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Pro-Argin™ Technology:
New Research on Superior Dentin
Hypersensitivity Relief with Stain Removal

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Pro-Argin™ Technology: New Research on Superior Dentin Hypersensitivity Relief with Stain Removal

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Dentin hypersensitivity: The effects of an arginine-calcium carbonate and fluoride desensitizing dentifrice

Dentin hypersensitivity is a common occurrence and is often a chief concern among patients. Dentin hypersensitivity incidence has been reported to be around 57% of the adult population. It is manifested as short, sharp bursts of pain, triggered by external stimuli at sites of exposed dentin.

Treatments to relieve dentin hypersensitivity are based on one of two major approaches: (1) the interruption of the neural response to pain stimuli, or (2) the occlusion of exposed and open tubules to block the hydrodynamic mechanism of pain stimulation.

The successful management of dentin hypersensitivity is often very challenging for the dental professional. The cause of the pain and the description of the discomfort reported by the patient can vary.

This Special Issue of the *American Journal of Dentistry* presents the results of studies performed testing the 8.0% arginine-calcium carbonate with fluoride

desensitizing dentifrice. The Introduction paper is an overview of dentin hypersensitivity. One paper shows that the new dentifrice occludes dentin tubules with material including calcium, phosphate, and carbonate. Another paper shows the results of a single direct application of the desensitizing dentifrice, using a finger, to give instant relief (which is maintained with regular brushing). This paper is followed by a study showing the lasting results after 8 weeks of use of the desensitizing dentifrice. The final paper shows the additional whitening effect of the dentifrice after 8 weeks of use.

These papers will add to the body of knowledge and effective treatment options for dentin hypersensitivity. The *Journal* thanks Colgate-Palmolive Company, the manufacturer of the arginine-calcium carbonate desensitizing dentifrice, for sponsoring this Special Issue.

Franklin García-Godoy, DDS, MS
Editor

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Recent advances in dentin hypersensitivity: Clinically proven treatments for instant and lasting sensitivity relief

DIANE CUMMINS, PHD

ABSTRACT: Purpose: To provide a brief overview of the diagnosis, epidemiology, etiology and clinical management of dentin hypersensitivity, to discuss technical approaches to relieve sensitivity, with special emphasis on dentin tubule occlusion and the clinical evidence for efficacy of desensitizing toothpastes based upon this approach, and to summarize the science behind a new dentifrice technology, based upon arginine and calcium carbonate, and the clinical evidence which proves that it delivers both instant and lasting relief of dentin hypersensitivity. **Results:** Clinical studies have shown that a new toothpaste, containing arginine and calcium carbonate (known as Pro-Argin™ technology) with 1450 ppm fluoride, offers clinically proven instant and lasting relief of dentin hypersensitivity. Three 8-week clinical studies have shown that this new toothpaste provides statistically significantly superior efficacy in reducing sensitivity to market leading desensitizing toothpastes containing 2% potassium ion. Importantly, three further clinical studies have shown that a single direct topical application of toothpaste to sensitive teeth, using a fingertip or cotton swab followed by 1 minute of massage, resulted in instant relief of dentin hypersensitivity and that the relief was maintained with subsequent twice-daily brushing. Mechanism of action studies have shown that this technology physically seals dentin tubules with a plug that contains arginine, calcium carbonate and phosphate. This plug, which is resistant to normal pulpal pressures and to acid challenge, effectively reduces dentin fluid flow and thereby relieves sensitivity. A new whitening variant of this desensitizing toothpaste, containing the Pro-Argin technology, fluoride and a high cleaning calcium carbonate system, has now been clinically and scientifically validated. This toothpaste works by the same mechanism of action as its non-whitening counterpart and is clinically proven to provide both instant and lasting relief of sensitivity, while providing proven efficacy in removal of extrinsic stains. No difference in desensitizing efficacy was observed between the whitening and non-whitening versions. (*Am J Dent* 2010;23 Sp Is A:3A-13A).

CLINICAL SIGNIFICANCE: The results of a series of clinical studies support the conclusion that a new toothpaste containing 8.0% arginine, a high cleaning calcium carbonate system, and 1450 ppm fluoride provides statistically significant relief of dentin hypersensitivity immediately after direct topical application and during regular twice daily brushing, as well as statistically significant removal of extrinsic stains.

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Introduction

Dentin hypersensitivity is characterized by short, sharp pain arising from exposed dentin in response to external stimuli, typically thermal, evaporative, tactile, osmotic or chemical, and which cannot be ascribed to any other form of dental defect or disease.^{1,2} The most frequently experienced pain from dentin hypersensitivity is 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.^{1,3,4} As several oral conditions can give rise to dental pain, such as untreated caries, a split tooth or a cracked cusp, the correct attribution of dental pain to dentin hypersensitivity is essential to assess appropriate treatment options.^{5,6}

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.^{1,7,8} Tactile, cold and osmotic stimuli all trigger rapid fluid outflow. Heat, on the other hand, triggers a slow retreat of dentin fluid, and the resultant pressure change activates the nerve fibers in a less dramatic fashion, consistent with the observation that cold is generally more problematic to sufferers than is heat.¹ 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. Scanning

electron microscopy has shown that tubules in clinically characterized “sensitive” exfoliated teeth are eight times more numerous, and two times larger in diameter, and are open, whereas tubules in “non-sensitive” teeth are fewer, smaller, and usually blocked.^{9,10} 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

Dentin can become exposed through gingival recession or through enamel loss. Gingival recession and exposure of the underlying dentin are caused by overzealous tooth brushing and improper tooth brushing technique, or by periodontal disease and its surgical and non-surgical treatment.^{1,11} Based on *in vitro* and *in situ* studies, it appears that normal tooth brushing does not cause significant enamel loss. However, erosion from acidic foods and drinks, in combination with tooth brushing, can result in significant tooth wear on any aspect of the tooth surface, especially the cervical area.^{1,12-14} Experts have concluded that gingival recession, rather than cervical enamel loss, is the key pre-disposing factor for dentin hypersensitivity.¹

Exposed dentin tubules are loosely occluded by a coating, known as the smear layer, comprised of protein components and calcium phosphate deposits derived from saliva. On the basis of *in vitro* studies, it has been suggested that both chem-

ical and physical forces can remove the smear layer to open exposed dentin tubules.¹ While there seems little doubt that acidic foods and drinks are able to remove the smear layer and soften dentin rendering the surface-softened dentin tissue susceptible to physical forces, such as tooth brushing, clinical data suggest that physical forces alone are not a key factor in removing the smear layer and opening exposed dentin tubules.^{1,7}

Dentin hypersensitivity is typically experienced by the adult population, age range from 20-49 years, with peak incidence between 30-39 years. A slightly higher incidence of dentin hypersensitivity has been observed in females, which may reflect oral hygiene and dietary practices. The buccal cervical regions of the permanent teeth are the most commonly affected surfaces, with canine, pre-molar and incisor teeth being more frequently affected than molars.^{1,5} Studies of the prevalence of dentin hypersensitivity have reported levels in the range 4-57% in general dental practice settings, others have suggested levels of 15-25% are typical. The reported wide variations have been attributed to different methods of assessment, self-reported or professional clinical diagnosis, the population base and setting, and behavioral factors, such as oral hygiene habits and intake of acidic foods and drinks.^{1,5,7,12} Not surprisingly, levels of dentin hypersensitivity are higher, ranging from 60-98%, in patients following periodontal treatment.^{1,5,11}

In 1982, dentin hypersensitivity was described as an enigma, because it was frequently encountered and poorly understood.¹⁵ While there is still much to learn, subsequent advances in our scientific understanding have made a comprehensive approach to sensitivity management possible. Specifically, the dental professional is advised to follow six steps with their patients:¹

- Correct diagnosis of dentin hypersensitivity based upon history and clinical examination;
- Differential diagnosis, to exclude other conditions giving rise to similar pain symptoms;
- Treatment of all secondary conditions with symptoms similar to dentin hypersensitivity;
- Identification of etiologic and predisposing factors, particularly dietary and oral hygiene habits, pertinent to erosion and abrasion;
- Removal or minimization of etiologic and predisposing factors through dietary advice and oral hygiene instruction;
- Recommendation or provision of treatment based upon individual needs.

Providing treatment to meet individual needs is typically initiated by the dental professional recommending use of desensitizing toothpaste, because this may result in significant relief of dentin hypersensitivity for the majority of individuals. When use of a desensitizing toothpaste is insufficient, a second step may be home use prescription fluoride products, which can offer additional benefits. Professionally applied in-office products may be suitable for patients with additional treatment needs.²

PRODUCTS TO ALLEVIATE DENTIN HYPERSENSITIVITY

Two primary approaches to the development and validation of products to treat dentin hypersensitivity have been

investigated:

- Interruption of the neural response to pain stimuli; and
- Occlusion of exposed and open dentin tubules to block the hydrodynamic mechanism of pain stimulation.

Interruption of the neural response to pain stimuli: Clinical evidence of the effectiveness of potassium-based toothpaste

Potassium salts have been shown to interrupt the neural response to pain stimuli. In fact, they are the only ingredients that have been validated for the relief of sensitivity *via* this mechanism. The vast majority of desensitizing toothpastes, representing approximately 10% of the global toothpaste market, contain a potassium salt to “numb” the pain of dentin hypersensitivity.^{16,17} In most countries, potassium nitrate (5%), potassium chloride (3.75%) and potassium citrate (5.5%) are used interchangeably in desensitizing toothpaste, as each of these salts provides 2% potassium ion, which is the clinically proven active entity for sensitivity relief. In the United States, however, desensitizing toothpastes typically contain 5% potassium nitrate, to meet FDA regulations.¹⁸ Because of the versatility of potassium salts to changes in product formulation, most potassium-based toothpastes contain other ingredients to provide additional benefits, such as fluoride for cavity protection, an anti-bacterial ingredient for plaque and gingivitis control, crystal inhibitors and high cleaning abrasives for tartar control and whitening, respectively.

A recent review identified published clinical studies that support that toothpaste formulations containing potassium nitrate,¹⁹⁻³¹ potassium chloride^{32,33} and potassium citrate,^{25,34} are significantly more effective in reducing dentin hypersensitivity than regular fluoride toothpaste. The addition of fluoride to potassium-based toothpaste, for cavity prevention, does not negatively impact the sensitivity relief efficacy.^{22-24,33} Likewise, the addition of other benefit agents, such as plaque and tartar control ingredients, to potassium-based toothpaste does not impact efficacy.²⁶⁻²⁸ While potassium-based toothpaste can provide effective relief, these clinical studies have repeatedly shown that it takes at least 2 weeks of twice daily use to show measurable reductions in sensitivity and longer time periods, generally 4 to 8 weeks, to demonstrate significant levels of pain relief. Based upon the available data, it appears that potassium-based toothpastes do not provide instant relief of dentin hypersensitivity, an important benefit to consumers which will be discussed in more detail below.

While there is a substantial evidence base for recommending the use of a potassium-based desensitizing toothpaste, some authors have reported that these toothpastes are no more effective than regular fluoride toothpaste,³⁵⁻³⁷ suggesting that support for the efficacy of potassium-based desensitizing toothpaste is equivocal.^{3,5,38,39} Differences in clinical results have been attributed to differences among clinical study parameters, especially population and scoring methods, and to the well known Hawthorne effect. The fact that placebo control products can reduce sensitivity by as much as 40% from baseline has significantly impacted the ability to differentiate the efficacy of a test product in some studies.^{3,39}

In vitro studies of the mechanism of action of potassium salts have shown that they can dramatically reduce the excitability of intra-dental nerves. Specifically, raising the concentration of potassium ion significantly above the physiological level in the extra-cellular fluid induces depolarization of the nerve cells, a brief excitatory burst, following which the nerves become unresponsive to excitatory stimuli. Some divalent cations, such as calcium and strontium, are also able to suppress nerve activity *in vitro*, but they do so to a much lesser extent than potassium.⁴⁰ The action of potassium salts in these mechanism studies does not reflect their effects, in terms of their slow time to action or limited duration of action, in clinical studies. This is because the potassium ion has to diffuse from the oral cavity into the dentin tubules, then through the dentin tubules against the flow of dentin fluid to the site of action at the interface of the inner dentin surface and the pulp chamber, *i.e.*, the nerve endings. Further, to induce depolarization of the nerves and achieve significant pain relief, the concentration of potassium must build up in the fluid surrounding the nerve ending, which typically takes a period of 4 to 8 weeks, and be maintained at that level on an ongoing basis. If and when treatment with potassium-based products is ceased, elevated levels of potassium at the site of action are diffused, and sensitivity relief is lost.

Occlusion of exposed and open dentin tubules to block the hydrodynamic mechanism of pain stimulation: Approaches

The principle of occluding dentin tubules to block the hydrodynamic mechanism of pain stimulation is a seemingly straightforward one.⁴⁰ Yet, there are multiple and complex ways in which different agents and products could potentially act to partially or completely occlude tubules. In simple theoretical terms, these ways might include:

- Creation of a “natural” smear layer – mechanical forces, such as professional burnishing of sensitive dentin surfaces, have been hypothesized to encourage natural oral constituents to interact with the dentin surface and loosely occlude the tubules;
- Deposition of a thin film coating – professionally-applied polymer-based materials, such as restorative resins or dentin bonding agents, have been suggested to create an “artificial smear layer” on the exposed dentin surface and over the open tubules;
- Deposition of a layer of fine particles – 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; and
- Induction of natural mineral formation *in situ* – new technologies, such as the Pro-Argin technology^a and NovaMin bioactive glass,^b are believed to bind to the exposed dentin surface and within the openings of the dentin tubules to mediate the formation of biological mineral.

In reality, however, these approaches to tubule occlusion are neither discrete, nor mutually exclusive. Furthermore, all approaches to tubule occlusion are not equal. Importantly,

they are theoretical until proven to be effective in well designed and executed clinical studies, as will be discussed in the following sections.

EVIDENCE FOR THE EFFECTS OF DENTIFRICE COMPONENTS ON THE CREATION AND DESTRUCTION OF SMEAR LAYERS

In the past, dentists have used mechanical procedures, such as burnishing of exposed root surfaces, to create a “natural” layer of dentin-derived mineral and denatured protein on the exposed surface and reduce dentin hypersensitivity. This practice has stimulated dental researchers to explore the formation and destruction of these so-called “smear” layers.

Addy and coworkers⁴¹⁻⁴³ have taken the lead in this area of research by conducting a range of *in vitro* studies and by suggesting that their observations may be of relevance to the *in vivo* treatment of dentin hypersensitivity. Among these studies, Absi *et al*⁴² demonstrated that tooth brushing could either create or remove a smear layer on dentin specimens *in vitro*, depending on the conditions of treatment. First, they suggested that brushing with toothpaste could offer therapeutic action by mechanically forming a smear layer. Second, and in diametric opposition to therapeutic action, they indicated that brushing in the presence of dietary acids could cause smear layer removal. In separate studies, Addy *et al*⁴¹ and Absi *et al*⁴³ showed that “smear layers” formed after brushing dentin specimens *in vitro* varied widely in composition and were largely comprised of lightly retentive deposits of toothpaste abrasive, some of which showed some resistance to water and acid washing. They are not naturally-derived layers of dentin-mineral and denatured protein.

The results of these *in vitro* experiments confirm for the author of this paper that creation of a smear layer and deposition of a thin layer of fine particles are neither discrete nor mutually exclusive routes to potentially occlude dentin tubules.

More recently, based upon *in vitro* studies of dentin wear, Moore & Addy⁴⁴ have suggested that toothpaste surfactants and abrasives are able to remove the natural smear layer on dentin and cause dentin surface loss. On the basis of their observations, these authors suggested that certain “mild” surfactants and “gentle” abrasives might have advantages over their more traditional counterparts in toothpastes marketed for the relief of dentin hypersensitivity.⁴⁴ While an independent *in vitro* study has recently been presented,⁴⁵ this hypothesis does not appear to have been clinically validated in well designed *in vivo* studies. To this author’s knowledge, there are no published clinical studies supporting the hypothesis that “mild” surfactants, such as tegobetaine, have benefits in reducing dentin hypersensitivity over the traditional surfactant, sodium lauryl sulfate, *in vivo*. Given the passage of 5 years since the first suggestion⁴⁴ regarding the potential advantages of mild surfactants, this lack of published clinical data is, perhaps, surprising. On the other hand, published clinical data show that the hypothesis that “gentle” abrasives may have benefits in toothpastes for dentin hypersensitivity over traditional abrasives has actually been refuted. Specifically, a clinical study compared toothpastes with relative dentin abrasivity (RDA) values of 60 and 210 for their effects on dentin hypersensitivity

when used twice daily during regular tooth brushing for 8 weeks. The study showed that the high and low RDA toothpastes did not differentially affect the response of subjects with existing dentin hypersensitivity, indicating that effects seen *in vitro* do not seem to be material to clinical performance of products designed to reduce dentin sensitivity *in vivo*.⁴⁶

Tubule occlusion *via* deposition of a layer of fine particles: Clinical evidence of the effectiveness of strontium-based toothpaste, stannous-based toothpaste, and silica abrasives

Strontium chloride (10%) was the first tubule blocking ingredient to be introduced into toothpaste, being commercialized as Sensodyne,^b approximately 50 years ago.⁴⁰ Because of the incompatibility of strontium chloride with fluoride, the original Sensodyne was a fluoride-free product. Strontium chloride can still be found in toothpaste in some markets, but it was largely replaced by potassium nitrate in the 1970s, because potassium had been hailed as “a superior desensitizer”.¹⁶ Over the subsequent 20 years or so, two substantive changes have been made to strontium-based toothpaste: one was to replace the original abrasive, diatomaceous earth, with silica; the other was to add fluoride and replace strontium chloride with strontium acetate (8%), with which fluoride is compatible.

While there appears to be a reasonable basis of evidence in support of the clinical efficacy of potassium-based toothpaste,⁴⁷ this does not appear to be the case for strontium-based toothpaste. In 1994, Zappa⁴⁸ summarized the results of early clinical studies on strontium chloride toothpaste and stated: “In summary, self-applied 10% strontium chloride hexahydrate desensitizing toothpaste seems to be effective in relieving the pain of tooth sensitivity. However, not all studies supported this conclusion and, in direct comparison with other active agents, the efficacy of strontium chloride is uncertain.”

More recently, in 2007, Jackson⁴⁹ summarized studies published subsequent to Zappa’s review and concluded: “In none of these studies was a consistent, significant improvement in patients’ symptoms of dentine hypersensitivity observed for strontium-based products compared with the negative control toothpaste. It can, therefore, be concluded that strontium salts appear to have only a minimal effect in reducing the symptoms of dentine hypersensitivity.”

The author of this paper has reviewed the published literature and has independently concluded that there is a paucity of conclusive clinical data on the efficacy of strontium-based toothpaste. While a systematic review of the available studies is not possible, because they differ substantially in many aspects of their design, the brief summary presented in Table 1 is informative.

As a first observation, these studies were run over an extended time period, from 1961 to 1997, during which our understanding of dentin hypersensitivity has increased considerably. In particular, it is important to note that the knowledge available today on how best to design and conduct clinical studies on dentin hypersensitivity, especially on selection and validation of clinical measurement methods, was not available to early investigators. In fact, it was not until the last of these strontium toothpaste studies had been published, *i.e.*, in 1997, that guidelines for dentin hypersensi-

tivity clinical trials were published.⁵⁰

The earliest studies were, in essence, uncontrolled “case” studies with a simple telephone call-back to determine patient self-assessment of sensitivity relief. Each of these monadic studies showed qualitative improvements *versus* baseline, for many individuals, suggesting that use of 10% strontium chloride toothpaste might be helpful to patients with dentin hypersensitivity.⁵¹⁻⁵⁴ Controlled clinical studies have also demonstrated monadic reductions (reductions *versus* baseline) in patients’ symptoms of dentin hypersensitivity, but they fail to provide conclusive evidence that strontium-based toothpaste provides superior efficacy over negative control toothpaste without strontium.

Four studies, using widely different study designs, have shown reductions in dentin hypersensitivity for 10% strontium chloride toothpaste *versus* a negative control.⁵⁵⁻⁵⁸ In one study, involving periodontal patients and patient self-assessment, Blitzer⁵⁵ reported that 75% of patients using the strontium chloride toothpaste felt “complete” relief from sensitivity symptoms compared to less than 25% using a placebo control. In another study,⁵⁶ using the tooth hypersensitivity index, larger reductions in sensitivity for users of 10% strontium chloride toothpaste after 3, 8, 15, 20, or 30 days use compared to formalin-based toothpaste were reported. In a third study,⁵⁷ using objective (tactile and thermal) and subjective (questionnaire) measures, statistically significant reductions on all measures for the 10% strontium chloride toothpaste after 4, 8, and 12 weeks’ use were reported, compared to the placebo control toothpaste. In a fourth study,⁵⁸ involving periodontal patients and objective (tactile, cold water, and air blast) measures, significantly reduced sensitivity after 1, 3 and 7 weeks’ use of strontium chloride toothpaste post-surgery was reported, whereas sensitivity was only significantly reduced after 7 weeks’ use of the placebo toothpaste.

On the other hand, several studies, most of them more recent than those discussed above, have shown no benefit for the use of strontium-based toothpaste over negative or placebo controls. In one study, using an explorer to elicit patient response, Shapiro *et al*⁵⁹ reported that reductions in dentin hypersensitivity perceived after 4 weeks’ use of 10% strontium chloride toothpaste were no longer evident after 8 weeks’ use. In another study,⁶⁰ using cold air, thermo-electric probe and patient subjective assessments, it was shown that Sensodyne with 10% strontium chloride was less effective than three experimental silica-based toothpastes (one contained 8% strontium acetate, one contained 8% strontium acetate and fluoride, and the other contained fluoride alone) and was no more effective than a formalin-based control. The authors attributed the observed reductions in dentin hypersensitivity to the presence of silica abrasive in the three experimental toothpastes and stated that “The results of this study support the recently reported minimal action of Sensodyne [with strontium chloride] in the treatment of dentin hypersensitivity” and “It is apparent that there is no convincing evidence that either strontium or fluoride salts occlude tubules either directly, or indirectly.”⁶⁰

It is important to note, however, that the dentin hypersensitivity benefits attributed to the presence of silica abrasive in these strontium toothpastes have not been reproduced in

Table 1. Summary of dentin hypersensitivity clinical studies conducted on toothpastes containing a strontium salt.

| Study reference | Test product | Control product | Study duration | Sensitivity measures | Summary of overall results |
|---|---|---|-----------------------------------|--|--|
| Ross, 1961 ⁵¹ | 10% SrCl ₂ toothpaste | None | Up to 1 month | Subjective assessment of improvement from baseline | 83% of subjects perceived complete to good relief |
| Cohen, 1961 ⁵² | 10% SrCl ₂ toothpaste | None | Up to 3 months | Subjective assessment of improvement from baseline | 87% of subjects perceived complete to good relief |
| Zelman & Hillyer, 1963 ⁵³ | 10% SrCl ₂ toothpaste | None | Up to 3 months | Subjective assessment of improvement from baseline | 56% of subjects perceived complete to good relief |
| Meffert & Hoskins, 1964 ⁵⁴ | 10% SrCl ₂ toothpaste | None | Up to 3 months | Subjective assessment of improvement from baseline | 78% of subjects perceived complete to good relief |
| Blitzer, 1967 ⁵⁵ | 10% SrCl ₂ toothpaste | Placebo control | 30 days | Subjective assessment of improvement from baseline | SrCl ₂ > placebo (P < 0.05) after 30 days |
| Shapiro <i>et al</i> , 1970 ⁵⁹ | 10% SrCl ₂ toothpaste | MFP control Placebo control | 8 weeks | Subjective response to explorer | No significant differences between products on overall measure; SrCl ₂ > MFP control ~ placebo control in sub-analysis after 8 weeks (P < 0.05) |
| Uchida <i>et al</i> , 1980 ⁵⁸ | 10% SrCl ₂ | Placebo | 8 weeks (post-surgery) | Explorer, thermal (cold water), air blast | SrCl ₂ significantly reduced average pain scores after 1, 3 and 7 weeks use; placebo significantly reduced pain scores after 7 weeks only |
| Tarbet <i>et al</i> , 1982 ²⁹ / Kanapka, 1982 ³⁰ | 5% KNO ₃ | 10% Sr Cl ₂ (also contained two other products Protect with 2% sodium citrate and Thermodent with 1.4% formaldehyde) | 4 weeks | Electrical and cold air | 5% KNO ₃ > 10% Sr Cl ₂ (P < 0.05) at 1, 2, 3, and 4 weeks |
| Minkoff & Axelrod, 1987 ⁵⁷ | 10% SrCl ₂ | Placebo control | 12 weeks | Yeaple probe, air blast, subject questionnaire | SrCl ₂ > placebo control after 4 weeks (subjective); after 8 weeks (air blast); and at 12 weeks (tactile) |
| Addy <i>et al</i> , 1987 ⁶⁰ | 8% Sr acetate/ silica base 8% Sr acetate + fluoride/silica base | Silica control Sensodyne with 10% SrCl ₂ / diatomous earth (contained one other test product) | 6 weeks | Cold air, thermo-electric probe (0 and 5°C), subjective assessment | Sr acetate ~ Sr acetate + F ~ silica control > Sensodyne (P < 0.05) |
| Dabas & Swadia, 1989 ⁵⁶ | 10% SrCl ₂ | Formalin toothpaste control | 20 days | Thermal | Complete relief in 85% subjects using test <i>versus</i> 52% using control |
| Gillam <i>et al</i> , 1992 ⁶² | 10% SrCl ₂ / low RDA silica base | Sensodyne with 10% SrCl ₂ / diatomous earth | 8 weeks use; 12 weeks post use | Yeaple probe, air blast subjective assessment | Significant effects <i>versus</i> baseline; no significant differences between products; effects remain 12 weeks post use |
| Pearce <i>et al</i> , 1994 ⁶¹ | 8% Sr acetate/ silica base | Sensodyne with 10% SrCl ₂ / diatomous earth Fluoride control | 12 weeks | Yeaple probe, air blast, subjective assessment | Significant effects <i>versus</i> baseline; no significant differences between products |
| Gillam <i>et al</i> , 1996 ³⁷ | 8% Sr acetate + fluoride | KCl/MFP positive control MFP control | 6 weeks | Yeaple probe, air blast, subjective assessment | Significant effects <i>versus</i> baseline; no significant differences between products |
| Silverman <i>et al</i> , 1996 ³¹ | 10% SrCl ₂ | KNO ₃ KNO ₃ /MFP Placebo control | 8 weeks | Tactile, cold air, subjective assessment | KNO ₃ + ~ KNO ₃ /MFP > SrCl ₂ ~ placebo after 8 weeks (P < 0.005) |
| West <i>et al</i> , 1997 ³⁶ | 8% Sr acetate + fluoride | KNO ₃ /NaF Negative control | 6 weeks | Yeaple probe, air blast, subjective assessment | Significant effects <i>versus</i> baseline; no significant differences between products |

other studies which included silica-based toothpastes. In 1994, Pearce *et al*⁶¹ compared the same strontium toothpastes; 8% strontium acetate and fluoride in a silica base and 10% strontium chloride in a diatomous earth base to a calcium-based fluoride-only control toothpaste. They showed that all three groups experienced reduced sensitivity, however, there

were no significant differences between the two desensitizing toothpastes, or between the desensitizing toothpastes and the control product. Gillam *et al*⁶² also failed to demonstrate a benefit for formulating with a silica abrasive. In a two cell study, significant reductions in sensitivity (tactile, air blast and subjective measures) were observed after 8 weeks of product

use, but there was no discernible advantage for a silica-based 8% strontium acetate toothpaste compared to a diatomous earth-based 10% strontium chloride toothpaste. While these results strongly reinforce existing doubt on the efficacy of strontium-based toothpastes, they question the hypothesis that there is an advantage to formulating toothpaste with a silica abrasive. In reality, most potassium-based toothpastes are formulated with a silica abrasive and, typically, they neither effectively occlude dentin tubules, nor significantly reduce dentin fluid flow.

Studies have directly compared the efficacy of toothpaste containing a potassium salt with toothpaste containing a strontium salt. In a four cell study, after 4 weeks' use, Tarbet *et al*²⁹ and Kanapka *et al*³⁰ showed that 5% potassium nitrate toothpaste was statistically significantly more effective in reducing sensitivity (electrical, cold air, and subjective measures) than 10% strontium chloride toothpaste. Silverman *et al*³¹ compared the effects of two toothpastes containing 5% potassium nitrate, one with and one without fluoride, to toothpaste containing 10% strontium chloride and to a placebo control. After 8 weeks' use, both potassium-based toothpastes were found to be significantly superior to 10% strontium chloride toothpaste (cold air and subject-perceived pain) and all three were significantly more effective than the placebo. In addition, Gillam *et al*³⁷ reported the results of a study comparing the efficacy of three fluoride toothpastes, one containing 3.75% potassium chloride (Sensodyne F^b), one containing 8% strontium acetate (Macleans Sensitive^b), and the other a control (Aquafresh^b). After 6 weeks' product use, tactile, air blast and subject assessment scores were significantly reduced for all users. However, there were no significant differences between products. Likewise, West *et al*³⁶ reported the results of a study comparing the efficacy of three fluoride toothpastes, one containing 5% potassium nitrate (Aquafresh Sensitive), one containing 8% strontium acetate (Macleans Sensitive), and a control (Aquafresh). Again, after 6 weeks' product use, tactile, air blast and subject assessment scores were significantly reduced for all users, but there were no significant differences between products. Thus, in both studies, the toothpaste containing 8% strontium acetate (Macleans Sensitive) did not perform better than the negative control (Aquafresh).

The literature suggests three potential mechanisms of action for strontium salts. First, as indicated above, nerve depolarization is possible. Second, because of its chemical similarity to calcium, strontium could, in principle, replace lost calcium in the hydroxyapatite lattice to strengthen de-mineralized enamel and/or dentin. Third, strontium salts may deposit a layer of fine particles to occlude dentin tubules. In fact, there is remarkably little scientific evidence to support any of these potential mechanisms.^{40,63} Although the third has been proposed to be the most likely of the three mechanisms,^{64,65} a hydraulic conductance study showed that strontium salts deposited on dentin, which visually occlude the tubules, do not rapidly alter dentin permeability.⁶⁵

In summary, clinical data do not provide conclusive evidence of the efficacy of strontium-containing toothpaste, rather they indicate that strontium-based toothpaste is no more effective in reducing dentin hypersensitivity than regular fluo-

ride toothpaste. Furthermore, clinical data support the conclusion that strontium-based toothpaste is less effective in reducing dentin hypersensitivity than potassium-based toothpaste. Based upon the available evidence, it appears most unlikely that strontium-based toothpaste can provide either instant or lasting relief of dentin hypersensitivity.^{47,67}

Stannous fluoride has been used in toothpaste since the 1960s, initially as a source of fluoride for cavity prevention. From the 1980s onwards, the potential oral health benefits of stannous fluoride have been explored, including the ability of stannous fluoride containing anhydrous gels to relieve dentin hypersensitivity.⁶⁸⁻⁷⁰ More recently, toothpaste formulations have been shown to be more effective in reducing sensitivity than placebo control products.⁷¹⁻⁷³ Typically, stannous fluoride formulations have been shown to provide significant reductions in dentin hypersensitivity after 4 or more weeks of twice daily use.^{47,67-73} In two virtually identical studies, a toothpaste containing 0.454% stannous fluoride and sodium hexameta-phosphate was shown to significantly reduce sensitivity, on both tactile and air blast measures, compared to sodium fluoride toothpaste, after 4 and 8 weeks' use.^{71,72}

To this author's knowledge, there are no published head-to-head clinical studies comparing the efficacy of stannous fluoride to potassium-based toothpaste. Based upon the available clinical evidence, it seems highly unlikely that stannous-based toothpaste can provide instant relief of dentin hypersensitivity.^{47,67} Despite its proven efficacy, stannous fluoride has not been widely available in the desensitizing toothpaste market. The well known negatives of tooth staining and poor taste are possible reasons for this.

Stannous is believed to work by precipitating insoluble metal compounds on dentin surfaces, thereby occluding or partially occluding open dentin tubules.⁷³ As recently as 2008, however, Addy⁷⁴ stated: "Evidence for dentine hypersensitivity actives in toothpastes is completely lacking, although experiments using 'actives' in solution, such as stannous salts, indicate that tubules can be blocked."

As there are few published data on stannous toothpastes, the possibility that stannous salts precipitate to occlude or partially occlude dentin tubules has not been shown to result in reduced dentin fluid flow and, thereby linked to reduced dentin hypersensitivity. In contrast to the Pro-Argin technology described in recent publications, and summarized below, strontium and stannous toothpastes do not induce deposition of "natural" calcium and phosphate.^{47,67}

Returning to the question of whether silica abrasives can effectively occlude dentin tubules and significantly reduce sensitivity, the answer is some do, but most do not. In recent years, silica manufacturers have devoted considerable effort to understanding the properties of synthetic silica systems and to developing novel materials with enhanced characteristics, such as improved cleaning and reduced abrasivity. Likewise, toothpaste manufacturers have developed products using these novel materials to provide new consumer benefits, such as dentin hypersensitivity relief. While much of this learning is proprietary, it is clear from patents and patent applications that some specially designed silica abrasives may effectively occlude tubules. However, most silicas neither adhere strongly enough to the exposed dentin surface nor penetrate tubules

sufficiently well to provide effective tubule occlusion. Moreover, the patent literature clearly demonstrates that it is not simply a matter of adding a specially designed silica to a toothpaste; the formulation itself must be specially designed to ensure effective adhesion and retention of the silica on the dentin surface for an extended time period. Recently, a new toothpaste containing a “specially designed” silica abrasive in a “specially designed” toothpaste formulation has been shown to occlude dentin tubules and reduce hydraulic conductance *in vitro*, and to significantly reduce dentin hypersensitivity *in vivo*, thereby providing effective sensitivity relief.⁷⁵⁻⁷⁷ The new understanding that underpins these latest developments, that not all silica abrasives and formulations containing them are equal, may help explain the irreproducible results on toothpaste containing silica abrasives reported several years ago.

Tubule occlusion by induction of natural mineral formation *in situ*: Clinical evidence of the effectiveness of calcium phosphate particle deposition from toothpaste

Recent advances in scientific understanding of dentin hypersensitivity have triggered research into new treatments that will not only alleviate the symptoms of dentin hypersensitivity, but will target the underlying causes. Markowitz & Pashley³ proposed to develop and validate new treatments that can render dentin significantly more resistant to both mechanical and chemical attack. First, by increasing the mineral density of the dentin surface itself, it would be possible to improve resistance to wear by both acid erosion and abrasion. Second, by plugging and sealing open tubules with a calcium- and phosphate-containing dentin-like substance, it would be possible to block diffusion through the tubules into the dentin sub-surface, thereby further increasing acid resistance. They also suggested that the ideal dentin hypersensitivity treatment would mimic the natural desensitizing process that leads to spontaneous occlusion of open dentin tubules over time; a successful treatment would render dentin non-sensitive and sclerotic, such a state being more desirable than open, patent, sensitive dentin. The authors concluded that any treatment that completely seals dentin tubules will restore that surface to a healthy state.³

The concept of delivering calcium and phosphate from a dentifrice vehicle has been of long standing interest; in the first instance, for cavity protection and, more recently, for sensitivity relief. The principle of bringing calcium and phosphate ions together 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 compatible with and stable in a dentifrice vehicle, particularly one containing fluoride, yet 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 deposition of amorphous calcium phosphate on the tooth surface have been investigated, published clinical data demonstrating effective sensitivity relief from products delivering amorphous calcium phosphate are sparse. In one clinical study, a previously marketed two-phase toothpaste containing calcium sulfate, and ammonium phosphate and sodium fluoride, was reported

to be more effective in alleviating sensitivity, assessed as the number of teeth becoming insensitive by the conclusion of the 8-week study, than a conventional fluoride toothpaste and an experimental toothpaste containing calcium and phosphate salts and fluoride, as monofluorophosphate.⁷⁸ In a more recent study, an anhydrous, single-phase fluoride toothpaste, containing calcium sulfate, di-potassium phosphate and baking soda, shown to modify the cosmetic appearance of enamel surfaces by filling surface defects and to occlude dentin tubules *in vitro*, was shown to reduce dentin hypersensitivity more effectively than a control toothpaste.⁷⁹

Novel “biomaterials”, in the form of calcium phosphor-silicates, have also been shown to have potential to release calcium and phosphate upon exposure to an aqueous environment to deliver relief of sensitivity. Bioglass particles in a specially formulated dentifrice were shown to occlude dentin tubules, whereas other formulations with the same ingredient were shown to be ineffective.⁸⁰ In a single published clinical study,⁸¹ a silica-based dentifrice containing 5% NovaMin, as the commercially available bioglass is now known, was compared to a commercial desensitizing toothpaste containing strontium chloride and to a placebo control for its effects in reducing sensitivity. Using visual analogue scales, and air blast and cold water stimuli, the NovaMin dentifrice was shown to be significantly more effective than both the strontium chloride and placebo control toothpastes after 6 weeks’ use. Interestingly, there were no significant differences between the strontium chloride and placebo toothpaste groups, further confirming the lack of efficacy of strontium-based toothpaste. This dentifrice containing 5% NovaMin has been compared to two commercial silica-based desensitizing toothpastes containing 2% potassium ion in *in vitro* mechanism of action studies:⁸² their abilities to occlude dentin tubules were assessed by scanning electron microscopy, and to reduce dentin fluid flow were measured by hydraulic conductance. All three toothpastes significantly reduced dentin permeability. Post-treatment challenges for 1 minute with 6% citric acid and 24 hours post-treatment immersion in artificial saliva both resulted in partial loss of the occlusion achieved with the NovaMin toothpaste. The potassium-containing silica-based toothpastes varied significantly in their responses to these two different challenge conditions, clearly illustrating that the behavior of silica-based toothpastes varies and that potassium-based toothpastes do not necessarily result in effective occlusion.

While these preliminary results appear promising, significantly more research is required on each of these two technologies: in particular, multiple independent clinical studies are needed on each technology to validate the efficacy of these dentifrices in reducing dentin hypersensitivity.

The development and validation of a new technology, Pro-Argin, based upon saliva’s role in the natural process of tubule occlusion: Clinical and scientific evidence for instant and lasting relief of sensitivity

Saliva plays a role in naturally reducing dentin hypersensitivity by transporting calcium and phosphate into dentin tubules to induce tubule plugging and by forming a surface

Table 2. Summary of results of 8-week clinical studies comparing the efficacy in reducing dentin hypersensitivity of a new toothpaste containing 8.0% arginine, calcium carbonate and fluoride to desensitizing toothpaste containing 2% potassium ion.

| Reference | Products tested | N | Baseline-adjusted mean tactile sensitivity scores | | | Baseline-adjusted mean air blast sensitivity scores | | |
|--|-----------------|----|---|---------|---------|---|---------|---------|
| | | | 2 weeks | 4 weeks | 8 weeks | 2 weeks | 4 weeks | 8 weeks |
| Ayad <i>et al</i> , 2009 ⁸⁶ | Test ① | 38 | 23.12* | 36.21* | 47.34* | 1.86* | 1.09* | 0.34* |
| | Control ② | 39 | 19.90 | 29.59 | 39.00 | 2.22 | 1.54 | 0.93 |
| Docimo <i>et al</i> , 2009 ⁸⁷ | Test ① | 40 | 26.45* | 40.98* | 45.40* | 1.65* | 0.92* | 0.49* |
| | Control ② | 40 | 19.30 | 31.52 | 40.47 | 2.17 | 1.35 | 0.69 |
| Docimo <i>et al</i> , 2009 ⁸⁸ | Test ① | 40 | 25.87* | 40.75* | 45.63* | 1.59* | 0.89* | 0.45* |
| | Control ③ | 40 | 18.63 | 31.62 | 40.88 | 1.91 | 1.21 | 0.68 |

① Toothpaste containing 8.0% arginine and 1450 ppm fluoride as sodium monofluorophosphate (MFP) in a calcium carbonate base.^a

② 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.^b

③ Sensodyne Total Care Gentle Whitening toothpaste containing 2% potassium ion, as 5% potassium nitrate, and 1450 ppm fluoride, as NaF in a silica base.^b

* Statistically significant difference at $P < 0.05$ between test and control based on ANCOVA comparison of baseline-adjusted means.

protective layer of salivary glycoprotein with calcium and phosphate. Because alkaline pH favors these processes, salivary factors that maintain slightly alkaline pH *in vivo* have been suggested to favor occlusion. Investigations of the science underpinning the mechanisms of natural occlusion have resulted in the development of a new “saliva-based composition” comprising arginine, an amino acid which is positively charged at physiological pH, bicarbonate, which is a pH buffer, and calcium carbonate, which is a source of calcium. A product (ProClude^c) based upon this composition has recently been marketed in the USA for the management of tooth sensitivity during professionally administered prophylaxis treatment. Clinical studies have shown that this desensitizing prophylaxis paste is effective in providing instant sensitivity relief, when burnished onto sensitive teeth following scaling and root planing procedures, and that this sensitivity relief lasts for at least 28 days following a single treatment.⁸³ In addition, an *in vitro* study⁸³ of mechanism of action has demonstrated tubule occlusion. A recent clinical study⁸⁴ sponsored by the Colgate-Palmolive Company has confirmed that this in-office desensitizing paste provides instant sensitivity relief, when applied after professional cleaning procedures, and that the treatment effects last for at least 28 days. Another study⁸⁵ also showed that the desensitizing paste provides instant relief of dentin hypersensitivity when applied prior to dental prophylaxis.

Colgate has further developed this innovative technology by combining the key components, arginine and calcium carbonate, with fluoride to provide a significant advance in everyday treatment of dentin hypersensitivity.^{47,67} A new dentifrice containing 8.0% arginine, calcium carbonate, and 1450 ppm fluoride, as MFP, has been clinically proven to provide lasting relief of sensitivity and superior relief to the market leading desensitizing toothpaste brand. A summary of the results from three 8-week clinical studies is given in Table 2. In all three studies,⁸⁶⁻⁸⁸ the new arginine-containing toothpaste provided highly significant reductions in sensitivity from baseline after 2, 4, and 8 weeks of product use. In addition, all three studies⁸⁶⁻⁸⁸ demonstrated that the arginine-containing toothpaste provides superior relief compared to Sensodyne toothpastes containing 2% potassium ion as the active ingredient. More important to the patient suffering from sensitivity is the fact that the arginine-containing

toothpaste provides instant relief of dentin hypersensitivity when applied directly to the sensitive tooth and massaged for 1 minute. A summary of the results of three clinical studies is given in Table 3. These results show that the arginine-containing toothpaste significantly reduces sensitivity immediately following direct application and that the relief is maintained with continued twice daily brushing. The results also show that neither the desensitizing toothpaste containing 2% potassium ion nor regular fluoride toothpaste provides instant relief when directly applied in the same manner. This reproducible clinical finding is particularly intriguing because it is the first time that any desensitizing toothpaste has been clinically proven to provide significant relief of sensitivity instantly following topical direct application.⁸⁹⁻⁹¹ The fact that the arginine-containing toothpaste provides instant relief, whereas the leading desensitizing toothpaste technology (2% potassium ion, 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, including confocal laser scanning microscopy (CLSM), scanning electron microscopy (SEM) and atomic force microscopy (AFM), have provided insight into the mechanism of action of the Pro-Argin technology, confirming that the technology effectively plugs and seals dentin tubules and that the occlusion achieved is resistant to acid challenge. CLSM studies have also shown that the arginine is delivered to the inner surfaces of dentin tubules within the occluded dentin plug. Chemical mapping using energy dispersive x-ray (EDX) has shown that the material on the dentin surface and occluded within the dentin tubules primarily consists of calcium and phosphate. Electron spectroscopy for chemical analysis (ESCA) has confirmed these observations and, in addition, has identified the presence of carbonate.⁹² Hydraulic conductance has shown that the occlusion achieved with the arginine-containing toothpaste 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 7 days of pulpal pressure and after treatment with strong acid.⁹²

Kleinberg⁸³ suggested that the arginine physically adsorbs onto the surface of the calcium carbonate *in vivo*, forming a positively charged agglomerate which readily binds to the negatively charged dentin on the exposed surfaces and within

Table 3. Summary of results of clinical studies evaluating the immediate effects on dentin hypersensitivity of direct application of a new toothpaste containing 8.0% arginine, calcium carbonate and fluoride compared to desensitizing toothpaste containing 2% potassium ion, and regular fluoride toothpaste.

| Reference | Products tested | N | Baseline adjusted Mean tactile sensitivity scores | | | Baseline-adjusted Mean air blast sensitivity scores | | |
|--|-----------------|----|--|-------------|----------|--|-------------|----------|
| | | | Baseline | Immediately | 3/7 days | Baseline | Immediately | 3/7 days |
| Ayad <i>et al</i> , 2009 ⁸⁹ | Test ❶ | 41 | 11.46 | 33.17* | 33.29* | 2.90 | 1.26* | 1.17* |
| | Control 1 ❷ | 40 | 10.88 | 14.38 | 16.25 | 2.93 | 2.24 | 2.11 |
| | Control 2 ❸ | 39 | 10.90 | 13.85 | 14.10 | 2.95 | 2.50 | 2.50 |
| Nathoo <i>et al</i> , 2009 ⁹⁰ | Test ❶ | 42 | 12.38 | 35.36* | 39.17* | 2.33 | 0.92* | 0.60* |
| | Control 1 ❷ | 41 | 11.95 | 13.54 | 15.85 | 2.43 | 2.29 | 2.01 |
| | Control 2 ❸ | 42 | 12.38 | 12.62 | 13.93 | 2.23 | 2.19 | 2.06 |
| Schiff <i>et al</i> , 2009 ⁹¹ | Finger tip | 84 | 10.00 | 29.17** | 29.17** | 2.55 | 1.08** | 1.10** |
| | Cotton swab | 84 | 10.00 | 28.21** | 29.05** | 2.62 | 1.13** | 1.08** |

❶ Toothpaste containing 8.0% arginine and 1450 ppm fluoride, as MFP, in a calcium carbonate base.^a

❷ Toothpaste containing 5% potassium nitrate and 1450 ppm fluoride, as NaF, in a silica base.^a

❸ Control toothpaste containing 1450 ppm fluoride.^a

* Statistically significant difference at $P < 0.05$ between test and control 1 and between test and control 2 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.

the tubules. In addition, the pH of the arginine-calcium carbonate agglomerate is sufficiently alkaline to facilitate deposition of calcium and phosphate from saliva and/or dentin fluid. The results of the mechanism of action studies are consistent with Kleinberg's hypothesis and support that interaction of arginine and calcium carbonate *in vivo* triggers deposition of phosphate, in addition to arginine, calcium, and carbonate on the dentin surface and within the dentin tubules.⁹²

A new whitening variant of this desensitizing toothpaste, containing the Pro-Argin technology, fluoride and a high cleaning calcium carbonate abrasive system, has now been developed and validated in a series of scientific and clinical studies. This special issue reports the results of these studies. In the first paper,⁹³ the mechanism of action studies demonstrate that this new desensitizing toothpaste with gentle whitening action works by the same mechanism of action as its non-whitening counterpart, by rapidly and effectively occluding dentin tubules with material containing calcium, phosphate and carbonate that is resistant to acid challenge. The second paper⁹⁴ presents the results of a 3-day clinical study in which the new desensitizing toothpaste is proven to provide significant instant relief after applying the product by fingertip directly onto the sensitive tooth and massaging for 1 minute; the relief was maintained after 3 days of subsequent brushing. No difference in efficacy was shown between the new toothpaste and the previously tested "original" non-whitening desensitizing toothpaste containing the Pro-Argin technology, whereas a control toothpaste did not provide significant instant relief under the same conditions of use. The third paper⁹⁵ presents the results of an 8-week clinical study in which the new desensitizing toothpaste is proven to provide significant lasting relief of sensitivity after 2, 4 and 8 weeks' use. No difference in efficacy was shown between the new toothpaste and the previously tested "original" non-whitening counterpart, whereas a control toothpaste did not provide significant lasting relief. Finally, the fourth paper⁹⁶ presents the results of an 8-week clinical study in which the new desensitizing toothpaste with a whitening benefit was com-

pared to the "original" non-whitening desensitizing toothpaste for its ability to remove extrinsic stains. In comparison to the control, the results showed that the new desensitizing toothpaste with the Pro-Argin technology and a gentle whitening benefit removed significantly more stain after both 4 and 8 weeks' use.

The Pro-Argin technology offers unique opportunities to both dental professionals and their patients alike. The in-office desensitizing product is clinically proven to provide instant sensitivity relief prior to and after dental procedures, such as scaling and root planing, while two dentifrice variants, one with whitening benefits, are clinically proven to provide instant and lasting relief of dentin hypersensitivity and superior relief of hypersensitivity compared to Sensodyne toothpastes containing 2% potassium ion as the active ingredient.

- a. Colgate-Palmolive, New York, NY, USA.
- b. Glaxo SmithKline, Middlesex, UK.
- c. Ortek Therapeutics, New York, NY, USA.

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Mode of action studies on a new desensitizing dentifrice containing 8.0% arginine, a high cleaning calcium carbonate system and 1450 ppm fluoride

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ABSTRACT: Purpose: To ascertain the mode of action of a new Pro-Argin™ formula desensitizing dentifrice with a gentle whitening benefit containing 8.0% arginine, a high cleaning calcium carbonate system and sodium monofluorophosphate, utilizing a range of state-of-the-art surface techniques. **Methods:** Confocal laser scanning microscopy (CLSM) and scanning electron microscopy (SEM) were used to assess tubule occlusion. Electron spectroscopy for chemical analysis (ESCA) was used to identify the composition of the occlusive material. CLSM was also used to identify the location of the arginine within the occluded dentin tubule and to demonstrate the resistance of the occlusion to an acid challenge. **Results:** The CLSM and SEM studies demonstrated that the arginine-calcium carbonate technology in this new Pro-Argin formula sensitivity dentifrice was highly effective in occluding dentin tubules. ESCA showed that the dentin surface deposit contained high levels of calcium, phosphorous, oxygen and carbonate. CLSM also confirmed that the arginine incorporated into the dentin plug, and the dentin plug resisted an acid challenge. (*Am J Dent* 2010;23 Sp Is A:14A-19A).

CLINICAL SIGNIFICANCE: The arginine and calcium carbonate in a new Pro-Argin formula desensitizing dentifrice with a gentle whitening benefit work together to deposit a protective layer on the dentin surface for effective occlusion of dentin.

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Introduction

Dentin hypersensitivity is an acute condition that results in dental pain. This pain occurs because the dental pulp and associated nerves become exposed to the external oral environment. In a healthy condition, the dental pulp is covered by dentin which is protected by enamel above the gingiva and cementum below the gingiva. The pain commonly occurs when the surface of the root becomes exposed through gingival recession.^{1,2} Gingival recession may occur naturally with age, but it is more typically associated with over-aggressive toothbrushing or periodontal disease. Just as the enamel covers and protects the underlying dentin from external stimuli, the gingiva protects the underlying cementum and root dentin. Once the gingiva has receded, the protective cementum can readily be removed so that the dentin tubules are exposed and opened. This channel can then transmit the pain producing stimuli.

The hydrodynamic theory best explains the mechanism of dentin hypersensitivity, and this is widely accepted as how dentin hypersensitivity occurs.³⁻⁵ External stimuli such as temperature (hot or cold), evaporative, osmotic or pressure change cause dentin fluid movement. It is this fluid movement that results in short and sharp pain responses in the nerve fibers.⁶ The pain is generally transient in nature, occurring instantly after the stimulus and then quickly diminishing.⁷⁻⁹

There are two primary approaches to treating dentin hypersensitivity. The first approach involves the interference of nerve transmission. Potassium salts are commonly used in this approach.⁷⁻⁹ Potassium depolarizes the nerve fibers, which interferes with the transmission of the pain response. Most over-the-counter commercial dentifrices for relieving dentin hypersensitivity are formulated with a potassium salt.

The main disadvantage of this approach is that the relief is neither immediate nor long lasting. The reason for this is twofold. First, the potassium ions must diffuse through the dentin tubules against a positive flow of dentin fluid. Second, these ions must build up and remain at elevated concentrations in order for the nerve fibers to remain depolarized, and this build up takes time. Reductions in dentin hypersensitivity may be seen after twice daily use of the product for 2 weeks. However, to demonstrate significant dentin hypersensitivity relief compared to a regular fluoride dentifrice, it generally takes twice daily use of the product for 4 to 8 weeks. Further, if treatment is discontinued, concentrations of potassium around the nerve fibers diminish and sensitivity relief is lost.⁹

The second approach to treating dentin hypersensitivity is to occlude the open dentin tubules. In this approach, fluid within the tubule is isolated from the external stimuli so there is no fluid movement to trigger a pain response.⁷⁻⁹ There are several means of occluding dentin tubules, ranging from invasive techniques, such as laser etching the dentin surface,¹⁰ to non-invasive methods, such as application of a gel or use of a toothpaste containing an occluding agent.¹¹ Some marketed dentifrices contain occluding agents, specifically one of either strontium or stannous salts. While the published clinical data on strontium-based toothpastes are equivocal, comparative clinical data show strontium-based toothpaste to be less effective than potassium-based toothpastes.⁹ Stannous-based toothpastes have been shown to provide reductions in dentin hypersensitivity after 4 weeks of twice daily use.^{9,12,13} Both strontium and stannous salts are believed to work by precipitating insoluble metal compounds on the dentin surface to occlude or partially occlude the open dentin tubules.^{12,13} One disadvantage of the strontium chloride is fluoride incompatibility.

bility, so this strontium salt is not ideal for a daily use toothpaste. Stannous salts, on the other hand, have the disadvantages of poor taste and tooth staining.⁹

Previous publications have reported a breakthrough technology, termed Pro-Argin technology, with 8.0% arginine and calcium carbonate, which was shown to effectively occlude dentin tubules.^{9,14} Clinical studies also demonstrate that a dentifrice containing 8.0% arginine, calcium carbonate and 1450 ppm fluoride provided superior relief of dentin hypersensitivity compared to a leading dentifrice with 2% potassium ion as the active agent.^{15,16} The studies confirmed that this breakthrough technology works differently than other technologies that occlude dentin tubules in that: 1) arginine and calcium are 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.^{9,14}

This paper reviewed the mode of action with *in vitro* studies of a new Pro-Argin desensitizing dentifrice^a with a whitening benefit containing 8.0% arginine, a high cleaning calcium carbonate system and sodium monofluorophosphate, to ascertain the effectiveness of occlusion of dentin tubules. State-of-the-art surface techniques were used to assess the effectiveness of the dentifrice. Confocal laser scanning microscopy (CLSM) and scanning electron microscopy (SEM) have been used to assess tubule occlusion. Electron spectroscopy for chemical analysis (ESCA) has been used to identify the composition of the occlusive material. In addition, CLSM has also been used to identify the location of the arginine within the occluded dentin tubule and to demonstrate the resistance of the occlusion to an acid challenge.

Materials and Methods

Preparation of dentin specimens for all surface analysis experiments - Dentin slices, approximately 800 μ -thick, were cut from the crown section of human molars in a parallel manner, slightly below the enamel-dentin junction, using a water-cooled, diamond-blade saw. Typically, two to five usable specimens were obtained from each tooth. The dentin slices were then polished on one side using 600 grit wet paper and a polishing wheel to create an even and uniform surface. The specimens were further polished by using a polishing cloth (Microcloth^b), which was wetted with a 5 μ alumina slurry.

The side that was polished magnified printed text when the specimen was placed over it. Each specimen was polished for approximately 30 seconds to make each specimen shiny. The dentin slices were then examined under a microscope to confirm that the surface was uniformly polished. The polished specimens were then placed in a jar of deionized water and sonicated for 10 minutes to remove the polishing abrasive. After sonication, the specimens were rinsed with water.

The tubules were opened by etching the dentin specimens in a Petri dish with a 1% citric acid solution, using mild agitation for 20 seconds. After etching, the specimens were rinsed with deionized water, then placed in a jar of deionized water and finally sonicated once again for 10 minutes. The etched and sonicated specimens were stored in a phosphate buffer saline (PBS, pH= 7).

Selection of dentin specimens for all surface analysis experiments - CLSM was used to inspect the dentin specimens to ensure that the tubules were open and the surface was uniform and free of debris. This ensured that the specimens were of sufficient quality to be used for further experiments. The CLSM was operated in reflectance mode using the 488 nm laser line. A x50 material science dry lens was used to view the specimens with a x4 zoom.

Treatment of specimens - Dentin specimens were placed on a microscope slide with the polished side up. A piece of double-sided tape was used to hold the dentin sample to the microscope slide. The sample was wetted with PBS buffer, and then test product was applied to the dentin surface, mixed with the PBS and spread across the entire surface using gentle strokes and a camel hair brush. The samples were left undisturbed for 15 minutes at room temperature. After this, the samples were placed in a jar containing 30 ml of PBS buffer, where they remained for 15 minutes while stirring. The samples were then gently rinsed to ensure removal of any excess product from the surface. This treatment was repeated five times and done in duplicate. For dentin specimens that were used as negative controls without treatment of the test product, the exact procedure was followed with the use of the brush only. The samples were dried prior to analysis by CLSM.

Test product - The test product was a dentifrice that contained 8.0% arginine in a high cleaning calcium carbonate-base.^a The dentifrice also contained 1450 ppm fluoride as sodium monofluorophosphate.

Evaluation of dentin occlusion and analysis of the surface composition - Dentin specimens before and after treatment were examined by CLSM and SEM. Five dentin disks were prepared. Prior to treatment, the dentin disks were examined by low energy SEM, to ensure that the dentin tubules were in an open unoccluded state. Each sample served as its own baseline. The samples were then examined a second time by low voltage SEM to determine the effect of the arginine-calcium carbonate paste on dentin tubule occlusion. After evaluation of tubule occlusion by SEM, the samples were studied by ESCA to quantitatively determine the elemental composition of the surface.

The extent of dentin occlusion and resistance to acid challenge - A CLSM was used to visualize the dentin occlusion and the effect of an acid challenge. The 488 nm line from the argon laser, along with a PLO APO x50 objective, was used in the experiments. Dentin specimens were occluded as described above. CLSM was used to visualize changes in the occluded surface both from XY (top) and XZ (side) perspectives after exposure of the occluded dentin specimens to cola.^c The specimens were exposed to acidic conditions simulating consumption of an acidic beverage by immersing the specimens in 10 ml of cola in a small Petri dish with mild agitation for 1 minute. After 1 minute, the samples were rinsed with deionized water and viewed by CLSM. This procedure was repeated to examine the effects of two acid challenges.

Location of arginine in the dentin - Dye-binding experiments were conducted to determine if arginine could be detected in

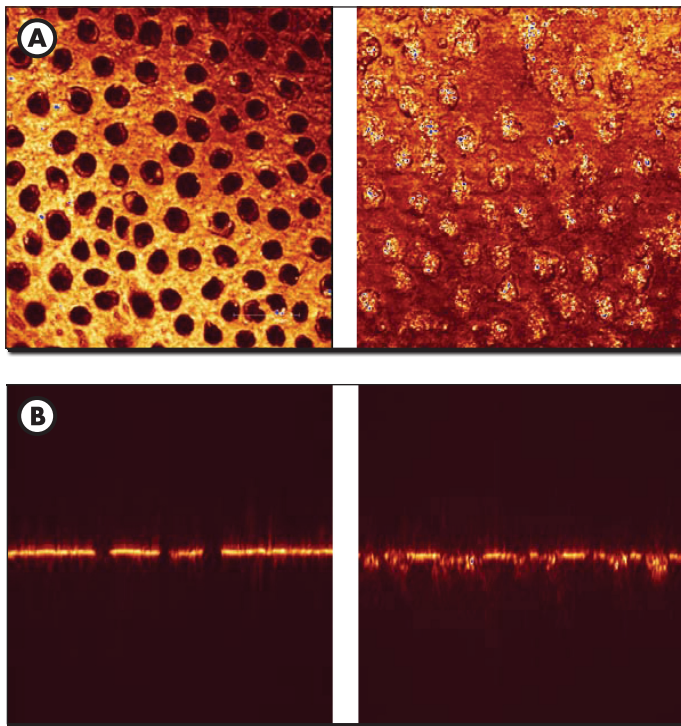


Fig. 1. Dentin specimens before (on left) and after (on right) treatment with the Pro-Argin formula. **A.** XY view. **B.** XZ view.

the dentin tubules by using 5(6) fluorescein isothiocyanate mixed isomer dye (FITC). FITC is specific for amino groups. Dentin specimens occluded by treating with the dentifrice were immersed in FITC dye and viewed by CLSM in the fluorescence and reflectance mode. An untreated dentin specimen with open tubules was used as a control.

Results

Confocal laser scanning microscopy - The CLSM images of dentin specimens before and after treatment with the dentifrice containing 8.0% arginine, a high cleaning calcium carbonate system and sodium monofluorophosphate are shown in Fig. 1. The results showed that there was complete occlusion of the dentin tubules after treatment with the dentifrice, and the tubules were no longer exposed. These results demonstrate that the arginine-calcium carbonate technology is highly effective in occluding open dentin tubules and effective when delivered in a fluoride dentifrice.

Scanning electron microscopy - SEM was used to obtain high resolution images of dentin treated with the dentifrice. The SEM images are shown in Fig. 2. The SEM analysis shows that treatment with the 8.0% arginine, a high cleaning calcium carbonate and sodium monofluorophosphate dentifrice was highly effective in occluding dentin tubules, confirming the results of the CLSM.

Confocal laser scanning microscopy and dye-binding experiments - Dentin specimens that were treated with the dentifrice were examined by CLSM in the fluorescence mode and reflectance mode. FITC dye, which is specific for amino groups, was used to stain the dentin samples. The reflectance mode was used to disclose the solid surfaces. The fluorescence mode was used to show where the dye was concentrated. The specimens were viewed in both the XY and

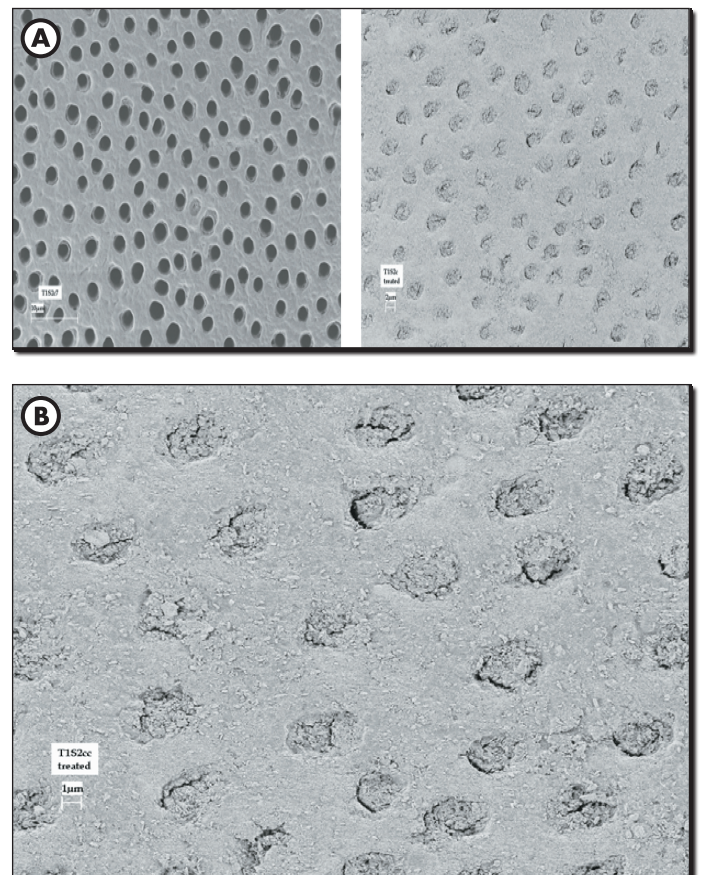


Fig. 2. Scanning electron micrographs of dentin surfaces before and after treatment. **A.** Before (on left) and after (on right) treatment with the Pro-Argin formula (x5000 magnification). **B.** After treatment view with x10000 magnification.

XZ mode. Figure 3 shows the results of the dye-binding experiments.

Both the reflectance and fluorescence mode images showed that the untreated dentin specimens contained tubules that were completely open. After treatment, the reflectance mode image in the XY orientation shows that the tubules were completely occluded. This was confirmed in the XZ view. In the fluorescence mode, the fluorescent signal from the FITC dye was intensely concentrated in the area where the tubules were present. The XZ view illustrates that the dye has indeed penetrated into the dentin tubule and is located within the solid plug. These results provide evidence that arginine directs the calcium carbonate into the open dentin tubule, where it becomes incorporated into the dentin plug.

Acid resistance of occluded tubules - In order to determine whether the dentin tubules remained plugged after exposure to an acidic beverage, dentin samples that were occluded with the dentifrice containing 8.0% arginine, a high cleaning calcium carbonate system and fluoride were exposed to cola for a total of 2 minutes to simulate the consumption of an acidic beverage. The integrity of the dentin surface and the occluded dentin tubules was examined before and after exposure to the cola by CLSM. Figure 4 shows the results of the CLSM analysis of the XY and XZ views.

The CLSM images of the occluded dentin samples show that the tubules remain occluded after a 2-minute exposure to cola. This result demonstrates that the occluding layer is resis-

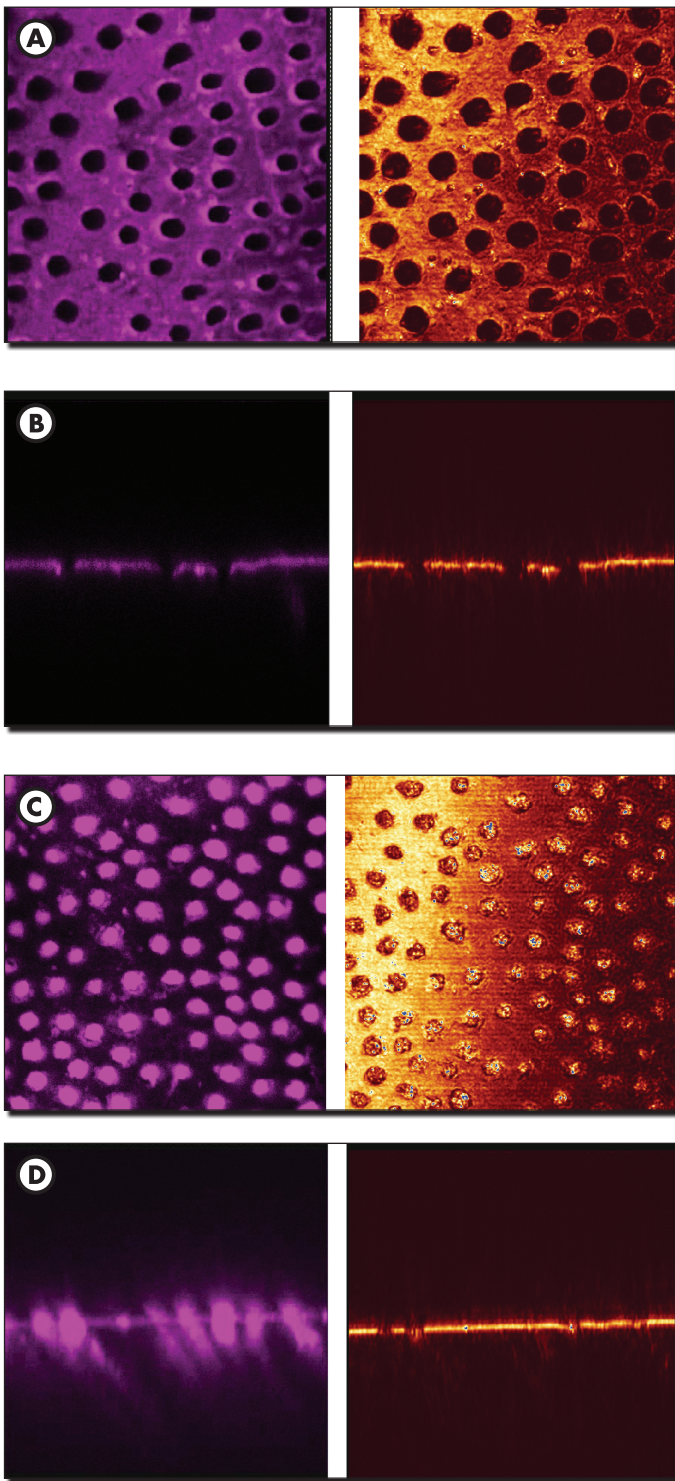


Fig. 3. Confocal microscopy images of dentin specimens before and after Pro-Argin treatment. Fluorescence mode (on left) and reflectance mode (on right) **A.** Untreated XY view. **B.** Untreated XZ view. **C.** Treated XY view. **D.** Treated XZ view.

tant to an acid challenge from a typical beverage that may be consumed following use of the product.

Chemical analysis of the dentin surface before and after treatment - ESCA was conducted on dentin samples before and after treatment with the dentifrice containing 8.0% arginine, a high cleaning calcium carbonate system and fluoride to characterize the chemical composition of the surface. The results are shown in the Table.

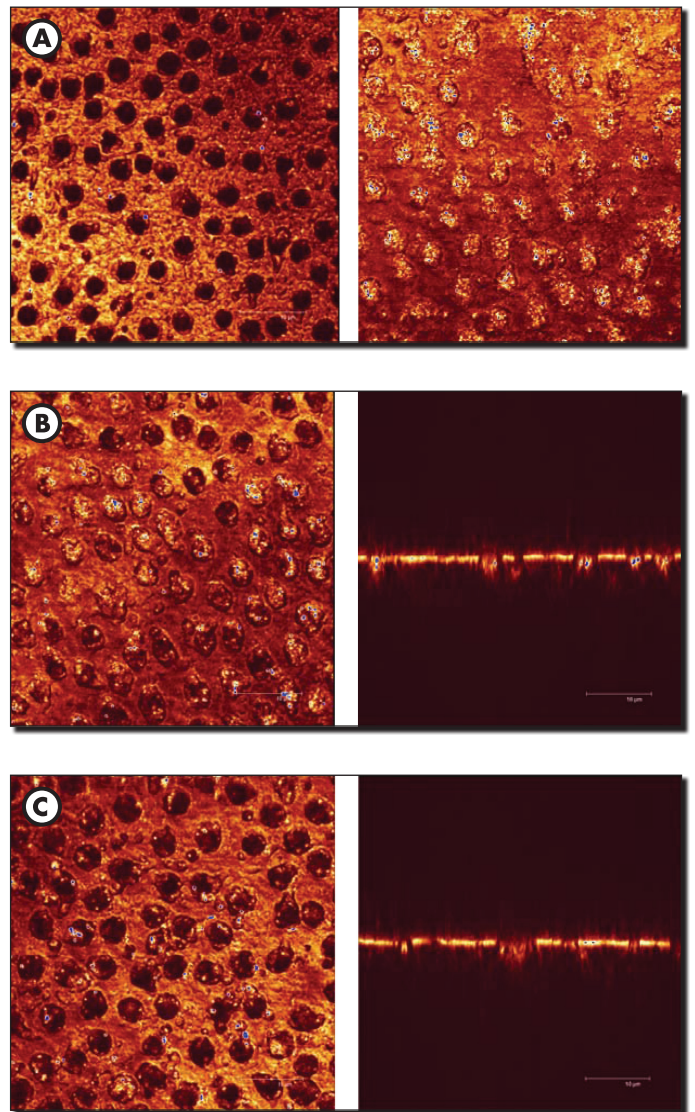


Fig. 4. Confocal microscopy images of dentin specimens. **A.** XY view before treatment (on left) and after (on right) treatment. **B.** After 1-minute exposure to cola (XY view on left and XZ view on right). **C.** After 2-minute exposure to cola (XY view on left and XZ view on right).

Table. ESCA analysis of dentin samples before and after treatment.

| | C _{Total} | CO ₃ | O | N | Atomic Percent | | | |
|-----------|--------------------|-----------------|-------|-------|----------------|------|------|------|
| | | | | | Ca | P | Na | Si |
| Dentin | | | | | | | | |
| Untreated | 54.05* | 0 | 24.73 | 18.13 | 1.67 | 1.18 | 0.04 | 0.22 |
| Treated | 37.16 | 2.80 | 42.98 | 1.20 | 9.64 | 6.98 | 1.10 | 0.63 |

*Average of duplicate samples.

The ESCA analysis of the dentin surface before treatment shows high levels of carbon, oxygen and nitrogen. The levels of calcium and phosphorus are significantly lower. This result is consistent with the fact that the dentin surface is demineralized following acid treatment to open the tubules, which would cause the collagen matrix to be exposed. No carbon in the form of carbonate was detected on the surface. Treatment with the arginine-containing dentifrice resulted in a dramatically different surface composition. Levels of carbon and nitrogen decreased, and the carbon associated with car-

bonate was detected. Calcium, oxygen, and phosphorus levels increased, which is consistent with re-mineralization of the dentin surface and occlusion of the dentin tubules by a dentin-like mineral containing calcium, phosphate and some calcium carbonate.

Discussion

State-of-the-art surface techniques and *in vitro* studies demonstrate that a new Pro-Argin desensitizing dentifrice with a whitening benefit containing 8.0% arginine, a high cleaning calcium carbonate system and sodium monofluorophosphate effectively occlude dentin tubules. These results are in complete agreement with similar studies conducted with currently marketed sensitivity products with the breakthrough Pro-Argin technology.¹⁴ Based on the mechanism of action proposed by Kleinberg¹⁷ in earlier research studies, the combination of arginine and calcium carbonate acts by forming a plug that occludes the 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 occlude the dentin tubules. The current research confirms that mode of action.

The CLSM and SEM micrographs of the dentin surface show that the Pro-Argin technology is highly effective in occluding open dentin tubules. The CLSM images also confirm the acid resistance of the dentin plug even after 2 minutes of exposure to a common acidic beverage, cola. The ESCA results of the untreated dentin specimens that were etched with acid to open and expose the dentin tubules showed high levels of carbon, oxygen and nitrogen and low levels of calcium and phosphorus. This indicated that the surface was substantially demineralized and primarily composed of the supporting collagen matrix. After treatment with the Pro-Argin formula, however, chemical analysis of the dentin surface showed that the levels of calcium and phosphorus increased dramatically with a decrease in carbon and nitrogen. Carbonate was also detected on the dentin surface after treatment. These results provide evidence that the treated surface had remineralized, and was covered by a dentin-like mineral of calcium, phosphate and some calcium carbonate, with effective occlusion of the open dentin tubules.

Dye-binding experiments using CLSM in both the fluorescence and reflectance mode using the amine-specific dye FITC provided evidence that arginine was present in the dentin tubules. In the reflectance mode, which detects reflections from the solid surfaces, the results showed that the dentin tubules were completely occluded. In the fluorescence mode, which shows where the dye is concentrated, the results showed that the fluorescence from FITC was highly concentrated within the occluded tubules. No dye was observed in the unoccluded tubules. As arginine has amine groups that bind to FITC, these results provide evidence that arginine is present in the tubules along with a solid substance. This result indicates that arginine is delivered to the dentin and helps attract and bind calcium carbonate to the dentin surface and

within dentin tubules to form a solid that occludes the open dentin tubules.

The studies and results described in this paper confirm that a new Pro-Argin desensitizing dentifrice with a whitening benefit occludes open dentin tubules in the same manner as the in-office desensitizing paste and fluoride-containing toothpaste, two currently marketed oral care products containing the Pro-Argin technology. The new dentifrice has been clinically proven to provide both significant instant and lasting dentin hypersensitivity relief^{18,19} and a whitening benefit.²⁰ As proven with the currently marketed Pro-Argin desensitizing products, the new dentifrice containing 8.0% arginine, a high cleaning calcium carbonate system and fluoride blocks the pathway to sensitivity pain by effectively occluding and sealing open dentin tubules and by depositing a dentin-like material containing calcium and phosphate on the dentin surface. The acid resistance demonstrated ensures that the relief from sensitivity is also lasting. This new Pro-Argin desensitizing dentifrice is the latest advance in dentin hypersensitivity relief that also provides an additional whitening benefit.¹⁹

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Instant dentin hypersensitivity relief of a new desensitizing dentifrice containing 8.0% arginine, a high cleaning calcium carbonate system and 1450 ppm fluoride: A 3-day clinical study in Chengdu, China

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ABSTRACT: Purpose: To compare, with a double-blind, randomized, parallel-design clinical study, the hypersensitivity efficacy of a new Pro-Argin™ formula dentifrice containing 8.0% arginine, a high cleaning calcium carbonate system and 1450 ppm fluoride to a previously validated Pro-Argin formula dentifrice containing 8.0% arginine, calcium carbonate and 1450 ppm fluoride, and to a control toothpaste containing calcium carbonate and 1450 ppm fluoride, instantly after a single direct topical self-application using a fingertip, and after subsequent brushing for 3 days. **Methods:** Qualifying subjects from the Chengdu, China area who presented two hypersensitive teeth with a tactile score of 10 to 50 grams, and an air blast score of 2 or 3, participated in this study. The first phase of the study consisted of a single topical application of the assigned product directly onto the hypersensitive surface of each of the two hypersensitive teeth. Study subjects applied a pea-size amount of their toothpaste onto the hypersensitive surface and massaged for 1 minute. The second phase of the study consisted of twice-daily at-home brushing with the toothpaste for 3 days. **Results:** All one hundred and twenty-two (122) subjects complied with the study protocol and completed the study. There was good balance among the three groups at baseline. The mean tactile sensitivity scores for the new Pro-Argin formula dentifrice, the previously validated Pro-Argin formula dentifrice, and the control dentifrice were at baseline 14.88, 14.76 and 14.38, and after direct application were 28.90, 29.02 and 15.88, and after 3 days of brushing were 34.51, 33.41 and 16.00, respectively. The mean air blast scores at baseline were 2.11, 2.12 and 2.15, and after direct application were 1.21, 1.18 and 2.06, and after 3 days of brushing were 0.80, 0.83 and 1.93, respectively. Immediately after direct application and after 3 days of brushing, for both the tactile and air blast sensitivity scores, the differences between the two dentifrices containing 8.0% arginine and the control were statistically significant. There were no statistically significant differences between the two 8.0% arginine dentifrices immediately after direct application and after 3 days of brushing. (*Am J Dent* 2010;23 Sp Is A:20A-27A).

CLINICAL SIGNIFICANCE: The two tested dentifrices containing 8.0% arginine, calcium carbonate and 1450 ppm fluoride provide significant improvements in dentin hypersensitivity relative to a control dentifrice immediately after a single topical self-application by fingertip and after 3 days of brushing following such topical self-application. The efficacy of the two dentifrices containing 8.0% arginine were not significantly different from each other.

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Introduction

Dentin hypersensitivity is defined as pain arising from exposed dentin, typically in response to external stimuli, such as thermal, tactile, osmotic or chemical, that cannot be explained by any other form of dental defect or pathology.¹ Up to 57% of patients have been reported to be affected by this potential quality of life altering condition.¹⁻⁴ As the incidence of dentin hypersensitivity is expected to rise as a result of changing diets, longer life expectancy, and longer retention of the dentition, there is a need for effective management strategies that deliver rapid action and represent realistic and practical alternatives for most sufferers of this condition.^{4,5}

Tactile, thermal and osmotic-chemical triggers of dentin hypersensitivity are frequently present during appointments with oral care professionals, as well as during the conduct of the normal activities of daily living, such as eating, drinking, rinsing, tooth brushing, and even breathing.⁶ The overall dental health impact of dentin hypersensitivity on a particular individual may ultimately correlate with the degree of discomfort experienced.⁷ In the absence of effective pain relief strategies, individuals who experience hypersensitive responses to otherwise harmless stimu-

li may understandably elect to modify specific behaviors and re-establish their oral care priorities, leading typically to poor compliance with routine oral hygiene maintenance regimens and decreased acceptance of treatment recommendations from their oral care providers. Sufferers may present inadequate levels of plaque control, putting themselves at increased risk for caries and periodontal complications.^{6,8}

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

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

Published consensus and expert opinion statements recommend the use of at-home desensitizing products as the first-line of treatment for this condition, along with management strategies to reduce etiologic and predisposing factors for dentin hypersensitivity.^{2,17} Desensitizing toothpastes for daily use are often recommended for this indication, as these represent non-invasive treatments that have been proven to provide relief for most individuals, when used over time.^{3,4,18-20} Slow onset of action and difficulty to deliver the desensitizing agent to specific hypersensitive sites have been considered disadvantages of desensitizing toothpastes.²¹ Most desensitizing toothpastes contain one of a number of potassium salts. Potassium-based toothpastes are thought to decrease the excitability of intradental nerves as a result of gradual penetration of the potassium ion into dentin tubules,^{18,22-25} although this has never been confirmed in intact human teeth.¹⁷ In clinical trials, potassium-based toothpastes have been shown to take at least 2 weeks of twice daily use to show measurable reductions in hypersensitivity and longer periods, generally 4 to 8 weeks or more, to demonstrate maximum effectiveness.^{3,4}

A recent review of biological approaches to therapy proposed that the ideal dentin hypersensitivity treatment should mimic natural desensitizing processes leading to spontaneous occlusion of open dentin tubules.²⁶ Kleinberg *et al*²⁷ developed a dentin hypersensitivity treatment consisting of 8.0% arginine, an amino acid found in saliva, bicarbonate and calcium carbonate. This desensitizing technology enhances saliva's natural process of plugging and sealing open dentin tubules. When applied to exposed dentin, open dentin tubules are sealed with a plug that reduces dentin hypersensitivity.⁴ This novel technology has been introduced as a desensitizing prophylaxis paste, with 8.0% arginine and calcium carbonate, for professional application. Results from clinical studies^{28,29} have demonstrated the efficacy of this professional product in providing instant and lasting (28 days) dentin hypersensitivity relief after a single in-office application of the product. In view of the impressive results observed with the professional product, a new desensitizing toothpaste containing 8.0% arginine, calcium carbonate and 1450 ppm fluoride, as sodium monofluorophosphate (MFP), was developed for regular, twice daily brushing. Three 8-week double blind, randomized clinical trials have demonstrated the superior clinical efficacy in reducing dentin hypersensitivity of this dentifrice relative to market-leading potassium based toothpastes when used twice daily during regular tooth brushing.³⁰⁻³²

In addition to the regular brushing studies,³⁰⁻³² direct topical

self-application studies³⁸⁻⁴⁰ were conducted to investigate if the toothpaste containing 8.0% arginine, calcium carbonate and 1450 ppm fluoride could provide instant sensitivity relief, and whether the effects were superior to those of a benchmark desensitizing toothpaste containing 2% potassium ion and 1450 ppm fluoride, and to those of a control toothpaste containing 1450 ppm fluoride alone. These clinical studies have demonstrated the superior clinical efficacy in providing instant sensitivity relief.

The objective of this double-blind, randomized clinical trial was: (1) to compare the efficacy in reducing dentin hypersensitivity of a toothpaste containing 8.0% arginine, a high cleaning calcium carbonate system and 1450 ppm fluoride, to a toothpaste containing 8.0% arginine, calcium carbonate and 1450 ppm fluoride and a control toothpaste containing calcium carbonate and 1450 ppm fluoride, instantly after a single direct topical self-application of the assigned toothpaste using a fingertip and after subsequent unsupervised brushing twice daily for 3 days; and (2) to investigate if a different form of the abrasive system, high cleaning calcium carbonate or calcium carbonate, affects the efficacy of the product with the Pro-Argin technology.

Materials and Methods

This 3-day, parallel-group, double-blind, stratified, and randomized clinical study was conducted at the State Key Laboratory of Oral Diseases, Sichuan University, Chengdu, China. One hundred and twenty-two adult subjects (44 males and 78 females with mean age of 56.28 years \pm 10.67) were enrolled in the study based upon the following criteria:

- 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.
- Subjects were required to possess a minimum of two hypersensitive teeth which were anterior to the molars and demonstrated cervical erosion/abrasion or gingival recession; and for which a tactile hypersensitivity stimuli score of 10 to 50 grams of force (Yeaple Probe) and an air blast stimuli score of 2 or 3 (Schiff Cold Air Sensitivity Scale) were presented at the baseline examination.
- Subjects were required to be available for the 3-day duration of the study, and to sign an informed consent form.
- 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.
- Subjects were also excluded from the study if they were current users of anticonvulsants, antihistamines, antidepressants, sedatives, tranquilizers, anti-inflammatory drugs or daily analgesics.
- Pregnant or lactating women, individuals who were participating in any other clinical study or who had participated in a desensitizing study or who used any desensitizing agents within the previous 3 months, were not allowed to participate in the study.

Qualifying subjects reported to the clinical facility having refrained from all oral hygiene procedures and from chewing gum for 8 hours, and from eating and drinking for 4 hours prior to the baseline examinations. Two hypersensitive teeth per study subject that satisfied the tactile and air blast sensitivity enrollment criteria were identified for evaluation throughout the study. Subjects were stratified according to mean baseline tactile and air blast hypersensitivity scores and were randomly assigned within strata to one of the following study treatments: Group 1 - test toothpaste with 8.0% arginine, a high cleaning calcium carbonate system and 1450 ppm fluoride as MFP (Pro-Argin Formula Desensitizing Toothpaste with Whitening^a), Group 2 - positive control toothpaste with 8.0% arginine, calcium carbonate and 1450 ppm fluoride as MFP (Pro-Argin Formula Desensitizing Toothpaste^a) and Group 3 - negative control toothpaste with calcium carbonate and 1450 ppm fluoride as MFP^a (Control). All three toothpastes were provided in white over-wrapped tubes to ensure the double-blind design.

The first phase of the study consisted of applying the assigned toothpaste with a fingertip directly onto the buccal-cervical area of exposed dentin on each of the two baseline-designated hypersensitive teeth per subject. During a supervised session at the clinic site, subjects self-applied a pea-size amount (approximately 0.3 grams) of their assigned product directly onto the hypersensitive surface of the study teeth and massaged each tooth for 1 minute. For the second phase of the study, subjects took their assigned product home and were provided with a soft-bristled toothbrush for unsupervised tooth brushing for a total of 3 days. At-home brushing instructions to study subjects consisted of brushing their teeth for 1 minute, twice daily, using only the toothpaste and toothbrush provided, and to refrain from any other oral hygiene procedures throughout the duration of the study. There were no 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 immediately after fingertip topical application of the assigned product and after 3 days of product use. Subjects were requested to return to the clinical facility for the 3-day follow-up visit, having refrained from all oral hygiene procedures and chewing gum for 8 hours and from eating and drinking for 4 hours prior to their scheduled visit. All examinations were performed by the same dental examiner, using the same procedures as employed at baseline.

Tactile hypersensitivity assessment^{33,34} - Hypersensitivity assessment in response to tactile stimuli was done using an Electronic Force Sensing Probe (Yeaple Probe Model 200A^b) that was calibrated daily by the study examiner. Scores were recorded in terms of a quantified, reproducible force (grams) applied by use of an attached #19 explorer tip. After presetting the probe to 10 grams, the probe tip was stroked over the exposed dentin perpendicular to the examined surface of the hypersensitive teeth. Subsequent passes were made, each time with the applied force increased by 10 grams, until the subject indicated that he/she was experiencing discomfort, or until the maximum force of 50 grams had been reached. A force of 50 grams was considered the cutoff point as the higher scores on this index correspond to lower levels of dentin hypersensitivity.

Table 1. Summary of age & gender for subjects who completed the clinical study.

| Toothpaste treatment | Number of subjects | | | Age | |
|----------------------------|--------------------|--------|-------|------|-------|
| | Male | Female | Total | Mean | Range |
| Pro-Argin with Whitening ① | 14 | 27 | 41 | 57.5 | 38-70 |
| Pro-Argin ② | 14 | 27 | 41 | 56.4 | 25-70 |
| Control ③ | 16 | 24 | 40 | 54.9 | 23-70 |

① Toothpaste containing 8.0% arginine, a high cleaning calcium carbonate system and 1450 ppm fluoride as MFP.

② Toothpaste containing 8.0% arginine, calcium carbonate and 1450 ppm fluoride as MFP.

③ Control toothpaste with calcium carbonate and 1450 ppm fluoride as MFP.

Table 2. Summary of the baseline tactile hypersensitivity and air blast hypersensitivity scores, for subjects who completed the 3-day clinical study.

| Parameter | Toothpaste treatment | n | Baseline summary (Mean ± S.D.)* |
|----------------------------|----------------------------|----|---------------------------------|
| Tactile hypersensitivity | Pro-Argin with whitening ① | 41 | 14.88 ± 5.97 |
| | Pro-Argin ② | 41 | 14.76 ± 6. |
| | Control ③ | 40 | 14.38 ± 4.56 |
| Air blast hypersensitivity | Pro-Argin with whitening ① | 41 | 2.11 ± 0.31 |
| | Pro-Argin ② | 41 | 2.12 ± 0.31 |
| | Control ③ | 40 | 2.15 ± 0.32 |

① Toothpaste containing 8.0% arginine, a high cleaning calcium carbonate and 1450 ppm fluoride as MFP.

② Toothpaste containing 8.0% arginine, calcium carbonate and 1450 ppm fluoride as MFP.

③ Control toothpaste with calcium carbonate and 1450 ppm fluoride as MFP.

* No statistically significant difference was indicated between the three treatment groups at baseline with respect to either tactile hypersensitivity or air blast hypersensitivity scores.

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 1 second from a distance of approximately 1 cm.
- 3) The Schiff Cold Air Sensitivity Scale³⁵ was used to assess subject response to this stimulus. This scale is scored as follows:

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

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

Statistical methods - Statistical analyses were performed separately for the tactile hypersensitivity assessments and air blast hypersensitivity assessments. Comparisons of the treat-

Table 3. Summary of the immediate after topical application mean tactile hypersensitivity scores for subjects who completed the 3-day clinical study.

| Treatment | n | Immediate after topical application summary (Mean ± S.D.) | Within-treatment analysis | | Between-treatment comparison | | | |
|--|----|---|-----------------------------|---------------------------|---------------------------------|---------------------------|---------------------------------|---------------------------|
| | | | Percent change ^④ | Significance ^⑤ | vs. Pro-Argin Toothpaste | | vs. Control Toothpaste | |
| | | | | | Percent Difference ^⑥ | Significance ^⑧ | Percent Difference ^⑦ | Significance ^⑨ |
| Pro-Argin Toothpaste with whitening ^① | 41 | 28.90 ± 14.12 | 94.2% | P< 0.05 | -0.4% | NS | 82.0% | P< 0.05 |
| Pro-Argin Toothpaste ^② | 41 | 29.02 ± 14.28 | 96.6% | P< 0.05 | ---- | ---- | 82.7% | P< 0.05 |
| Control Toothpaste ^③ | 40 | 15.88 ± 5.30 | 10.4% | P< 0.05 | ---- | ---- | ---- | ---- |

- ① Toothpaste containing 8.0% arginine, a high cleaning calcium carbonate system and 1450 ppm fluoride as MFP.
- ② Toothpaste containing 8.0% arginine, calcium carbonate and 1450 ppm fluoride as MFP.
- ③ Control toothpaste containing calcium carbonate and 1450 ppm fluoride as MFP.
- ④ Percent change exhibited immediately after topical application relative to the baseline mean. A positive value indicates an improvement in mean tactile hypersensitivity at the immediately after topical application examination.
- ⑤ Significance of paired *t*-test comparing the baseline and the immediate after topical application examinations.
- ⑥ Difference between the immediate after topical application means expressed as a percentage of the immediate after topical application mean for the Pro-Argin Toothpaste. A positive value indicates an improvement in mean tactile hypersensitivity scores relative to the Pro-Argin Toothpaste.
- ⑦ Difference between the immediate after topical application means expressed as a percentage of the immediate after topical application mean for the control toothpaste. A positive value indicates an improvement in mean tactile hypersensitivity scores relative to the control toothpaste.
- ⑧ Significance of ANCOVA comparison of baseline-adjusted means.

Table 4. Summary of the immediate after topical application mean air blast hypersensitivity scores for subjects who completed the 3-day clinical study.

| Treatment | n | Immediate after topical application summary (Mean ± S.D.) | Within-treatment analysis | | Between-treatment comparison | | | |
|--|----|---|-----------------------------|---------------------------|---------------------------------|---------------------------|---------------------------------|---------------------------|
| | | | Percent change ^④ | Significance ^⑤ | vs. Pro-Argin Toothpaste | | vs. Control Toothpaste | |
| | | | | | Percent difference ^⑥ | Significance ^⑧ | Percent difference ^⑦ | Significance ^⑨ |
| Pro-Argin Toothpaste with whitening ^① | 41 | 1.21 ± 0.40 | 42.7% | P< 0.05 | -2.5% | NS | 41.3% | P< 0.05 |
| Pro-Argin Toothpaste ^② | 41 | 1.18 ± 0.52 | 44.3% | P< 0.05 | ---- | ---- | 42.7% | P< 0.05 |
| Control Toothpaste ^③ | 40 | 2.06 ± 0.43 | 4.2% | NS | ---- | ---- | ---- | ---- |

- ① Toothpaste containing 8.0% arginine, a high cleaning calcium carbonate system and 1450 ppm fluoride as MFP.
- ② Toothpaste containing 8.0% arginine, calcium carbonate and 1450 ppm fluoride as MFP.
- ③ Control toothpaste with calcium carbonate and 1450 ppm fluoride as MFP.
- ④ Percent change exhibited immediately after topical application relative to the baseline mean. A positive value indicates a reduction in mean air blast hypersensitivity at the immediately after topical application examination.
- ⑤ Significance of paired *t*-test comparing the baseline and the immediate after topical application examinations.
- ⑥ Difference between the immediate after topical application means expressed as a percentage of the immediate after topical application mean for the Pro-Argin Toothpaste. A positive value indicates a reduction in mean air blast hypersensitivity scores relative to the Pro-Argin Toothpaste.
- ⑦ Difference between the immediate after topical application means expressed as a percentage of the immediate after topical application mean for the control toothpaste. A positive value indicates a reduction in mean air blast hypersensitivity scores relative to the control toothpaste.
- ⑧ Significance of ANCOVA comparison of baseline-adjusted means.

ment groups with respect to baseline tactile scores and air blast scores were performed using analysis of variance (ANOVA). Within-treatment comparisons of the baseline *versus* follow-up tactile hypersensitivity and air blast hypersensitivity scores were performed using paired *t*-tests. Comparisons of the treatment groups with respect to baseline-adjusted mean tactile hypersensitivity and air blast hypersensitivity scores at the follow-up examinations were performed using analyses of covariance (ANCOVA). All statistical tests of hypotheses were two-sided, and employed a level of significance of $\alpha=0.05$.

Results

One hundred and twenty-two subjects complied with the protocol, and completed the 3-day clinical study. A summary of the gender and age of the study population is presented in Table 1. The treatment groups did not differ significantly with respect to either of these characteristics. Throughout the study, there

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

Baseline data

Table 2 presents a summary of the mean tactile and air blast scores measured at the baseline examination. For tactile-induced hypersensitivity, the mean baseline scores were 14.88 for the Pro-Argin Formula Desensitizing Toothpaste with Whitening group, 14.76 for the Pro-Argin Formula Desensitizing Toothpaste group and 14.38 for the Control group. For air blast-induced hypersensitivity, the mean baseline scores were 2.11 for the Pro-Argin Formula Desensitizing Toothpaste with Whitening group, 2.12 for the Pro-Argin Formula Desensitizing Toothpaste group and 2.15 for the Control group. No statistically significant differences were indicated between the treatment groups with respect to either baseline mean hypersensitivity score.

Table 5. Summary of the 3-day mean tactile hypersensitivity scores for subjects who completed the 3-day clinical study.

| Treatment | n | 3-day summary (Mean ± S.D.) | Within-treatment analysis | | Between-treatment comparison vs. Pro-Argin Toothpaste | | | |
|---|----|-----------------------------------|--------------------------------|---------------------------|---|---------------------------|------------------------------------|---------------------------|
| | | | Percent change ^④ | Significance ^⑤ | Percent difference ^⑥ | Significance ^⑥ | Percent difference ^⑦ | Significance ^⑧ |
| Pro-Argin Toothpaste with whitening ^① | 41 | 34.51 ± 13.41 | 131.9% | P< 0.05 | 3.3% | NS | 115.7% | P< 0.05 |
| Pro-Argin Toothpaste ^② | 41 | 33.41 ± 13.06 | 126.4% | P< 0.05 | ----- | ----- | 108.8% | P< 0.05 |
| Control Toothpaste ^③ | 40 | 16.00 ± 5.91 | 11.3% | P< 0.05 | ----- | ----- | ----- | ----- |

^① Toothpaste containing 8.0% arginine, high cleaning calcium carbonate and 1450 ppm fluoride as MFP.

^② Toothpaste containing 8.0% arginine, calcium carbonate and 1450 ppm fluoride as MFP.

^③ Control toothpaste with calcium carbonate and 1450 ppm fluoride as MFP.

^④ Percent change exhibited by the 3-day mean relative to the baseline mean. A positive value indicates an improvement in mean tactile hypersensitivity at the 3-day examination.

^⑤ Significance of paired *t*-test comparing the baseline and 3-day examinations.

^⑥ Difference between 3-day means expressed as a percentage of the 3-day mean for the Pro-Argin Toothpaste. A positive value indicates an improvement in mean tactile hypersensitivity scores relative to the Pro-Argin Toothpaste.

^⑦ Difference between 3-day means expressed as a percentage of the 3-day mean for the control toothpaste. A positive value indicates an improvement in mean tactile hypersensitivity score relative to the control toothpaste.

^⑧ Significance of ANCOVA comparison of baseline-adjusted means.

Immediate after topical application data

Tactile hypersensitivity - Table 3 presents a summary of the mean tactile hypersensitivity scores measured immediately after fingertip topical self-application of the assigned product. The mean tactile hypersensitivity scores recorded immediately after topical product application were 28.90 for the Pro-Argin Formula Desensitizing Toothpaste with Whitening group, 29.02 for the Pro-Argin Formula Desensitizing Toothpaste group and 15.88 for the Control group. The percent changes from baseline were 94.2% for the Pro-Argin Formula Desensitizing Toothpaste with Whitening group, 96.6% for the Pro-Argin Formula Desensitizing Toothpaste group and 10.4% for the Control group, all of which were statistically significant.

Relative to the Control groups, the Pro-Argin Formula Desensitizing Toothpaste with Whitening and Pro-Argin Formula Desensitizing Toothpaste groups exhibited statistically significant improvements in mean tactile hypersensitivity scores immediately after topical product application (82.0% and 82.7%, respectively). Relative to the Pro-Argin Formula Desensitizing Toothpaste group, the Pro-Argin Formula Desensitizing Toothpaste with Whitening group did not exhibit a statistically significant difference in mean tactile hypersensitivity scores immediately after topical application of the product (0.4%).

Air blast hypersensitivity - Table 4 presents a summary of the mean air blast hypersensitivity scores measured immediately after fingertip topical self-application of the assigned product. The mean air blast hypersensitivity scores recorded immediately after topical application of the product were 1.21 for the Pro-Argin Formula Desensitizing Toothpaste with Whitening group, 1.18 for the Pro-Argin Formula Desensitizing Toothpaste group and 2.06 for the Control group. The mean percent reductions from baseline were 42.7% for the Pro-Argin Formula Desensitizing Toothpaste with Whitening group, 44.3% for the Pro-Argin Formula Desensitizing Toothpaste group and 4.2% for the Control group; the reductions for both Pro-Argin formula groups were statistically significant.

Relative to the Control groups, the Pro-Argin Formula Desensitizing Toothpaste with Whitening and Pro-Argin

Formula Desensitizing Toothpaste groups exhibited statistically significant improvements in mean air blast hypersensitivity scores immediately after topical product application (41.3% and 42.7%, respectively). Relative to the Pro-Argin Formula Desensitizing Toothpaste group, the Pro-Argin Formula Desensitizing Toothpaste with Whitening group did not exhibit a statistically significant difference in mean air blast hypersensitivity scores immediately after topical application of the product (2.5%).

Three-day data

Tactile hypersensitivity - Table 5 presents a summary of the mean tactile hypersensitivity scores measured after 3 days of at-home brushing with the assigned product, subsequent to the single fingertip topical self-application performed at the beginning of the study. The mean 3-day tactile hypersensitivity scores were 34.51 for the Pro-Argin Formula Desensitizing Toothpaste with Whitening group, 33.41 for the Pro-Argin Formula Desensitizing Toothpaste group and 16.00 for the Control group. The percent changes from baseline were 131.9% for the Pro-Argin Formula Desensitizing Toothpaste with Whitening group, 126.4% for the Pro-Argin Formula Desensitizing Toothpaste group and 11.3% for the Control group, all of which were statistically significant.

Relative to the Control groups, the Pro-Argin Formula Desensitizing Toothpaste with Whitening and Pro-Argin Formula Desensitizing Toothpaste groups exhibited statistically significant improvements in mean tactile hypersensitivity scores after 3 days of product use (115.7% and 108.8%, respectively). Relative to the Pro-Argin Formula Desensitizing Toothpaste group, the Pro-Argin Formula Desensitizing Toothpaste with Whitening group did not exhibit a statistically significant difference in mean tactile hypersensitivity scores after 3 days of product use (3.3%).

Air blast hypersensitivity - Table 6 presents a summary of the mean air blast hypersensitivity scores measured after 3 days of at-home brushing with the assigned product, subsequent to the single fingertip topical self-application performed at the beginning of the study. The mean 3-day air blast hypersen-

Table 6. Summary of the 3-day air blast hypersensitivity scores for subjects who completed the 3-day clinical study.

| Treatment | n | 3-day summary (Mean \pm S.D.) | Within-treatment analysis | | Between-treatment comparison vs. Pro-Argin Toothpaste | | | |
|---|----|---------------------------------------|--------------------------------|---------------------------|---|---------------------------|------------------------------------|---------------------------|
| | | | Percent change ^④ | Significance ^⑤ | Percent difference ^⑥ | Significance ^⑥ | Percent difference ^⑦ | Significance ^⑧ |
| Pro-Argin Toothpaste with whitening ^① | 41 | 0.80 \pm 0.40 | 62.1% | P< 0.05 | 3.6% | NS | 58.5% | P< 0.05 |
| Pro-Argin Toothpaste ^② | 41 | 0.83 \pm 0.44 | 60.8% | P< 0.05 | ----- | ----- | 57.0% | P< 0.05 |
| Control Toothpaste ^③ | 40 | 1.93 \pm 0.42 | 10.2% | P< 0.05 | ----- | ----- | ----- | ----- |

^① Toothpaste containing 8.0% arginine, a high cleaning calcium carbonate system and 1450 ppm fluoride as MFP.

^② Toothpaste containing 8.0% arginine, calcium carbonate and 1450 ppm fluoride as MFP.

^③ Control toothpaste with calcium carbonate and 1450 ppm fluoride as MFP.

^④ Percent change exhibited by the 3-day mean relative to the baseline mean. A positive value indicates a reduction in mean air blast hypersensitivity at the 3-day examination.

^⑤ Significance of paired *t*-test comparing the baseline and 3-day examinations.

^⑥ Difference between 3-day means expressed as a percentage of the 3-day mean for the Pro-Argin Toothpaste. A positive value indicates a reduction in mean air blast hypersensitivity scores relative to the Pro-Argin Toothpaste.

^⑦ Difference between 3-day means expressed as a percentage of the three day mean for the control toothpaste. A positive value indicates a reduction in mean air blast hypersensitivity scores relative to the control toothpaste.

^⑧ Significance of ANCOVA comparison of baseline-adjusted means.

sitivity scores were 0.80 for the Pro-Argin Formula Desensitizing Toothpaste with Whitening group, 0.83 for the Pro-Argin Formula Desensitizing Toothpaste group and 1.93 for the Control group. The mean percent reductions from baseline were 62.1% for the Pro-Argin Formula Desensitizing Toothpaste with Whitening group, 60.8% for the Pro-Argin Formula Desensitizing Toothpaste group and 10.2% for the Control group, all of which were statistically significant.

Relative to the Control groups, the Pro-Argin Formula Desensitizing Toothpaste with Whitening and Pro-Argin Formula Desensitizing Toothpaste groups exhibited statistically significant improvements in mean air blast hypersensitivity scores after 3 days of product use (58.5% and 57.0%, respectively). Relative to the Pro-Argin Formula Desensitizing Toothpaste group, the Pro-Argin Formula Desensitizing Toothpaste with Whitening group did not exhibit a statistically significant difference in mean air blast hypersensitivity scores after 3 days of product use (3.6%).

Discussion

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

occlusion blocks fluid movement to inhibit the hydrodynamic mechanism.^{4,36}

Demands for the management of dentin hypersensitivity are expected to increase as the adult population lives longer and retains their teeth later in life, and as populations of all age groups engage in lifestyles and behaviors that promote dentin exposure through gingival recession or erosion of protective tooth surfaces. At-home use of desensitizing products has been considered a realistic and practical means of treating most patients.³⁷ Given that they are widely available, cost effective, non-invasive and simple to use, desensitizing toothpastes are, consequently, recommended as the first line of treatment for the control of dentin hypersensitivity. Among the reported disadvantages of desensitizing toothpastes are that they have a relatively slow onset of action and that they do not directly deliver their desensitizing agents to specific hypersensitive sites.²⁰ The tested regimen of use for the desensitizing toothpaste containing 8.0% arginine, calcium carbonate and 1450 ppm fluoride offers the prospect of a desensitizing treatment alternative that can be used daily and provides significant instant hypersensitivity relief following fingertip application of the product directly onto the hypersensitive area of teeth.

An adult population with history of dentin hypersensitivity was enrolled for participation in this study. Before product application, hypersensitivity symptoms were successfully stimulated in all the teeth included in the trial and tactile and air blast scores were recorded as baseline hypersensitivity values. Dentin hypersensitivity was re-evaluated immediately after topical paste application and after 3 days of twice daily brushing with the product. The clinical results of this study confirm the results from similar other two independent studies^{38,40} previously conducted in New Jersey, USA and Mississauga, Canada.

It could, perhaps, be speculated that the dramatic dentin hypersensitivity relief observed after massaging the Pro-Argin formula desensitizing toothpaste directly onto hypersensitive dentin results, at least in part, from the massaging process itself. The results for the control group, however, clearly show that

massaging with toothpaste per se provides only minor relief. The results of this study, which demonstrate that both Pro-Argin formula desensitizing toothpastes, with either high cleaning calcium carbonate or calcium carbonate, provide instant sensitivity relief when applied directly to hypersensitive teeth, are consistent with the findings of the *in vitro* mechanism of action studies that show effective deposition of a calcium-rich dentin plug and complete occlusion of open dentin tubules.³⁶ Subsequent twice daily brushing with either Pro-Argin formula desensitizing toothpaste helps maintain the instant plugging effect achieved by direct application.

The results of this double-blind clinical study support the conclusions that: (1) a single fingertip topical self-application of a toothpaste containing 8.0% arginine, a high cleaning calcium carbonate system and 1450 ppm fluoride, or a toothpaste containing 8.0% arginine, calcium carbonate and 1450 ppm fluoride, directly onto the hypersensitive surface of teeth, provides significant instant improvements in dentin hypersensitivity relative to identical application of a control toothpaste with 1450 ppm fluoride; (2) 3 days of brushing with both 8.0% arginine toothpastes, subsequent to the single topical self-application of the product, provides significant improvements in dentin hypersensitivity relative to identical application of the control toothpaste; (3) the instant sensitivity relief benefit afforded by direct topical self-application of both Pro-Argin formula desensitizing toothpastes is maintained by subsequent regular twice daily brushing for, at least, a period of 3 days; and (4) there is no statistically significant difference between the two Pro-Argin formula toothpastes in providing instant and 3-day sensitive relief, indicating that the exchange of a high cleaning calcium carbonate system for calcium carbonate does not affect product efficacy.

- a. Colgate-Palmolive, New York, NY, USA.
- b. Xinix Research Inc., Portsmouth, NH, USA.

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Dentin hypersensitivity reduction of a new toothpaste containing 8.0% arginine and 1450 ppm fluoride: An 8-week clinical study on Chinese adults

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ABSTRACT: Purpose: To present the results of an 8-week dentin hypersensitivity clinical study in which the efficacy of a new Pro-Argin formula toothpaste, with gentle whitening benefits, containing 8.0% arginine, a high cleaning calcium carbonate system, and 1450 ppm fluoride as sodium monofluorophosphate (MFP) was compared to that of a commercial Pro-Argin™ formula toothpaste containing 8.0% arginine, calcium carbonate, and 1450 ppm fluoride as MFP and a negative control toothpaste containing calcium carbonate and 1450 ppm fluoride as MFP. **Methods:** An 8-week clinical study, with 121 subjects, was conducted in Chengdu, Sichuan, China, using a double-blind, stratified, three-treatment design. Tactile and air blast sensitivity assessments were used to compare the efficacy of the three products. **Results:** This clinical study demonstrated that the new Pro-Argin formula toothpaste provided a significant reduction in dentin hypersensitivity when used over a period of 8 weeks. The study also showed that the new toothpaste provided significantly greater reductions ($P < 0.05$) in dentin hypersensitivity in response to tactile (64.4%, 71.1%, and 61.0%) and air blast (40.7%, 58.8.0%, and 74.4%) stimuli than the negative control toothpaste containing 1450 ppm fluoride after 2, 4, and 8 weeks of product use, respectively. The results for the new toothpaste did not differ significantly from those of the positive control toothpaste at all time points in the study. (*Am J Dent* 2010;23 Sp Is A:28A-35A).

CLINICAL SIGNIFICANCE: A new Pro-Argin formula toothpaste with whitening benefits, containing 8.0% arginine, a high cleaning calcium carbonate system, and 1450 ppm fluoride, provides significantly greater dentin hypersensitivity relief ($P < 0.05$) compared to a negative control toothpaste after 2, 4, and 8 weeks of product use. It provides hypersensitivity relief that is not statistically significantly different than the positive control Pro-Argin formula toothpaste after 2, 4, and 8 weeks of product use.

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Introduction

Dentin hypersensitivity is commonly characterized by a sharp pain of short duration, which arises from exposed dentin in response to an external stimulus. The cause of the pain cannot be associated with any other type of dental problem. The pain trigger is usually a thermal (cold temperature), tactile (toothbrush or dental instrument), osmotic (sweet), or dehydrating (air blast) stimulus.¹ Dentin hypersensitivity is typically experienced when the root of the tooth has been exposed to the oral environment as a result of gingival recession. Gingival recession may occur naturally, although it may be compounded by poor oral hygiene habits, such as overzealous and/or improper tooth brushing, or it may result from surgical or non-surgical periodontal treatment. Dentin hypersensitivity occurs more frequently in the cervical area of the roots, where the cementum is very thin. As people live longer, healthier lives and maintain their dentitions, there will be an increased demand on dental professionals to manage the sensitivity of cervically exposed dentin, as well as any secondary issues that may arise from the discomfort associated with dentin hypersensitivity. Unfortunately, for many patients who suffer from dentin hypersensitivity, tooth brushing may be more difficult and can result in persistent and continued accumulation of dental plaque. This increase in dental plaque may lead to an increased incidence of caries, gingivitis, and more serious periodontal problems.²

Several theories have been proposed to explain the mechanism of dentin hypersensitivity, including the odonto-

blast transducer theory, the dentin receptor theory, and the hydrodynamic theory.^{3,4} Scientific evidence supports the hydrodynamic theory (modified by Brännström⁵ in 1963), which assumes that fluid movement within the dentin tubules is the basis for the transmission of painful sensations. Non-noxious stimuli at the tooth surface cause fluid movement within the dentin tubules, affecting the pulpal mechanoreceptors and resulting in the sensation of pain.

In order to address this problem, and provide patients with improved oral comfort and quality of life, a number of agents have been proposed to help control dentin hypersensitivity and relieve discomfort. These products range from those that can be used by the patient at home to others that must be applied in the dental office by a dental professional. One approach by which this can be achieved is to reduce the diameter of open dentin tubules in order to limit the displacement of fluids within them (decreased hydrodynamic flow), thereby, blocking neurotransmission and decreasing the response to painful stimuli. According to Trowbridge & Silver,⁶ this could be achieved by forming a smear layer on the exposed dentin, using topical agents that form insoluble precipitates within the tubules, or by blocking the entrance to tubules with plastic resins. This approach has been most extensively applied in professionally administered products.

The most common products used by patients to relieve pain from dentin hypersensitivity are desensitizing dentifrices; specifically, toothpastes containing potassium salts. Potassium salts (*i.e.*, potassium nitrate, potassium citrate, and potassium chloride) have been used extensively as desensi-

tizing agents, based upon a second approach to relief of discomfort. In effect, the potassium ion is believed to have a depolarizing effect on electrical nerve conduction, causing nerve fibers to be less excitable to the stimuli,⁷ thereby reducing the patient's sensation of pain.

Arginine, an essential amino acid, has been identified as an ingredient with potential oral health benefits. Kleinberg⁸ demonstrated in an early work that a combination of arginine bicarbonate and calcium carbonate can be deposited on exposed dentin surfaces to physically block and seal open dentin tubules. More recently, the Colgate-Palmolive Company has evaluated a novel toothpaste with Pro-Argin^a technology, comprising arginine and calcium carbonate, and 1450 ppm fluoride as sodium monofluorophosphate (MFP). Clinical studies have demonstrated that this toothpaste is highly effective in reducing dentin hypersensitivity, and *in vitro* mechanism of action studies have shown that this novel technology works by occluding dentin tubules.⁹⁻¹²

This 8-week clinical trial compared the efficacy in reducing dentin hypersensitivity of a new Pro-Argin formula toothpaste^a containing 8.0% arginine and 1450 ppm fluoride as MFP, and a high cleaning calcium carbonate system for gentle whitening benefits to a commercial Pro-Argin formula toothpaste^a containing 8.0% arginine and 1450 ppm fluoride as MFP in a calcium carbonate base and a negative control toothpaste containing calcium carbonate and 1450 ppm fluoride, as MFP^a over an 8-week period.

Materials and Methods

This 8-week, single-center, parallel-group, double-blind, stratified, and randomized clinical study was conducted at the Key State Laboratory of Oral Diseases, Chengdu, Sichuan, China. Subjects were recruited from the patient population of the college. One hundred twenty-one subjects (44 males, 77 females with a mean age of 56.5 ± 10.0 years) were selected based on the following criteria:

- Subjects had to be between 18 and 70 years of age, in generally good health, with no history of allergies or idiosyncrasies to dentifrice ingredients.
- 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 10-50 grams of force (Yeaple probe^b) and an air blast stimulus score of 2 or 3 (Schiff Cold Air Sensitivity Scale) were presented at the baseline examination.
- Subjects needed to be available for the duration of the study, and to sign an informed consent form.
- Subjects were excluded from the study if they had gross oral pathology, chronic disease, advanced periodontal disease, treatment for periodontal disease (within the last 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.
- Subjects that had orthodontic appliances were excluded from the study.

- Subjects were excluded from the study if they began taking anticonvulsants, antihistamines, antidepressants, sedatives, tranquilizers, anti-inflammatory drugs or daily analgesics within 1 month prior to the start of the study or if they started taking them during the course of the study.

- Pregnant or lactating women, individuals who were participating in any other clinical study or who had participated in a desensitizing dentifrice study or who used a desensitizing dentifrice within the last 3 months, were not allowed to participate in the study.

- 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 4 hours, were also excluded from the study.

Prospective study subjects reported to the clinical facility having refrained from all oral hygiene procedures and chewing gum for 8 hours, and having refrained from eating and drinking for 4 hours prior to their examination. All prospective subjects who met the inclusion/exclusion criteria and signed an informed consent form received a baseline tactile hypersensitivity and an air blast 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 list was followed to determine what toothpaste was assigned to each study subject. Such randomized assignment resulted in study groups that were balanced on the basis of mean tactile and air blast dentin hypersensitivity baseline scores:

Test toothpaste 1 – New sensitive toothpaste (Pro-Argin^a) containing 8.0% arginine and 1450 ppm fluoride, as MFP, with a high cleaning calcium carbonate system for gentle whitening.

Test toothpaste 2 – Commercial sensitive toothpaste (Pro-Argin^a) containing 8.0% arginine and 1450 ppm fluoride as MFP in a calcium carbonate base.

Control toothpaste – Commercial toothpaste (Colgate Cavity Protection^a) containing 1450 ppm MFP in a calcium carbonate base.

Qualifying subjects took their assigned product home for unsupervised tooth brushing for a total of 8 weeks. Subject at-home brushing instructions consisted of brushing their teeth for 1 minute, twice daily, using only the toothpaste and toothbrush provided, and to refrain from any other oral hygiene procedures throughout the duration of the study. There were no other restrictions regarding diet or smoking habits during the course of the study. Subjects were also instructed to refrain from all oral hygiene procedures and chewing gum for 8 hours, and eating and drinking for 4 hours prior to their follow-up hypersensitivity evaluations.

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 2 weeks, 4 weeks and 8 weeks of product use. All examinations were performed by the same dental examiner, using the same

Table 1. Summary of age & gender for subjects who completed the 8-week clinical study.

| Treatment | Number of subjects | | | Age* | |
|----------------------|--------------------|---------|-------|------|-------|
| | Male* | Female* | Total | Mean | Range |
| Test toothpaste 1 ❶ | 13 | 27 | 40 | 57.3 | 38-78 |
| Test toothpaste 2 ❷ | 14 | 26 | 40 | 56.7 | 35-70 |
| Control toothpaste ❸ | 17 | 24 | 41 | 55.5 | 37-69 |

❶ Pro-Argin whitening toothpaste containing 8.0% arginine, high cleaning calcium carbonate and 1450 ppm fluoride as MFP.

❷ Pro-Argin toothpaste^a containing 8.0% arginine, calcium carbonate and 1450 ppm fluoride as MFP.

❸ Control toothpaste containing calcium carbonate and 1450 ppm fluoride as MFP (Colgate Cavity Protection^a).

* No statistically significant difference was indicated between the three treatment groups with respect to either gender or age.

procedures as employed at baseline. 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^b electronic force sensing probe. The application of this probe for dental hypersensitivity testing utilizing a #19 explorer tip at a pre-set force measured in grams was employed.

Teeth were evaluated for tactile hypersensitivity^{10,11} in the following manner:

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 sensitivity assessment - Air blast sensitivity was assessed by directing a 1-second blast of air onto the exposed buccal root surface of the sensitive tooth, from a distance of 1 centimeter, using the air component of a dental air/water syringe. After shielding the adjacent proximal teeth from the air blast through the placement of two fingers, the air blast was applied with a pressure of 60 p.s.i. (\pm 5 p.s.i) and a temperature of 70°F (\pm 3°F) for 1 second.

Sensitivity was recorded in accordance with the air sensitivity scale as described by Schiff *et al*¹³ as follows:

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

Table 2. Summary of the baseline tactile hypersensitivity and air blast hypersensitivity scores, for subjects who completed the 8-week clinical study.

| Parameter | Treatment | n | Baseline summary (Mean \pm S.D.)* |
|-----------------------|----------------------|----|-------------------------------------|
| Tactile sensitivity | Test toothpaste 1 ❶ | 40 | 16.38 \pm 7.51 |
| | Test toothpaste 2 ❷ | 40 | 15.00 \pm 6.89 |
| | Control toothpaste ❸ | 41 | 16.59 \pm 7.54 |
| Air blast sensitivity | Test toothpaste 1 ❶ | 40 | 2.13 \pm 0.29 |
| | Test toothpaste 2 ❷ | 40 | 2.13 \pm 0.32 |
| | Control toothpaste ❸ | 41 | 2.13 \pm 0.34 |

❶ Pro-Argin whitening toothpaste containing 8.0% arginine, high cleaning calcium carbonate and 1450 ppm fluoride as MFP.

❷ Pro-Argin toothpaste containing 8.0% arginine, calcium carbonate and 1450 ppm fluoride as MFP.

❸ Control toothpaste containing calcium carbonate and 1450 ppm fluoride as MFP.

* No statistically significant difference was indicated between the three treatment groups at baseline with respect to either tactile or air blast hypersensitivity scores.

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 tonsillar and pharyngeal areas.

Statistical methods - Statistical analyses were performed separately for the tactile sensitivity assessments and air blast sensitivity assessments. Comparisons of the treatment groups with respect to baseline tactile scores and air blast scores were performed using ANOVA. Within-treatment comparisons of the baseline *versus* follow-up tactile sensitivity and air blast sensitivity scores were performed using paired *t*-tests. Comparisons of the treatment groups with respect to baseline-adjusted tactile sensitivity and air blast sensitivity scores at the follow-up examinations were performed using ANCOVA. All statistical tests of hypotheses were two sided and employed a level of significance of $\alpha = 0.05$.

Results

One-hundred-twenty-one subjects complied with the protocol, and completed the 8-week clinical study. A summary of the gender and age of the study population is presented in Table 1. The treatment groups did not differ significantly with respect to either of these characteristics. Throughout the study, there were no adverse events on the oral soft or hard tissues of the oral cavity observed by the examiner, or reported by the subjects when questioned.

Baseline data - Table 2 presents a summary of the tactile and air blast hypersensitivity score means measured at the baseline examination for all subjects. For tactile hypersensitivity, the mean baseline scores were 16.38 for the Test toothpaste 1 group, 15.00 for the Test toothpaste 2 group and 16.59 for the Control toothpaste group. For air blast hypersensitivity, the mean baseline scores were 2.13 for the Test toothpaste 1 group, 2.13 for the Test toothpaste 2 group and 2.13 for the Control toothpaste group. No statistically significant difference was indicated between the treatment groups with

Table 3. Summary of the 2-week tactile hypersensitivity scores for subjects who completed the 8-week clinical study.

| Treatment | n | 2-week summary (Mean ± S.D.) | Within-treatment analysis | | Between-treatment comparison | | | |
|---------------------------------|----|------------------------------|-----------------------------|---------------------------|---------------------------------|---------------------------|---------------------------------|---------------------------|
| | | | Percent change ^④ | Significance ^⑤ | vs. Test toothpaste 2 | vs. Control toothpaste | vs. Test toothpaste 2 | vs. Control toothpaste |
| | | | | | Percent difference ^⑥ | Significance ^③ | Percent difference ^⑦ | Significance ^③ |
| Test toothpaste 1 ^① | 40 | 36.50 ± 12.26 | 122.8% | P< 0.05 | 2.1% | NS | 64.4% | P< 0.05 |
| Test toothpaste 2 ^② | 40 | 35.75 ± 11.91 | 138.3% | P< 0.05 | ----- | ----- | 61.0% | P< 0.05 |
| Control toothpaste ^③ | 41 | 22.20 ± 10.37 | 33.8% | P< 0.05 | ----- | ----- | ----- | ----- |

- ① Pro-Argin whitening toothpaste containing 8.0% arginine, high cleaning calcium carbonate and 1450 ppm fluoride as MFP.
- ② Pro-Argin toothpaste containing 8.0% arginine, calcium carbonate and 1450ppm fluoride as MFP.
- ③ Control toothpaste containing calcium carbonate and 1450ppm fluoride as MFP.
- ④ Percent change exhibited by the 2-week mean relative to the baseline mean. A positive value indicates an improvement in tactile hypersensitivity at the 2-week examination.
- ⑤ Significance of paired *t*-test comparing the baseline and the 2-week examinations.
- ⑥ Difference between the 2-week means expressed as a percentage of the 2-week mean for the Test toothpaste 2. A positive value indicates an improvement in tactile hypersensitivity scores in the row heading than for the Test toothpaste 2.
- ⑦ Difference between the 2-week means expressed as a percentage of the 2-week mean for the Control toothpaste. A positive value indicates an improvement in tactile hypersensitivity scores in the row heading than for the Control toothpaste.
- ⑧ Significance of ANCOVA comparison of baseline-adjusted means.

Table 4. Summary of the 2-week air blast hypersensitivity scores for subjects who completed the 8-week clinical study.

| Treatment | n | 2-week summary (Mean ± S.D.) | Within-treatment analysis | | Between-treatment comparison | | | |
|---------------------------------|----|------------------------------|-----------------------------|---------------------------|---------------------------------|---------------------------|---------------------------------|---------------------------|
| | | | Percent change ^④ | Significance ^⑤ | vs. Test toothpaste 2 | vs. Control toothpaste | vs. Test toothpaste 2 | vs. Control toothpaste |
| | | | | | Percent difference ^⑥ | Significance ^③ | Percent difference ^⑦ | Significance ^③ |
| Test toothpaste 1 ^① | 40 | 1.18 ± 0.56 | 44.6% | P< 0.05 | -1.7% | NS | 40.7% | P< 0.05 |
| Test toothpaste 2 ^② | 40 | 1.16 ± 0.68 | 45.5% | P< 0.05 | ----- | ----- | 41.7% | P< 0.05 |
| Control toothpaste ^③ | 41 | 1.99 ± 0.45 | 6.6% | P< 0.05 | ----- | ----- | ----- | ----- |

- ① Pro-Argin whitening toothpaste containing 8.0% arginine, high cleaning calcium carbonate and 1450 ppm fluoride as MFP.
- ② Pro-Argin toothpaste containing 8.0% arginine, calcium carbonate and 1450ppm fluoride as MFP.
- ③ Control toothpaste containing calcium carbonate and 1450ppm fluoride as MFP.
- ④ Percent change exhibited by the 2-week mean relative to the baseline mean. A positive value indicates an improvement in air blast hypersensitivity scores at the 2-week examination.
- ⑤ Significance of paired *t*-test comparing the baseline and the 2-week examinations.
- ⑥ Difference between the 2-week means expressed as a percentage of the 2-week mean for the Test toothpaste 2. A positive value indicates an improvement in air blast hypersensitivity scores in the row heading than for the Test toothpaste 2.
- ⑦ Difference between the 2-week means expressed as a percentage of the 2-week mean for the Control toothpaste. A positive value indicates a reduction in air blast hypersensitivity scores in the row heading than for the Control toothpaste.
- ⑧ Significance of ANCOVA comparison of baseline-adjusted means.

groups with respect to either tactile or air blast hypersensitivity scores at baseline.

2-WEEK DATA

Tactile hypersensitivity - Table 3 presents a summary of the tactile hypersensitivity scores measured after 2 weeks of product use.

Comparisons versus baseline - The mean 2-week tactile hypersensitivity scores were 36.50 for the Test toothpaste 1 group, 35.75 for the Test toothpaste 2 group and 22.20 for the Control toothpaste group. The percent changes from baseline were 122.8.0% for the Test toothpaste 1 group, 138.3% for the Test toothpaste 2 group and 33.8.0% for the Control toothpaste group, all of which were statistically significant.

Comparison between treatment groups - Relative to the Control toothpaste group, both the Test toothpaste 1 and Test toothpaste 2 groups exhibited statistically significant improvements in tactile hypersensitivity scores after 2 weeks of product use (64.4% and 61.0% respectively).

Relative to the Test toothpaste 1 group, the Test toothpaste 2 group did not exhibit a statistically significant improvement in tactile hypersensitivity scores after 2 weeks of product use (2.1%).

Air blast hypersensitivity - Table 4 presents a summary of the air blast hypersensitivity scores measured after 2 weeks of product use.

Comparisons versus baseline - The mean 2-week air blast hypersensitivity scores were 1.18 for the Test toothpaste 1 group, 1.16 for the Test toothpaste 2 group and 1.99 for the Control toothpaste group. The percent changes from baseline were 44.6% for the Test toothpaste 1 group, 45.5% for the Test toothpaste 2 group and 6.6% for the Control toothpaste group, all of which were statistically significant.

Comparison between treatment groups - Relative to the Control toothpaste group, both the Test toothpaste 1 and Test toothpaste 2 groups exhibited statistically significant reductions in air blast hypersensitivity scores after 2 weeks of product use (40.7% and 41.7% respectively).

Table 5. Summary of the 4-week tactile hypersensitivity scores for subjects who completed the 8-week clinical study.

| Treatment | n | 4-week summary (Mean ± S.D.) | Within-treatment analysis | | Between-treatment comparison vs. Test toothpaste 2 | | | |
|---------------------------------|----|------------------------------------|--------------------------------|---------------------------|--|---------------------------|------------------------------------|---------------------------|
| | | | Percent change ^④ | Significance ^⑤ | Percent difference ^⑥ | Significance ^⑥ | Percent difference ^⑦ | Significance ^⑧ |
| Test toothpaste 1 ^① | 40 | 45.50 ± 6.58 | 177.8% | P< 0.05 | 2.0% | NS | 71.1% | P< 0.05 |
| Test toothpaste 2 ^② | 40 | 44.62 ± 7.79 | 197.5% | P< 0.05 | ----- | ----- | 67.8% | P< 0.05 |
| Control toothpaste ^③ | 41 | 26.59 ± 11.64 | 60.3% | P< 0.05 | ----- | ----- | ----- | ----- |

^①Pro-Argin whitening toothpaste containing 8.0% arginine, high cleaning calcium carbonate and 1450 ppm fluoride as MFP.

^②Pro-Argin toothpaste containing 8.0% arginine, calcium carbonate and 1450ppm fluoride as MFP.

^③Control toothpaste containing calcium carbonate and 1450ppm fluoride as MFP.

^④Percent change exhibited by the 4-week mean relative to the baseline mean. A positive value indicates an improvement in tactile hypersensitivity at the 4-week examination.

^⑤Significance of paired *t*-test comparing the baseline and the 4-week examinations.

^⑥Difference between the 4-week means expressed as a percentage of the 4-week mean for the Test toothpaste 2. A positive value indicates an improvement in tactile hypersensitivity scores in the row heading than for the Test toothpaste 2.

^⑦Difference between the 4-week means expressed as a percentage of the 4-week mean for the Control toothpaste. A positive value indicates an improvement in tactile hypersensitivity scores in the row heading than for the Control toothpaste.

^⑧Significance of ANCOVA comparison of baseline-adjusted means.

Table 6. Summary of the 4-week air blast hypersensitivity scores for subjects who completed the 8-week clinical study.

| Treatment | n | 4-week summary (Mean ± S.D.) | Within-treatment analysis | | Between-treatment comparison vs. Test toothpaste 2 | | | |
|---------------------------------|----|------------------------------------|--------------------------------|---------------------------|--|---------------------------|------------------------------------|---------------------------|
| | | | Percent change ^④ | Significance ^⑤ | Percent difference ^⑥ | Significance ^⑥ | Percent difference ^⑦ | Significance ^⑧ |
| Test toothpaste 1 ^① | 40 | 0.75 ± 0.55 | 64.8% | P< 0.05 | 1.3% | NS | 58.8% | P< 0.05 |
| Test toothpaste 2 ^② | 40 | 0.76 ± 0.64 | 64.3% | P< 0.05 | ----- | ----- | 58.2% | P< 0.05 |
| Control toothpaste ^③ | 41 | 1.82 ± 0.38 | 14.6% | P< 0.05 | ----- | ----- | ----- | ----- |

^①Pro-Argin whitening toothpaste containing 8.0% arginine, high cleaning calcium carbonate and 1450 ppm fluoride as MFP.

^②Pro-Argin toothpaste containing 8.0% arginine, calcium carbonate and 1450 ppm fluoride as MFP.

^③Control toothpaste containing calcium carbonate and 1450 ppm fluoride as MFP.

^④Percent change exhibited by the 4-week mean relative to the baseline mean. A positive value indicates a reduction in air blast hypersensitivity scores at the 4-week examination.

^⑤Significance of paired *t*-test comparing the baseline and the 4-week examinations.

^⑥Difference between the 4-week means expressed as a percentage of the 4-week mean for the Test toothpaste 2. A positive value indicates a reduction in air blast hypersensitivity scores in the row heading than for the Test toothpaste 2.

^⑦Difference between the 4-week means expressed as a percentage of the 4-week mean for the Control toothpaste. A positive value indicates a reduction in air blast hypersensitivity scores in the row heading than for the Control toothpaste.

^⑧Significance of ANCOVA comparison of baseline-adjusted means.

Relative to the Test toothpaste 1 group, the Test toothpaste 2 group did not exhibit a statistically significant reduction in air blast hypersensitivity scores after 2 weeks of product use (1.7%).

4-WEEK DATA

Tactile hypersensitivity - Table 5 presents a summary of the tactile hypersensitivity scores measured after 4 weeks of product use.

Comparisons versus baseline - The mean 4-week tactile hypersensitivity scores were 45.50 for the Test toothpaste 1 group, 44.62 for the Test toothpaste 2 group and 26.59 for the Control toothpaste group. The percent changes from baseline were 177.8.0% for the Test toothpaste 1 group, 197.5% for the Test toothpaste 2 group and 60.3% for the Control toothpaste group, all of which were statistically significant.

Comparison between treatment groups - Relative to the Control toothpaste group, both the Test toothpaste 1 and Test toothpaste 2 groups exhibited statistically significant im-

provements in tactile hypersensitivity scores after 4 weeks of product use (71.1% and 67.8.0% respectively).

Relative to the Test toothpaste 1 group, the Test toothpaste 2 group did not exhibit a statistically significant improvement in tactile hypersensitivity scores after 4 weeks of product use (2.0%).

Air blast hypersensitivity - Table 6 presents a summary of the air blast hypersensitivity scores measured after 4 weeks of product use.

Comparisons versus baseline - The mean 4-week air blast hypersensitivity scores were 0.75 for the Test toothpaste 1 group, 0.76 for the Test toothpaste 2 group and 1.82 for the Control toothpaste group. The percent changes from baseline were 64.8.0% for the Test toothpaste 1 group, 64.3% for the Test toothpaste 2 group and 14.6% for the Control toothpaste group, all of which were statistically significant.

Comparison between treatment groups - Relative to the Control toothpaste group, both the Test toothpaste 1 and Test toothpaste 2 groups exhibited statistically significant reduc-

Table 7. Summary of the 8-week tactile hypersensitivity scores for subjects who completed the 8-week clinical study.

| Treatment | n | 8-week summary (Mean ± S.D.) | Within-treatment analysis | | Between-treatment comparison | | | |
|---------------------------------|----|------------------------------|-----------------------------|---------------------------|---------------------------------|---------------------------|---------------------------------|---------------------------|
| | | | Percent change ^④ | Significance ^⑤ | vs. Test toothpaste 2 | vs. Control toothpaste | vs. Test toothpaste 2 | vs. Control toothpaste |
| | | | | | Percent difference ^⑥ | Significance ^⑧ | Percent difference ^⑦ | Significance ^⑨ |
| Test toothpaste 1 ^① | 40 | 48.50 ± 4.11 | 196.1% | P< 0.05 | 1.0% | NS | 61.0% | P< 0.05 |
| Test toothpaste 2 ^② | 40 | 48.00 ± 4.91 | 220.0% | P< 0.05 | ---- | ---- | 59.4% | P< 0.05 |
| Control toothpaste ^③ | 41 | 30.12 ± 12.57 | 81.6% | P< 0.05 | ---- | ---- | ---- | ---- |

- ① Pro-Argin whitening toothpaste containing 8.0% arginine, high cleaning calcium carbonate and 1450 ppm fluoride as MFP.
- ② Pro-Argin toothpaste containing 8.0% arginine, calcium carbonate and 1450 ppm fluoride as MFP.
- ③ Control toothpaste containing calcium carbonate and 1450 ppm fluoride as MFP.
- ④ Percent change exhibited by the 8-week mean relative to the baseline mean. A positive value indicates an improvement in tactile hypersensitivity at the 8-week examination.
- ⑤ Significance of paired *t*-test comparing the baseline and the 8-week examinations.
- ⑥ Difference between the 8-week means expressed as a percentage of the 8-week mean for the Test toothpaste 2. A positive value indicates an improvement in tactile hypersensitivity scores in the row heading than for the Test toothpaste 2.
- ⑦ Difference between the 8-week means expressed as a percentage of the 8-week mean for the Control toothpaste. A positive value indicates an improvement in tactile hypersensitivity scores in the row heading than for the Control toothpaste.
- ⑧ Significance of ANCOVA comparison of baseline-adjusted means.

Table 8. Summary of the 8-week air blast hypersensitivity scores for subjects who completed the 8-week clinical study.

| Treatment | n | 8-week summary (Mean ± S.D.) | Within-treatment analysis | | Between-treatment comparison | | | |
|---------------------------------|----|------------------------------|-----------------------------|---------------------------|---------------------------------|---------------------------|---------------------------------|---------------------------|
| | | | Percent change ^④ | Significance ^⑤ | vs. Test toothpaste 2 | vs. Control toothpaste | vs. Test toothpaste 2 | vs. Control toothpaste |
| | | | | | Percent difference ^⑥ | Significance ^⑧ | Percent difference ^⑦ | Significance ^⑨ |
| Test toothpaste 1 ^① | 40 | 0.44 ± 0.56 | 79.3% | P< 0.05 | -15.8% | NS | 74.4% | P< 0.05 |
| Test toothpaste 2 ^② | 40 | 0.38 ± 0.52 | 82.2% | P< 0.05 | ---- | ---- | 77.9% | P< 0.05 |
| Control toothpaste ^③ | 41 | 1.72 ± 0.46 | 19.2% | P< 0.05 | ---- | ---- | ---- | ---- |

- ① Pro-Argin whitening toothpaste containing 8.0% arginine, high cleaning calcium carbonate and 1450 ppm fluoride as MFP.
- ② Pro-Argin toothpaste containing 8.0% arginine, calcium carbonate and 1450 ppm fluoride as MFP.
- ③ Control toothpaste containing calcium carbonate and 1450 ppm fluoride as MFP.
- ④ Percent change exhibited by the 8-week mean relative to the baseline mean. A positive value indicates a reduction in air blast hypersensitivity scores at the 8-week examination.
- ⑤ Significance of paired *t*-test comparing the baseline and the 8-week examinations.
- ⑥ Difference between the 8-week means expressed as a percentage of the 8-week mean for the Test toothpaste 2. A positive value indicates a reduction in air blast hypersensitivity scores in the row heading than for the Test toothpaste 2.
- ⑦ Difference between the 8-week means expressed as a percentage of the 8-week mean for the Control toothpaste. A positive value indicates a reduction in air blast hypersensitivity scores in the row heading than for the Control toothpaste.
- ⑧ Significance of ANCOVA comparison of baseline-adjusted means.

tions in air blast hypersensitivity scores after 4 weeks of product use (58.8.0% and 58.2% respectively).

Relative to the Test toothpaste 1 group, the Test toothpaste 2 group did not exhibit a statistically significant reduction in air blast hypersensitivity scores after 4 weeks of product use (1.3%).

8-WEEK DATA

Tactile hypersensitivity - Table 7 presents a summary of the tactile hypersensitivity scores measured after 8 weeks of product use.

Comparisons versus baseline - The mean 8-week tactile hypersensitivity scores were 48.50 for the Test toothpaste 1 group, 48.00 for the Test toothpaste 2 group and 30.12 for the Control toothpaste group. The percent changes from baseline were 196.1% for the Test toothpaste 1 group, 220.0% for the Test toothpaste 2 group and 81.6% for the Control toothpaste group, all of which were statistically significant.

Comparison between treatment groups - Relative to the Control toothpaste group, both the Test toothpaste 1 and Test toothpaste 2 groups exhibited statistically significant improvements in tactile hypersensitivity scores after 8 weeks of product use (61.0% and 59.4% respectively).

Relative to the Test toothpaste 1 group, the Test toothpaste 2 group did not exhibit a statistically significant improvement in tactile hypersensitivity scores after 8 weeks of product use (1.0%).

Air blast hypersensitivity - Table 8 presents a summary of the air blast hypersensitivity scores measured after 8 weeks of product use.

Comparisons versus baseline - The mean 8-week air blast hypersensitivity scores were 0.44 for the Test toothpaste 1 group, 0.38 for the Test toothpaste 2 group and 1.72 for the Control toothpaste group. The percent changes from baseline were 79.3% for the Test toothpaste 1 group, 82.2% for the Test toothpaste 2 group and 19.2% for the Control toothpaste group, all of which were statistically significant.

Comparison between treatment groups - Relative to the Control toothpaste group, both the Test toothpaste 1 and Test toothpaste 2 groups exhibited statistically significant reductions in air blast hypersensitivity scores after 8 weeks of product use (74.4% and 77.9% respectively).

Relative to the Test toothpaste 1 group, the Test toothpaste 2 group did not exhibit a statistically significant reduction in air blast hypersensitivity scores after 8 weeks of product use (15.8.0%).

Discussion

Dentin hypersensitivity is a relatively common problem seen in clinical practice. It is characterized by a sharp, transient pain in response to a sensory stimulus, which can impact the quality of life through its effects on eating, drinking, brushing teeth, and breathing.¹⁴ This condition affects nearly 40 million Americans,¹⁵ approximately one in five adults, and can be seen in all age groups.¹⁶ Patients who have received periodontal therapy are four times more at risk at developing hypersensitivity than the general population.¹⁷ Epidemiologic research suggests that prevalence peaks between 30 and 40 years of age. As individuals retain their dentitions for longer and as diets change, it is reasonable to expect that there will be a higher incidence of oral complaints related to dentin hypersensitivity, and with that an increase in requests for treatment.

A number of professional and over-the-counter products have been developed to help alleviate the pain associated with dentin hypersensitivity. For example, potassium salts have been added to dentifrices as sensitivity reducing agents for many years. There is a body of clinical evidence that demonstrates that potassium-based toothpastes are effective in reducing dentin hypersensitivity; however, some investigators have reported that potassium-based toothpastes are no more effective than regular fluoride toothpaste.¹⁸⁻²⁰

Another approach that has been investigated by the dental research community is to occlude dentin tubules, or at least reduce their diameter, with a technology that coats the dentin surface and fills the openings of the tubules. This approach has primarily been used to manage sensitivity in the form of products applied by dental professionals using either a varnish or precipitates.²¹ Such an approach reduces the movement of fluids in the dentin tubule, and results in the blockage of painful stimuli. While several *in vitro* studies have shown occlusion of dentin tubules with calcium phosphate,²¹⁻²⁴ there is a paucity of clinical data proving efficacy *in vivo*.

Arginine, an amino acid, has been investigated in combination with calcium carbonate for its ability to occlude dentin tubules and reduce pain from dentin hypersensitivity.⁸ This technology has recently been further developed by the Colgate-Palmolive Company and sold in a toothpaste containing 8.0% arginine, calcium carbonate, and 1450 ppm fluoride as sodium monofluorophosphate.⁹⁻¹²

The results of this double-blind clinical study support the conclusions that a new sensitive toothpaste with whitening benefits, containing 8.0% arginine, a high cleaning calcium carbonate system, and 1450 ppm fluoride, provides significantly greater dentin hypersensitivity relief ($P < 0.05$) than a negative control toothpaste after 2, 4, and 8 weeks of

product use. The results for the new Pro-Argin formula toothpaste with whitening benefits did not significantly differ from those of the positive control toothpaste containing 8.0% arginine, calcium carbonate and 1450 ppm fluoride.

- a. Colgate-Palmolive, New York, NY, USA.
- b. Yeaple Research, Pittsford, NY, USA.

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Dr. Que is Lecturer, Dr. Fu is a dentist, Dr. Lin is a dentist and Dr. Hu is Professor and Chair, The Key State Laboratory of Oral Diseases, Sichuan University, Chengdu, Sichuan, China. Dr. Zhang is Director, Dr. Panagakos is Director, and Dr. DeVizio is Vice-President, Colgate-Palmolive Technology Center, Piscataway, New Jersey, USA. Mr. Mateo is a statistical consultant, LRM Statistical Consulting, Hoboken, New Jersey, USA.

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Extrinsic stain removal efficacy of a new desensitizing dentifrice containing 8.0% arginine, calcium carbonate and 1450 ppm fluoride

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ABSTRACT: Purpose: To evaluate the extrinsic stain removal efficacy of a new Pro-Argin™ formula whitening dentifrice containing 8.0% arginine, a high cleaning calcium carbonate and 1450 ppm fluoride, as monofluorophosphate, after brushing twice daily for 4 and 8 weeks. **Methods:** At the baseline visit, 92 adult subjects were stratified based on their Lobene Stain Index scores and randomized into two treatment groups; one using the new Pro-Argin formula whitening dentifrice (test group) and the other using the original Pro-Argin formula dentifrice (control group). Subjects were instructed to brush twice daily for the duration of the study. Tooth stain evaluations were conducted as stain area and stain intensity according to the Lobene Stain Index. **Results:** All 92 enrolled subjects complied with the protocol and completed the 8-week study. Baseline scores demonstrated no significant differences between the two treatment groups for the evaluated area and intensity parameters of stain ($P > 0.05$). At both the 4- and 8-week post-use evaluations, subjects brushing with the test dentifrice demonstrated significant reductions for all stain parameters *versus* the control ($P < 0.05$). Relative to the control group, the test group demonstrated reductions in mean stain intensity scores of 9.7% and 17.9% at the 4- and 8-week evaluations, respectively. Corresponding reductions in mean stain area scores for the test group relative to the control were 11.7% and 20.8% at the 4- and 8-week evaluations, respectively. (*Am J Dent* 2010;23 Sp Is A:36A-40A).

CLINICAL SIGNIFICANCE: In comparison to the Pro-Argin formula control dentifrice, the results of this investigation demonstrated significantly more stain removal following the use of the new Pro-Argin formula whitening dentifrice containing 8.0% arginine, a high cleaning calcium carbonate and 1450 ppm fluoride, as monofluorophosphate, after 4 and 8 weeks' product use.

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Introduction

Tooth discoloration is a common concern for many individuals because it readily occurs on the anterior teeth, where it can be easily perceived by the affected individual and by others. The healthy and attractive appearance of the dentition has been reported to play a significant role in the quality of life and well-being of most people.^{1,2} For many, tooth staining is a cosmetic concern that can be indicative of inadequate oral hygiene and personal care. Surveys of dental professionals indicate that stained teeth is a frequent reason for patient visits to have a prophylaxis.³

Dentistry has traditionally been associated with the treatment and prevention of disease, while also meeting increasing cosmetic demands from and expectations of patients. Manufacturers of oral care products also respond to such needs as the removal of tooth stains by developing effective technologies to address this cosmetic indication, in addition to desired therapeutic functions, such as caries protection and the reduction of dentin hypersensitivity.

Tooth staining can be of intrinsic or extrinsic origin. Intrinsic tooth stains are the result of the binding of undesirable pigments or chromogens into enamel or dentin.⁴ The incorporation of these stains into these tooth structures occurs primarily during the tooth development process and its remediation relies mainly on vital or non-vital tooth bleaching procedures and/or on relatively invasive restorative treatment alternatives. Extrinsic tooth staining occurs as the result of the binding of chromogenic components in certain foods, drinks, medications and tobacco products to the salivary pellicle on tooth sur-

faces.^{5,6} The accumulation of extrinsic stain can also be influenced by poor oral hygiene and the stain removal efficacy of dentifrices for daily use.⁷ The physical forces of brushing, combined with the ingredients in dentifrices, enhance stain removal,^{1,8} thus, daily brushing with toothpaste represents a convenient method for the control of extrinsic tooth stain between professional dental cleanings.

A new Pro-Argin formula dentifrice⁸ has been formulated to offer both dentin hypersensitivity relief and improved whitening benefits. The objective of this clinical study was to evaluate the extrinsic stain removal efficacy following twice daily brushing for 4 and 8 weeks of the new dentifrice containing 8.0% arginine, a high cleaning calcium carbonate and 1450 ppm fluoride, as monofluorophosphate.

Materials and Methods

Subjects and study design - The study population was comprised of subjects (age range 27-65 years) in good oral and general health. Prospective voluntary participants who indicated an interest in the study were scheduled for an oral examination by a dentist at the West China College of Stomatology. The clinical protocol and informed consent were reviewed and approved by The Institutional Review Board of Sichuan Committee for Oral Health prior to the start of the study. Individuals who completed the informed consent process and met the selection criteria were enrolled. Inclusion criteria for the study consisted of subject's availability for the 8-week duration of the study, the presence of at least seven anterior teeth that were free of large restorations, intrinsic stain or

Table 1. Summary of age and gender, for subjects who completed the 8-week clinical study.

| Treatment | Number of subjects | | | Age ^③ | |
|---------------------------------|--------------------|---------------------|-------|------------------|-------|
| | Male ^② | Female ^② | Total | Mean | Range |
| Test dentifrice ^① | 30 | 16 | 46 | 43.2 | 28-61 |
| Control dentifrice ^② | 32 | 14 | 46 | 42.5 | 27-65 |

- ① Pro-Argin whitening dentifrice containing 8.0% arginine, a high cleaning calcium carbonate and 1450 ppm fluoride as MFP.^a
- ② Pro-Argin dentifrice containing 8.0% arginine, calcium carbonate and 1450 ppm fluoride as MFP.^a
- ③ No statistically significant difference was indicated between the two treatment groups with respect to either gender or age.

dental prosthetic crowns which might interfere with the scoring of extrinsic stains. Subjects also needed to illustrate clinical evidence of a tendency to form extrinsic stain on anterior teeth by presenting a minimum mean Lobene Stain Index Area score of 0.5 and a minimum mean Lobene Stain Intensity Index score of 0.5.⁹ Excluded from participation were individuals who had advanced periodontal disease, were taking prescription medications that might interfere with the study outcome, had received a dental prophylaxis during the 2 weeks prior to the study baseline examination, wore a removable partial denture or had orthodontic bands or brackets, were pregnant or lactating, or had participated in any other clinical study or panel test within 30 days prior to the start of the study.

This clinical study employed a randomized, single-center, double-blind, two-arm, parallel-group design. Subjects who met the inclusion/exclusion criteria received a baseline extrinsic tooth stain examination and oral soft tissue assessment. The study subjects were stratified on the basis of their baseline extrinsic stain examination scores and randomly assigned to participate in one of the two study groups.

Dentifrices tested and study procedures - The dentifrices used in the study were two formulations containing the Pro-Argin technology for the relief of dentin hypersensitivity. The test product was a whitening dentifrice containing 8.0% arginine, a high cleaning calcium carbonate and 1450 ppm fluoride^a and the control product was the dentifrice containing 8.0% arginine, calcium carbonate and 1450 ppm fluoride,^a previously validated^{10,11} for efficacy in instant and lasting hypersensitivity relief. Both dentifrices were supplied in over-wrapped tubes and assigned a unique code for randomized allocation to subjects. The subjects and the study examiner remained blinded to product assignment. While enrolled subjects were not instructed to alter their daily diet or other habits, they were instructed to discontinue the use of all other dentifrices, mouthwashes, gums, and other oral hygiene formulations for the duration of the study. All subjects were provided with their assigned dentifrice, soft-bristled adult size toothbrush and were directed to brush twice daily for the 8-week duration of the study. Subjects were requested to return to the clinical facility for follow-up examinations at 4 and 8 weeks. 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.

Clinical scoring procedures - All clinical examinations were conducted under constant lighting conditions. Using the stan-

Table 2. Summary of the baseline stain area and stain intensity scores, for subjects who completed the 8-week clinical study.

| Parameter | Treatment | n | Baseline summary (Mean ± S.D.) ^③ |
|-----------------|---------------------------------|----|---|
| Stain Area | Test dentifrice ^① | 46 | 2.42 ± 0.48 |
| | Control dentifrice ^② | 46 | 2.41 ± 0.47 |
| Stain Intensity | Test dentifrice ^① | 46 | 2.05 ± 0.53 |
| | Control dentifrice ^② | 46 | 2.06 ± 0.47 |

- ① Pro-Argin whitening dentifrice containing 8.0% arginine, a high cleaning calcium carbonate and 1450 ppm fluoride as MFP.
- ② Pro-Argin dentifrice containing 8.0% arginine, calcium carbonate and 1450 ppm fluoride as MFP.
- ③ No statistically significant difference was indicated between the two treatment groups at baseline with respect to either stain area or stain intensity scores.

dard method described by Lobene, each tooth was scored separately using four point area and intensity scales ranging from:

Stain area:

- 0 = No stain detected;
- 1 = Stain up to one third of the region;
- 2 = Stain up to two thirds of the region;
- 3 = Stain over more than two thirds of the region.

Stain intensity:

- 0 = No stain;
- 1 = Light stain – yellow/tan;
- 2 = Moderate stain – medium brown;
- 3 = Heavy stain – dark brown/black.

A mean stain intensity score and a mean stain area score were calculated for each subject per examination.

Statistical methods - Statistical analyses were performed separately for the stain area assessments and stain intensity assessments. Comparisons of the treatment groups with respect to baseline mean stain area scores and mean stain intensity scores were performed using independent *t*-tests. Comparisons between the treatment groups with respect to gender were performed using a chi-square test and, for age, an independent *t*-test. Within-treatment comparisons of the baseline *versus* follow-up mean stain area and mean stain intensity scores were performed using a paired *t*-test. Comparisons of the treatment groups with respect to baseline-adjusted stain area and stain intensity scores at the follow-up examinations were performed using an analysis of covariance (ANCOVA). Analyses were conducted by Minitab.^b All statistical tests of hypotheses were two-sided, and results at P < 0.05 reported as significant.

Results

A total of 92 subjects complied with the protocol, and completed the 8-week clinical study. A summary of the gender and age of the study population is presented in Table 1. The treatment groups did not differ significantly with respect to either of these characteristics. Throughout the study, there were no adverse effects on the oral soft or hard tissues of the oral cavity which were observed by the examiner, or reported by the subjects when questioned.

The two treatment groups were balanced (P > 0.05) at baseline on the basis of mean stain area scores and mean stain intensity scores (Table 2).

Table 3. Summary of the 4-week stain area scores, for subjects who completed the 8-week clinical study.

| Treatment | n | 4-week summary (Mean \pm S.D.) | Within treatment analysis | | Between-treatment comparison | |
|---------------------------------|----|----------------------------------|-----------------------------|---------------------------|---------------------------------|---------------------------|
| | | | Percent change ^③ | Significance ^④ | Percent difference ^⑤ | Significance ^⑥ |
| Test dentifrice ^① | 46 | 2.03 \pm 0.57 | 16.1% | P < 0.05 | 11.7% | P < 0.05 |
| Control dentifrice ^② | 46 | 2.30 \pm 0.56 | 4.6% | P < 0.05 | | |

① Pro-Argin whitening dentifrice containing 8.0% arginine, a high cleaning calcium carbonate and 1450 ppm fluoride as MFP.

② Pro-Argin dentifrice containing 8.0% arginine, calcium carbonate and 1450 ppm fluoride as MFP.

③ Percent change exhibited by the 4-week mean relative to the baseline mean. A positive value indicates a reduction in stain area scores at the 4-week examination.

④ Significance of paired *t*-test comparing the baseline and the 4-week examinations.

⑤ Difference between the 4-week means expressed as a percentage of the 4-week mean for the Control dentifrice. A positive value indicates a reduction in stain area scores for the Test dentifrice relative to the Control dentifrice.

⑥ Significance of ANCOVA comparison of baseline-adjusted means.

Table 4. Summary of the 8-week stain area scores, for subjects who completed the 8-week clinical study.

| Treatment | n | 8-week summary (Mean \pm S.D.) | Within treatment analysis | | Between-treatment comparison | |
|---------------------------------|----|----------------------------------|-----------------------------|---------------------------|---------------------------------|---------------------------|
| | | | Percent change ^③ | Significance ^④ | Percent difference ^⑤ | Significance ^⑥ |
| Test dentifrice ^① | 46 | 1.56 \pm 0.61 | 35.5% | P < 0.05 | 20.8% | P < 0.05 |
| Control dentifrice ^② | 46 | 1.97 \pm 0.63 | 18.3% | P < 0.05 | | |

① Pro-Argin whitening dentifrice containing 8.0% arginine, a high cleaning calcium carbonate and 1450 ppm fluoride as MFP.

② Pro-Argin dentifrice containing 8.0% arginine, calcium carbonate and 1450 ppm fluoride as MFP.

③ Percent change exhibited by the 8-week mean relative to the baseline mean. A positive value indicates a reduction in stain area scores at the 8-week examination.

④ Significance of paired *t*-test comparing the baseline and the 8-week examinations.

⑤ Difference between the 8-week means expressed as a percentage of the 8-week mean for the Control dentifrice. A positive value indicates a reduction in stain area scores for the Test dentifrice relative to the Control dentifrice.

⑥ Significance of ANCOVA comparison of baseline-adjusted means.

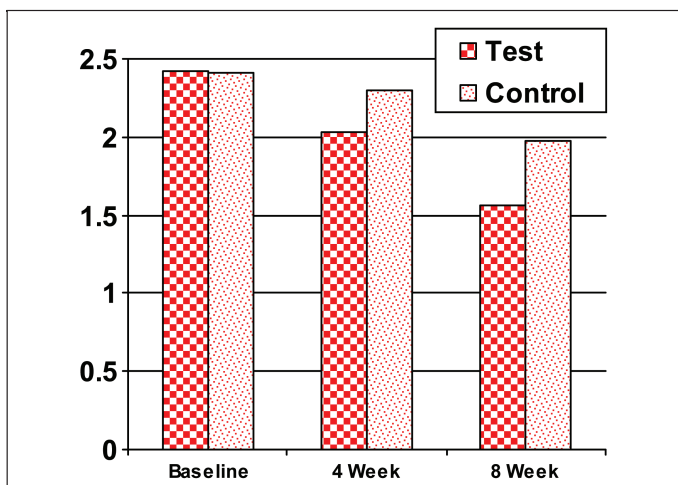


Fig. 1. Mean Lobene Stain Area scores.

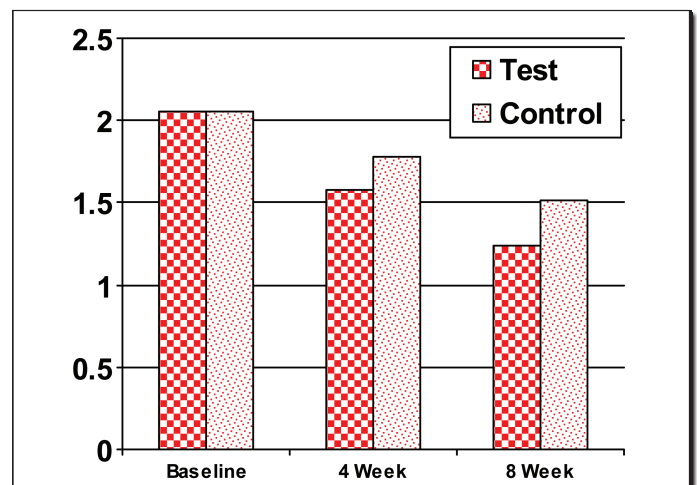


Fig. 2. Mean Lobene Stain Intensity scores.

Stain area - The effect of twice daily brushing with the assigned dentifrices on stain area is shown in Tables 3 and 4 and graphically in Fig. 1. After 4 weeks of product use, the assessment of stain area demonstrated a statistically significant ($P < 0.05$) reduction from baseline scores for subjects assigned to the test group (16.1%) and for subjects assigned to the control group (4.6%). After 8 weeks of product use, the assessment of stain area examination demonstrated a statistically significant ($P < 0.05$) reduction from baseline scores for subjects assigned to the test group (35.5%) and for subjects assigned to the control group (18.3%).

Relative to the control group, subjects assigned to the test group exhibited a statistically significant reduction in mean stain area scores after 4 weeks of twice a day product use (11.7%). In addition, relative to the control group, subjects assigned to the test group exhibited a statistically significant reduction in mean stain area scores after 8 weeks of twice a day product use (20.8%).

Stain intensity - The effect of twice daily brushing with the assigned dentifrices on stain intensity is shown in Tables 5 and 6 and graphically in Fig. 2. After 4 weeks of product use, the assessment of stain intensity demonstrated a statistically

Table 5. Summary of the 4-week stain intensity scores, for subjects who completed the 8-week clinical study.

| Treatment | n | 4-week summary (Mean ± S.D.) | Within treatment analysis | | Between-treatment comparison | |
|---------------------------------|----|------------------------------|-----------------------------|---------------------------|---------------------------------|---------------------------|
| | | | Percent change ^③ | Significance ^④ | Percent difference ^⑤ | Significance ^⑥ |
| Test dentifrice ^① | 46 | 1.58 ± 0.53 | 22.9% | P< 0.05 | 9.7% | P< 0.05 |
| Control dentifrice ^② | 46 | 1.75 ± 0.50 | 15.0% | P< 0.05 | | |

- ① Pro-Argin whitening dentifrice containing 8.0% arginine, a high cleaning calcium carbonate and 1450 ppm fluoride as MFP.
- ② Pro-Argin dentifrice containing 8.0% arginine, calcium carbonate and 1450 ppm fluoride as MFP.
- ③ Percent change exhibited by the 4-week mean relative to the baseline mean. A positive value indicates a reduction in stain area scores at the 4-week examination.
- ④ Significance of paired *t*-test comparing the baseline and the 4-week examinations.
- ⑤ Difference between the 4-week means expressed as a percentage of the 4-week mean for the Control dentifrice. A positive value indicates a reduction in stain area scores for the Test dentifrice relative to the Control dentifrice.
- ⑥ Significance of ANCOVA comparison of baseline-adjusted means.

Table 6. Summary of the 8-week stain intensity scores, for subjects who completed the 8-week clinical study.

| Treatment | n | 8-week summary (Mean ± S.D.) | Within treatment analysis | | Between-treatment comparison | |
|---------------------------------|----|------------------------------|-----------------------------|---------------------------|---------------------------------|---------------------------|
| | | | Percent change ^③ | Significance ^④ | Percent difference ^⑤ | Significance ^⑥ |
| Test dentifrice ^① | 46 | 1.24 ± 0.46 | 39.5% | P< 0.05 | 17.9% | P< 0.05 |
| Control dentifrice ^② | 46 | 1.51 ± 0.50 | 26.7% | P< 0.05 | | |

- ① Pro-Argin whitening dentifrice containing 8.0% arginine, a high cleaning calcium carbonate and 1450 ppm fluoride as MFP.
- ② Pro-Argin dentifrice containing 8.0% arginine, calcium carbonate and 1450 ppm fluoride as MFP.
- ③ Percent change exhibited by the 8-week mean relative to the baseline mean. A positive value indicates a reduction in stain area scores at the 8-week examination.
- ④ Significance of paired *t*-test comparing the baseline and the 8-week examinations.
- ⑤ Difference between the 8-week means expressed as a percentage of the 8-week mean for the Control dentifrice. A positive value indicates a reduction in stain area scores for the Test dentifrice relative to the Control dentifrice.
- ⑥ Significance of ANCOVA comparison of baseline-adjusted means.

significant (P< 0.05) reduction from baseline scores for subjects assigned to the test group (22.9%) and for subjects assigned to the control group (15.0%). After 8 weeks of product use, the assessment of stain intensity demonstrated a statistically significant (P< 0.05) reduction from baseline scores for subjects assigned to the test group (39.5%) and for subjects assigned to the control group (26.7%)

Relative to the control group, subjects assigned to the test group exhibited a statistically significant reduction in mean stain intensity scores after 4 weeks of twice a day product use (9.7%). In addition, relative to the control group, subjects assigned to the test group exhibited a statistically significant reduction in mean stain intensity scores after 8 weeks of twice a day product use (17.9%).

Discussion

This clinical investigation examined stain removal after unsupervised twice daily brushing for 4 and 8 weeks using an adult soft bristled toothbrush and a new Pro-Argin formula sensitivity dentifrice with a whitening benefit. Stain examinations for the entire study were conducted using the Lobene Stain Index, an assessment that provides numerical scores for extrinsic stains on the enamel and is widely reported in the literature.^{12,13}

The results at the 4- and 8-week evaluations were consistent. The average stain area and stain intensity scores following the use of either toothpaste demonstrated statistically significant improvements from its respective baseline values. Statistical

analyses comparing the two toothpastes demonstrated superior stain removal efficacy by the test dentifrice at the two follow-up examinations. Relative to the control group, subjects assigned to the test dentifrice exhibited statistically significant improvements in stain area and stain intensity parameters of extrinsic stain removal after 4 weeks and after 8 weeks of twice a day brushing applications.

The test dentifrice utilized in this investigation contains the combination of 8.0% arginine and calcium carbonate, known as Pro-Argin technology, for the relief of dentin hypersensitivity. Multiple randomized clinical trials^{10,11,14-18} have documented the efficacy of dentifrices formulated with this technology for superior, instant and lasting dentin hypersensitivity relief. Dentifrices containing 8.0% arginine and calcium carbonate with levels of 1100 and 1450 ppm fluoride, have been shown to provide sensitivity relief by blocking and sealing open dentin tubules with a protective layer that is resistant to acid challenge.¹⁹ The results of the present clinical study support the improved extrinsic stain removal efficacy as an added cosmetic benefit to the tested sensitivity relief dentifrice containing 8.0% arginine, a high cleaning calcium carbonate and 1450 ppm fluoride. The results of clinical trials^{20,21} and *in vitro* studies²² included in this special issue publication, document that the Pro-Argin technology in this whitening formulation retains its sensitivity relief efficacy through the deposit of a robust and resilient protective layer on the dentin surface for effective occlusion of dentin tubules, to provide instant and superior dentin hypersensitivity relief.

- a. Colgate-Palmolive Co., New York, NY, USA.
- b. Minitab, State College, PA, USA.

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Dr. Yin and Dr. Li are Lecturers, Dr. He is a dentist, Dr. Ma is a dentist and PhD student, and Dr. Hu is Professor and Chair, The State Key Laboratory of Oral Diseases, Sichuan University, Chengdu, Sichuan, China. Dr. Zhang is Director of Clinical Dental Research, Dr. Delgado is Manager of Clinical Dental Research, Dr. DeVizio is Vice President of Clinical Dental Research, Colgate-Palmolive Technology Center, Piscataway, NJ, USA. Mr. Mateo is a statistical consultant, LRM Statistical Consulting, Hoboken, NJ, USA.

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