

Randomized Clinical Trial of the Efficacy of Dentifrices Containing 1.5% Arginine, an Insoluble Calcium Compound and 1450 ppm Fluoride Over Two Years

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Abstract

- **Objective:** A double blind, randomized, unsupervised, parallel-group clinical trial was conducted on over 5,500 children in Sichuan Province, China. This clinical trial compared the anti-caries efficacy of two test dentifrices to that of a control dentifrice.
- **Methods:** The test dentifrices contained 1.5% arginine, 1450 ppm fluoride as sodium monofluorophosphate (MFP), and an insoluble calcium compound (either dicalcium phosphate or calcium carbonate). The positive control dentifrice contained 1450 ppm fluoride as sodium fluoride (NaF), in a silica base. The children were randomly assigned one of the toothpastes, and children residing in the same household were assigned the same dentifrice to use at home, twice a day.
- **Results:** Three calibrated dentists examined the children at baseline, as well as after one and two years of product use. After one year of product use, there were no statistically significant differences among the three groups with respect to decayed, missing, and filled teeth (DMFT) or to decayed, missing, and filled surfaces (DMFS). After two years of product use, subjects in the two test groups using the dentifrices containing 1.5% arginine, 1450 ppm fluoride as MFP, and an insoluble calcium compound had a statistically significant reduction in DMFT increments of 20.5% and in DMFS increments of 19.6% when compared to subjects in the group using the positive control dentifrice. After two years, there were no statistically significant differences with respect to DMFT or DMFS between the two groups using the dentifrices containing 1.5% arginine, 1450 ppm fluoride as MFP, and an insoluble calcium compound.
- **Conclusion:** The use of the two test dentifrices demonstrated significant reductions in decayed, missing, and filled teeth and surfaces, however there was no statistically significant difference between the two test dentifrices clinically after two years of using the toothpastes. The results of this two-year clinical investigation support the conclusion that dentifrices containing 1.5% arginine, an insoluble calcium compound, and 1450 ppm fluoride as MFP provide superior protection against caries lesion cavitation compared to a positive control dentifrice containing only 1450 ppm fluoride as NaF.

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Introduction

According to the U.S. Department of Health and Human Service's Oral Health Initiative, dental caries is still "the single most common chronic childhood disease."¹ In addition, the U.S. National Center for Health Statistics Survey identified over 54% of children ages 6–9 who have had at least one cavity.² To address these findings, several of the oral health objectives of the U.S. Healthy People 2020 initiative involve the reduction in the incidence of caries in children, adolescents, and adults.³ One way to address this is through the use of an oral hygiene procedure of tooth brushing with fluoride toothpaste. Fluoride toothpastes have been widely used for over forty years and remain one of the standards for the preven-

tion of dental caries. The Cochrane Collaboration found that children who brush their teeth at least daily with fluoride toothpaste have a lower incidence of caries.⁴ Fluoride toothpaste has contributed significantly to the worldwide decrease in dental caries.⁵ Recently, the etiology, prevalence, and risk factors associated with dental caries were reviewed along with several important scientific concepts that will shape the future of caries research.⁶ These concepts were discussed in the broader framework of the metabolic integrity and diversity of dental plaque, as well as the roles that cariogenic bacteria, pH, and dietary sugars play.

Fluoride targets the tooth surface to arrest and reverse the caries

process. However, fluoride has limitations under pathogenic conditions, because it does not target dental plaque as its primary mode of action. New strategies to deliver superior caries prevention would ideally complement the effects of fluoride while targeting plaque pathogenicity. Despite sustained research in this area, few conceptual approaches to reduce plaque pathogenicity have progressed to clinically validated cost-effective products.⁶ An exception to this is the development and validation of innovative dentifrices containing 1.5% arginine, an insoluble calcium compound, and fluoride. Initial research a decade ago identified an arginine-based technology that would help raise the pH in the oral cavity and counter caries metabolic pathways. The anti-caries effect of this technology was demonstrated in two caries clinical studies.^{7,8} More recently, this technology has been expanded to be based on 1.5% arginine and an insoluble calcium compound, and combined with fluoride into a dentifrice. This dentifrice has been validated in a number of clinical and laboratory studies, with the clinical studies ranging from six months to two years. Five studies of six months duration have assessed the efficacy of dentifrices containing this technology in arresting and reversing (remineralizing) early, reversible enamel lesions and root caries lesions in children and adults, and is superior to dentifrices with only fluoride.⁹⁻¹³ In addition, a previous two-year caries clinical trial conducted on children in Thailand has demonstrated the significantly greater protection that these dentifrices can provide as opposed to a dentifrice with only fluoride.¹⁴ Finally, *in situ* clinical studies have shown that these dentifrices inhibit demineralization and enhance remineralization more effectively than dentifrices with fluoride alone.¹⁵ In these studies, two sources of insoluble calcium, dicalcium phosphate and calcium carbonate, were evaluated and are interchangeable with no impact on efficacy.

Additional research with this dentifrice containing 1.5% arginine, an insoluble calcium compound, and 1450 ppm fluoride as MFP has focused on its ability to modulate plaque metabolism and to increase ammonia production.¹⁶ This results in an increase in plaque pH and helps restore a pH-neutral environment. The authors concluded that the modulation of the plaque environment enhances utilization of the arginine deminase system, which is a key pathway through which ammonia is produced. The increase in pH was confirmed in a follow-up study.¹⁷ Subjects using this dentifrice containing 1.5% arginine, an insoluble calcium compound, and 1450 ppm fluoride as MFP had significantly higher plaque pH values before, as well as after a sucrose challenge than those using a silica-based dentifrice containing 1450 ppm sodium fluoride. Furthermore, subjects using the dentifrice containing 1.5% arginine, an insoluble calcium compound, and 1450 ppm fluoride as MFP also produced higher levels of ammonia and lower levels of lactic acid.

The confirmatory two-year, double-blind, three-treatment, parallel, randomized clinical trial reported here investigated the efficacy of two dentifrices containing 1.5% arginine, an insoluble calcium compound, and 1450 ppm fluoride as sodium monofluorophosphate (MFP) in preventing caries lesion cavitation compared to a dentifrice with 1450 ppm fluoride as sodium fluoride alone. The two sources of insoluble calcium compound, dicalcium phosphate and calcium carbonate were directly compared in this study.

Materials and Methods

This double blind, randomized, parallel group clinical investigation was conducted in Sichuan Province, China, where the fluoride level in tap water is less than 0.3 ppm.¹⁸ Prior to initiation of the study, the protocol and pertinent documents were reviewed and approved by the Institutional Review Board of West China College of Stomatology, Sichuan University. Schools were randomly selected to take part in the study based on the known caries risk of their students, levels of cooperation of the staff, students, and parents/guardians, and low population mobility determined during previous studies in the area and pilot investigations. Study participants volunteering to take part were school children ages 7–12 years. They had written informed consent to take part from a parent or legal guardian. Six thousand and seventy four children were screened at baseline and entered into the study. They were selected based on the following inclusion and exclusion criteria.

Inclusion Criteria

- Children in elementary or middle school who had at least four fully erupted permanent molars and at least one erupted permanent central or lateral incisor.

Exclusion Criteria

- Presence of orthodontic appliances.
- Any condition which, in the opinion of the investigator, would hinder participation by the potential subject. The reason for any such exclusion would be carefully documented by the investigator.
- Participation in any other clinical study during the three months preceding the clinical study.
- History of allergies or other adverse reactions to arginine, or oral care products or their ingredients

Study Design

Qualified subjects were randomly assigned to one of the three study treatments using a randomization table generated centrally by the study statistician following the revised version of the FDI Principal Requirements for Controlled Trials of Caries Preventive Agents.¹⁹ The three study treatments were:

- i. Test Dentifrice 1 containing 1.5% arginine, dicalcium phosphate, and 1450 ppm fluoride as MFP (Colgate-Palmolive Company, New York, NY, USA);
- ii. Test Dentifrice 2 containing 1.5% arginine, calcium carbonate, and 1450 ppm fluoride as MFP (Colgate-Palmolive Company, New York, NY, USA);
- iii. Positive Control Dentifrice containing 1450 ppm fluoride as NaF in a silica base (Procter & Gamble Company, Cincinnati, OH, USA).

Each subject was provided with three 100 ml tubes of their assigned dentifrice and three adolescent-size soft-bristled manual toothbrushes every three months for their exclusive use at home. Subjects in the same household were assigned to the same treatment group. To maintain the blinding of the investigation, the tubes of dentifrice were completely over-wrapped with white tape so that neither the examiners nor the subjects were aware of the identity of the product they were using. Participants were instructed to brush their teeth twice daily (morning and evening) at home. No instructions on post-brushing rinsing behavior were provided and subjects brushed

as per their established daily routine. Subjects were instructed not to use any other oral hygiene products, such as mouthrinses, dental floss, or other dentifrices. School teachers advised parents/guardians to help remind students about at-home tooth brushing. The school teachers also educated the students about the importance of at-home tooth brushing to ensure that, within the constraints of a home use unsupervised setting, subjects brushed their teeth twice daily. When the subjects received new supplies of dentifrice and toothbrush, the clinical team checked and reviewed returned/used dentifrices to help ensure compliance.

The sample size per group was estimated, based on previous investigations conducted in the population, using the following assumptions: (1) a two-year study period; (2) three-treatment groups; (3) coefficient of variation = 1.1; (4) power = 0.8; (5) $\alpha = 0.05$, two sided t-test; (6) a 10% difference between products; and (7) 10% annual attrition of subjects. With these assumptions, the required minimum sample size to satisfy the American Dental Association criterion for superior efficacy (10% difference between test and control products) at the end of the two years of product use was 1,920 subjects per group.

Clinical examinations were performed in school classrooms using portable dental equipment at baseline, and after one year and two years of product use using the criteria and methods described by the U.S. National Institute of Dental Research.²⁰

Clinical Examination and Scoring Procedure for Coronal Caries

Caries examinations were conducted by three trained and calibrated examiners in accordance with the established criteria^{20,21} after cleaning and drying the teeth. Each of the three examiners performed clinical examinations on the same subjects (approximately 2000) at baseline, and after one year and two years of product use. The examinations were conducted using a halogen light source with an attached dental mouth mirror (Miltex, Inc, York, PA, USA) and a WHO CPI probe (Shanghai Medical Instruments [Group] Ltd., Shanghai, China). A visual-tactile assessment of dental caries status was made using the probe to confirm continuity of the enamel surface. The status of all tooth surfaces for each permanent tooth was assessed, with the exception of any third molars. Subsequently, decayed, missing, and filled teeth (DMFT) and decayed, missing, and filled surfaces (DMFS) scores were calculated for each participant, and then the mean DMFT and DMFS scores were calculated for each dentifrice group.

Examiner Calibration

Training and calibration of the three caries examiners were conducted by an experienced clinician (Professor Deyu Hu, West China College of Stomatology, Sichuan University, Chengdu, China). The first part of the training and calibration was a discussion of diagnostic criteria, examination methods, and procedures. In the second part, the examiners were calibrated for inter- and intra-examiner reliability using a representative sample of subjects. The inter- and intra-examiner reliability was quantified through the calculation of an overall Kappa statistic, which is a widely used measure of reliability for categorical parameters and expresses the degree of improvement over random agreement. A threshold of ≥ 0.75 was used to qualify the examiners. Examiners were calibrated before the baseline measurements and then recalibrated annually.

Oral Soft and Hard Tissue Assessment

Using the same dental light and dental mirror used for the caries assessments, the three dental examiners visually examined the oral cavity and peri-oral area of each subject, whom they had evaluated for caries. 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 tonsillar and pharyngeal areas.

Adverse Events

Adverse events were obtained from interviews with each subject and from the dental examination by each examiner at each appointment.

Statistical Analyses

Statistical analyses were performed for the incremental DMFT and incremental DMFS scores for all subjects completing the study. Comparisons of the treatment groups with respect to baseline scores were performed using conventional analyses of variance (ANOVAs). Comparisons between the treatment groups with respect to gender were performed using chi-square tests and for age by ANOVA. Comparisons among treatment groups with respect to baseline-adjusted incremental DMFT and incremental DMFS scores after one year and two years were performed using analyses of covariance (ANCOVAs) on the per-protocol population. Post-ANCOVA pair-wise comparisons of the study treatments were performed using the Tukey test for multiple comparisons. All statistical tests of hypotheses were two-sided and employed a level of significance of $\alpha = 0.05$.

Results

Eight elementary schools in Sichuan Province, China, with a total of 6,301 subjects, were first approached to take part; 6,285 consented and 6,074 met the inclusion criteria and were assigned to one of the three study groups (Figure 1). A total of 5,669 students completed all phases of the study.

Inter- and intra-examiner calibration was performed for each of the three examination periods. The overall Kappa statistic for inter- and intra-examiner reproducibility of DMFT and DMFS was 0.82, which indicates a high level of agreement within and among the three examiners.

No adverse effects on the oral hard or soft tissues were observed by the examiners or reported by the subjects.

Baseline Data

The gender and age of the population who completed the study (per-protocol population) for the three study groups are presented in Figure 1. The three groups did not differ statistically significantly ($p > 0.05$) with respect to gender, but they did have a small difference with respect to age.

Summaries of the baseline data for the DMFT and DMFS scores for the subjects who completed the study are presented in Table I. The mean \pm standard deviation scores at baseline for DMFT for Test Dentifrice 1, Test Dentifrice 2, and Positive Control Dentifrice were 0.43 ± 0.83 , 0.43 ± 0.86 , and 0.46 ± 0.86 , respectively. The mean \pm standard deviation scores at baseline for DMFS were 0.56 ± 1.10 for Test Dentifrice 1, 0.56 ± 1.15 for Test Dentifrice 2, and

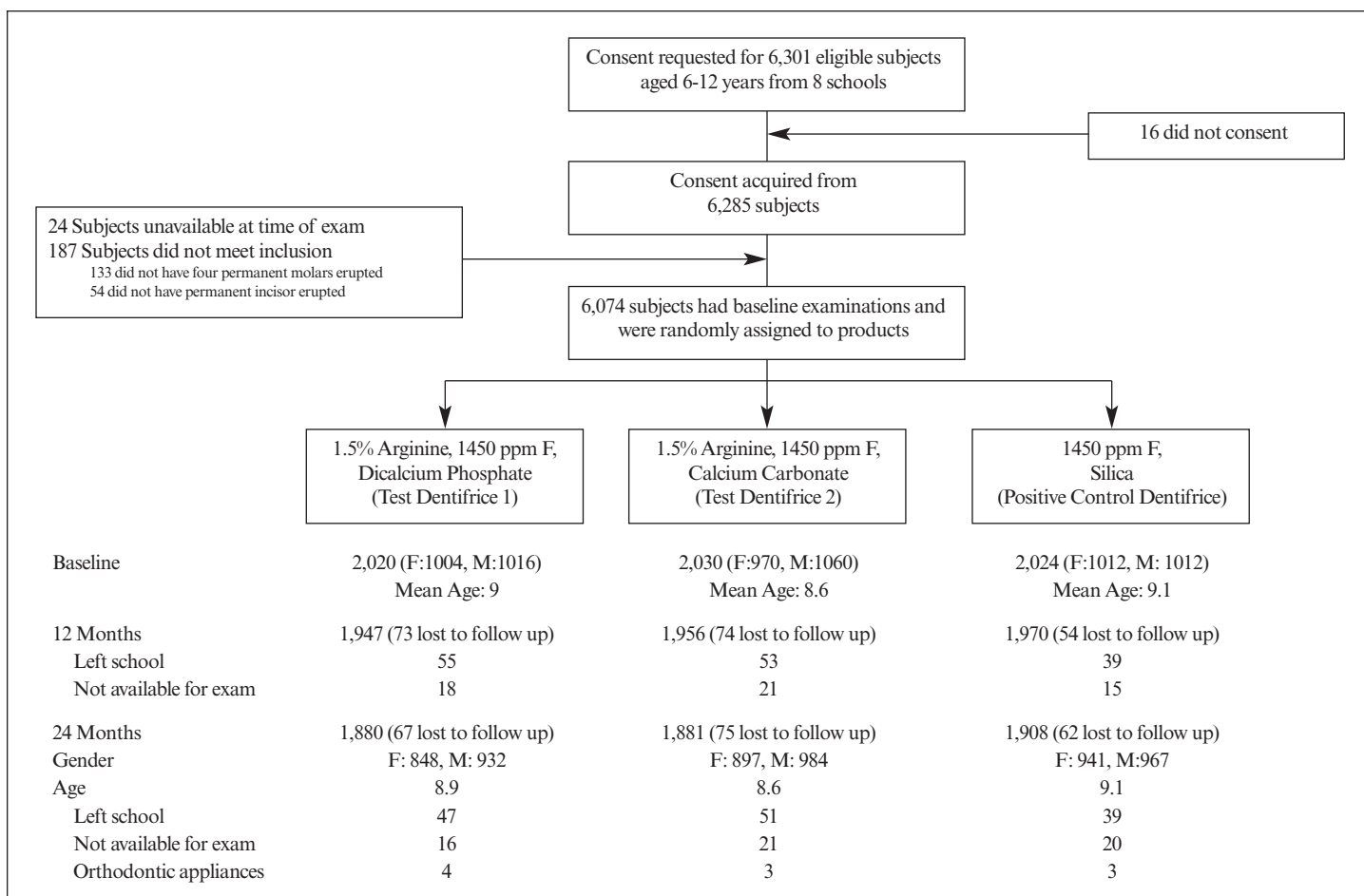


Figure 1. Disposition of subjects in the two-year clinical study.

Table I

Summary of the Mean (\pm SD) Baseline DMFT and DMFS Scores and One- and Two-Year Caries Increments for Subjects Who Completed the Two-Year Clinical Investigation.

Treatment	N	DMFT (Mean \pm SD)			DMFS (Mean \pm SD)		
		Baseline	One-Year Increment	Two-Year Increment	Baseline	One-Year Increment	Two-Year Increment
Test Dentifrice 1	1,880	0.43 \pm 0.83	0.19 \pm 0.57	0.31 \pm 0.67	0.56 \pm 1.10	0.24 \pm 0.80	0.41 \pm 0.95
Test Dentifrice 2	1,881	0.43 \pm 0.86	0.19 \pm 0.55	0.31 \pm 0.66	0.56 \pm 1.15	0.24 \pm 0.76	0.41 \pm 0.97
Positive Control Dentifrice	1,908	0.46 \pm 0.86	0.21 \pm 0.56	0.39 \pm 0.71	0.60 \pm 1.20	0.26 \pm 0.73	0.51 \pm 0.97

0.60 \pm 1.20 for the Positive Control Dentifrice. No statistically significant ($p > 0.05$) differences in either DMFT or DMFS were indicated among the three groups at baseline (Table II).

One-Year Data Incremental DMFT and DMFS Scores

The mean incremental DMFT scores measured after one year of product use are shown in Table I and were 0.19 \pm 0.57, 0.19 \pm 0.55, and 0.21 \pm 0.56 for Test Dentifrice 1, Test Dentifrice 2, and Positive Control Dentifrice, respectively. After one year of product use, no statistically significant ($p > 0.05$) differences were indicated among the three dentifrice groups with respect to reductions in incremental DMFT scores.

The mean incremental DMFS scores measured after one year of product use are shown in Table I and were 0.24 \pm 0.80, 0.24 \pm 0.76, and 0.26 \pm 0.73 for Test Dentifrice 1, Test Dentifrice 2, and Positive Control Dentifrice, respectively. Likewise, no statistically significant ($p > 0.05$) differences were indicated among the three

Table II

Summary of the Statistical Significances of Differences Between Subjects in the Three Groups for Those Completing the Two-Year Clinical Investigation

Dentifrice Comparison	Significant ($p < 0.05$) Pair-Wise Comparisons			
	DMFT Increment		DMFS Increment	
	One-Year	Two-Year	One-Year	Two-Year
Test Dentifrice 1 x Test Dentifrice 2	NS	NS	NS	NS
Test Dentifrice 1 x Positive control	NS	20.5%	NS	19.6%
Test Dentifrice 2 x Positive control	NS	20.5%	NS	19.6%

dentifrice groups with respect to reductions in incremental DMFS scores after one year of product use (Table II).

Two-Year Data Incremental DMFT and DMFS Scores

The mean incremental DMFT scores measured after two years of product use are presented in Table I. They were 0.31 \pm 0.67, 0.31

± 0.66 , and 0.39 ± 0.71 for Test Dentifrice 1, Test Dentifrice 2, and Positive Control Dentifrice, respectively. Relative to the Positive Control Dentifrice, both Test Dentifrice 1 and Test Dentifrice 2 exhibited statistically significant ($p < 0.05$) reductions of 20.5% each in incremental DMFT scores (Table II). However, no statistically significant ($p > 0.05$) difference was observed between the two test dentifrices in incremental DMFT scores after two years of product use (Table II).

The mean incremental DMFS scores measured after two years of product use are also shown in Table I. They were 0.41 ± 0.95 , 0.41 ± 0.97 , and 0.51 ± 0.97 for Test Dentifrice 1, Test Dentifrice 2, and Positive Control Dentifrice, respectively. Relative to the Positive Control Dentifrice, both Test Dentifrice 1 and Test Dentifrice 2 exhibited statistically significant ($p < 0.05$) reductions of 19.6% (Table II) in incremental DMFS scores after two years of product use. The incremental DMFS scores for the two test dentifrices after two years of product use, however, were not statistically significantly ($p > 0.05$) different from each other (Table II).

Discussion

Fluoride has been included in dentifrices for its anti-caries benefits, and its anti-caries efficacy has been documented.^{4,22} However, significant enhancements to the clinical efficacy of dentifrices formulated with 1450 ppm fluoride, the maximum permitted level of fluoride in mass marketed dentifrices, have not been forthcoming until recently, despite active research on new ingredients and innovative formulations. A new technology based upon 1.5% arginine and an insoluble calcium compound in combination with 1450 ppm fluoride has demonstrated promise, providing statistically significant and clinically meaningful anti-caries efficacy compared to dentifrices with only 1450 ppm fluoride.¹⁴

The results of the current two-year clinical investigation confirm that two dentifrices containing 1.5% arginine, an insoluble calcium compound (as dicalcium phosphate or calcium carbonate), and 1450 ppm fluoride provide significant reductions in incremental DMFT and DMFS scores compared to a positive control dentifrice containing 1450 ppm fluoride alone. In addition, the two arginine-containing dentifrices with either dicalcium phosphate or calcium carbonate provided the same levels of efficacy in preventing the formation of new cavitated caries lesions. Both sources of insoluble calcium compound, dicalcium phosphate and calcium carbonate, were included in this confirmatory study since both abrasive systems are typically available to consumers. Importantly, the percentage reductions in mean caries increment after two years for the two dentifrices relative to the fluoride-only, positive control dentifrice exceed the accepted criterion for superior anti-caries efficacy of 10%,^{23,24} highlighting the clinical relevance of the results. As with the previous two-year clinical study, the DMFT increments of between 0.31 and 0.39 are relatively small and are likely reflective of the inclusion of low to moderate risk subjects in the study.¹⁴

Most recently, the results from a two-year study that assessed the benefit of an enhanced oral health promotion program were published and document the positive effect a dentifrice containing 1.5% arginine, an insoluble calcium compound, and 1450 ppm fluoride as MFP.²⁵ These results indicated that the subjects participating in a closely supervised school-based brushing program and using a dentifrice containing 1.5% arginine, an insoluble calcium com-

pound, and 1450 ppm fluoride as MFP demonstrated a reduction in DMFT of 26.9% and a reduction in DMFS of 34.1% when only dentine lesions were analyzed, as compared to subjects in the control group who used a dentifrice with 1000 ppm fluoride who participated in an unsupervised school-based brushing program.

A body of evidence has been published to demonstrate the superiority of a dentifrice containing 1.5% arginine, insoluble calcium, and 1450 ppm fluoride to dentifrices containing only fluoride. These include studies demonstrating the arresting and reversing early enamel lesions,¹¹⁻¹³ examining rehardening of adult root surface lesions,^{9,10} measuring the demineralization/remineralization of enamel in intra-oral studies,¹⁵ and monitoring of plaque metabolism studies.^{16,17} Furthermore, a two-year clinical study has demonstrated that a fluoride-free toothpaste containing 1.5% arginine provided equivalent anti-caries efficacy to a silica-based toothpaste containing 1100 ppm fluoride, indicating that arginine can provide clinically meaningful caries prevention.⁷ All of these studies support the overall superiority of arginine-containing dentifrices to fluoride dentifrices in the prevention of caries.

Other researchers have discovered a positive association between the *in situ* ammonia production from salivary arginine via the arginine deiminase system (ADS) in dental plaque and a reduced caries experience.^{26,27} This indicates the importance of ammonia production in caries prevention. An additional study has shown that an anti-caries effect may be expected from an arginine-containing, fluoride-free toothpaste and is due to an enhancement of ADS activity.²⁸

Conclusion

The results of this two-year clinical investigation support the conclusion that dentifrices containing 1.5% arginine, an insoluble calcium compound, and 1450 ppm fluoride as MFP provide superior protection against caries lesion cavitation compared to a positive control dentifrice containing only 1450 ppm fluoride as NaF.

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