toothpaste after two, four, and eight weeks of use.[25-28] More importantly, four additional double-blind, randomized clinical studies have demonstrated that toothpaste containing 8.0% arginine and 1450 ppm fluoride as MFP in a calcium carbonate base provides statistically significant relief of dentin hypersensitivity immediately following direct application to sensitive teeth and one minute of massage, compared to a potassium-based desensitizing toothpaste and a regular fluoride toothpaste. The potassium-based desensitizing toothpaste, in contrast, did not provide significant relief compared to the regular fluoride toothpaste.[29-32]

Among the variety of agents and materials used historically to occlude dentin tubules, strontium acetate has attracted renewed interest. A recent literature review identified a range of clinical studies on the effects of strontium-based toothpastes on dentin hypersensitivity when used during routine brushing for periods of four to 12 weeks; however, the review determined that many of the double-blind controlled studies showed no significant benefit for 10% strontium chloride or 8% strontium acetate toothpastes as compared to regular fluoride toothpaste. For this reason, that author concluded that: 1) the evidence for the efficacy of strontium-based toothpaste in reducing dentin hypersensitivity during long-term use is, at best, equivocal; and 2) there is no evidence to suggest that strontium-based toothpaste can provide immediate relief of sensitivity when directly applied to sensitive teeth.[24]

A recent clinical study, which compared the effects of 8% strontium acetate toothpaste to regular fluoride toothpaste immediately after direct application and after a subsequent three days of twice-daily brushing, reported that 8% strontium acetate toothpaste reduced dentin hypersensitivity immediately after direct application.[33] Although the 8% strontium acetate toothpaste was not compared to the previously validated 8.0% arginine/calcium carbonate-based toothpaste, it appeared that the effects observed for the 8% strontium acetate toothpaste were substantially lower than those previously reported for the 8.0% arginine/calcium carbonate-based toothpaste.[29-32]

The objective of this parallel, double-blind, stratified, and randomized clinical study was to compare the clinical efficacy of a toothpaste containing 8% strontium acetate and 1040 ppm fluoride as sodium fluoride (NaF) in a silica base (test), to that of a positive control toothpaste containing 8.0% arginine and 1450 ppm fluoride as sodium monofluorophosphate (MFP) in a calcium carbonate base, and to a negative control toothpaste containing 1100 ppm fluoride as NaF in a silica base in reducing dentin hypersensitivity immediately after a single self-application, as well as after twice-daily brushing for seven days.

## Materials and Methods

Prior to the initiation of the study, the protocol and the letter of informed consent were approved by the Institutional Review Board (IRB) of Loma Linda University. A total of 150 healthy adults, ages 18 to 70 years, participated in the study. Subjects were required to be available for the study duration and to sign an informed consent form. To be eligible for participating in the study, each subject had to have a minimum of two dentin hypersensitive teeth among incisors, canines, and premolars, with cervical erosion/abrasion or gingival recession, as determined by a tactile hypersensitivity stimulus score of 10 to 50 grams of force using a calibrated Yeaple Electronic Pressure Sensitive Probe (Model 200A; Yeaple Research, Pittsford, NY, USA) and an air blast stimulus score of 2 or 3 (Schiff Cold Air Sensitivity Scale). Subjects with any of the following conditions were excluded from the study: gross oral pathology; chronic oral diseases; advanced periodontal disease; treatment for periodontal disease within one year; and sensitive teeth with a mild mobility (mobility index > 1), extensive or defective restorations, suspected pulpitis, caries, cracked enamel, or removable partial dentures. The exclusion was also applied to the following conditions: current use of anticonvulsants, antihistamines, antidepressants, sedatives, tranquilizers, anti-inflammatory drugs, or daily analgesics; pregnant or lactating women; participation in a desensitizing dentifrice study or use of a desensitizing dentifrice within the last three months; currently participating in another clinical study; history of allergy to oral care/personal care consumer products or the test products of the present study; or any existing medical conditions that precluded them from not eating and drinking for a period of four hours.

The study was a three-cell, double-blind, parallel-group, stratified and randomized clinical investigation. Subjects and the clinical examiner were fully blinded to product assignment and application. The three toothpastes provided to the principal investigator were over-wrapped with white tape and identified only with a code. The clinical examiner was not present when the toothpaste was directly applied to the sensitive teeth in the first phase of the study.

Each enrolled study participant was randomly assigned to one of the three treatment groups which were balanced using the baseline tactile and air blast hypersensitivity scores. The three toothpastes were: 1) Test, a toothpaste containing 8% strontium acetate and 1040 ppm fluoride as NaF in a silica base (marketed as Sensodyne® Rapid Relief Toothpaste, GlaxoSmithKline, Weybridge, Surrey, UK); 2) Positive Control, a toothpaste containing 8.0% arginine and 1450 ppm fluoride as MFP in a calcium carbonate base (marketed as Colgate® Sensitive Pro-Relief™ Toothpaste and elmex® Sensitive Professional™ Toothpaste, Colgate-Palmolive Company, New York, NY, USA); and 3) Negative Control, a toothpaste containing 1100 ppm fluoride as NaF in a silica base (Crest® Cavity Protection Toothpaste, Procter & Gamble Co., Cincinnati, OH, USA).

Subjects were instructed to refrain from oral hygiene procedures and chewing gum for eight hours, and from eating and drinking for four hours prior to their scheduled baseline examination. After the baseline evaluation of oral tissues and dentin hypersensitivity of the two identified teeth using the Yeaple Tactile Probe and Schiff Cold Air Blast Method,[34] each subject topically self-applied a pea-size amount (approximately 0.3 grams) of their assigned toothpaste directly onto each of his/her hypersensitive teeth using a fingertip by massaging each tooth for 60 seconds before expectoration. The same tactile and air blast hypersensitivity examinations were then conducted again by the same examiner.

The same toothpaste was used by the subjects at home for seven days. At-home brushing instructions 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 products and procedures throughout the duration of the study. There were no restrictions regarding diet or smoking habits. Subjects returned to the clinic after seven days, again refraining from oral hygiene procedures and chewing gum for eight hours, and eating and drinking for four hours prior to their scheduled final examinations. Assessments of oral tissues and tactile and air blast dentin hypersensitivity were repeated by the same examiner using the same methods. At each visit, each subject was also interviewed regarding adverse events and the use of concomitant medications. Subjects and study examiner remained fully blinded to product assignment and application for the duration of the study.

For the measurement of Yeaple tactile hypersensitivity, the instrument was calibrated daily following manufacturer's instructions. Scores were recorded in terms of the quantified reproducible force (grams applied through a #19 explorer tip) that was required to elicit discomfort using the established procedures.[35,36] Briefly, the subject was instructed to respond at the point where he or she first experienced discomfort. The explorer tip of the probe was applied to the buccal surface of each hypersensitive tooth at the CEJ. The explorer tip was stroked perpendicular to the tooth beginning at a pre-set force of 10 grams, and increased by 10-gram increments until the subject experienced discomfort, or until 50 grams of force was applied.

For evaluating the air blast hypersensitivity, the tooth to be examined was isolated from the adjacent teeth (mesial and distal) by placing the examiner's fingers over the adjacent teeth. Air was delivered from a standard dental unit air syringe at 60 psi (± 5 psi) and 72˚F (± 3°F), directed at the exposed buccal surface of the hypersensitive tooth for one second from a distance of approximately 1 cm. The Schiff Cold Air Sensitivity Scale[34] was used to assess subject response to this stimulus as follows:

0 = Subject did not respond to air stimulus;
1 = Subject responded to air stimulus but did not request discontinuation of stimulus;
2 = Subject responded to air stimulus and requested discontinuation or moved from stimulus;
3 = Subject responded to air stimulus, considered stimulus to be painful, and requested discontinuation of the stimulus.

The oral soft and hard tissue examination included visual assessment of the soft and hard palate, gingival and buccal mucosa, mucogingival fold areas, tongue, sublingual and submandibular areas, salivary glands, and the tonsilar and pharyngeal areas.

Comparisons of the treatment groups with respect to gender were performed using a chi-square analysis; for age, the analysis of variance (ANOVA) was used. The tactile and air blast scores were calculated separately by averaging the values measured on the two qualified teeth for each subject, and the data were analyzed using ANOVA. The paired t-test was performed to examine the within-treatment effects. The treatment groups, with respect to baseline-adjusted tactile hypersensitivity and air blast hypersensitivity scores at the follow-up examinations, were compared using analysis of covariance (ANCOVA). If a statistically significant difference was detected among the treatment groups by ANCOVA analysis, a *post hoc* Tukey's Multiple Comparison test was performed on the pair-wise comparisons. All statistical tests were two-sided using a significance level of $\alpha = 0.05$.

## Results

All 150 subjects completed the study. As shown in Table I, the demographic compositions are comparable among the three groups. The average age was 37.4, 36.8, and 35.9, and the females accounted for 60%, 58%, and 56% for the positive control toothpaste group, the test toothpaste group, and the negative control toothpaste group, respectively. The race composition was also similar among the three groups (Table II).

Table III presents the baseline Yeaple tactile and Schiff air blast hypersensitivity scores; there were no significant differences among the three groups. The baseline tactile force to induce sensitivity was 15.9, 16.3, and 16.0 grams for the positive control toothpaste group, the test toothpaste group, and the negative control toothpaste group, respectively. The baseline air blast sensitivity scores were 2.45, 2.46, and 2.43 for the positive control toothpaste group, the test toothpaste group, and the negative control toothpaste group, respectively.

**Table I**
Age and Gender Composition of the Three Study Groups

| Group[1] | Gender | | | Age | |
|---|---|---|---|---|---|
| | Male | Female | Total | Mean[2] | Range |
| Positive Control Toothpaste | 20 | 30 | 50 | 37.4 | 18–63 |
| Test Toothpaste | 21 | 29 | 50 | 36.8 | 18–69 |
| Negative Control Toothpaste | 22 | 28 | 50 | 35.9 | 18–61 |

[1]Positive Control toothpaste marketed as Colgate Sensitive Pro-Relief and elmex Sensitive Professional. Test toothpaste marketed as Sensodyne Rapid Relief, and Negative Control toothpaste marketed as Crest Cavity Protection.
[2]There were no significant differences among the three groups.

**Table II**
Race Composition of the Three Study Groups

| Group[1] | Race Distribution | | | | |
|---|---|---|---|---|---|
| | White | Hispanic | Asian | African-American | Other |
| Positive Control Toothpaste | 18 | 22 | 4 | 6 | 0 |
| Test Toothpaste | 15 | 25 | 0 | 9 | 1 |
| Negative Control Toothpaste | 15 | 23 | 3 | 9 | 0 |

[1]Positive Control toothpaste marketed as Colgate Sensitive Pro-Relief and elmex Sensitive Professional. Test toothpaste marketed as Sensodyne Rapid Relief, and Negative Control toothpaste marketed as Crest Cavity Protection.

**Table III**
Baseline Yeaple Tactile and Schiff Air Blast Hypersensitivity Scores

| Group[1] | n | Yeaple Tactile Force (g)[2] | Schiff Air Blast[2] |
|---|---|---|---|
| Positive Control Toothpaste | 50 | 15.9 ± 6.98 | 2.45 ± 0.38 |
| Test Toothpaste | 50 | 16.3 ± 6.13 | 2.46 ± 0.40 |
| Negative Control Toothpaste | 50 | 16.0 ± 6.55 | 2.43 ± 0.10 |

[1]Positive Control toothpaste marketed as Colgate Sensitive Pro-Relief and elmex Sensitive Professional. Test toothpaste marketed as Sensodyne Rapid Relief, and Negative Control toothpaste marketed as Crest Cavity Protection.
[2]Mean ± SD. There were no significant differences among three groups.

Immediately after a single direct application of the toothpastes, the mean tactile force increased to 36.1, 20.0, and 18.9 grams for the positive control toothpaste group, the test toothpaste group, and the negative control toothpaste group, respectively (Table IV).

When the tactile data were compared among the three groups, the positive control toothpaste was significantly more effective ($p < 0.05$) than the test toothpaste (80.5%) and the negative control toothpaste (91.0%) in reducing tactile hypersensitivity immediately after a single direct application (Table IV). There was no statistically significant difference between the test toothpaste and the negative control toothpaste, which means that the test toothpaste did not provide significant instant relief.

Immediately after a single direct application of the toothpastes, the mean air blast sensitivity scores decreased to 1.16, 1.98, and 2.10 for the positive control toothpaste group, the test toothpaste group, and the negative control toothpaste group, respectively (Table V).

The analysis of the between-treatment effects on air blast hypersensitivity scores showed that the positive control toothpaste was significantly more effective ($p < 0.05$) in reducing air blast hypersensitivity immediately after a single application than the test toothpaste (41.4%) and the negative control toothpaste (44.8%). There was no statistically significant difference between the test toothpaste and the negative control toothpaste (Table V), which confirms that the test toothpaste did not provide significant instant relief.

The seven-day results showed further improvement of the scores after twice-daily brushing with the three toothpastes (Figures 1 and 2). As shown in Table VI, the mean tactile force that induced hypersensitivity was 40.3 g for the positive control toothpaste, 30.5 g for the test toothpaste, and 28.0 g for the negative control toothpaste. The between-treatment analysis showed that the positive control toothpaste maintained its superiority compared to the test toothpaste (32.1%) and the negative control toothpaste (43.9%), and the differences were significant ($p < 0.05$). Again, there was no statistically significant difference between the test toothpaste and the negative control toothpaste (Table VI).

Table VII presents the results of the seven-day air blast hypersensitivity assessment. The overall data were consistent with and supportive of those obtained from the Yeaple tactile method (Figure 1 and Table VI). The analysis of the between-treatment effects showed that after seven days, the positive control toothpaste group maintained a significantly higher reduction in air

**Table IV**
Yeaple Tactile Sensitivity Force (Gram) Immediately After a Single Application

| Group[1] | n | Immediately Post-Application (Mean ± SD) | Within-Treatment Analysis | | Between-Treatment Comparisons | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | vs. Test Toothpaste | | vs. Negative Control Toothpaste | |
| | | | % Change[2] | p-value[3] | % Difference[4] | p-value[5] | % Difference[6] | p-value[5] |
| Positive Control Toothpaste | 50 | 36.1 ± 10.17 | 127.0 | < 0.05 | 80.5 | < 0.05 | 91.0 | < 0.05 |
| Test Toothpaste | 50 | 20.0 ± 10.69 | 22.7 | < 0.05 | — | — | 5.8 | NS |
| Negative Control Toothpaste | 50 | 18.9 ± 9.22 | 18.1 | < 0.05 | — | — | — | — |

[1]Positive Control toothpaste marketed as Colgate Sensitive Pro-Relief and elmex Sensitive Professional. Test toothpaste marketed as Sensodyne Rapid Relief, and Negative Control toothpaste marketed as Crest Cavity Protection.
[2]Percent change comparing the immediate post-application to the baseline. A positive value indicates an increased tactile score at the immediate post-application examination.
[3]Significance of paired t-test comparing the baseline and the immediate post-application examination means.
[4]Percentage difference between Positive Control toothpaste and Test toothpaste; a positive value indicates more reduction for Positive Control in tactile hypersensitivity as compared to Test toothpaste.
[5]Significance of ANCOVA comparison of baseline-adjusted means.
[6]Percentage difference between Positive Control toothpaste or Test toothpaste and the Negative Control toothpaste; a positive value indicates more reduction in tactile hypersensitivity for Positive Control toothpaste or Test toothpaste as compared to Negative Control toothpaste.

**Table V**
Schiff Air Blast Hypersensitivity Scores Immediately After a Single Application

| | | | | | Between-Treatment Comparisons | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | vs. Test Toothpaste | | vs. Negative Control Toothpaste | |
| Group[1] | n | Immediately Post-Application (Mean ± SD) | Within-Treatment Analysis % Change[2] | p-value[3] | % Difference[4] | p-value[5] | % Difference[6] | % Change[2] |
| Positive Control Toothpaste | 50 | 1.16 ± 0.68 | 52.7 | < 0.05 | 41.4 | < 0.05 | 44.8 | < 0.05 |
| Test Toothpaste | 50 | 1.98 ± 0.64 | 19.5 | < 0.05 | — | — | 5.7 | NS |
| Negative Control Toothpaste | 50 | 2.10 ± 0.65 | 13.6 | < 0.05 | — | — | — | — |

[1]Positive Control toothpaste marketed as Colgate Sensitive Pro-Relief and elmex Sensitive Professional. Test toothpaste marketed as Sensodyne Rapid Relief, and Negative Control toothpaste marketed as Crest Cavity Protection.
[2]Percent change comparing the immediate post-application to the baseline. A positive value indicates an increased air blast score at the immediate post-application examination.
[3]Significance of paired t-test comparing the baseline and the immediate post-application examination means.
[4]Percentage difference between Positive Control toothpaste and Test toothpaste; a positive value indicates more reduction for Positive Control in air blast hypersensitivity as compared to Test toothpaste.
[5]Significance of ANCOVA comparison of baseline-adjusted means.
[6]Percentage difference between Positive Control toothpaste or Test toothpaste and the Negative Control toothpaste; a positive value indicates more reduction in air blast hypersensitivity for Positive Control toothpaste or Test toothpaste as compared to Negative Control toothpaste.

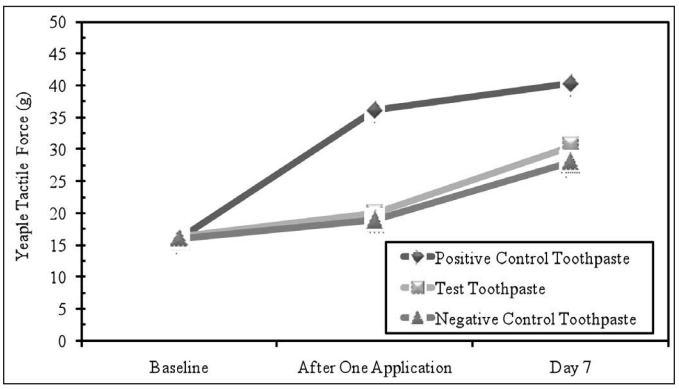



**Figure 1.** *Mean Yeaple tactile forces (g) at baseline, immediately after a single application, and after twice-daily tooth brushing for seven days. Positive Control toothpaste marketed as Colgate Sensitive Pro-Relief and elmex Sensitive Professional, Test toothpaste marketed as Sensodyne Rapid Relief, and Negative Control toothpaste marketed as Crest Cavity Protection.*

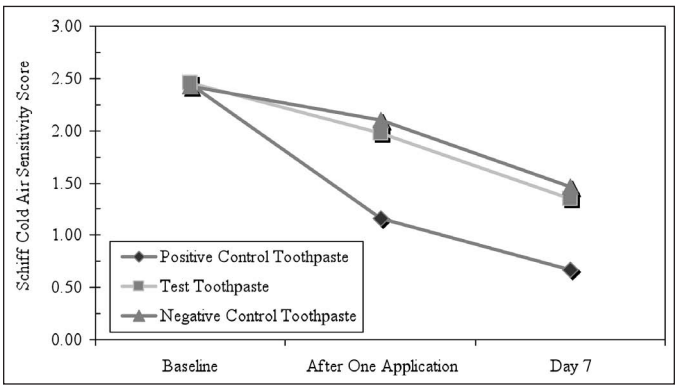



**Figure 2.** *Mean Schiff air blast hypersensitivity scores at baseline, immediately after a single application, and after twice-daily tooth brushing for seven days. Positive Control toothpaste marketed as Colgate Sensitive Pro-Relief and elmex Sensitive Professional, Test toothpaste marketed as Sensodyne Rapid Relief, and Negative Control toothpaste marketed as Crest Cavity Protection.*

blast hypersensitivity ($p < 0.05$) as compared to the test toothpaste group (50.4%) and the negative control toothpaste group (54.1%). Again, there was no statistically significant difference between the test toothpaste group and the negative control toothpaste group (Table VII), which means that the test toothpaste did not provide sensitivity relief after seven days of twice-daily brushing compared to the negative control toothpaste.

No adverse events were reported by subjects during the course of the study. There were no changes in oral hard and soft tissues detected in any of the three groups at any of the visits.

**Table VI**
Yeaple Tactile Sensitivity Force (Gram) Twice-Daily Tooth Brushing for Seven Days

| | | | | | Between-Treatment Comparisons | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | vs. Test Toothpaste | | vs. Negative Control Toothpaste | |
| Group[1] | n | Seven-Day Post-Application (Mean ± SD) | Within-Treatment Analysis % Change[2] | p-value[3] | % Difference[4] | p-value[5] | % Difference[6] | p-value[5] |
| Positive Control Toothpaste | 50 | 40.3 ± 12.31 | 153.5 | < 0.05 | 32.1 | < 0.05 | 43.9 | < 0.05 |
| Test Toothpaste | 50 | 30.5 ± 14.44 | 87.1 | < 0.05 | — | — | 8.9 | NS |
| Negative Control Toothpaste | 50 | 28.0 ± 12.74 | 75.0 | < 0.05 | — | — | — | — |

[1]Positive Control toothpaste marketed as Colgate Sensitive Pro-Relief and elmex Sensitive Professional. Test toothpaste marketed as Sensodyne Rapid Relief, and Negative Control toothpaste marketed as Crest Cavity Protection.
[2]Percent change comparing the seven-day post-application to the baseline. A positive value indicates an increased tactile score at the seven-day post-application examination.
[3]Significance of paired t-test comparing the baseline and the seven-day post-application examination means.
[4]Percentage difference between Positive Control toothpaste and Test toothpaste; a positive value indicates more reduction for Positive Control in tactile hypersensitivity as compared to Test toothpaste.
[5]Significance of ANCOVA comparison of baseline-adjusted means.
[6]Percentage difference between Positive Control toothpaste or Test toothpaste and the Negative Control toothpaste; a positive value indicates more reduction in tactile hypersensitivity for Positive Control toothpaste or Test toothpaste as compared to Negative Control toothpaste.

**Table VII**
Schiff Air Blast Hypersensitivity Scores Twice-Daily Tooth Brushing for Seven Days

| | | | | | Between-Treatment Comparisons | | | |
|---|---|---|---|---|---|---|---|---|
| | | | Within-Treatment Analysis | | vs. Test Toothpaste | | vs. Negative Control Toothpaste | |
| Group[1] | n | Seven-Day Post-Application (Mean ± SD) | % Change[2] | p-value[3] | % Difference[4] | p-value[5] | % Difference[6] | p-value[5] |
| Positive Control Toothpaste | 50 | 0.67 ± 0.71 | 72.7 | < 0.05 | 50.4 | < 0.05 | 54.1 | < 0.05 |
| Test Toothpaste | 50 | 1.35 ± 0.87 | 45.1 | < 0.05 | — | — | 7.5 | NS |
| Negative Control Toothpaste | 50 | 1.46 ± 0.83 | 39.9 | < 0.05 | — | — | — | — |

[1]Positive Control toothpaste marketed as Colgate Sensitive Pro-Relief and elmex Sensitive Professional. Test toothpaste marketed as Sensodyne Rapid Relief, and Negative Control toothpaste marketed as Crest Cavity Protection.
[2]Percent change comparing the seven-day post-application to the baseline. A positive value indicates an increased air blast score at the seven-day post-application examination.
[3]Significance of paired t-test comparing the baseline and the seven-day post-application examination means.
[4]Percentage difference between Positive Control toothpaste and Test toothpaste; a positive value indicates more reduction for Positive Control in air blast hypersensitivity as compared to Test toothpaste.
[5]Significance of ANCOVA comparison of baseline-adjusted means.
[6]Percentage difference between Positive Control toothpaste or Test toothpaste and the Negative Control toothpaste; a positive value indicates more reduction in air blast hypersensitivity for Positive Control toothpaste or Test toothpaste as compared to Negative Control toothpaste.

## Discussion

The well-balanced demographic compositions, including age, gender, and race, provide evidence of comparability of the parameters among the three study groups. In addition, the age range, gender ratio, and race distribution of the subjects in the present study are representative of the general population of the study site, which further supports the relevancy of the results for this sample of patients.

On the basis of clinical efficacy studies demonstrating relief of sensitivity compared to regular fluoride toothpaste, toothpastes containing potassium salts as active ingredients are recommended by dental professionals as the first line of treatment for dentin hypersensitivity. However, clinical data indicate that the effect of potassium-based toothpastes is gradual, needing an extended period of two weeks or longer of twice-daily brushing to provide significant relief from dentin hypersensitivity.[24] Despite the availability of clinical efficacy data, there have been questions and debate on the desensitizing efficacy of potassium-based toothpaste. Specifically, a Cochrane systemic review[37] and meta-analysis of a subset of six randomized, controlled clinical studies led its authors to conclude that the clinical efficacy in reducing dentin hypersensitivity of potassium-containing toothpastes is equivocal.

Approximately 50 years ago, prior to the widespread adoption of potassium as a desensitizer, strontium chloride was incorporated into toothpaste because it was believed to treat tooth sensitivity by occluding dentin tubules. More recently, strontium acetate has been used in desensitizing toothpastes because of its compatibility with fluoride.[17] However, data on their clinical efficacy for the relief of dentin hypersensitivity are inconsistent and equivocal.[24,38,39] The overall evidence on clinical efficacy of strontium-based toothpastes for reducing dentin hypersensitivity is not as strong as that for the potassium-based toothpastes.[24]

The present study evaluated the clinical effectiveness of three commercial dentifrices in reducing dentin hypersensitivity immediately after a single self-application, as well as after a subsequent twice-daily brushing for a period of seven days. The test toothpaste contained 8% strontium acetate and 1040 ppm fluoride as NaF in a silica base, newly marketed as Sensodyne Rapid Relief. The study contained both a positive and a negative control, this being appropriate to demonstrate comparative efficacy among different formulations. Study validation can be achieved by showing that the positive control was statistically better than the negative control in reducing dentin hypersensitivity at each of the two measurement time points, *i.e.*, immediately after direct application and after a subsequent seven days of twice-daily brushing.

The positive control product containing 8.0% arginine and 1450 ppm fluoride as MFP in a calcium carbonate base, marketed as Colgate Sensitive Pro-Relief and elmex Sensitive Professional, was selected because it has been clinically proven to provide statistically significant dentin hypersensitivity relief immediately after direct application, compared to a potassium-based desensitizing toothpaste and a regular fluoride toothpaste in multiple independent clinical studies.[29-32]

The negative control, Crest Cavity Protection, was a regular fluoride toothpaste that is similar to the test product in that it contains 1100 ppm fluoride as NaF in a silica base. The inclusion of the negative control was also important to allow the study to establish and factor out the reductions in dentin hypersensitivity associated with the use of regular fluoride toothpaste. Observations at both the immediate and short-term (seven-day) measurement points may be attributed to the well-known placebo or Hawthorne effect.[40]

The results of the present study confirm that a toothpaste containing 8.0% arginine and 1450 ppm fluoride as MFP in a calcium carbonate base (Colgate Sensitive Pro-Relief/elmex Sensitive Professional) provides statistically significant relief of dentin hypersensitivity immediately after direct application, and after a period of subsequent twice-daily brushing compared to regular fluoride toothpaste, and to the test toothpaste containing 8% strontium acetate and 1040 ppm fluoride. The results are highly consistent for both tactile and air blast stimulated sensitivity evaluations, and are also in close agreement with the results of previous independent studies published in peer-reviewed scientific journals.[25-29,31,32]

In summary, the results demonstrate statistically significant efficacy differences between the positive control, test dentifrice,

and negative control, both immediately and at a seven-day time point. These differences are all in favor of the positive control, indicating that the toothpaste containing 8.0% arginine and 1450 ppm fluoride in a calcium carbonate base (Colgate Sensitive Pro-Relief/elmex Sensitive Professional) is superior in providing immediate and lasting relief of dentin hypersensitivity compared to the strontium acetate toothpaste (Sensodyne Rapid Relief). The results also show that there are no statistical differences between the test toothpaste with 8% strontium acetate and 1040 ppm fluoride (Sensodyne Rapid Relief) and the negative control, a regular fluoride toothpaste, on either tactile or air blast measures at either the immediate or seven-day time point.

## Conclusions

The results of this double-blind, randomized, controlled, parallel-design clinical study support the following conclusions:

1. Toothpaste containing 8.0% arginine and 1450 ppm fluoride in a calcium base (marketed as Colgate Sensitive Pro-Relief and elmex Sensitive Professional) offers significant relief of dentin hypersensitivity immediately after a single fingertip topical self-application, and after a subsequent seven-day period of twice-daily brushing relative to a toothpaste containing 8% strontium acetate and 1040 ppm fluoride (marketed as Sensodyne Rapid Relief) and to a regular fluoride toothpaste.
2. Toothpaste containing 8% strontium acetate and 1040 ppm fluoride (marketed as Sensodyne Rapid Relief) does not provide significant relief of dentin hypersensitivity immediately after a single fingertip topical self-application, and after a subsequent seven-day period of twice-daily brushing relative to a regular fluoride toothpaste.

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# Comparative Evaluation of the Efficacy of Three Commercially Available Toothpastes on Dentin Hypersensitivity Reduction: An Eight-Week Clinical Study

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**Abstract**

- **Objective:** The objective of this eight-week, single-center, three-cell, double-blind, and randomized clinical study was to evaluate the dentin hypersensitivity reduction efficacy of three commercially available toothpastes: 1) Colgate® Sensitive Pro-Relief™ Toothpaste (also marketed as elmex® Sensitive Professional™); 2) Sensodyne® Rapid Relief Toothpaste; and (3) Crest® Cavity Protection Toothpaste.
- **Methods:** 150 subjects, having two teeth with tactile and air blast hypersensitivity, were assigned to one of the three study groups (50/group). Subjects were then asked to brush their teeth for one minute, twice daily, with the given toothpaste. The dentin hypersensitivity and oral tissues were evaluated at baseline, two weeks, four weeks, and eight weeks. Comparison of the treatment groups with respect to gender was conducted using a chi-square analysis, and with respect to age and baseline hypersensitivity scores was performed using the analysis of variance (ANOVA). Within-treatment effects were analyzed using the paired t-test, while the analysis of covariance (ANCOVA) was used to examine between-treatment effects. The *post hoc* Tukey test was performed for pair-wise comparisons. All statistical tests were two-sided using a significance level of $\alpha = 0.05$.
- **Results:** After two, four, and eight weeks of daily use of the products, all three groups showed a statistically significant reduction from baseline in tactile and air blast dentin hypersensitivity ($p < 0.05$). Colgate Sensitive Pro-Relief toothpaste produced a significant improvement in mean tactile and air blast dentin hypersensitivity scores, and was more effective than Sensodyne Rapid Relief toothpaste and Crest Cavity Protection toothpastes ($p < 0.05$).
- **Conclusion:** Colgate Sensitive Pro-Relief Toothpaste, used twice daily, significantly reduces dentin hypersensitivity, and is significantly more effective in reducing dentin hypersensitivity than Sensodyne Rapid Relief Toothpaste and Crest Cavity Protection Toothpaste.

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## Introduction

Dentin hypersensitivity may be experienced after the root surfaces of an individual are exposed to the oral environment via gingival recession or periodontal treatment. Once the root is exposed and the cementum subsequently eroded, the exposed dentin is subjected to exterior stimuli. These stimuli are most commonly of a thermal, osmotic, electrical, chemical, or dehydrating nature. The host then feels a pain, termed "dentinalgia"[1] that has been described as "short, sharp, and cannot be ascribed to any other form of dental defect or pathology."[2] This frequent clinical condition has long been a dilemma for both patients and dental practitioners, and with teeth being maintained longer there is an increased demand placed upon the dental practitioner to manage the sensitivity of cervically exposed dentin.

Many theories have been used to explain the mechanisms of dentin hypersensitivity. An early hypothesis was the dentin receptor mechanism theory, which suggested that dentin hypersensitivity is caused by the direct stimulation of sensory nerve endings in dentin;[3] today this theory is not well accepted. Another theory was proposed by Rapp, *et al*.[4] suggesting that odontoblasts act as receptor cells, mediating changes in the membrane potential of the odontoblasts via synaptic junction with nerves. This could result in the sensation of pain from the nerve endings located in the pulpodentinal border. This theory, like the previous one, has some shortcomings, and is not well accepted by the scientific community.

The theory that is widely accepted to explain dentin hypersensitivity-related pain is the "hydrodynamic theory" as described

by Brännström and Astron.[5] This theory states that the pain sensation is caused by the activation of mechanoreceptors in intratubular nerves or in the superficial pulp due to changes of the flow and/or volume of fluid within dentin tubules.[5,6]

The management of dentin hypersensitivity has consisted of using dentifrices containing potassium salts for nerve depolarization and disruption of a neural response to pain stimuli as the first line of action. This method, albeit effective, has two shortcomings: 1) it does not address the cause of the problem (open dentin tubules); and 2) it does not provide immediate relief. A number of other agents have been investigated for the treatment of hypersensitive teeth, with varying degrees of effectiveness. They include formaldehyde, sodium fluoride, dibasic sodium citrate, sodium monofluorophosphate, sodium silicofluoride, silver nitrate, calcium hydroxide, and strontium chloride. Some of these compounds have been incorporated into dentifrices for daily use.[7,8] However, strong evidence of the clinical efficacy of many of these ingredients has been elusive, with some (*i.e.*, formaldehyde) being associated with allergic reactions or soft tissue damage.[9] In recent years, a novel technology using an amino acid found in saliva (arginine) has shown great promise for the treatment of dentin hypersensitivity as it acts on the open dentin tubules to block the pathway to pain.[10] This new technology utilizes 8.0% arginine and calcium carbonate with 1450 ppm fluoride as sodium monofluorophosphate (MFP) in a toothpaste formula that has been shown to obliterate the dentin tubules, hence reducing the dentin flow and significantly alleviating the pain sensation.[11-13]

The objective of this parallel, double-blind, stratified, and randomized clinical study was to compare the clinical efficacy of the new Colgate® Sensitive Pro-Relief™ Toothpaste (also marketed as elmex® Sensitive Professional™) to that of Sensodyne® Rapid Relief Toothpaste and Crest® Cavity Protection Toothpaste in reducing dentin hypersensitivity after two, four, and eight weeks of twice-daily brushing.

## Materials and Methods

After Institutional Review Board (IRB) approval of the protocol and the letter of informed consent, a total of 150 healthy adults, ages 20 to 69 years, participated in the study. Subjects were required to be available for the study duration and to sign the informed consent form. To be eligible for participation in the study, each subject had to have a minimum of two teeth with dentin hypersensitivity among incisors, canines, and premolars, with cervical erosion/abrasion or gingival recession, as determined by a tactile hypersensitivity stimulus score of 10 to 50 grams of force using a calibrated Yeaple Electronic Pressure Sensitive Probe (Model 200A; Yeaple Research, Pittsford, NY, USA), and an air blast stimulus score of 2 or 3 (Schiff Cold Air Sensitivity Scale). Subjects with any of the following conditions were excluded from the study: gross oral pathology; chronic oral diseases; advanced periodontal disease; treatment for periodontal disease within one year; sensitive teeth with mild mobility (mobility index > 1), extensive or defective restorations, suspected pulpitis, caries, cracked enamel; or teeth used as abutments for removable partial dentures. The exclusion also applied to the following conditions: current use of anticonvulsants, antihistamines, antidepressants, sedatives, tranquilizers, anti-inflammatory drugs, or daily analgesics; pregnant or lactating women; participation in a desensitizing dentifrice study or use of a desensitizing dentifrice within the last three months; currently participating in another clinical study; history of allergy to oral care/personal care consumer products or the test products of the present study; or any existing medical conditions that precluded them from not eating and drinking for a period of four hours.

The study was a three-cell, double-blind, parallel-group, stratified, and randomized clinical investigation. Each enrolled study participant was randomly assigned to one of the three treatment groups which were balanced using the baseline tactile and air blast hypersensitivity scores. The three toothpastes were: 1) Colgate Sensitive Pro-Relief containing 8.0% arginine, calcium carbonate, and 1450 ppm fluoride as MFP (Colgate-Palmolive Co., New York, NY, USA); 2) Sensodyne Rapid Relief containing 8% strontium acetate and 1040 ppm fluoride as NaF (Glaxo-SmithKline Co., Weybridge, Surrey, UK); and 3) Crest Cavity Protection containing 1100 ppm fluoride as NaF (Procter & Gamble Co., Cincinnati, OH, USA).

Subjects were instructed to refrain from oral hygiene procedures and chewing gum for eight hours, and from eating and drinking for four hours prior to their scheduled baseline examination. After the baseline evaluation of oral tissues and dentin hypersensitivity of the two identified teeth using the Yeaple tactile probe and Schiff cold air blast method,[14] each subject was given their assigned toothbrush and toothpaste to use for the duration of the study. At-home instructions 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 products and procedures throughout the duration of the study

All tested dentifrices were supplied in their original packaging and overwrapped with a white label to mask the identity of the product. A log of the dispensed products was kept and all clinical supplies were refurbished as needed. There were no restrictions regarding diet or smoking habits. Subjects returned to the clinic after two weeks, four weeks, and eight weeks, again refraining from oral hygiene procedures and chewing gum for eight hours, and eating and drinking for four hours prior to their scheduled examinations. Assessments of oral tissues and tactile and air blast dentin hypersensitivity were repeated by the same examiner using the same methods. At each visit, each subject was also interviewed regarding adverse events and the use of concomitant medications.

For the measurement of Yeaple tactile hypersensitivity, the instrument was calibrated daily following manufacturer's instructions. Scores were recorded in terms of the quantified reproducible force (grams applied using a #19 explorer tip) that was required to elicit discomfort with the established procedures.[15,16] Briefly, the subject was instructed to respond at the point where he or she first experienced discomfort. The explorer tip of the probe was applied to the buccal surface of each hypersensitive tooth at the CEJ. The explorer tip was stroked perpendicular to the tooth beginning at a pre-set force of 10 grams, and increased by 10-gram increments until the subject experienced discomfort, or until 50 grams of force was applied.

For evaluating the air blast hypersensitivity, the tooth to be examined was isolated from the adjacent teeth by placing the

examiner's fingers over the adjacent teeth. Air was delivered from a standard dental unit air syringe at 60 psi (± 5 psi) and 70˚F (± 3˚F), directed at the exposed buccal surface of the hypersensitive tooth for one second from a distance of approximately one cm. The Schiff Cold Air Sensitivity Scale[14] was used to assess subject response to this stimulus, as follows:

0 = Subject did not respond to air stimulus;
1 = Subject responded to air stimulus but did not request discontinuation of stimulus;
2 = Subject responded to air stimulus and requested discontinuation or moved from stimulus;
3 = Subject responded to air stimulus, considered stimulus to be painful, and requested discontinuation of the stimulus.

The oral tissue examination included visual assessment of the soft and hard palate, gingival and buccal mucosa, mucogingival fold areas, tongue, sublingual and submandibular areas, salivary glands, and the tonsilar and pharyngeal areas.

Comparisons of the treatment groups with respect to gender were performed using a chi-square analysis; for age, the analysis of variance (ANOVA) was used. The tactile and air blast scores were calculated separately by averaging the values measured on the two qualified teeth for each subject, and the data were analyzed using the ANOVA. The paired t-test was performed to examine within-treatment effects. The treatment groups, with respect to baseline-adjusted tactile hypersensitivity and air blast hypersensitivity scores at the follow-up examinations, were compared using the analysis of covariance (ANCOVA). If a statistically significant difference was detected among the treatment groups by the ANCOVA analysis, a *post hoc* Tukey Multiple Comparison test was performed on the pair-wise comparisons. All statistical tests were two-sided using a significance level of $\alpha = 0.05$.

## Results

All one-hundred and fifty (150) subjects complied with the protocol and completed the eight-week clinical study. A summary of the gender and age of the study population is presented in Table I. Throughout the study, there were no adverse events on the soft or hard tissues of the oral cavity observed by the examiner or reported by the subjects when questioned. Table II presents a summary of the mean tactile and air blast hypersensitivity scores measured at the baseline examination. For tactile hypersensitivity, the mean baseline scores were 11.60 for the Colgate Sensitive Pro-Relief Toothpaste group, 11.90 for the Sensodyne Rapid Relief Toothpaste group, and 12.10 for the Crest Cavity Protection Toothpaste group. For air blast hypersensitivity, the mean baseline scores were 2.50 for the Colgate Sensitive Pro-Relief Toothpaste group, 2.43 for the Sensodyne Rapid Relief Toothpaste group, and 2.37 for the Crest Cavity Protection Toothpaste group. No statistically significant differences were indicated among the treatment groups with respect to either tactile or air blast hypersensitivity scores at baseline.

### *Two-Week Clinical Data—Tactile Hypersensitivity*

Table III presents a summary of the tactile hypersensitivity scores measured after two weeks of product use.

**Comparisons versus Baseline.** The mean two-week tactile hypersensitivity scores were 27.20 for the Colgate Sensitive Pro-Relief Toothpaste group, 19.20 for the Sensodyne Rapid Relief Toothpaste group, and 16.30 for the Crest Cavity Protection Toothpaste group. The percent changes from baseline were 134.5% for the Colgate Sensitive Pro-Relief Toothpaste group, 61.3% for the Sensodyne Rapid Relief Toothpaste group, and 34.7% for the Crest Cavity Protection Toothpaste group, all of which were statistically significant.

**Comparison Between Treatment Groups.** Relative to the Sensodyne Rapid Relief Toothpaste group and Crest Cavity Protection Toothpaste group, the Colgate Sensitive Pro-Relief Toothpaste group exhibited statistically significant improvements in tactile hypersensitivity scores after two weeks of product use (41.7% and 66.9%, respectively).

Relative to the Crest Cavity Protection Toothpaste group, the Sensodyne Rapid Relief Toothpaste group exhibited a small, but statistically significant improvement in tactile hypersensitivity scores after two weeks of product use (17.8%).

**Table I**
Summary of Age and Gender for Subjects Who Completed the Eight-Week Clinical Study

| | Number of Subjects | | | Age | |
|---|---|---|---|---|---|
| Treatment | Male | Female | Total | Mean | Range |
| Colgate Sensitive Pro-Relief* Toothpaste | 15 | 35 | 50 | 39.4 | 20–69 |
| Sensodyne Rapid Relief Toothpaste | 14 | 36 | 50 | 37.6 | 23–61 |
| Crest Cavity Protection Toothpaste | 17 | 33 | 50 | 39.8 | 23–65 |

*Also marketed as elmex Sensitive Professional.

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

| Parameter | Treatment | n | Baseline Summary (Mean ± SD)[1] |
|---|---|---|---|
| Tactile Sensitivity | Colgate Sensitive Pro-Relief* Toothpaste | 50 | 11.60 ± 3.26 |
| | Sensodyne Rapid Relief Toothpaste | 50 | 11.90 ± 3.63 |
| | Crest Cavity Protection Toothpaste | 50 | 12.10 ± 3.79 |
| Air Blast Sensitivity | Colgate Sensitive Pro-Relief Toothpaste | 50 | 2.50 ± 0.43 |
| | Sensodyne Rapid Relief Toothpaste | 50 | 2.43 ± 0.38 |
| | Crest Cavity Protection Toothpaste | 50 | 2.37 ± 0.41 |

*Also marketed as elmex Sensitive Professional.
[1]No statistically significant differences were indicated among the three treatment groups at baseline with respect to either tactile hypersensitivity or air blast hypersensitivity scores.

**Table III**
Summary of the Two-Week Tactile Hypersensitivity Scores for Subjects Who Completed the Eight-Week Clinical Study

| | | | Within-Treatment Analysis | | Between-Treatment Comparison | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | vs. Sensodyne Rapid Relief Toothpaste | | vs. Crest Cavity Protection Toothpaste | |
| Treatment | n | Two-Week Summary (Mean ± SD) | Percent Change[1] | Sig.[2] | Percent Difference[3] | Sig.[5] | Percent Difference[4] | Sig.[5] |
| Colgate Sensitive Pro-Relief* Toothpaste | 50 | 27.20 ± 8.76 | 134.5% | $p < 0.05$ | 41.7% | $p < 0.05$ | 66.9% | $p < 0.05$ |
| Sensodyne Rapid Relief Toothpaste | 50 | 19.20 ± 5.19 | 61.3% | $p < 0.05$ | — | — | 17.8% | $p < 0.05$ |
| Crest Cavity Protection Toothpaste | 50 | 16.30 ± 4.61 | 34.7% | $p < 0.05$ | — | — | — | — |

*Also marketed as elmex Sensitive Professional.
[1]Percent change exhibited by the two-week mean relative to the baseline mean. A positive value indicates an improvement in tactile hypersensitivity at the two-week examination.
[2]Significance of paired t-test comparing the baseline and the two-week examinations.
[3]Difference between the two-week means expressed as a percentage of the two-week mean for the Sensodyne Rapid Relief Toothpaste. A positive value indicates an improvement in tactile hypersensitivity scores relative to the Sensodyne Rapid Relief Toothpaste.
[4]Difference between the two-week means expressed as a percentage of the two-week mean for the Crest Cavity Protection Toothpaste. A positive value indicates an improvement in tactile hypersensitivity scores relative to the Crest Cavity Protection Toothpaste.
[5]Significance of ANCOVA comparison of baseline-adjusted means.

***Two-Week Clinical Data—Air Blast Hypersensitivity***

Table IV presents a summary of the air blast hypersensitivity scores measured after two weeks of product use.

**Comparisons versus Baseline.** The mean two-week air blast hypersensitivity scores were 1.45 for the Colgate Sensitive Pro-Relief Toothpaste group, 1.93 for the Sensodyne Rapid Relief Toothpaste group, and 2.04 for the Crest Cavity Protection Toothpaste group. The percent changes from baseline were 42.0% for the Colgate Sensitive Pro-Relief Toothpaste group, 20.6% for the Sensodyne Rapid Relief Toothpaste group, and 13.9% for the Crest Cavity Protection Toothpaste group, all of which were statistically significant.

**Comparison Between Treatment Groups.** Relative to the Sensodyne Rapid Relief Toothpaste group and Crest Cavity Protection Toothpaste group, the Colgate Sensitive Pro-Relief Toothpaste group exhibited statistically significant reductions in air blast hypersensitivity scores after two weeks of product use (24.9% and 28.9%, respectively).

Relative to the Crest Cavity Protection Toothpaste group, the Sensodyne Rapid Relief Toothpaste group did not exhibit a statistically significant reduction in air blast hypersensitivity scores after two weeks of product use (5.4%).

***Four-Week Clinical Data—Tactile Hypersensitivity***

Table V presents a summary of the tactile hypersensitivity scores measured after four weeks of product use.

**Comparisons versus Baseline.** The mean four-week tactile hypersensitivity scores were 42.50 for the Colgate Sensitive Pro-Relief Toothpaste group, 27.90 for the Sensodyne Rapid Relief Toothpaste group, and 17.70 for the Crest Cavity Protection Toothpaste group. The percent changes from baseline were 266.4% for the Colgate Sensitive Pro-Relief Toothpaste group, 134.5% for the Sensodyne Rapid Relief Toothpaste group, and 46.3% for the Crest Cavity Protection Toothpaste group, all of which were statistically significant.

**Comparison Between Treatment Groups.** Relative to the Sensodyne Rapid Relief Toothpaste group and Crest Cavity Protection Toothpaste group, the Colgate Sensitive Pro-Relief Toothpaste group exhibited statistically significant improvements in tactile hypersensitivity scores after four weeks of product use

**Table IV**
Summary of the Two-Week Air Blast Hypersensitivity Scores for Subjects Who Completed the Eight-Week Clinical Study

| | | | Within-Treatment Analysis | | Between-Treatment Comparison | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | vs. Sensodyne Rapid Relief Toothpaste | | vs. Crest Cavity Protection Toothpaste | |
| Treatment | n | Two-Week Summary (Mean ± SD) | Percent Change[1] | Sig.[2] | Percent Difference[3] | Sig.[5] | Percent Difference[4] | Sig.[5] |
| Colgate Sensitive Pro-Relief* Toothpaste | 50 | 1.45 ± 0.62 | 42.0% | $p < 0.05$ | 24.9% | $p < 0.05$ | 28.9% | $p < 0.05$ |
| Sensodyne Rapid Relief Toothpaste | 50 | 1.93 ± 0.42 | 20.6% | $p < 0.05$ | — | — | 5.4% | NS |
| Crest Cavity Protection Toothpaste | 50 | 2.04 ± 0.38 | 13.9% | $p < 0.05$ | — | — | — | — |

*Also marketed as elmex Sensitive Professional.[1]
Percent change exhibited by the two-week mean relative to the baseline mean. A positive value indicates a reduction in air blast hypersensitivity at the two-week examination.
[2]Significance of paired t-test comparing the baseline and the two-week examinations.
[3]Difference between the two-week means expressed as a percentage of the two-week mean for the Sensodyne Rapid Relief Toothpaste. A positive value indicates a reduction in air blast hypersensitivity scores relative to the Sensodyne Rapid Relief Toothpaste.
[4]Difference between the two-week means expressed as a percentage of the two-week mean for the Crest Cavity Protection Toothpaste. A positive value indicates a reduction in air blast hypersensitivity scores relative to the Crest Cavity Protection Toothpaste.
[5]Significance of ANCOVA comparison of baseline-adjusted means.

**Table V**
Summary of the Four-Week Tactile Hypersensitivity Scores for Subjects Who Completed the Eight-Week Clinical Study

| | | | Within-Treatment Analysis | | Between-Treatment Comparison | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | vs. Sensodyne Rapid Relief Toothpaste | | vs. Crest Cavity Protection Toothpaste | |
| Treatment | n | Four-Week Summary (Mean ± SD) | Percent Change[1] | Sig.[2] | Percent Difference[3] | Sig.[5] | Percent Difference[4] | Sig.[5] |
| Colgate Sensitive Pro-Relief* Toothpaste | 50 | 42.50 ± 5.91 | 266.4% | $p < 0.05$ | 52.3% | $p < 0.05$ | 140.1% | $p < 0.05$ |
| Sensodyne Rapid Relief Toothpaste | 50 | 27.90 ± 6.23 | 134.5% | $p < 0.05$ | — | — | 57.6% | $p < 0.05$ |
| Crest Cavity Protection Toothpaste | 50 | 17.70 ± 4.19 | 46.3% | $p < 0.05$ | — | — | — | — |

*Also marketed as elmex Sensitive Professional.
[1]Percent change exhibited by the four-week mean relative to the baseline mean. A positive value indicates an improvement in tactile hypersensitivity at the four-week examination.
[2]Significance of paired t-test comparing the baseline and four-week examinations.
[3]Difference between the four-week means expressed as a percentage of the four-week mean for the Sensodyne Rapid Relief Toothpaste. A positive value indicates an improvement in tactile hypersensitivity scores relative to the Sensodyne Rapid Relief Toothpaste.
[4]Difference between the four-week means expressed as a percentage of the four-week mean for the Crest Cavity Protection Toothpaste. A positive value indicates an improvement in tactile hypersensitivity scores relative to the Crest Cavity Protection Toothpaste.
[5]Significance of ANCOVA comparison of baseline-adjusted means.

(52.3% and 140.1%, respectively).

Relative to the Crest Cavity Protection Toothpaste group, the Sensodyne Rapid Relief Toothpaste group exhibited a statistically significant improvement in tactile hypersensitivity scores after four weeks of product use (57.6%).

### *Four-Week Clinical Data—Air Blast Hypersensitivity*

Table VI presents a summary of the air blast hypersensitivity scores measured after four weeks of product use.

**Comparisons versus Baseline.** The mean four-week air blast hypersensitivity scores were 0.60 for the Colgate Sensitive Pro-Relief Toothpaste group, 1.44 for the Sensodyne Rapid Relief Toothpaste group, and 1.99 for the Crest Cavity Protection Toothpaste group. The percent changes from baseline were 76.0% for the Colgate Sensitive Pro-Relief Toothpaste group, 40.7% for the Sensodyne Rapid Relief Toothpaste group, and 16.0% for the Crest Cavity Protection Toothpaste group, all of which were statistically significant.

**Comparison Between Treatment Groups.** Relative to the Sensodyne Rapid Relief Toothpaste group and Crest Cavity Protection Toothpaste group, the Colgate Sensitive Pro-Relief Toothpaste group exhibited statistically significant reductions in air blast hypersensitivity scores after four weeks of product use (58.3% and 69.8%, respectively).

Relative to the Crest Cavity Protection Toothpaste group, the Sensodyne Rapid Relief Toothpaste group exhibited a statistically significant reduction in air blast hypersensitivity scores after four weeks of product use (27.6%).

### *Eight-Week Clinical Data—Tactile Hypersensitivity*

Table VII presents a summary of the tactile hypersensitivity scores measured after eight weeks of product use.

**Comparisons versus Baseline.** The mean eight-week tactile hypersensitivity scores were 46.60 for the Colgate Sensitive Pro-Relief Toothpaste group, 36.30 for the Sensodyne Rapid Relief Toothpaste group, and 18.90 for the Crest Cavity Protection Toothpaste group. The percent changes from baseline were 301.7% for the Colgate Sensitive Pro-Relief Toothpaste group, 205.0% for the Sensodyne Rapid Relief Toothpaste group, and 56.2% for the Crest Cavity Protection Toothpaste group, all of which were statistically significant.

**Table VI**
Summary of the Four-Week Air Blast Hypersensitivity Scores for Subjects Who Completed the Eight-Week Clinical Study

| | | | Within-Treatment Analysis | | Between-Treatment Comparison | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | vs. Sensodyne Rapid Relief Toothpaste | | vs. Crest Cavity Protection Toothpaste | |
| Treatment | n | Four-Week Summary (Mean ± SD) | Percent Change[1] | Sig.[2] | Percent Difference[3] | Sig.[5] | Percent Difference[4] | Sig.[5] |
| Colgate Sensitive Pro-Relief* Toothpaste | 50 | 0.60 ± 0.35 | 76.0% | $p < 0.05$ | 58.3% | $p < 0.05$ | 69.8% | $p < 0.05$ |
| Sensodyne Rapid Relief Toothpaste | 50 | 1.44 ± 0.39 | 40.7% | $p < 0.05$ | — | — | 27.6% | $p < 0.05$ |
| Crest Cavity Protection Toothpaste | 50 | 1.99 ± 0.38 | 16.0% | $p < 0.05$ | — | — | — | — |

*Also marketed as elmex Sensitive Professional.
[1]Percent change exhibited by the four-week mean relative to the baseline mean. A positive value indicates a reduction in air blast hypersensitivity at the four-week examination.
[2]Significance of paired t-test comparing the baseline and the four-week examinations.
[3]Difference between the four-week means expressed as a percentage of the four-week mean for the Sensodyne Rapid Relief Toothpaste. A positive value indicates a reduction in air blast hypersensitivity scores relative to the Sensodyne Rapid Relief Toothpaste.
[4]Difference between the four-week means expressed as a percentage of the four-week mean for the Crest Cavity Protection Toothpaste. A positive value indicates a reduction in air blast hypersensitivity scores relative to the Crest Cavity Protection Toothpaste.
[5]Significance of ANCOVA comparison of baseline-adjusted means.

**Table VII**
Summary of the Eight-Week Tactile Hypersensitivity Scores for Subjects Who Completed the Eight-Week Clinical Study

| | | | Within-Treatment Analysis | | Between-Treatment Comparison | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | vs. Sensodyne Rapid Relief Toothpaste | | vs. Crest Cavity Protection Toothpaste | |
| Treatment | n | Eight-Week Summary (Mean ± SD) | Percent Change[1] | Sig.[2] | Percent Difference[3] | Sig.[5] | Percent Difference[4] | Sig.[5] |
| Colgate Sensitive Pro-Relief* Toothpaste | 50 | 46.60 ± 3.97 | 301.7% | $p < 0.05$ | 28.4% | $p < 0.05$ | 146.6% | $p < 0.05$ |
| Sensodyne Rapid Relief Toothpaste | 50 | 36.30 ± 7.20 | 205.0% | $p < 0.05$ | — | — | 92.1% | $p < 0.05$ |
| Crest Cavity Protection Toothpaste | 50 | 18.90 ± 4.20 | 56.2% | $p < 0.05$ | — | — | — | — |

*Also marketed as elmex Sensitive Professional.
[1]Percent change exhibited by the eight-week mean relative to the baseline mean. A positive value indicates an improvement in tactile hypersensitivity at the eight-week examination.
[2]Significance of paired t-test comparing the baseline and the eight-week examinations.
[3]Difference between the eight-week means expressed as a percentage of the eight-week mean for the Sensodyne Rapid Relief Toothpaste. A positive value indicates an improvement in tactile hypersensitivity scores relative to the Sensodyne Rapid Relief Toothpaste.
[4]Difference between the eight-week means expressed as a percentage of the eight-week mean for the Crest Cavity Protection Toothpaste. A positive value indicates an improvement in tactile hypersensitivity scores relative to the Crest Cavity Protection Toothpaste.
[5]Significance of ANCOVA comparison of baseline-adjusted means.

**Comparison Between Treatment Groups.** Relative to the Sensodyne Rapid Relief Toothpaste group and Crest Cavity Protection Toothpaste group, the Colgate Sensitive Pro-Relief Toothpaste group exhibited statistically significant improvements in tactile hypersensitivity scores after eight weeks of product use (28.4% and 146.6%, respectively).

Relative to the Crest Cavity Protection Toothpaste group, the Sensodyne Rapid Relief Toothpaste group exhibited a statistically significant improvement in tactile hypersensitivity scores after eight weeks of product use (92.1%).

### *Eight-Week Clinical Data—Air Blast Hypersensitivity*

Table VIII presents a summary of the air blast hypersensitivity scores measured after eight weeks of product use.

**Comparisons versus Baseline.** The mean eight-week air blast hypersensitivity scores were 0.35 for the Colgate Sensitive Pro-Relief Toothpaste group, 0.89 for the Sensodyne Rapid Relief Toothpaste group, and 1.92 for the Crest Cavity Protection Toothpaste group. The percent changes from baseline were 86.0% for the Colgate Sensitive Pro-Relief Toothpaste group, 63.4% for the Sensodyne Rapid Relief Toothpaste group, and 19.0% for the Crest Cavity Protection Toothpaste group, all of which were statistically significant.

**Comparison Between Treatment Groups.** Relative to the Sensodyne Rapid Relief Toothpaste group and Crest Cavity Protection Toothpaste group, the Colgate Sensitive Pro-Relief Toothpaste group exhibited statistically significant reductions in air blast hypersensitivity scores after eight weeks of product use (60.7% and 81.8%, respectively).

Relative to the Crest Cavity Protection Toothpaste group, the Sensodyne Rapid Relief Toothpaste group exhibited a statistically significant reduction in air blast hypersensitivity scores after eight weeks of product use (53.6%).

## Discussion

This double-blind clinical study provided an investigative comparison of the efficacy of three commercially available toothpastes with respect to dentin hypersensitivity reduction after

**Table VIII**
Summary of the Eight-Week Air Blast Hypersensitivity Scores for Subjects Who Completed the Eight-Week Clinical Study

| | | | Within-Treatment Analysis | | Between-Treatment Comparison | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | vs. Sensodyne Rapid Relief Toothpaste | | vs. Crest Cavity Protection Toothpaste | |
| Treatment | n | Eight-Week Summary (Mean ± SD) | Percent Change[1] | Sig.[2] | Percent Difference[3] | Sig.[5] | Percent Difference[4] | Sig.[5] |
| Colgate Sensitive Pro-Relief* Toothpaste | 50 | 0.35 ± 0.35 | 86.0% | $p < 0.05$ | 60.7% | $p < 0.05$ | 81.8% | $p < 0.05$ |
| Sensodyne Rapid Relief Toothpaste | 50 | 0.89 ± 0.38 | 63.4% | $p < 0.05$ | — | — | 53.6% | $p < 0.05$ |
| Crest Cavity Protection Toothpaste | 50 | 1.92 ± 0.36 | 19.0% | $p < 0.05$ | — | — | — | — |

*Also marketed as elmex Sensitive Professional.
[1]Percent change exhibited by the eight-week mean relative to the baseline mean. A positive value indicates a reduction in air blast hypersensitivity at the eight-week examination.
[2]Significance of paired t-test comparing the baseline and eight-week examinations.
[3]Difference between the eight-week means expressed as a percentage of the eight-week mean for the Sensodyne Rapid Relief Toothpaste. A positive value indicates a reduction in air blast hypersensitivity scores relative to the Sensodyne Rapid Relief Toothpaste.
[4]Difference between the eight-week means expressed as a percentage of the eight-week mean for the Crest Cavity Protection Toothpaste. A positive value indicates a reduction in air blast hypersensitivity scores relative to the Crest Cavity Protection Toothpaste.
[5]Significance of ANCOVA comparison of baseline-adjusted means.

two, four, and eight weeks of at-home brushing, two times per day over an eight-week period.

Toothpastes have been widely used in the treatment of dentin hypersensitivity because of their low cost and ease of use for home application. The mechanism of action of a desensitizing toothpaste is either nerve depolarization (potassium-based toothpaste) or the obliteration of dentin tubules by the precipitation of insoluble deposits on the dentin surface. Potassium-based toothpastes, when used for several weeks, have been reported to alleviate the discomfort associated with dentin hypersensitivity. Although widely popular among dental professionals, the real efficacy of these potassium-based products is still open to question.[6]

The present study compared Colgate Sensitive Pro-Relief Toothpaste to Sensodyne Rapid Relief and Crest Cavity Protection Toothpastes regarding their clinical effectiveness in reducing dentin hypersensitivity after two, four, and eight weeks of twice-daily brushing. Relative to the Sensodyne Rapid Relief Toothpaste group and Crest Cavity Protection Toothpaste group, subjects assigned to the Colgate Sensitive Pro-Relief Toothpaste group exhibited superior efficacy, providing statistically significant improvements in tactile hypersensitivity scores after two weeks (41.7% and 66.9%, respectively), four weeks (52.3% and 140.1%, respectively), and eight weeks (28.4% and 146.6%, respectively).

The superior efficacy of Colgate Sensitive Pro-Relief was confirmed by the air blast sensitivity test results. Relative to the Sensodyne Rapid Relief Toothpaste group and Crest Cavity Protection Toothpaste group, subjects assigned to the Colgate Sensitive Pro-Relief Toothpaste group exhibited statistically significant reductions in air blast hypersensitivity scores after two weeks of twice-daily product use (24.9% and 28.9%, respectively), four weeks of twice-daily product use (58.3% and 69.8%, respectively), and eight weeks of twice-daily product use (60.7% and 81.8%, respectively).

## Conclusion

Colgate Sensitive Pro-Relief Toothpaste, used twice daily, significantly reduces dentin hypersensitivity and is significantly more effective than Sensodyne Rapid Relief Toothpaste and Crest Cavity Protection Toothpaste. Colgate Sensitive Pro-Relief Toothpaste is the latest new tool in the armament of the modern dentist.

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# Clinical Efficacy in Reducing Dentin Hypersensitivity of a Dentifrice Containing 8.0% Arginine, Calcium Carbonate, and 1450 ppm Fluoride Compared to a Dentifrice Containing 8% Strontium Acetate and 1040 ppm Fluoride Under Consumer Usage Conditions Before and After Switch-Over

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**Abstract**

- **Objective:** The objective of this 16-week, double-blind, randomized, switch-over design study was to compare the efficacy in reducing dentin hypersensitivity of a dentifrice containing 8.0% arginine, calcium carbonate, and 1450 ppm fluoride as sodium monofluorophosphate (Colgate® Sensitive Pro-Relief™ [also marketed as elmex® Sensitive Professional™]) to a desensitizing dentifrice containing 8% strontium acetate and 1040 ppm fluoride as sodium fluoride (Sensodyne® Rapid Relief) under relevant consumer usage conditions.
- **Methods:** Qualifying subjects from the San Francisco, CA, 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 Cold Air Sensitivity Scale), participated in this two-phase double-blind study. Subjects were randomly assigned to one of two test groups. The first phase of the study consisted of twice-daily at-home brushing with the first assigned dentifrice for eight weeks. The second phase of the study consisted of switching product use to the second assigned dentifrice for a second eight-week period. Dentin hypersensitivity examinations, which comprised tactile and air blast hypersensitivity measures, as well as examinations of oral hard and soft tissues, were conducted at baseline, at the completion of the first study phase, and at two weeks and eight weeks of the second phase.
- **Results:** One-hundred and twenty-one subjects complied with the study protocol and completed the study. *Study Phase I:* Subjects who brushed twice daily for eight weeks with the arginine/calcium carbonate dentifrice experienced statistically significant improvements in mean tactile and air blast hypersensitivity scores (51.3% and 39.4%, respectively) relative to that experienced by subjects who brushed with the strontium acetate dentifrice. *Study Phase II:* Subjects who brushed with the arginine/calcium carbonate dentifrice for the first eight weeks of the study and then switched to brush with the strontium acetate dentifrice for the second eight weeks of the study, did not exhibit further improvements in mean tactile or mean air blast hypersensitivity scores after two and eight weeks of switch-over product use. However, subjects who brushed with the strontium acetate dentifrice for the first eight weeks of the study and then switched to brush with the arginine/calcium carbonate dentifrice exhibited statistically significant improvements in mean tactile and air blast hypersensitivity scores two weeks (35.2% and 29.9%, respectively) and eight weeks (40.3% and 35.3%, respectively) after product switch-over. Relative to the subjects who switched from twice-daily brushing with the arginine/calcium carbonate dentifrice to brush with the strontium acetate dentifrice, those who switched from brushing with the strontium acetate dentifrice to brush with the arginine/calcium carbonate dentifrice exhibited statistically significant improvements in mean tactile hypersensitivity scores (10.3%) and in mean air blast hypersensitivity scores (16.3%) eight weeks after product switch-over.
- **Conclusion:** Eight weeks of brushing with Colgate Sensitive Pro-Relief (elmex Sensitive Professional) provides significant reductions in mean dentin hypersensitivity relative to the identical use of Sensodyne Rapid Relief. Additionally, the dentin hypersensitivity reductions achieved by twice-daily brushing with Sensodyne Rapid Relief are significantly improved by switching to twice-daily brushing with Colgate Sensitive Pro-Relief (elmex Sensitive Professional) for two and eight weeks. Further, the dentin hypersensitivity reductions achieved by twice-daily brushing with Colgate Sensitive Pro-Relief (elmex Sensitive Professional) are not improved by switching to twice-daily brushing with Sensodyne Rapid Relief for two or eight weeks. Eight weeks' use of Colgate Sensitive Pro-Relief (elmex Sensitive Professional), after having used Sensodyne Rapid Relief for an initial eight-week time period, provides statistically significant improvements in dentin hypersensitivity relative to eight weeks' use of the Sensodyne Rapid Relief.

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## Introduction

Dentin hypersensitivity is characterized by a short, sharp pain arising from exposed dentin in response to external stimuli, typically thermal, dehydrating, tactile, osmotic, or chemical, and which cannot be ascribed to any other form of dental defect or disease.[1,2] This condition is a significant clinical problem that can start as early as adolescence and is quite prevalent among adults,[3] often interfering with quality of life of sufferers.[4-7]

To be hypersensitive, dentin must be exposed and the exposed tubules must be open and patent to the pulp.[1,8] The hydrodynamic theory (modified by Brännström in 1963) ascribes fluid movement within the dentin tubules as the basis for the transmission of painful sensations.[9,10] In 1994, Nahri, *et al*. 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.[11] Specifically, the theory suggests that an external stimulus contacts exposed dentin triggering a pressure change in the dentin fluid. As a consequence, fluid movement transmits a signal to the odontoblast process, thereby carrying the stimulus from the tooth surface toward the afferent nerve ending in the dentin tubule resulting in pain. It is, therefore, understandable that the pain caused by this change is transient in that once the stimulus is removed or dissipates, the pressure within the tubule returns to normal and the pain subsides. The overall dental health impact of dentin hypersensitivity on a particular individual may ultimately correlate with the degree of discomfort experienced.

Therapeutic management of dentin hypersensitivity varies widely from products that are applied by the dental professional in-office, to everyday use at home. Not many products have undergone extensive clinical evaluation, and others have shown equivocal efficacy.[12] Many clinicians recommend daily at-home use of desensitizing dentifrices as the first-line of treatment for their patients. This at-home treatment option for sensitivity relief is cost-effective, safe, non-invasive, simple to use, and typically results in improvement for the majority of individuals.[12-16]

Two treatment approaches have been used to provide relief of dentin hypersensitivity: one is to interfere with the transmission of the neural response to pain stimuli; the other is to occlude open tubules to block the hydrodynamic mechanism. The majority of desensitizing dentifrices for at-home use targets the former approach, and contains a potassium salt in the form of potassium nitrate, potassium citrate, or potassium chloride as the active ingredient. Clinical and mechanism of action studies have shown that 2% potassium ion is the active entity, and this can be dosed as any one of the three commonly used salts. The potassium ion is believed to have a hyperpolarizing effect on electrical nerve conduction, causing nerve fibers to be less excitable to external stimuli, thereby reducing the patient's sensation of pain. In clinical trials, potassium-based dentifrices 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.[13,14] Patients may follow at-home treatment recommendations to use a potassium-based dentifrice and achieve noticeable hypersensitivity relief, but when and if the use of the potassium-based product is ceased, elevated levels of potassium at the site of action are diffused, and the symptoms return.

Saliva can play a critical role in naturally reducing dentin hypersensitivity. It supplies calcium and phosphate ions which can enter open dentin tubules and, over time, block the tubules from external stimuli by forming a surface protective layer consisting of perceptible aggregates of a combination of salivary glycoproteins with calcium phosphate.[17] 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 providing effective pain relief.[18] Effective occlusion of open dentin tubules reduces dentin fluid flow, thereby decreasing the response to painful stimuli via blockage of the hydrodynamic mechanism. Kleinberg[17] proposed that the combination of arginine and calcium carbonate is able to deposit on exposed dentin surfaces to physically block and seal open dentin tubules and reduce dentin hypersensitivity, mimicking saliva's natural process. This concept was further evaluated by the Colgate-Palmolive Company, and desensitizing dentifrices containing 8.0% arginine, calcium carbonate, and 1450 ppm fluoride as sodium monofluorophosphate (MFP) were developed for regular, twice-daily brushing. Clinical studies have demonstrated the efficacy of such dentifrices in reducing dentin hypersensitivity.[19-28] *In vitro* mechanism of action studies have shown that an in-office desensitizing paste and dentifrices containing the arginine and calcium carbonate technology, known as the Pro-Argin™ technology, work by occluding dentin tubules, and show that 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.[29,30] These studies confirm that this technology works differently than other technologies that occlude dentin tubules in that: 1) arginine and calcium are also naturally found in saliva; and 2) arginine and calcium carbonate work together to accelerate the natural mechanisms of occlusion by depositing a dentin-like material, containing calcium and phosphate, within the dentin tubules to form a plug and a protective layer on the dentin surface, thereby repairing sensitive parts of teeth.[31]

Strontium chloride was introduced in a dentifrice form approximately 50 years ago as tubule blocking technology for the treatment of dentin hypersensitivity, before it was largely replaced by potassium nitrate in the 1970s. Available clinical data support the conclusions that the strontium-containing dentifrice is less effective than the potassium-based technology in reducing dentin hypersensitivity, and no more effective than a regular fluoride dentifrice.[32-34] While controlled clinical studies doubt the dentin hypersensitivity relief efficacy of strontium-based dentifrices, recent publications support the efficacy of a commercially available strontium acetate dentifrice formulation.[35,36] The objective of this 16-week, single-center, two-treatment, randomized, switch-over design clinical study was to evaluate the efficacy in reducing dentin hypersensitivity of a dentifrice containing 8.0% arginine, calcium carbonate, and 1450 ppm fluoride as sodium monofluorophosphate (marketed as Colgate® Sensitive Pro-Relief™ and elmex® Sensitive Professional™, Colgate-Palmolive Company, New York, NY, USA) compared to a dentifrice containing 8% strontium acetate and 1040 ppm fluoride as sodium fluoride (marketed as Sensodyne® Rapid Relief Toothpaste, GlaxoSmithKline,

Weybridge, UK) after eight weeks' use of the first assigned dentifrice, and after a subsequent eight weeks' use of the second switch-over dentifrice to represent relevant consumer usage conditions (as consumers typically switch dentifrices without a wash-out period).

## Materials and Methods

One-hundred and twenty-four subjects voluntarily enrolled in this 16-week single-center, double-blind, two-treatment, randomized, switch-over design clinical trial. The study was conducted in San Francisco, CA, USA and the protocol, including its informed consent form, was approved by the Institutional Review Board of Concordia Clinical Research, Cedar Knolls, NJ, USA. Subjects were enrolled in the study based on the following criteria:

***Inclusion 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) were presented at the baseline examination.

(iii) Subjects were required to be available for the 16-week duration of the study, and to sign an informed consent form.

***Exclusion Criteria***

(i) 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.

(ii) Subjects were also excluded from the study if they began taking anticonvulsants, antihistamines, antidepressants, sedatives, tranquilizers, anti-inflammatory drugs, or daily analgesics within one month prior to the start of the study, or if they started taking them during the course of the study.

(iii) Pregnant or lactating women.

(iv) 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.

(v) Subjects with a history of allergy to the test products, or allergies to oral care/personal care consumer products or their ingredients, or subjects with existing medical conditions which precluded them from not eating and drinking for periods up to four hours, were also excluded from the study.

***Phase I***

Prospective study subjects reported to the clinical facility having refrained from all oral hygiene procedures and chewing gum for eight hours, and from eating and drinking for four hours prior to their examination. All prospective subjects who met the inclusion/exclusion criteria and signed an informed consent form received a baseline tactile dentin hypersensitivity evaluation and an air blast dentin hypersensitivity evaluation, along with an oral soft and hard tissue assessment.

For each subject who qualified for participation in the study, two hypersensitive teeth that satisfied the tactile and air blast hypersensitivity enrollment criteria were identified for evaluation throughout the study. A randomization assignment process was followed to determine which dentifrice was assigned to each study subject. Such randomized assignment resulted in two study groups that were balanced on the basis of mean tactile and air blast dentin hypersensitivity baseline scores: Population A—Subjects assigned to use the dentifrice containing 8.0% arginine, calcium carbonate, and 1450 ppm fluoride as MFP for the first eight weeks of the study; and Population B—Subjects assigned to use the dentifrice containing 8% strontium acetate and 1040 ppm fluoride as sodium fluoride for the first eight weeks of the study. All dentifrices were provided in overwrapped tubes to ensure the double-blind design.

Following treatment assignment, subjects were provided with a soft-bristled toothbrush and their assigned dentifrice. Subjects' at-home brushing instructions consisted of brushing 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 other 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 after eight weeks of product use. Subjects were requested to return to the clinical facility 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. Subjects were also interviewed with respect to the presence of adverse events and the use of concomitant medications.

***Phase II***

The dentin hypersensitivity scores and oral soft tissue assessment outcomes of the eight-week visit marked the end of the first phase of the study and the beginning of the second phase of the study. The tactile and air blast dentin hypersensitivity scores recorded at this visit (eight-week scores) served as the interim values for the second phase of the study. There was no washout period between Phase I and Phase II to represent relevant conditions of consumer product switch-over.

For the second phase of the study, all subjects remained in the study group to which they were assigned for Phase I of the study, but they switched to use the alternative test dentifrice for the second phase of the study: Population A—subjects assigned

to conduct the first phase of the study using the arginine/calcium carbonate dentifrice were assigned to conduct the second phase of the study using the strontium acetate dentifrice. Population B—subjects assigned to conduct the first phase of the study using the strontium acetate dentifrice were assigned to conduct the second phase of the study using the arginine/calcium carbonate dentifrice. All dentifrices were, again, provided in over-wrapped tubes to ensure the double-blind design.

All participants discontinued use of the product assigned for Phase I and returned all study products dispensed for completion of this initial phase of the study. For Phase II of the study, subjects were provided with a new soft-bristled toothbrush and their second assigned dentifrice. As in Phase I, subjects' at-home instructions consisted of brushing their teeth for one minute, twice daily, using only the dentifrice and toothbrush provided for this second phase of the study, and to refrain from any other oral hygiene procedures throughout the duration of the study. There were no other 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 after two weeks of switch-over product use (10-week examinations) and after eight weeks of switch-over product use (16-week examinations). Subjects were requested to return to the clinical facility for all follow-up visits, 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 and the eight-week examinations. Subjects were also interviewed with respect to the presence of adverse events and the use of concomitant medications.

### *Tactile Sensitivity Assessment*

Tactile hypersensitivity was assessed by use of the Yeaple Model 200A electronic force sensing probe (Yeaple Research, Pittsford, NY, USA). The application of this probe for dentin hypersensitivity testing, utilizing a #19 explorer tip at a pre-set force measured in grams, was employed.

Teeth were evaluated for tactile hypersensitivity in the following manner:[37,38]

1. The subject was instructed to respond at the point where he/she first experienced discomfort.
2. The explorer tip of the probe was applied to the buccal surface of each hypersensitive tooth at the CEJ.
3. The explorer tip was stroked perpendicular to the tooth beginning at a pre-set force of 10 grams and increased by 10 gram increments until the subject experienced discomfort, or until 50 grams of force was applied.

Subject-wise scores were calculated by averaging the values measured on the two baseline-designated study teeth.

### *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[39] 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.

Subject-wise scores were calculated by averaging the values measured on the two baseline-designated study teeth.

### *Oral Soft and Hard Tissue Assessment*

The dental examiner visually examined the oral cavity and peri-oral area using a dental light and dental mirror. This examination included an evaluation of the soft and hard palate, gingival mucosa, buccal mucosa, mucogingival fold areas, tongue, sublingual and submandibular areas, salivary glands, and the tonsilar and pharyngeal areas.

### *Statistical Methods*

The data corresponding to study subjects who complied with the protocol and completed all dentin hypersensitivity examinations were included for statistical analyses. Statistical analyses were performed separately for the tactile hypersensitivity assessments and air blast hypersensitivity assessments. Comparisons of the treatment groups with respect to gender were performed using a chi-square analysis, and for age an analysis of variance (ANOVA) was performed.

**Phase I.** Comparisons of the treatment groups with respect to mean baseline tactile hypersensitivity scores and mean baseline air blast hypersensitivity scores were performed using an analysis of variance (ANOVA). Within-treatment comparisons of the mean baseline versus mean 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 and air blast hypersensitivity scores at the follow-up examinations were performed using analyses of covariance (ANCOVA).

**Phase II.** In Phase II of the study, the same analyses were performed as in Phase I of the study, with the mean eight-week tactile hypersensitivity and air blast hypersensitivity scores serving as the interim values for comparison purposes.

All statistical tests of hypothesis were two-sided, and employed a level of significance of $\alpha = 0.05$.

## Results

One-hundred and twenty-one subjects complied with the protocol and completed the 16-week study. Three subjects did not complete the study due to either protocol non-compliance or an event unrelated to product use. A summary of the gender and age

of the study populations is presented in Table I. The treatment groups did not differ significantly with respect to either of these characteristics.

**Table I**
Summary of Age and Gender for Subjects
Who Completed the 16-Week Clinical Study

| | Number of Subjects | | | Age[3] | |
|---|---|---|---|---|---|
| Study Groups | Male | Female | Total | Mean | Range |
| Population A[1] | 25 | 36 | 61 | 34.8 | 19-60 |
| Population B[2] | 26 | 34 | 60 | 33.8 | 20-52 |

[1]Sampled population assigned to brush with the dentifrice containing 8.0% arginine, calcium carbonate, and 1450 ppm MFP for the first eight weeks of the study, and then switched to brush with the dentifrice containing 8% strontium acetate and 1040 ppm NaF for the second eight weeks of the study.
[2]Sampled population assigned to brush with the dentifrice containing 8% strontium acetate and 1040 ppm NaF for the first eight weeks of the study, and then switched to brush with the 8.0% arginine, calcium carbonate, and 1450 ppm MFP dentifrice for the second eight weeks of the study.
[3]No statistically significant difference was indicated between the two study groups with respect to either gender or age.

### *Adverse Events*

Throughout the study, there were no adverse events on the soft or hard tissues of the oral cavity 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 hypersensitivity scores measured at the baseline examination for those subjects who completed the clinical study. For tactile hypersensitivity, the mean baseline scores were 10.00 for both treatment groups. For air blast sensitivity, the mean baseline scores were 2.82 for Population A (arginine/calcium carbonate dentifrice users) and 2.77 for Population B (strontium acetate dentifrice users). No statistically significant differences were indicated between the treatment groups with respect to either baseline mean dentin hypersensitivity scores.

### *Eight-Week Data (Phase I)*

**Tactile Hypersensitivity.** Table III presents a summary of the mean tactile hypersensitivity scores measured after eight weeks of at-home brushing with the assigned product. A positive percent change indicates an improvement from baseline.

**Table II**
Summary of the Baseline Tactile and
Air Blast Hypersensitivity Scores for Subjects
Who Completed the 16-Week Clinical Study

| Parameter | Study Group | n | Baseline Summary (Mean ± SD)[3] |
|---|---|---|---|
| Tactile Sensitivity | Population A[1] | 61 | 10.00 ± 0.00 |
| | Population B[2] | 60 | 10.00 ± 0.00 |
| Air Blast Sensitivity | Population A[1] | 61 | 2.82 ± 0.27 |
| | Population B[2] | 60 | 2.77 ± 0.35 |

[1]Sampled population assigned to brush with the dentifrice containing 8.0% arginine, calcium carbonate, and 1450 ppm MFP for the first eight weeks of the study, and then switched to brush with the dentifrice containing 8% strontium acetate and 1040 ppm NaF for the second eight weeks of the study.
[2]Sampled population assigned to brush with the dentifrice containing 8% strontium acetate and 1040 ppm NaF for the first eight weeks of the study, and then switched to brush with the 8.0% arginine, calcium carbonate, and 1450 ppm MFP dentifrice for the second eight weeks of the study.
[3]No statistically significant difference was indicated between the two study groups at baseline with respect to either tactile sensitivity or air blast sensitivity scores.

***Comparisons Versus Baseline.*** The mean eight-week tactile hypersensitivity scores were 34.43 for Population A (arginine/calcium carbonate dentifrice users for the first eight weeks of the study) and 22.75 for Population B (strontium acetate dentifrice users for the first eight weeks of the study). The percent changes from baseline were 244.3% for Population A and 127.5% for Population B, both of which were statistically significant.

***Comparison Between Treatment Groups.*** Relative to Population B (strontium acetate dentifrice users), Population A (arginine/calcium carbonate dentifrice users) exhibited a statistically significant (51.3%) improvement in mean tactile hypersensitivity scores after eight weeks of product use.

**Air Blast Hypersensitivity.** Table IV presents a summary of the mean air blast hypersensitivity scores measured after eight weeks of at-home brushing with the assigned product. A positive percent change indicates an improvement from baseline.

***Comparisons Versus Baseline.*** The mean eight-week air blast hypersensitivity scores were 1.02 for Population A (arginine/

**Table III**
Phase I of the Clinical Study: Summary of the Eight-Week Mean Tactile
Hypersensitivity Scores for Subjects Who Completed the 16-Week Clinical Study

| | | Eight-Week Summary | Within-Treatment Analysis | | Between-Treatment Comparison | |
|---|---|---|---|---|---|---|
| Study Group | n | (Mean ± SD) | Percent Change[3] | Significance[4] | Percent Difference[5] | Significance[6] |
| Population A[1] | 61 | 34.43 ± 5.17 | 244.3% | $p < 0.05$ | 51.3% | $p < 0.05$ |
| Population B[2] | 60 | 22.75 ± 7.27 | 127.5% | $p < 0.05$ | | |

[1]Sampled population assigned to brush with the dentifrice containing 8.0% arginine, calcium carbonate, and 1450 ppm MFP for the first eight weeks of the study, and then switched to brush with the dentifrice containing 8% strontium acetate and 1040 ppm NaF for the second eight weeks of the study.
[2]Sampled population assigned to brush with the dentifrice containing 8% strontium acetate and 1040 ppm NaF for the first eight weeks of the study, and then switched to brush with the 8.0% arginine, calcium carbonate, and 1450 ppm MFP dentifrice for the second eight weeks of the study.
[3]Percent change exhibited by the eight-week mean relative to the baseline mean. A positive value indicates an improvement in tactile hypersensitivity at the eight-week examination.
[4]Significance of paired t-test comparing the baseline and the eight-week examinations.
[5]Difference between the eight-week means expressed as a percentage of the eight-week mean for Population B. A positive value indicates an improvement in tactile hypersensitivity scores for Population A relative to Population B.
[6]Significance of ANCOVA comparison of baseline-adjusted means.

**Table IV**
Phase I of the Clinical Study: Summary of the Eight-Week Mean Air Blast Hypersensitivity Scores for Subjects Who Completed the 16-Week Clinical Study

| Study Group | n | Eight-Week Summary (Mean ± SD) | Within-Treatment Analysis | | Between-Treatment Comparison | |
|---|---|---|---|---|---|---|
| | | | Percent Change[3] | Significance[4] | Percent Difference[5] | Significance[6] |
| Population A[1] | 61 | 1.02 ± 0.34 | 63.8% | $p < 0.05$ | 39.4% | $p < 0.05$ |
| Population B[2] | 60 | 1.67 ± 0.45 | 39.7% | $p < 0.05$ | | |

[1]Sampled population assigned to brush with the dentifrice containing 8.0% arginine, calcium carbonate, and 1450 ppm MFP for the first eight weeks of the study, and then switched to brush with the dentifrice containing 8% strontium acetate and 1040 ppm NaF for the second eight weeks of the study.
[2]Sampled population assigned to brush with the dentifrice containing 8% strontium acetate and 1040 ppm NaF for the first eight weeks of the study, and then switched to brush with the 8.0% arginine, calcium carbonate, and 1450 ppm MFP dentifrice for the second eight weeks of the study.
[3]Percent change exhibited by the eight-week mean relative to the baseline mean. A positive value indicates a reduction in air blast hypersensitivity scores at the eight-week examination.
[4]Significance of paired t-test comparing the baseline and the eight-week examinations.
[5]Difference between the eight-week means expressed as a percentage of the eight-week mean for Population B. A positive value indicates a reduction in air blast hypersensitivity scores for Population A relative to Population B.
[6]Significance of ANCOVA comparison of baseline-adjusted means.

calcium carbonate dentifrice users) and 1.67 for Population B (strontium acetate dentifrice users). The percent changes from baseline were 63.8% for Population A and 39.7% for Population B, both of which were statistically significant.

***Comparison Between Treatment Groups.*** Relative to Population B (strontium acetate dentifrice users), Population A (arginine/calcium carbonate dentifrice users) exhibited a statistically significant improvement in mean air blast hypersensitivity scores after eight weeks of product use (39.4%).

### *Ten-Week Data (Phase II)*

**Tactile Hypersensitivity.** Table V presents a summary of the mean tactile hypersensitivity scores measured after two weeks' use of the second assigned switch-over dentifrice. A positive percent change indicates an improvement from the eight-week tactile hypersensitivity scores obtained in Phase I of the study (Interim Values).

***Comparisons Versus Interim Values.*** The mean 10-week tactile hypersensitivity scores were 31.48 for Population A (population that switched from daily use of the arginine/calcium carbonate dentifrice to use of the strontium acetate dentifrice) and 30.75 for Population B (population that switched from daily use of the strontium acetate dentifrice to use of the arginine/calcium carbonate dentifrice). The percent changes from the eight-week scores were -8.6% for Population A and 35.2% for Population B, both of which were statistically significant.

***Comparison Between Treatment Groups.*** Relative to Population A, Population B did not exhibit a statistically significant improvement in mean tactile hypersensitivity scores from the eight-week scores after two weeks of switch-over product use (2.3%).

**Air Blast Hypersensitivity.** Table VI presents a summary of the mean air blast hypersensitivity scores measured after two weeks' use of the second assigned switch-over dentifrice. A positive percent change indicates an improvement from the eight-week air blast hypersensitivity scores obtained in Phase I of the study (Interim Values).

***Comparisons Versus Interim Values.*** The mean 10-week air blast hypersensitivity scores were 1.29 for Population A (population that switched from daily use of the arginine/calcium carbonate dentifrice to use of the strontium acetate dentifrice) and 1.17 for Population B (population that switched from daily use of the strontium acetate dentifrice to use of the arginine/calcium carbonate dentifrice). The percent changes from the eight-week scores were -26.5% for Population A and 29.9% for Population B, both of which were statistically significant.

**Table V**
Phase II of the Clinical Study: Summary of the 10-Week Mean Tactile Hypersensitivity Scores for Subjects Who Completed the 16-Week Clinical Study

| Study Group | n | 10-Week Summary (Mean ± SD) | Within-Treatment Analysis | | Between-Treatment Comparison | |
|---|---|---|---|---|---|---|
| | | | Percent Change[3] | Significance[4] | Percent Difference[5] | Significance[6] |
| Population A[1] | 61 | 31.48 ± 8.58 | – 8.6% | $p < 0.05$ | 2.3% | NS |
| Population B[2] | 60 | 30.75 ± 5.66 | 35.2% | $p < 0.05$ | | |

[1]Sampled population assigned to brush with the dentifrice containing 8.0% arginine, calcium carbonate, and 1450 ppm MFP for the first eight weeks of the study, and then switched to brush with the dentifrice containing 8% strontium acetate and 1040 ppm NaF for the second eight weeks of the study.
[2]Sampled population assigned to brush with the dentifrice containing 8% strontium acetate and 1040 ppm NaF for the first eight weeks of the study, and then switched to brush with the 8.0% arginine, calcium carbonate, and 1450 ppm MFP dentifrice for the second eight weeks of the study.
[3]Percent change exhibited by the 10-week mean relative to the eight-week mean. A positive value indicates an improvement in tactile hypersensitivity at the 10-week examination.
[4]Significance of paired t-test comparing the eight-week and the 10-week examinations.
[5]Difference between the 10-week means expressed as a percentage of the 10-week mean for Population A. A positive value indicates an improvement in tactile hypersensitivity scores for Population B relative to Population A.
[6]Significance of ANCOVA comparison of eight-week-adjusted means.

**Table VI**
Phase II of the Clinical Study: Summary of the 10-Week Mean Air Blast Hypersensitivity Scores for Subjects Who Completed the 16-Week Clinical Study

| Study Group | n | 10-Week Summary (Mean ± SD) | Within-Treatment Analysis | | Between-Treatment Comparison | |
|---|---|---|---|---|---|---|
| | | | Percent Change[3] | Significance[4] | Percent Difference[5] | Significance[6] |
| Population A[1] | 61 | 1.29 ± 0.41 | – 26.5% | p < 0.05 | 9.3% | NS |
| Population B[2] | 60 | 1.17 ± 0.53 | 29.9% | p < 0.05 | | |

[1]Sampled population assigned to brush with the dentifrice containing 8.0% arginine, calcium carbonate, and 1450 ppm MFP for the first eight weeks of the study and then switched to brush with the dentifrice containing 8% strontium acetate and 1040 ppm NaF for the second eight weeks of the study.
[2]Sampled population assigned to brush with the dentifrice containing 8% strontium acetate and 1040 ppm NaF for the first eight weeks of the study and then switched to brush with the 8.0% arginine, calcium carbonate, and 1450 ppm MFP dentifrice for the second eight weeks of the study.
[3]Percent change exhibited by the 10-week mean relative to the eight-week mean. A positive value indicates a reduction in air blast hypersensitivity at the 10-week examination.
[4]Significance of paired t-test comparing the eight-week and the 10-week examinations.
[5]Difference between the 10-week means expressed as a percentage of the 10-week mean for the Population A. A positive value indicates a reduction in air blast hypersensitivity scores for Population B relative to Population A.
[6]Significance of ANCOVA comparison of eight-week adjusted means.

***Comparison Between Treatment Groups.*** Relative to Population A, Population B did not exhibit a statistically significant improvement in mean air blast hypersensitivity scores from the eight-week scores after two weeks of switch-over product use (9.3%).

***Sixteen-Week Data (Phase II)***

**Tactile Hypersensitivity.** Table VII presents a summary of the mean tactile hypersensitivity scores measured after eight weeks' use of the second assigned switch-over dentifrice. A positive percent change indicates an improvement from the eight-week tactile hypersensitivity scores obtained in Phase I of the study (Interim Values).

***Comparisons Versus Interim Values.*** The 16-week tactile hypersensitivity scores were 28.93 for Population A (population that switched from daily use of the arginine/calcium carbonate dentifrice to use of the strontium acetate dentifrice) and 31.92 for Population B (population that switched from daily use of the strontium acetate dentifrice to use of the arginine/calcium carbonate dentifrice). The percent changes from the eight-week scores were –16.0% for Population A and 40.3% for Population B, both of which were statistically significant.

***Comparison Between Treatment Groups.*** Relative to Population A, Population B exhibited a statistically significant improvement in mean tactile hypersensitivity scores from the eight-week scores after eight weeks' use of the switch-over dentifrice (10.3%).

**Air Blast Hypersensitivity.** Table VIII presents a summary of the mean air blast hypersensitivity scores measured after eight weeks' use of the second assigned switch-over dentifrice. A positive percent change indicates an improvement from the eight-week air blast hypersensitivity scores obtained in Phase I of the study (Interim Values).

***Comparisons Versus Interim Values.*** The mean 16-week air blast hypersensitivity scores were 1.29 for Population A (population that switched from daily use of the arginine/calcium carbonate dentifrice to use of the strontium acetate dentifrice) and 1.08 for Population B (population that switched from daily use of the strontium acetate dentifrice to use of the arginine/calcium carbonate dentifrice). The percent changes from the eight-week scores were –26.5% for Population A and 35.3% for Population B, both of which were statistically significant.

***Comparison Between Treatment Groups.*** Relative to Population A, Population B exhibited a statistically significant improvement in mean air blast hypersensitivity scores from the eight-week scores after eight weeks' use of the switch-over dentifrice (16.3%).

**Table VII**
Phase II of the Clinical Study: Summary of the 16-Week Mean Tactile Hypersensitivity Scores for Subjects Who Completed the 16-Week Clinical Study

| Study Group | n | 16-Week Summary (Mean ± SD) | Within-Treatment Analysis | | Between-Treatment Comparison | |
|---|---|---|---|---|---|---|
| | | | Percent Change[3] | Significance[4] | Percent Difference[5] | Significance[6] |
| Population A[1] | 61 | 28.93 ± 3.03 | – 16.0% | p < 0.05 | 10.3% | p < 0.05 |
| Population B[2] | 60 | 31.92 ± 5.76 | 40.3% | p < 0.05 | | |

[1]Sampled population assigned to brush with the dentifrice containing 8.0% arginine, calcium carbonate, and 1450 ppm MFP for the first eight weeks of the study and then switched to brush with the dentifrice containing 8% strontium acetate and 1040 ppm NaF for the second eight weeks of the study.
[2]Sampled population assigned to brush with the dentifrice containing 8% strontium acetate and 1040 ppm NaF for the first eight weeks of the study and then switched to brush with the 8.0% arginine, calcium carbonate, and 1450 ppm MFP dentifrice for the second eight weeks of the study.
[3]Percent change exhibited by the 16-week mean relative to the 8-week mean. A positive value indicates an improvement in tactile hypersensitivity at the 16-week examination.
[4]Significance of paired t-test comparing the 8-week and the 16-week examinations.
[5]Difference between the 16-week means expressed as a percentage of the 16-week mean for Population A. A positive value indicates an improvement in tactile hypersensitivity scores for Population B relative to Population A.
[6]Significance of ANCOVA comparison of two 8-week adjusted means.

**Table VIII**
Phase II of the Clinical Study: Summary of the 16-Week Mean Air Blast Hypersensitivity Scores for Subjects Who Completed the 16-Week Clinical Study

| Study Group | n | 16-Week Summary (Mean ± SD) | Within-Treatment Analysis | | Between-Treatment Comparison | |
|---|---|---|---|---|---|---|
| | | | Percent Change[3] | Significance[4] | Percent Difference[5] | Significance[6] |
| Population A[1] | 61 | 1.29 ± 0.39 | – 26.5% | $p < 0.05$ | 16.3% | $p < 0.05$ |
| Population B[2] | 60 | 1.08 ± 0.20 | 35.3% | $p < 0.05$ | | |

[1]Sampled population assigned to brush with the dentifrice containing 8.0% arginine, calcium carbonate, and 1450 ppm MFP for the first eight weeks of the study, and then switched to brush with the dentifrice containing 8% strontium acetate and 1040 ppm NaF for the second eight weeks of the study.
[2]Sampled population assigned to brush with the dentifrice containing 8% strontium acetate and 1040 ppm NaF for the first eight weeks of the study, and then switched to brush with the 8.0% arginine, calcium carbonate, and 1450 ppm MFP dentifrice for the second eight weeks of the study.
[3]Percent change exhibited by the 16-week mean relative to the eight-week mean. A positive value indicates a reduction in air blast hypersensitivity at the 16-week examination.
[4]Significance of paired t-test comparing the eight-week and the 16-week examinations.
[5]Difference between the 16-week means expressed as a percentage of the 16-week mean for Population A. A positive value indicates a reduction in air blast hypersensitivity scores for Population B relative to Population A.
[6]Significance of ANCOVA comparison of eight-week adjusted means.

### *Summary Comparison of the Tactile Hypersensitivity Scores Over the 16-Week Study*

Figure 1 shows the results for the mean tactile hypersensitivity scores measured at baseline, after eight weeks of twice-daily brushing with the first assigned dentifrice, and after two weeks' and eight weeks' use of the second assigned switch-over dentifrice.

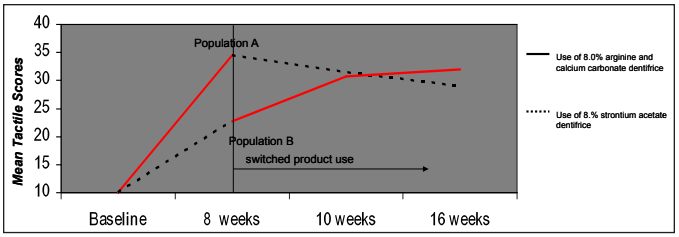



**Figure 1.** *Mean tactile hypersensitivity scores measured at baseline, after eight weeks of twice-daily brushing with the first assigned dentifrice, and after two weeks' and eight weeks' use of the second assigned switch-over dentifrice.*

### *Summary Comparison of the Air Blast Hypersensitivity Scores Over the 16-Week Study*

Figure 2 shows the results for the mean air blast hypersensitivity scores measured at baseline, after eight weeks of twice-daily brushing with the first assigned dentifrice, and after two weeks' and eight weeks' use of the second assigned switch-over dentifrice.

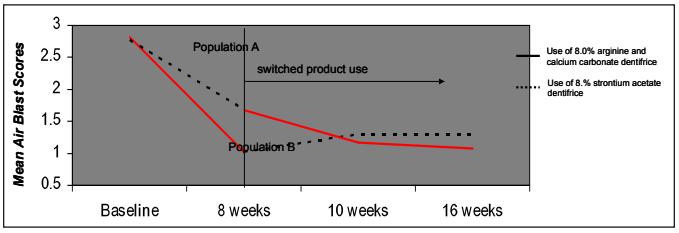



**Figure 2.** *Mean air blast hypersensitivity scores measured at baseline, after eight weeks of twice-daily brushing with the first assigned dentifrice, and after two weeks' and eight weeks' use of the second assigned switch-over dentifrice.*

## Discussion

Demands for the management of dentin hypersensitivity are expected to increase as the adult population lives longer and retains its teeth for 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.[7,40,41]

Therapeutic management of dentin hypersensitivity may involve a combination of at-home and in-office treatments. Desensitizing dentifrices 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 dentifrices represent a treatment option that, given regimen compliance, may be efficacious for most individuals, and are simple to use, cost effective, and widely available.[2,12,13,42] However, the slow, gradual build-up of the effects of most commercially available desensitizing dentifrices, and the associated negative aspects of some, such as poor taste and staining, may discourage sufferers of this distressing condition from achieving compliance to regular and sustained product use. Instead, sufferers may modify their behaviors to avoid inducing pain, and in ways that can further jeopardize their oral health and quality of life.[7] Product characteristics which may increase product compliance include instant onset of desensitizing action, lasting relief, ease of application, product efficacy, and no negative side effects. An ideal dentin hypersensitivity treatment would mimic the natural desensitizing process, including changes in dentin that lead to rapid and lasting occlusion of dentin tubules.[13,18]

Occluding open dentin tubules is one of the means of treating dentin hypersensitivity. In this approach, fluid within the tubule is isolated from external stimuli, resulting in a significant reduction or elimination of fluid movement to trigger a pain response. There are many means of occluding dentin tubules, ranging from invasive techniques such as laser etching of the dentin surface, to noninvasive methods such as the application of a gel or dentifrice containing an occluding agent.[12]

Pro-Argin, a new technology based upon arginine and calcium carbonate, has been developed and validated for the treatment of dentin hypersensitivity.[13] This technology can be delivered in the form of a dentifrice with fluoride for daily use, as well as a professionally applied desensitizing treatment. Dentifrices containing arginine in a calcium carbonate base with 1450 ppm fluoride as sodium monofluorophosphate have been developed, and clinical studies have demonstrated that these dentifrices are

highly effective in reducing dentin hypersensitivity, and have been clinically proven to provide faster and superior relief of dentin hypersensitivity compared to market-leading dentifrices containing 2% potassium ion as the active agent.[22-24] Moreover, it has been clinically proven that dentifrices with the Pro-Argin technology provide instant relief of dentin hypersensitivity when applied directly to each sensitive tooth and massaged for one minute, and the afforded relief is maintained with continued twice-daily brushing.[19,20,25,26,28]

Kleinberg, the inventor of the arginine and calcium carbonate technology for the treatment of dentin hypersensitivity, proposed the combination of arginine bicarbonate and calcium carbonate for deposition of a dentin-like layer on exposed dentin surfaces to physically block and seal open dentin tubules. He suggested that the positively charged arginine is attracted to the negatively charged dentin surface where it helps attract and adhere calcium carbonate to the dentin surface and deep into the tubules. The association of the arginine and calcium carbonate *in situ* provides an alkaline environment which encourages endogenous calcium and phosphate ions to deposit and further occlude the dentin tubules.[17] A range of state-of-the art imaging methods have been used to elucidate aspects of the mechanism of action of the arginine/calcium carbonate technology *in vitro*.[29,30] Confocal Laser Scanning Microscopy (CLSM) studies have demonstrated that the Pro-Argin technology is effective in occluding open dentin tubules, and that this occlusion is resistant to acid challenge. High resolution Scanning Electron Microscopy (SEM) and Atomic Force Microscopy (AFM) studies have confirmed tubule occlusion, and Electron Spectroscopy for Chemical Analysis (ESCA) and Energy Dispersive X-ray (EDX) studies have shown that the occluded mineral contains calcium, phosphate, and carbonate. In addition, hydraulic conductance experiments have shown that sequential treatments with the technology resulted in significant reductions in dentin permeability. They have also confirmed that the dentin occlusion is robust, as reduced permeability was maintained after seven days of pulpal pressure and after treatment with strong acid. Together, these results have clearly demonstrated that in-office and dentifrice products containing the Pro-Argin technology effectively reduce dentin hypersensitivity by sealing and plugging dentin tubules.

The efficacy of strontium-based dentifrices to reduce dentin hypersensitivity by blocking open dentin tubules has been historically described as "minimal" and "uncertain" by reviewers of published clinical study reports. Tarbet, *et al.*[32] and Kanapka[33] showed that a 5% potassium nitrate dentifrice was more effective in reducing sensitivity (electrical, cold air, and subjective measures) than a 10% strontium chloride dentifrice. Silverman, *et al.*[34] found that two 5% potassium nitrate dentifrices were significantly superior at reducing dentin hypersensitivity (cold air and subject-perceived pain) than a 10% strontium chloride dentifrice after eight weeks of product use. Gillam, *et al.*[43] and West, *et al.*[44] compared the sensitivity reduction efficacy (tactile, air blast, and subject assessment scores) after six weeks' product use of a dentifrice containing 8% strontium acetate (Macleans Sensitive) to 2% potassium ion dentifrices and a fluoride control dentifrice. In both studies, the dentifrice containing 8% strontium acetate did not perform better than the regular fluoride control. Recent publications, however, support the efficacy of a commercially available dentifrice with 8% strontium acetate and 1040 ppm fluoride as sodium fluoride (Sensodyne Rapid Relief).[35,36]

The objective of this 16-week, double-blind, randomized, switch-over design study was to provide an investigative comparison of the efficacy of two commercially available dentifrices, one containing 8.0% arginine, calcium carbonate, and 1450 ppm fluoride as MFP, and the other containing 8% strontium acetate and 1040 ppm fluoride as sodium fluoride, with respect to reducing dentin hypersensitivity after eight weeks of at-home brushing twice daily with the first assigned dentifrice, and after subsequent use of the second assigned switch-over dentifrice for eight weeks.

***Phase I of the Study***

After eight weeks of product use, study subjects who were assigned to use the arginine/calcium carbonate dentifrice exhibited statistically significant improvements in mean tactile-induced hypersensitivity scores and in mean air blast-induced hypersensitivity scores relative to subjects who used the strontium acetate dentifrice. These findings confirm the results from an eight-week brushing study conducted in Rome, Italy, which compared the efficacy of twice-daily brushing with the arginine/calcium carbonate dentifrice, the strontium acetate dentifrice, and a fluoride dentifrice control.[27]

***Phase II of the Study***

Subjects who brushed with the arginine/calcium carbonate dentifrice for the first eight weeks of the study, and then switched-over to brush with the strontium acetate dentifrice for the second phase of the study, did not exhibit improvements in mean tactile or mean air blast hypersensitivity scores after two and eight weeks' use of the strontium acetate dentifrice. However, subjects who brushed with the strontium acetate dentifrice for the first eight weeks of the study and then switched over to brush with the arginine/calcium carbonate dentifrice exhibited statistically significant improvements in mean tactile and air blast hypersensitivity scores after two and eight weeks' use of the arginine/calcium carbonate dentifrice.

Relative to subjects who switched from twice-daily brushing with the arginine/calcium carbonate dentifrice to brush with the strontium acetate dentifrice, those who switched from brushing with the strontium acetate dentifrice to brush with the arginine/calcium carbonate dentifrice did not exhibit statistically significant improvements in mean tactile hypersensitivity scores or in mean air blast hypersensitivity scores after two weeks of switch-over product use. However, after eight weeks' use of the second switch-over dentifrice, relative to subjects who switched from twice-daily brushing with the arginine/calcium carbonate dentifrice to brush with the strontium acetate dentifrice, those who switched from brushing with the strontium acetate dentifrice to brush with the arginine/calcium carbonate dentifrice exhibited statistically significant improvements in mean tactile hypersensitivity scores and in mean air blast hypersensitivity scores, which clearly demonstrates the superior efficacy of the arginine/calcium carbonate dentifrice.

## Conclusions

(i) The results of this double-blind clinical study support the conclusion that eight weeks of brushing with Colgate Sensitive Pro-Relief (elmex Sensitive Professional) provides significant reductions in mean dentin hypersensitivity relative to the identical use of Sensodyne Rapid Relief;

(ii) The dentin hypersensitivity reductions achieved by twice-daily brushing with Sensodyne Rapid Relief are significantly improved by switching to twice-daily brushing with Colgate Sensitive Pro-Relief (elmex Sensitive Professional) for two and eight weeks; and

(iii) The dentin hypersensitivity reductions achieved by twice-daily brushing with Colgate Sensitive Pro-Relief (elmex Sensitive Professional) are not improved by switching to twice-daily brushing with Sensodyne Rapid Relief for two or eight weeks. Eight-week's use of Colgate Sensitive Pro-Relief (elmex Sensitive Professional), after having used Sensodyne Rapid Relief for an initial eight-week time period, provides statistically significant improvements in dentin hypersensitivity relative to eight weeks' use of the Sensodyne Rapid Relief.

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