Efficacy of 1.23% APF gel applications on incipient carious lesions: a double-blind randomized clinical trial

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Abstract: The aim of this double-blind randomized clinical trial was to evaluate the efficacy of 1.23% APF gel application on the arrest of active incipient carious lesions in children. Sixty 7- to 12-year-old children, with active incipient lesions were included in the study. Children were divided randomly into 2 groups: 1.23% APF gel and placebo gel applications. Each group received 8 weekly applications of treatment. The lesions were re-evaluated at the 4th and 8th appointments. Poisson regression analysis was used to estimate relative risks of the presence of active white spot lesions. Groups showed similar results (PR = 1.67; CI 95% 0.69–3.98). The persistence of at least 1 active lesion was associated with a higher number of lesions in the baseline (PR = 2.67; CI 95% 1.19–6.03), but not with sugar intake (PR = 1.06; CI 95% 0.56–2.86) and previous exposure to fluoride dentifrice (PR = 1.26; CI 95% 0.49–2.29). The trial demonstrates the equivalence of the treatments. The use of the APF gel showed no additional benefits in this sample of children exposed to fluoridated water and dentifrice. The professional dental plaque removal in both groups may also account for the resulting equivalence of the treatments.

Descriptors: Fluorides, Topical; Dental Caries; Toothbrushing.

Introduction

Despite the decline of the prevalence of dental caries observed worldwide, there is still a considerable number of children presenting with the disease. The clinical features of dental caries may vary from a white spot to a cavity, if the disease is not controlled. Studies have indicated that initial carious lesions are significantly more prevalent than cavitated lesions[1,2] and that the presence of initial lesions is a predictor of caries increment in the permanent dentition.[3]

Preventive strategies must be employed to revert the changes provoked by the disease in enamel through a noninvasive treatment. Topical fluoride has been used as an adjunct in the treatment of initial caries lesions. Among the fluoride-containing applications, the use of professional acidulated phosphate fluoride (APF) is used widely. In an *in situ* study, the presence of fluoride played an important role in rehardening enamel.[4] Without plaque removal and under cariogenic challenge, the APF gel reduced demineralization in enamel when used alone. However, the use of fluoride dentifrice alone or in combination with APF gel showed no differences between groups regarding the reduction of enamel mineral loss.

Declaration of Interests: The authors certify that they have no commercial or associative interest that represents a conflict of interest in connection with the manuscript.

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Similar results were found in another study that assessed the reduction of lesion size.[5]

A randomized controlled clinical trial (RCT) showed no additional benefits after treating incipient carious lesions with APF, suggesting that the weekly supervised toothbrushing played a more important role.[6] Another study has shown the relevance of plaque disturbance in the arrest of incipient carious lesions, regardless of the use of fluoride.[7]

Most results, however, were obtained from *in situ* studies[4,5,8,9] and only a few of the studies were RCT,[6,7] which is recognized to be the most appropriate tool for comparing therapies. Further research on non-surgical treatment of incipient carious lesions is still needed.[10,11] A research on the best fluoride regimen to assist in the remineralization of early carious lesions is important in order to provide a stronger evidence-base for the use of professionally applied topical fluoride.[11] Furthermore, head-to-head comparisons of regimens and agents may provide more useful information.[12]

The aim of this double-blind RCT was to evaluate the efficacy of the application of 1.23% APF gel on the arrest of active incipient carious lesions in children receiving professional toothbrushing with fluoride dentifrice.

Methodology

Subjects and study design

A double-blind RCT trial was carried out in a public school in the city of Pelotas, Brazil. This research was approved by the Ethics Committee of the School of Dentistry of the University of São Paulo and the parents of the children signed a written consent form.

All children from 7 to 12 years old were recruited and examined. To be included in the study children had to have at least 1 active incipient non cavitated carious lesions on the buccal surfaces of upper permanent incisors and/or of lower permanent first molars. Incipient carious lesions were considered to be active if they showed a whitish, opaque (chalky) coloration, if they felt rough when the probe was gently moved across the surface,[13] and if they were close to the gingival margin. Children participating in any other preventive program were not included, as well as children with neurological or systemic diseases.

A pre-test was conducted on 30 children. After 8 weeks, the incidence of active lesions was 33.3% in the group of professional toothbrushing and placebo gel and 60% in the group of professional toothbrushing and fluoride gel application. Assuming that the difference in incidence between groups would be 27%, $\alpha = 0.05$ and $\beta = 0.20$, the sample size for each group was 30 children with at least 1 lesion.

Examination methods and evaluation

One previously trained dentist performed clinical examinations of the children at school under artificial illumination in regular chairs. The Plaque Index System,[14] with scores ranging from 0 to 3, was used to assess the buccal surfaces of teeth 16, 11, 26 and 31 and the lingual surfaces of teeth 36 and 46.[15] The children were classified as presenting a score < 1, 1–1.9 or ≥ 2. Dental caries were recorded using WHO criteria, as follows: decayed, missing or filled surface (DMFS),[16] and the corresponding severity of dental caries in children were categorized as 0–3 or > 3 surfaces. The clinical diagnosis of white spot lesions was made after adequately cleaning and drying the surface with compressed air. A visual-tactile examination was performed. A probe was used to gently check for surface texture and loss of tooth structure.[13] The reliability of the calibration was assessed by the Kappa test (kappa 0.80). Regarding the number of lesions, the children were classified as presenting 1–2 or > 2 non cavitated lesions.

The children were assigned randomly to either the placebo group (Group I) or the 1.23% APF (DFL, Sultan Topex, Rio de Janeiro, Brazil) treatment group (Group II). The allocation was concealed by opening an opaque randomization envelope containing papers with only the number of the group, 30 for Group I and 30 for Group II. Both the placebo and the fluoride gels were placed in similar bottles with different labels (I and II). The placebo gel was manufactured by a compounding pharmacy and both gels displayed the same characteristics (color, smell, consistency). The following procedures were performed at each weekly appointment for 8 weeks[6] by the operator:

- toothbrushing instructions,

- professional toothbrushing of the lesion areas for 15 s,
- drying of the buccal surface, and
- topical application of a 1.23% APF, according to the manufacturer's instructions, or placebo gel on the lesion, according to each group, using cotton swabs to minimize the ingestion of the gel.

Children were given toothbrushes (Colgate/Palmolive, São Bernardo do Campo, Brazil) and fluoridated dentifrice (1100 ppm NaF; Tandy, Colgate/Palmolive, São Bernardo do Campo, Brazil) to be used throughout this trial. It was emphasized that the children had to brush their teeth at home with the dentifrice. Furthermore, mothers were asked to control their children's dental hygiene procedure. Children did not participate in any additional type of preventive program.

The examiner performed the evaluation of the white spots after the 4th and 8th treatment sessions. Lesions were categorized as inactive if:

- they showed whitish, brownish or black coloration,
- enamel was shiny and felt hard or smooth when the tip of the probe was moved gently across the surface,
- there was no clinically detectable loss of substance, and
- lesion was located at some distance from the gingival margin,[13]

The participants, the care providers and the examiner who assessed the outcome, did not know which gel was used in each group, characterizing a double-blind study.

Questionnaire

A questionnaire was answered by the parents. To determine the socioeconomic status of the child's family, the scale of the ABIPEME (Associação Brasileira de Institutos de Pesquisa de Mercado) was used.[17] The children's diets were classified at baseline according to the frequency of sugar intake. Twenty most consumed foods containing sugar were selected, and each was given a value according to the frequency of consumption, as follows:

- never = 0,
- rarely = 1,
- weekly = 2, and
- daily = 5.

When the pattern of consumption scored 30 points or over, it was considered to be high and, when it scored lower than 30 points, it was considered to be moderate.[18]

Statistical analysis

Data were analyzed using Stata 10.0 (Stata Corporation, College Station, USA). Differences between groups were assessed using the chi-square test, Fisher's exact test, and *t*-test with Welch's correction. Poisson regression analysis was used to estimate relative risks of the children presenting at least 1 active white spot lesion after 8 weeks. First, the relative risk and 95% CI of each variable were estimated separately. Then, multivariate modeling was performed. The level of significance was set at 5%.

Results

Four hundred and thirty children were examined until the sample of 60 children was attained. Figure 1 shows the diagram of the RCT. One of the participants of the placebo group dropped out. A total of 112 active white spot lesions were present in 59 children. No adverse effects occurred.

The groups showed similarities in all the characteristics that were assessed (Table 1). The groups were also similar in relation to the DMFS caries index ($p = 0.74$, *t*-test with Welch's correction) which was around 7.5.

Table 2 presents the crude and multivariate model for the presence of white spot lesions after 8 weeks. The treatments showed similar results. The persistence of at least 1 active lesion was associated with a higher number of white spot lesions in baseline in crude analysis and also when adjusted for the group and sugar intake.

The majority of lesions (62%) showed arrest in the final evaluation. There was an increase in the percentage of inactive lesions when the results from the 4th and the 8th sessions were compared in both groups ($p < 0.01$) (Figure 2).

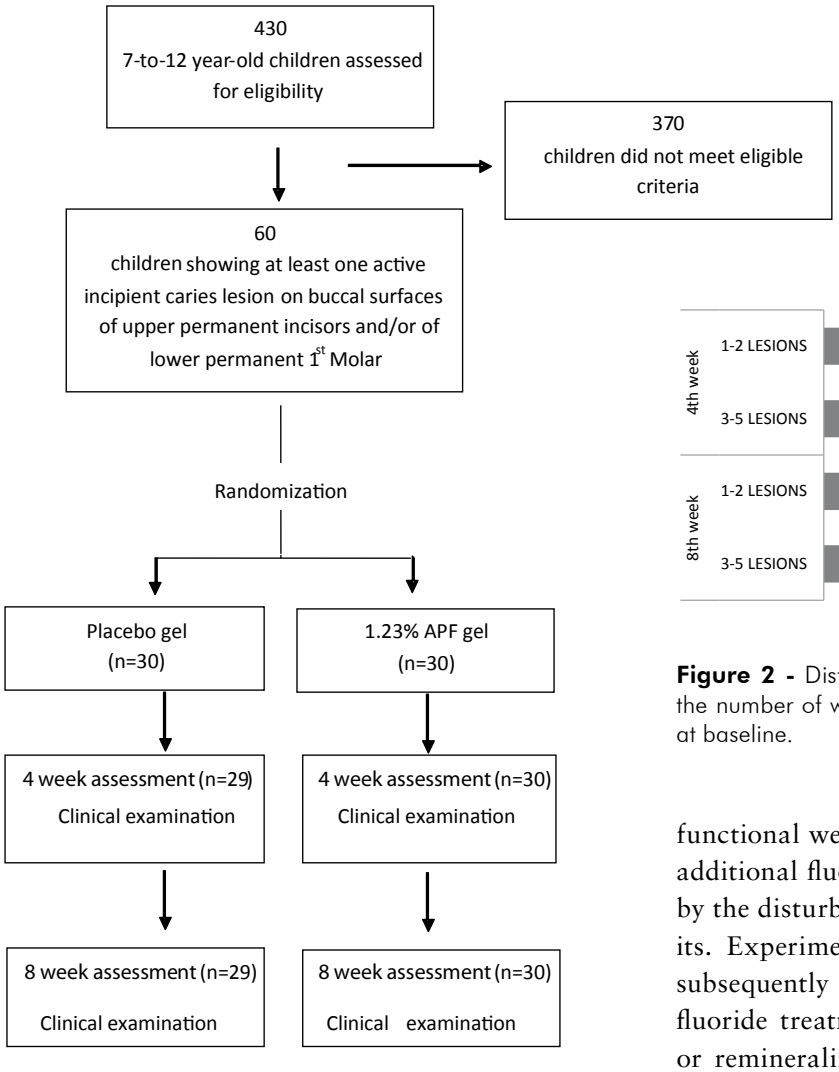

Figure 1 - Flowchart of the clinical trial.

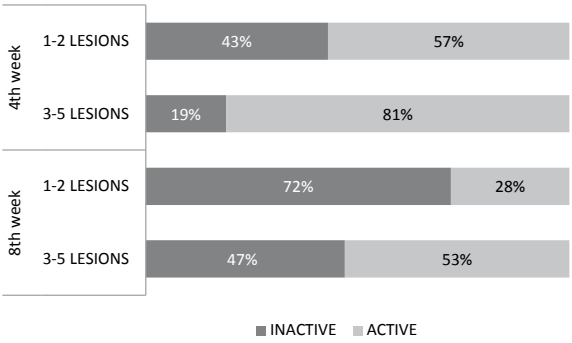

Figure 2 - Distribution of lesions after 4 and 8 weeks by the number of white spot lesions that the patient presented at baseline.

Discussion

The results did not show any additional effect of the APF gel on the arrest of enamel lesions compared to placebo gel after 8 weeks. Both groups received professional toothbrushing before the application of the gel at all sessions, and were advised to use fluoridated dentifrice at home. In both groups, the arrest of white spot lesions was observed. The biofilm control itself is an effective way to obtain arrest of lesions,[6] since it promotes mechanical wear of the lesion, what contributes to the improvement of its final aspect.[19]

Surface abrasion with some redeposition of minerals is believed to be responsible for the regression of lesions.[19] Holmen *et al.*[20] observed that functional wear and usual toothbrushing, with no additional fluoride, were responsible for the arrest by the disturbance and removal of bacterial deposits. Experimentally induced enamel lesions were subsequently remineralized *in vivo* without any fluoride treatment.[8] The enamel demineralization or remineralization effect can only be quantified in *in situ* and *in vitro* studies using invasive and analysis methods,[21] and not in *in vivo* studies, like the present one.

The caries-inhibiting effect of the fluoride gel was not clinically relevant in a study with children with low incidence of caries who were regular attendees of pediatric dental clinics and were receiving semi-annual check-ups with oral hygiene instruction and supervised toothbrushing with fluoride toothpaste.[22] Others studies[4,23,24] showed that toothbrushing with fluoridated dentifrices alone is able to lead to the arrest of white spot lesions.

It is noteworthy that children at high risk for dental caries might benefit from additional exposure to fluoride.[11] In a RCT of the efficacy of a high-fluoride gel self-applied by toothbrushing in children at high caries risk, it was found that self-

Table 1 - Characteristics of children by treatment group.

Variable	Placebo group		Experimental group		Total		*p*
	n	%	n	%	n	%	
Gender							0.71#
Female	11	37.9	9	30.0	20	33.9	
Male	18	62.1	21	70.0	39	66.1	
Age group							0.52#
7 to 9	15	51.7	19	63.3	34	57.2	
10 to 12	14	48.3	11	36.7	25	42.4	
Socioeconomic status							*Ŧ
A–B	0	-	2	6.7	2	3.4	
C	6	20.7	4	13.3	10	16.9	
D	16	55.2	12	40.0	28	47.5	
E	7	24.1	12	40.0	19	32.2	
Sugar intake							0.87#
Moderate	11	37.9	11	36.7	22	37.3	
High	18	62.1	19	63.3	37	63.7	
Number of lesions							0.07Ŧ
1 to 2	26	89.7	20	66.7	46	78.0	
3 to 5	3	10.3	10	33.3	13	22.0	
Plaque index							0.17Ŧ
< 1	1	3.4	1	3.3	2	3.4	
1–1.9	24	82.8	19	63.3	43	72.9	
≥ 2	4	13.8	10	33.3	14	23.7	
DMFS							0.19#
0–3	14	48.3	11	36.7	25	42.4	
≥ 4	15	51.7	19	63.3	34	57.6	

* Status C × D = 0.58, Status D × E = 0.29, Status C × E = 0.21 Ŧ Fisher exact test; # chi-square test.

Table 2 - Overall Relative Risk (RR), adjusted RR and respective 95% confidence intervals in the analysis of factors associated with presence of active white spot lesions after 8 weeks of treatment.

Variable	RR overall	95% CI (RR overall)	*p*	RR adjusted	95% CI (adjusted RR)	*p*
Group						
Placebo	1.00		0.07	1.00		0.26
Experimental	2.18	0.95–5.00		1.65	0.69–3.96	
No. of white spot lesions						
1–2	1.00		< 0.01	1.00		0.02
3–5	3.03	1.40–6.56		2.67	1.18–6.04	
Sugar intake						
Moderate	1.00		0.70	1.00		0.56
High	1.23	0.50–2.52		1.27	0.56–2.86	

application of fluoride gel at school benefits children from more disadvantaged communities who may brush less frequently at home, and therefore have the greatest potential to benefit from this program.[25] Children recruited for this study had active dental caries, an individual factor that increases risk. Besides this, children were recruited from a public school and had low socioeconomic status, characteristics recognized as risk factors for dental caries.

The professional toothbrushing throughout the clinical study and oral hygiene supervision of children by parents can mask the real benefit of fluoride gel application; thus, our results should be interpreted with caution. There was evidence from nine trials showing that the simultaneous use of a topical fluoride treatment with fluoride toothpaste results in an enhanced caries-inhibiting effect, compared with the use of toothpaste alone.[26] However, these results refer to preventive measures, whereas the present study assessed the arrest of incipient caries lesions. It is currently recognized that the effect of fluoride on the dynamics of the caries process and its success in preventing caries should not be confused with its arrest or reversal of carious lesions.

The evaluation of the use of fluoridated gel was short-term, enabling intense supervision and effective control of plaque removal. This period of time would be enough to allow the observation of clinical alterations showing the arrest of further demineralization of the lesions.[19] It is worth mentioning that among the lesions classified as active in the final examination, some presented clinical features of arrested caries, which reflects the dynamic nature of the caries process.[27] However, as improvement occurred between 4 and 8 weeks it is possible that better results could have been achieved with a longer period of follow-up. This seems to be particularly true in cases of children with a higher number of incipient carious lesions.

High numbers of active lesions may represent a "risk" to maintain white spot activity.[6] In this study, the numbers of lesions at baseline were also verified to interfere with the presence of white spot lesions after 8 weeks. Incipient carious lesions in children with many lesions would take longer to become inactive when compared to those of children with fewer lesions. Arrow[28] concluded that enamel caries progression was associated with baseline caries experience, showing that individuals with a high number of lesions are at higher caries risk. Further studies should address this question.

The sugar intake showed no influence on persistence of active white spot lesions. The relationship between sugar intake and incipient carious lesions occurs only when oral hygiene is poor.[29] A study with 6 year-old children showed that sweet consumption at least once a day was associated with a higher caries index. However, a low toothbrushing frequency was the main behavior risk factor for high levels of caries.[30]

Sample size calculation was conducted to detect a true difference based on the results of a pilot test. However results showed great variation from the pilot study. A limitation is that smaller differences, although important, would not be detected. However, this sample size calculation method was adopted because no other study was found with similar intervention tested. Thus, the results should be interpreted with caution.

Conclusion

The trial failed to demonstrate clear evidence of a difference in efficacy between groups and, thus, the equivalence of the treatments can be concluded. The use of fluoride gel showed no additional benefits in this sample of children exposed to fluoridated water and dentifrice. The professional dental plaque removal in both groups may also account for the equivalence of treatments obtained in this study.

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