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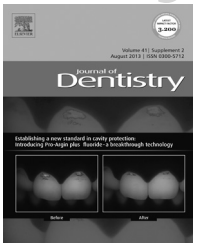

Comparing the efficacy of a dentifrice containing 1.5% arginine and 1450 ppm fluoride to a dentifrice containing 1450 ppm fluoride alone in the management of primary root caries

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ABSTRACT

Objective: To compare the efficacy of a new dentifrice containing 1.5% arginine and 1450 ppm fluoride to a positive control dentifrice containing 1450 ppm fluoride alone in arresting and reversing primary root caries lesions in adults.

Study design: A total of 3779 subjects from Piracicaba, Säo Paulo, Brazil were screened; 284 had at least one leathery primary root caries lesion and were eligible for the study. The new dentifrice contained 1.5% arginine, an insoluble calcium compound, and 1450 ppm fluoride, as sodium monofluorophosphate; the matched positive control dentifrice contained 1450 ppm fluoride. One lesion for each subject was selected for inclusion in the study and was examined at baseline, 3 and 6 months.

Results: A total of 253 subjects completed the study with 129 of 144 subjects included in the final statistical analysis for the test dentifrice and 124 of 140 for the positive control. The mean age of subjects was 45.7 (±9.19) years and 56.5% were female. After 6 months product use, 70.5% of root caries lesions improved for subjects using the arginine-containing dentifrice compared to 58.1% for subjects using the positive control. The difference in the number of root caries lesions becoming hard in the two groups was statistically significant ($p = 0.038$).

Conclusion: A new dentifrice containing 1.5% arginine, an insoluble calcium compound, and 1450 ppm fluoride, as sodium monofluorophosphate, provided statistically significantly superior efficacy in arresting and reversing active root caries lesions in adults compared to a matched positive control dentifrice containing fluoride alone.

1. Introduction

Despite the highly successful introduction of fluoride, dental caries remains a prevalent oral disease, and cavities remain a global public health problem. Historically, epidemiology research has emphasized dental caries in young people. Nonetheless, research shows that dental caries is important throughout life because caries prevalence and severity increases with age as secondary, or recurrent, caries begins

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to dominate over new primary lesions.[1] In addition, studies have reported an increase in the prevalence of root caries as a result of older adults retaining a higher number of teeth in their oral cavity. The possibility that exposed root surfaces are present in older adults increases the risk of caries development and progression.[2–5]

There is undisputed evidence that fluoride has a beneficial effect on de- and re-mineralization of both enamel and root dentin.[6–9] For this reason, brushing with fluoride toothpaste remains as the first line of defense against root caries, helping to remove plaque and acting as a fluoride delivery vehicle. In fact, it is one of the few interventions in dentistry which has survived the detailed scrutiny of the systematic review process.[10]

The extensive use of fluoridated dentifrice has led to a decrease in dental caries prevalence worldwide, including rapidly developing countries, such as Brazil.[11] Despite the evidence that fluoridated dentifrice has played a significant role in controlling caries development, it can not completely prevent dental caries – a disease continuum that progresses through a series of stages from the formation of a reversible early de-mineralized lesion to a cavity that can no longer be reversed.[1] One reason why fluoride cannot completely prevent the caries process is that dental caries is a complex, multi-factorial process; it involves residual dental plaque biofilm, a susceptible tooth surface, and sugar, and it occurs at the interface where bacterial metabolism of these dietary sugars produces acids. Fluoride is effective in preventing cavities because it targets the tooth surface where it reverses and repairs early caries lesions by driving calcium and phosphate back into the de-mineralized hydroxyapatite. It also strengthens the hydroxyapatite by integrating into the tooth structure as fluorapatite. In addition, fluoride is effective in preventing cavities because it reduces the critical pH below which calcium and phosphate ions are lost from the tooth surface, thereby reducing de-mineralization.[1] However, fluoride does not target the root cause–dental plaque. Therefore, there is good reason to believe that new technologies should be investigated that have the potential to complement and enhance the effects of fluoride by specifically targeting dental plaque to reduce its pathogenicity. This could, at least in principle, be accomplished by reducing the numbers of bacterial species within the plaque biofilm that are associated with caries, such as the mutans streptococci, or by modulating biofilm metabolism to reduce the production and effects of bacterial acid.[1]

Among the new technologies recently identified for their potential oral health benefits is a novel combination of arginine and an insoluble calcium compound. Arginine is a semi-essential amino acid found in many foods, including milk and its byproducts, meat, poultry, seafood, cereals and nuts, which is considered safe for use in toothpaste. The insoluble calcium may be in the form of calcium carbonate or dicalcium phosphate dihydrate. By utilising the arginine deiminase pathway in non-pathogenic, arginolytic organisms, such as *S. sanguis*, arginine is metabolized to ammonia which, in turn, can neutralize plaque acids and stabilize the residual plaque biofilm on susceptible tooth surfaces.[12,13] In so doing, arginine can help prevent shifts in biofilm flora to acid-producing bacteria, such as *S. mutans*, and maintain a ''healthy'' plaque after sugar challenge. Further, the insoluble calcium compound can act a reservoir of free calcium ions to augment the re-mineralization process helping to arrest and reverse early caries lesions to prevent cavities.[1]

In a 2-year caries clinical trial, a fluoride-free calcium-based toothpaste containing arginine bicarbonate was evaluated as an alternative to regular fluoride toothpaste. The results of the study show that the fluoride-free arginine/bicarbonate toothpaste reduced the formation of cavities as effectively as 1100 ppm fluoride toothpaste, demonstrating that the approach is valid and applicable to toothpaste.[14] Based upon the scientific literature, this new arginine-containing toothpaste is particularly noteworthy, as it is the first fluoride-free toothpaste to demonstrate comparable clinical efficacy in preventing cavities to the efficacy of 1100 ppm sodium fluoride toothpaste.[1]

Based upon the mechanism of action of arginine, which is complementary to the well-known mechanism of action of fluoride, arginine has the potential to significantly enhance the caries preventive benefits of traditional fluoride dentifrices. For this reason, a next generation dentifrice technology based upon 1.5% arginine and 1450 ppm fluoride, as monofluorophosphate, in a calcium base has been developed and clinically validated. Specifically, three coronal caries studies, using quantitative light-induced fluorescence (QLF) to measure changes in early caries lesions in children, have each shown that a new dentifrice containing 1.5% arginine and 1450 ppm fluoride in a calcium base is significantly more effective in arresting and reversing coronal caries lesions than a dentifrice containing 1450 ppm fluoride alone. Two additional studies have measured changes in root caries lesions in adults, and each has shown that the new dentifrice containing 1.5% arginine and 1450 ppm fluoride in a calcium base is significantly more effective in arresting and reversing root caries lesions than a dentifrice containing 1450 ppm fluoride alone. Furthermore, it has been proven to more effectively prevent the progression of caries to cavitation than dentifrice with fluoride alone. This Special Issue of Journal of Dentistry reports two of the coronal and one of the root caries clinical studies.[15–17] A Special Issue of Journal of Clinical Dentistry reports the additional coronal and root caries studies,[18,19] together with a series of *in situ* and *in vivo* mechanism of action studies which demonstrate that this new technology works by targeting dental plaque to modulate bacterial metabolism enhancing the production of ammonia which, in turn, helps neutralize bacterial acids to reduce fluctuations in plaque pH, thereby, reducing de-mineralization and enhancing re-mineralization of early caries lesions.[20,21]

The aim of this study was to test the hypothesis that the new dentifrice containing 1.5% arginine, an insoluble calcium compound, and 1450 ppm fluoride as sodium monofluorophosphate (MFP) is more effective than a matched, positive control dentifrice containing 1450 ppm fluoride alone in hardening primary root caries lesions in adults.

2. Materials and methods

This 6-month randomized controlled clinical study was conducted in groups of adults residing in Piracicaba, Sao Paulo, Brazil. The drinking water at the study site contains approximately 0.7 ppm fluoride. Approval to conduct the study was given by the Research Ethics Committee of the Piracicaba Dental School, Säo Paulo, Brazil.

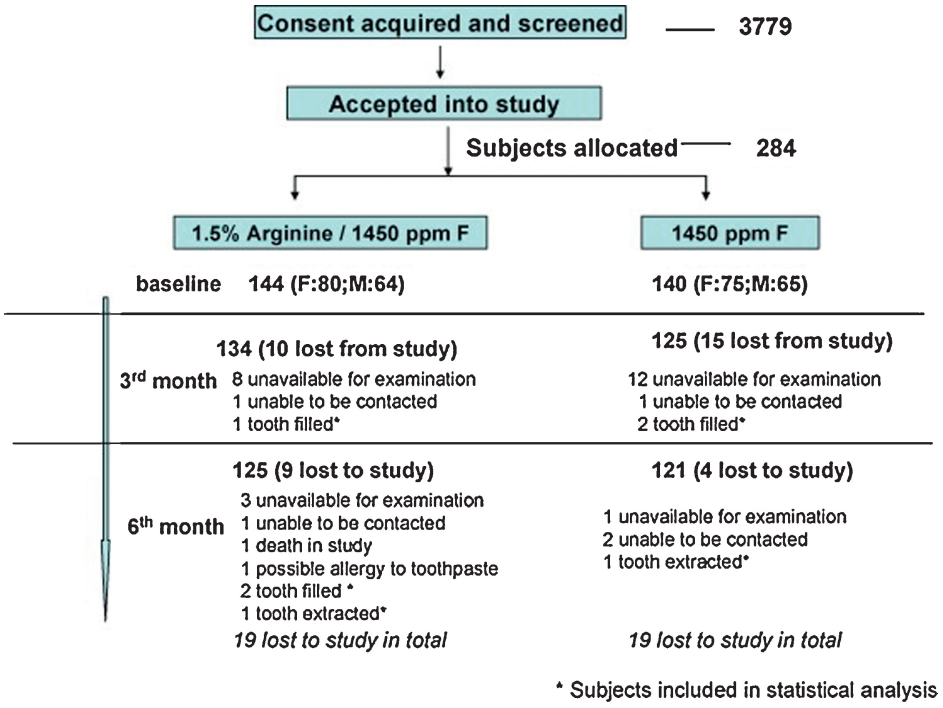

Fig. 1 – Disposition of subjects.

In order to participate in this study, male and female subjects had to be at least 30 years of age, have at least eight natural uncrowned teeth and at least one leathery root caries lesion. Subjects were excluded if they had advanced periodontal disease, had participated in another dental study during the previous 3 months, had a history of allergy to oral care or personal care consumer products or their ingredients, or were pregnant or nursing. A total of 3779 subjects were screened and of these 284 were found to meet the eligibility criteria, entered into the study and allocated to one of the two study products (Fig. 1).

Participants were allocated to one of two groups using a sequence of codes randomly generated by the study administrator. The two groups comprised a positive control group using a matched product containing 1450 ppm fluoride, as sodium monofluorophosphate (MFP), in a calcium base and an experimental group using the test product containing 1.5% arginine, and insoluble calcium compound, and 1450 ppm fluoride, as MFP. Because the two products contained the same abrasive system, the relative dentin abrasion (RDA) values were very similar, and both were much lower than the maximum permitted RDA for daily use toothpastes. Within the randomization, product allocation was stratified according age (two levels; 30–50 and 51–69) and number of lesions present (two levels; $\leq$4 and 5 or more).

Participants were instructed to brush at least twice daily with their assigned dentifrice and a Colgate plus Sensitive, compact head, soft toothbrush (Colgate-Palmolive, New York, NY) for 1 min. Prior to and during the course of the study, a dental professional provided participants with instruction in proper oral hygiene to ensure that the toothpaste was being used as recommended. Two tubes of dentifrice and a toothbrush were supplied to each subject at 6-week intervals. The tubes were individually labelled for each study participant and supplied in plain white containers to conceal the identity of the product. Only one type of toothpaste was assigned per family and additional tubes of toothpaste were available upon participant's request. A compliance check occurred in conjunction with the 6-week deliveries of toothpaste. To help ensure that products were being used by the study participants, at both the 3- and 6-month examinations, empty and partially used tubes were returned to the study site before additional toothpaste was supplied.

One leathery lesion for each subject was selected for inclusion in the study and examined at baseline, 3 and 6 months. When possible, lesions were chosen with clearly demarcated borders on the buccal surfaces of teeth. In cases where multiple suitable lesions were available, the most anterior lesion was selected.

3. Examination methods

Examinations were performed at baseline and after 3 and 6 months of product use by a single examiner. The clinical assessment commenced with an examination of the soft and hard tissues of the mouth. The methods described by Baysan et al. were used to perform a detailed assessment of the selected root caries lesion.[22]

3.1. *Dental plaque*

The amount of plaque overlying each lesion was measured using the Plaque Index of Silness and Loe and scored as follows[23]:

0 = no plaque.
1 = a thin film of plaque adhering to the gingival margin and adjacent area of the tooth. The plaque may be seen *in situ* only after using the probe on the tooth surface.
2 = Moderate accumulation of soft deposits within the gingival pocket or on the tooth and gingival margin which can be seen with the naked eye.
3 = Abundance of soft matter within the gingival pocket and/or on the tooth and gingival margin.

Dental plaque scores were recorded at the baseline examination to ensure that the groups were similar at baseline with respect to this variable.

3.2. *Lesion height, width and distance from the gingival margin*

The maximum height and width of the lesions was measured to the nearest 0.5 mm using standard periodontal probe with 1 mm markings (PCPUNC15, Hu Friedy, US). The product of these two values was calculated and used to estimate the ''area'' of the lesion which was used in statistical analysis. The distance from the gingival margin to the gingival border of the lesion was also measured to the nearest 0.5 mm.

3.3. *Hardness*

The hardness of each lesion was defined as follows: a soft lesion is one which permitted a sharp probe (No. 5 Sharp Explorer) to penetrate the lesion with ease, and there was no resistance to its withdrawal; a leathery lesion permitted a sharp probe to penetrate the surface, but there was some resistance to its withdrawal; a hard lesion is comparable in hardness to the surrounding sound root dentine.

3.4. *Statistical analysis*

The number of lesions becoming hard was compared for the two study groups using a Chi^2 test at the 3- and 6-month examinations. The number of lesions becoming hard at the 6-month examination was the primary outcome for the study. Further analysis using a logistic regression model was used to control for potential baseline imbalance of lesion characteristics. The level of statistical significance was set at $p < 0.05$.

4. Results

A total of 129 of 144 subjects were included in the final statistical analysis for the experimental group and 124 of 140 in the positive control group. Reasons for loss from the study are tabulated in Fig. 1. The mean age of subjects included in the final statistical analysis was 45.7 (±9.19) years and 56.5% were female.

4.1. *Baseline balance*

The baseline characteristics of plaque, lesion area, distance of the lesion from the gingival margin and number of lesions per subjects are shown in Table 1. It can be seen that there was some evidence of baseline imbalance with lesions tending to be larger in area ($p = 0.022$) in the arginine-containing dentifrice group than in the positive control group. The results of the logistic regression analysis, show in Table 3, indicate that these differences would increase the probability that a lesion would not become hard for the arginine-containing dentifrice group compared to the positive control.

4.2. *Lesion hardness*

Lesion hardness scores are shown in Table 2. At the baseline examination, in accordance with the inclusion criteria, all

Table 1 – Baseline mean plaque score, distance of lesion from the gingival margin (mm), lesion area (mm^2) and number of lesions for the two study groups (mean (SD)).

	1.5% Arginine/1450 MFP N = 129	1450 MFP N = 124	Significance of difference
Lesion plaque score	1.56 (1.01)	1.36 (1.00)	$p = 0.12$
Distance from Gingival margin	0.52 (0.82)	0.58 (0.84)	$p = 0.56$
Lesion area	4.11 (4.05)	3.06 (3.09)	$p = 0.022$
Number of lesions	3.35 (3.29)	3.46 (3.59)	$p = 0.80$

Table 2 – Cross-tabulation of baseline hardness with the 3- and 6-month scores for subjects completing the study or being withdrawn due to the tooth being filled or extracted for the two study groups.

Group		Baseline	3 months				6 months				
		Leathery	Soft	Leathery	Hard	Filled	Soft	Leathery	Hard	Filled	Extracted
1.5% Arginine/1450 MFP	*n*	129	0	89	39	1	0	34	91	3	1
	%	100	0	69.0	30.2	0.8	0	26.4	70.5	2.3	0.8
1450 MFP	*n*	124	1	71	50	2	2	47	72	2	1
	%	100	0.8	57.3	40.3	1.6	1.6	37.9	58.1	1.6	0.8

3 months; 1.5% Arginine/1450 ppm F 39/129 (30.2%) became hard compared to 1450 ppm F 50/121 (41.3%) $p = 0.093$; 6 months; 1.5% Arginine/1450 ppm F 91/129 (70.5%) became hard compared to 1450 ppm F 72/124 (58.1%) $p = 0.038$

Table 3 – Logistic regression analysis for lesion hardness at 6 months controlling for baseline mean plaque score, distance of lesion from the gingival margin (mm), lesion area (mm^2) and number of lesions.

	B coefficient (SE)	Sig.	Exp (B)	95.0% C.I. for Exp(B)	
				Lower	Upper
Plaque score	−0.57 (0.17)	0.001	0.568	0.411	0.784
Distance from gingival margin	0.85 (0.25)	0.001	2.329	1.431	3.791
Baseline lesion area	−0.07 (0.05)	0.14	0.934	0.852	1.023
Number of root caries lesions	−0.05 (0.05)	0.27	0.949	0.865	1.041
Group	0.88 (0.30)	0.004	2.410	1.332	4.359

Table 4 – Baseline mean plaque score, distance of lesion from the gingival margin (mm), lesion area (mm^2) and number of lesions for lesions classified as hard or not hard at the 6-month examination (mean (SD)).

	Not hard at 6-month examination N = 90	Hard at 6-month examination N = 163	Significance of difference
Lesion Plaque score	1.82 (0.87)	1.26 (1.02)	$p < 0.001$
Distance from Gingival margin	0.28 (0.50)	0.70 (0.93)	$p < 0.001$
Lesion area	4.69 (4.30)	2.99 (3.08)	$p = 0.001$
Number of lesions	4.34 (4.35)	2.88 (2.68)	$p = 0.004$

lesions were leathery. After 3 months of product use, 30.2% of lesions had become hard in the arginine-containing dentifrice group compared to 40.3% in the positive control. During the first 3 months of the study, one lesion was restored in the arginine-containing dentifrice group and two lesions were restored and one became soft in the positive control group. The difference in the number of lesions becoming hard in the arginine-containing dentifrice and positive control groups was not statistically significant at the 3-month examination ($p = 0.09$).

At the 6-month examination, 70.5% of lesions had become hard in the arginine-containing dentifrice group compared to 58.1% in the positive control group. During the 6 months of the study, three lesions were restored and one was extracted in the arginine-containing dentifrice group. In the positive control group, two lesions were restored, one was extracted and two became soft. The difference in the number of lesions becoming hard in the arginine-containing dentifrice and positive control groups was statistically significant ($p = 0.038$).

The unadjusted odds ratio for lesions becoming in the experimental group compared to the control was 1.73 (95% CI 1.03–2.91). A logistic regression analysis was used to assess the impact of the slight imbalance in baseline lesion characteristics by comparing the odds ratio of lesions becoming hard after controlling for baseline covariates (Table 3). The significance of the difference between the two groups increased from $p = 0.038$ to $p = 0.004$ using the logistic regression analysis. The odds ratio for lesions becoming hard between the two study groups increased to 2.41 (95% CI 1.33–4.36) when the baseline covariates were included.

4.3. *Baseline characteristics and lesion hardness at 6 months*

The baseline characteristics of subjects with lesions becoming hard at 6 months were compared to those that did not improve or became worse (Table 4). Lesions that became hard had the following baseline characteristics on average: lesions had less plaque ($p < 0.001$), were further from the gingival margin ($p < 0.001$), were smaller in area ($p < 0.001$) and were present in subjects who had fewer root caries lesions present ($p = 0.004$).

5. Discussion

The highly successful introduction of fluoride has led to a decrease in dental caries prevalence worldwide. Nonetheless, there is abundant caries prevalence and severity data that demonstrate that dental caries remains a global oral health problem.[1] Fluoridated dentifrice, in particular, has played a significant role in controlling the caries process and preventing the formation of cavities by acting upon de-mineralized tooth surfaces to re-mineralize and strengthen the enamel and, thereby, to reverse and repair early caries lesions. Fluoride also prevents de-mineralization because it reduces the critical pH below which calcium and phosphate ions are lost from the tooth surface.[1] However, fluoride can not completely prevent the caries process, because it does not act upon dental plaque.

For this reason, a new dentifrice containing 1.5% arginine, an insoluble calcium compound, and 1450 ppm fluoride, as monofluorophosphate, has been developed. The combination of arginine and an insoluble calcium compound complements and enhances the effects of a fluoride dentifrice by additionally targeting dental plaque to reduce its pathogenicity.[1] The arginine is metabolized to ammonia which helps to neutralize plaque acids, to prevent shifts in biofilm flora to acid-producing bacteria, such as *S. mutans*, and to maintain a ''healthy'' plaque after sugar challenge.[21] Further, the insoluble calcium compound acts a reservoir of free calcium ions to enhance the re-mineralization process.[20] This new dentifrice containing 1.5% arginine, an insoluble calcium compound, and 1450 ppm fluoride, as monofluorophosphate, has been clinically proven to arrest and reverse early caries lesions more effectively than control dentifrices containing fluoride both in children with early coronal caries lesions and in older

adults with active root caries.[15–19] Furthermore, it has been proven to more effectively prevent the progression of caries to cavitation than dentifrice with fluoride alone.[24]

Three coronal caries studies, using quantitative light-induced fluorescence (QLF) to measure changes in early caries lesions in children, have each shown that a new dentifrice containing 1.5% arginine, and insoluble calcium compound and 1450 ppm fluoride is significantly more effective in arresting and reversing coronal caries lesions than a dentifrice containing 1450 ppm fluoride alone.[15,16,18] In one study, the new dentifrice was compared to two control dentifrices: a matched positive control containing 1450 ppm fluoride alone and a matched fluoride-free negative control. After 6 months product use, improvements from baseline in the representative parameter ΔQ (lesion volume) were 50.7, 32.3 and 11.4% for the new arginine-containing dentifrice, the positive control dentifrice, and the negative control dentifrice, respectively. The differences between the negative control and the two fluoride containing dentifrices ($p < 0.001$), as well as the differences between the new dentifrice and the positive control ($p = 0.003$), were statistically significant.[18] In a second study, the new dentifrice was compared to two control dentifrices; a positive control containing 1450 ppm fluoride as sodium fluoride in a silica base and a matched fluoride-free negative control. After 6 months product use, improvements from baseline in the parameter ΔQ (lesion volume) were 50.6, 34.0 and 13.1% for the new arginine-containing dentifrice, the positive control dentifrice and the negative control dentifrice, respectively. Once again, the differences between the negative control and the two fluoride containing dentifrices ($p < 0.001$), as well as the differences between the new dentifrice and the positive control ($p = 0.008$), were statistically significant.[15] In a third study, the new dentifrice was compared to a matched positive control dentifrice containing 1450 ppm fluoride alone. After 6 months product use, improvements from baseline in the parameter ΔQ (lesion volume) were 44.6 and 28.9% for the new arginine-containing dentifrice and the positive control dentifrice, respectively. The difference between the new dentifrice and the positive control was statistically significant ($p < 0.001$).[16]

Two root caries studies in adults have each shown that the new dentifrice containing 1.5% arginine and 1450 ppm fluoride in a calcium base is significantly more effective in arresting and reversing root caries lesions than a dentifrice containing 1450 ppm fluoride alone. In one study, the new dentifrice was compared to two control dentifrices: a positive control containing 1450 ppm fluoride, as sodium fluoride, in a silica base, and a matched fluoride-free negative control. After 6 months product use, clinical hardness measures showed that only one lesion (0.7%) was worse in the new dentifrice group compared to 9.0 and 18.2% in the positive and negative control groups, respectively. In addition, 61.7, 56.0 and 27.0% lesions showed improvement for the new arginine-containing dentifrice, the positive control dentifrice and the negative control dentifrice, respectively. The differences in the distribution of lesion change scores between the negative control and the two fluoride containing dentifrices ($p < 0.001$), as well as the differences between the new dentifrice and the positive control ($p = 0.006$), were statistically significant.[19]

The clinical study reported in this paper is the second of the root caries studies and compared the new dentifrice to a matched positive control containing 1450 ppm. After 6 months product use, 70.5% of root caries lesions improved for subjects using the new dentifrice compared to 58.1% for subjects in the positive control group. The difference in the number of root caries lesions being hardened in the new dentifrice and positive control groups was statistically significant ($p < 0.05$). Thus, this study confirmed the hypothesis that the new dentifrice was more effective in hardening root caries lesions in adults than a marketed positive control dentifrice containing 1450 ppm fluoride alone. The results support the findings of the other four clinical studies.[15–19]

Together, these five studies show that a new dentifrice containing 1.5% arginine, an insoluble calcium compound, and 1450 ppm fluoride, as monofluorophosphate, is clinically proven to arrest and reverse early caries lesions more effectively in both children and adults than control dentifrices containing fluoride alone.

Finally, a 2-year conventional caries clinical study has proven that two dentifrices containing 1.5% arginine and 1450 ppm fluoride in a calcium base, one with di-calcium phosphate and the other with calcium carbonate, are significantly more effective in preventing the formation of cavitated caries lesions than a dentifrice containing 1450 ppm fluoride alone. Three trained and calibrated dentists examined the children at baseline and after one and two years using the National Institute of Dental Research Diagnostic Procedures and Criteria. The number of decayed, missing, and filled teeth (DMFT) and surfaces (DMFS) for the three study groups were very similar at baseline, with no statistically significant differences among groups. After one year, there were no statistically significant differences in caries increments among the three groups. After two years, the two groups using the dentifrices containing 1.5% arginine, an insoluble calcium compound and 1450 ppm F had statistically significantly ($p < 0.02$) lower DMFT increments (21.0% and 17.7% reductions, respectively) and DMFS increments (16.5% and 16.5%) compared to the control dentifrice. The differences between the two groups using the new dentifrices were not statistically significant. The results of this pivotal clinical study support the conclusion that dentifrices containing 1.5% arginine, an insoluble calcium compound, and 1450 ppm fluoride provide superior protection against caries lesion cavitation to dentifrices containing 1450 ppm fluoride alone.[24]

6. Conclusion

This study demonstrates that use of a new dentifrice containing 1.5% arginine, an insoluble calcium compound, and 1450 ppm fluoride, as monofluorophosphate, statistically significantly enhances the re-mineralization of root caries lesions as compared to use of a dentifrice containing fluoride alone.

Conflict of interest

Drs Zhang, Cummins and Ellwood are employees of the Colgate-Palmolive Company. Drs Souza, Tenuta and Cury

have no conflict of interest. Mr Mateo provided independent statistical review of the data for the Colgate-Palmolive Company on a consultancy basis.

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