Original Research
Cariology

Efficacy of fluoride gel in arresting active non-cavitated caries lesions: a randomized clinical trial

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Abstract: This study evaluated the efficacy of fluoride gel in arresting active non-cavitated caries lesions in permanent teeth. This randomized, triple-blind, placebo-controlled clinical trial randomized 100 schoolchildren aged 10.7 ± 2.2 years to test treatment (1.23% acidulated phosphate fluoride [APF] gel) or control treatment (placebo gel) for 4–6 applications at weekly intervals. Data collection included the visible plaque index, gingival bleeding index, visible plaque accumulation on the occlusal surfaces, eruption stage, and dental caries. The association between group and lesion arrestment was assessed using logistic regression, and estimates were adjusted for plaque accumulation over the lesion at baseline, surface type, and tooth type. Models were fitted using generalized estimating equations for accounting for the clustering of data (*i.e.*, the same individual contributed > 1 lesion). Ninety-eight children completed the study (48 fluoride and 50 placebo). When all dental surfaces were analyzed, the likelihood of lesion arrestment was similar between both groups ($p > 0.05$). A secondary analysis including only the occlusal lesions in molars showed that for teeth under eruption, lesions receiving the 1.23% APF gel were about 3-fold more likely to become arrested than lesions receiving the placebo gel (OR = 2.85; 95%CI = 1.23–6.61; $p = 0.01$). No significant difference was detected for molars with complete eruption ($p > 0.05$). The benefit of fluoride gel for arresting non-cavitated caries lesions could not be identified by clinical assessment in this short-term trial. Notwithstanding, when the cariogenic challenge was greater (as on the occlusal surfaces of erupting molars), 1.23% APF gel treatment was an important tool for caries control.

Keywords: Dental Caries; Fluorides, Topical; Tooth Eruption; Randomized Controlled Trial.

Introduction

The significant decline in caries prevalence observed in the last decades may be attributed essentially to the fluoridation of public water supply and the addition of fluoridated compounds to dentifrices.[1,2] This lower prevalence has been accompanied by a modification of the disease profile, with studies showing a lower proportion of cavitated lesions and a higher proportion of non-cavitated enamel lesions.[3,4] These lesions can

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be managed with proper biofilm control, control of sugar intake, and the use of fluoridated products.[5] Local factors such as the stage of the eruption of posterior teeth and their susceptibility for plaque accumulation may influence the effectiveness of the treatment for dental caries.[6]

Despite the well-known effectiveness of fluoride gel on caries prevention/inhibition,[7] its effectiveness to reverse incipient caries lesions has been recently questioned.[8] A systematic review has evaluated the effectiveness of professional topical fluoride application (gels and varnishes) on the reversal of incipient enamel caries lesions in primary and permanent teeth[8]. The study concluded that fluoride varnish appears to be effective; however, the authors concluded that further clinical trials evaluating the effectiveness of fluoride gel are still required. Only two studies evaluating fluoride gel met the inclusion criteria and were included in this review,[9,10] but no meta-analysis could be performed due to insufficient data.

The studies available in the literature on this topic showed no additional benefit of 1.23% acidulated phosphate fluoride (APF) gel compared to placebo gel.[9,10] However, it is important to emphasize that both studies evaluated the effectiveness of 1.23% APF gel concurrently with weekly professional/supervised tooth brushing, which precludes distinguishing the effects of fluoride from that of the mechanical disorganization of biofilm in reversing incipient enamel lesions. It is well known that mechanical disturbance of biofilm (without fluoride) performed weekly may be sufficient to control the progression of active enamel lesions,[11] which may justify the lack of significant difference between experimental groups in those studies.

Therefore, trying to dissociate the chemical effect of fluoride from the mechanical effect of toothbrushing, this study aimed to evaluate the efficacy of 1.23% APF gel in arresting active non-cavitated caries lesions in permanent teeth without interfering with the oral hygiene pattern of the subjects. Under this condition, we hypothesized that a treatment protocol using 1.23% APF gel would be more effective in arresting active non-cavitated caries lesions than using a placebo gel.

Methodology

This study was designed as a randomized, triple-blind, placebo-controlled clinical trial and was reported according to the CONSORT statement. Patients received either of the two interventions: test treatment (1.23% APF gel) or control treatment (placebo gel). The gels were manipulated and had their fluoride concentration checked in the laboratory prior to application.

Participants

Children presenting at least one active non-cavitated lesion (white spot lesion) on any permanent tooth surface were considered eligible for the study. No sex or age restrictions were imposed as long as they attended the schools included in the trial (school-aged participants). Patients using fixed orthodontic appliances and individuals with special needs or cognitive impairments were not included.

The sample size required for the study was calculated (www.openepi.com) using the following parameters: 30% difference between the success rates of the two groups (defined by the authors as a clinically relevant difference), power of 80%, and 95% significance level. A sample size of 45 patients per group was estimated. Fifty participants were included in each group, assuming a dropout rate of 10%

Data collection

Data were collected at four public schools from Santa Maria, southern Brazil, between August 2017 and July 2019 (one school per semester, contributing 25 children each, on average). The schoolchildren in this study had access to fluoridated water (0.7–0.8 ppm F) and to fluoridated toothpaste at home (> 1,000 ppm F).

A questionnaire was sent to parents/legal guardians of the selected children to gather information on socio-demographics (age, sex, mother's education) and behavioral characteristics (tooth brushing frequency and sugar intake frequency). Clinical examination was performed with the students in a supine position with the aid of a mirror, a millimeter periodontal probe, a ball-ended probe, cotton rolls, gauze, and artificial light. Initially, the visible plaque index (VPI)[12] and

the gingival bleeding index (GBI)[12] were recorded in four sites per tooth. In addition, the visible plaque accumulation on the occlusal surfaces of posterior teeth was also recorded, as follows: (0) no visible plaque, (1) hardly detectable plaque restricted to the groove-fossa system, (2) easily detectable plaque on the groove-fossa-system, and (3) occlusal surfaces partially or totally covered with heavy plaque accumulation.[13] To record the eruption stage of permanent molars, the following index was used: (1) occlusal surface partially erupted; (2) occlusal surface fully erupted, but more than half of the tooth buccal surface was covered with gingival tissue; (3) the occlusal surface fully erupted, and less than half of the tooth buccal surface was covered with gingival tissue; and (4) full occlusion.[13] After professional tooth cleaning and drying, all permanent teeth were examined for the severity and activity of caries lesions.

Regarding severity, lesions were classified as non-cavitated or cavitated. Activity assessment was performed based on the clinical features of the lesion, such as surface roughness, color, and light reflection. This criterion has been widely used in the dental literature[14,15] and has been recently validated to classify a patient's caries activity profile.[16] In this sense, an active non-cavitated lesion was defined as opaque enamel with a dull, whitish surface, and an inactive non-cavitated lesion as a white or brownish lesion with a shiny appearance.[14] Caries examination also included the presence of cavitated lesions, missing and filled surfaces in order to compute the dmfs/DMFS according to the WHO standards (cavity level)[17]. Once included in the study, subjects were randomized to either of the two intervention groups.

Interventions

Individuals assigned to the test group received topical application of 1.23% APF in wax molds adapted to the size of the arches to ensure homogeneous application of the product for 1 minute at all dental surfaces. The procedure was repeated every 7 days for 4 weeks. No professional cleaning was performed; dental surfaces were only dried with gauze prior to the gel application. The next week, individuals were clinically examined as previously described (5-week assessment). Participants with all lesions showing signs of arrestment had their treatment considered completed. Those who still had active lesions received two additional gel applications following the same protocol. One week later, caries lesions were examined again (7-week assessment). Subjects allocated to the control group received the same protocol using the placebo gel. Figure provides the study flowchart.

After the experimental period, all participants presenting lesions that remained active (irrespective of the group to which they were assigned) received fluoride varnish, oral hygiene instructions focused on the lesions, and dietary counseling according to individual needs.

Randomization

The sequence of allocation was obtained using Random Alocator software, and it was kept confidential in sequentially numbered sealed black envelopes. The envelopes were only opened after the completion of the baseline clinical examination. The subject was the unit of randomization.

Blinding

Both gels were manipulated with the same color, odor, taste, and consistency to assure blinding. The study participants, the examiner (ADN), and the researchers who implemented the interventions (BVF, LFBS, BSM, and NCC) were unaware of the experimental groups to which the subjects were assigned.

A member of the research team (LSA) was responsible for products coding and blinding maintenance.

Reliability

Clinical examinations were performed by a single examiner (ADN), previously trained and calibrated to the caries index[14] used in the study by a reference examiner (JEAZ). After theoretical training with photographs and practical training with the children, intra- and inter-examiner reliability was assessed through repeated examinations on 18 schoolchildren not included in the study sample, after a minimal time interval of 2 days. Intra- and inter-examiner unweighted Cohen's kappa values ≥ 0.82 were obtained. Intra-examiner reliability was

verified over the data collection, and the minimum kappa value was 0.80. Regarding VPI and GBI, clinical training was conducted under the supervision of the same reference examiner, but no calibration was performed due to the temporary nature of these conditions.

Data analysis

The primary outcome of this study was lesion arrestment at the end of the treatment protocol (either after 4 or 6 weeks of treatment), defined as the modification of lesion features from an active non-cavitated lesion at baseline to an inactive non-cavitated lesion at follow-up. As we intended to investigate the efficacy of fluoride gel "under optimal conditions", we adopted a per-protocol analysis, thus excluding the 2 children (4 lesions) lost to follow-up.

The association between group and arrestment was assessed using logistic regression. Models were fitted using generalized estimating equations to account for data clustering (*i.e.*, the same individual contributed > 1 lesion). The odds ratio (OR) and the 95% confidence intervals (CI) were estimated. Estimates were adjusted for plaque accumulation over the lesion at baseline, surface type, and tooth type, as these variables may influence the relationship between group and lesion arrestment. The unit of analysis was the lesion because lesions behaved differently in the same patient (some were arrested and others were not).

A secondary analysis was performed, including only the occlusal caries lesions in molars. In this case, the logistic regression models were performed after stratifying the sample by eruption stage (incomplete – scores 0, 1, or 2; or complete – score 4). Since the surface and the tooth types were the same, estimates were adjusted only for plaque accumulation over the lesion at baseline. Scores of baseline and final plaque accumulation on the occlusal surfaces were compared using the Wilcoxon test.

VPI and GBI at baseline and after 4-6 weeks were compared within the same group using the Wilcoxon test. A between-group comparison was performed using the Mann-Whitney test.

Data analysis was performed in SPSS, version 18.0. The level of significance was set at 5%.

Ethical aspects

The study protocol was registered at the Brazilian Clinical Trials Registry (ReBEC), UTN U1111-1200-9389, and approved by the Federal University of Santa Maria Research Ethics Committee, number 2.178.279. The research was conducted ethically, in accordance with the World Medical Association Declaration of Helsinki. All participants signed an assent term, and their parents/legal guardians signed a written informed consent form. Students were referred to operative treatment when necessary.

Results

As shown in Figure, all randomized schoolchildren completed the 4-week protocol; however, 2 children in the fluoride group who have not shown signs of lesion arrestment were lost to follow-up after the 5-week assessment (moved to another school during the study period). Therefore, a total of 98 children completed the study (50 placebo group and 48 fluoride group), with a mean ± SD age of 10.7 ± 2.2 years (ranging from 7 to 16).

Table 1 shows the baseline characteristics of the sample. No significant difference was observed between groups regarding age, sex, mother's education, tooth brushing, sugar intake, and caries prevalence at baseline. The mean ± SD dmfs/DMFS was also similar between the two groups (4.3 ± 6.0 in the placebo group and 2.9 ± 4.9 in the fluoride group; p = 0.22, Wald test). At the lesion level, 318 active non-cavitated lesions were included in the study, 184 in the placebo group, and 134 in the fluoride group. An even distribution was observed regarding the surface type, while most lesions were located in molars and presented plaque accumulation over the lesion at baseline. No significant difference between placebo and fluoride groups was detected at the lesion level. Each schoolchild contributed a mean ± SD of 4.2 ± 1.9 active lesions (ranging from 1 to 9); 4.5 ± 1.8 in the placebo group and 3.7 ± 2.0 in the fluoride group. After the treatment protocol, the mean ± SD number of arrested lesions per schoolchild was 2.2 ± 1.8 and 1.8 ± 1.4 in the placebo and fluoride groups, respectively.

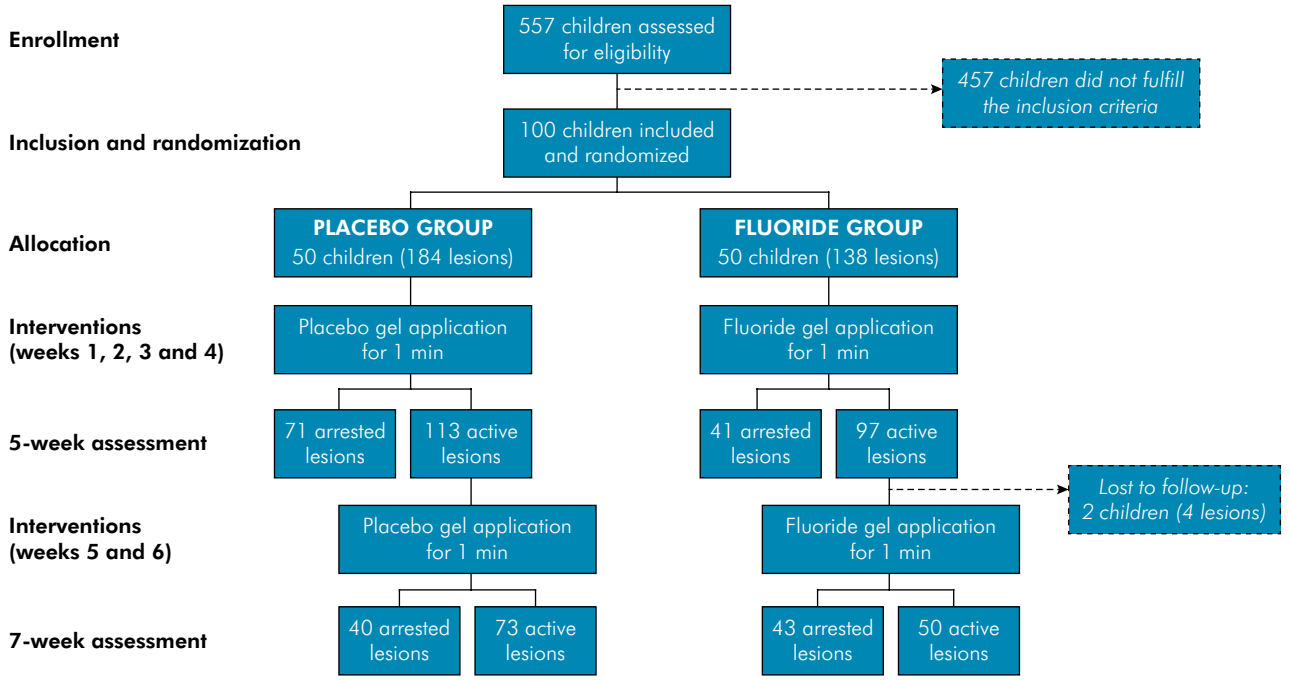

Figure. Study flowchart.

Table 2 describes VPI and GBI at baseline and after 4–6 weeks according to group. High levels of plaque accumulation were observed at baseline and a significant decrease over time followed in both groups ($p < 0.05$). Regarding gingivitis, low levels were found in both groups at both time points.

The relationship between group and lesion arrestment is presented in Table 3. When all dental surfaces were considered, the proportion of active lesions becoming arrested after the treatment protocols was similar between placebo and fluoride groups (60% and 63%, respectively), resulting in a similar likelihood of lesion arrestment (OR = 1.01, 95%CI = 0.81–1.27, p = 0.91).

A significant decrease in the mean occlusal plaque scores was detected in both subgroups (incomplete eruption, baseline mean score 2.18 ± 0.99 and final mean score 1.42 ± 1.16, $p < 0.05$; complete eruption, baseline mean 1.36 ± 1.09 and final mean score 1.00 ± 1.00, $p < 0.05$). Notwithstanding, molars with incomplete eruptions harbored thicker occlusal plaque over the study period.

The association between group and lesion arrestment including only the occlusal caries lesions on permanent molars stratified by eruption stage (incomplete and complete) is shown in Table 4. For teeth with incomplete eruption, fluoride gel showed greater efficacy in arresting caries lesion (61%) compared with the placebo group (33%), with a likelihood of arrestment approximately 3-fold greater among lesions receiving 1.23% APF gel for 4–6 weeks than among lesions receiving the placebo gel (OR= 2.85, 95%CI = 1.23–6.61, p = 0.01). No association was found when the eruption process was completed (OR = 1.02, 95%CI = 0.70–1.48, p = 0.92).

Discussion

This randomized placebo-controlled clinical trial evaluated the efficacy of 1.23% APF gel in arresting active non-cavitated caries lesions without interfering wittingly in the oral hygiene pattern of the patients. Our main findings were that a) plaque accumulation decreased significantly over the study period, and b) lesions exposed to fluoride gel behaved similar to the ones exposed to placebo gel, which is in agreement with the previous randomized clinical trials on this topic.[9,10] Notwithstanding, the fluoride gel was more effective than the placebo gel in sites that continued to present thick plaque, such as on the occlusal

Table 1. Sample description at the patient level and at the lesion level. n (%).

Variable	Placebo	Fluoride	Total	p-value
Patient level				
Age				
7-10 years	26 (52)	27 (56)	53 (54)	
11-16 years	24 (48)	21 (44)	45 (46)	0.67
Sex				
Girls	20 (40)	25 (52)	45 (46)	
Boys	30 (60)	23 (48)	53 (54)	0.23
Mother's education*				
Elementary school	24 (52)	25 (57)	49 (54)	
High school	22 (48)	19 (43)	41 (46)	0.66
Tooth brushing frequency*				
Once a day	5 (11)	8 (18)	13 (15)	
Twice a day	23 (50)	23 (52)	46 (51)	
Three times a day	18 (39)	13 (30)	31 (34)	0.48
Sugar intake frequency*				
≤ twice a day	24 (52)	25 (57)	49 (54)	
≥ three times a day	22 (48)	19 (43)	41 (46)	0.66
Caries prevalence (cavity level)				
dmfs/DMFS = 0	19 (38)	20 (42)	39 (40)	
dmfs/DMFS > 0	31 (62)	28 (58)	59 (60)	0.71
Total	50 (100)	48 (100)	98 (100)	
Lesion level				
Surface type				
Occlusal	83 (47)	63 (47)	146 (47)	
Smooth	98 (53)	71 (53)	169 (53)	0.96
Tooth type				
Anterior	59 (32)	29 (22)	88 (28)	
Pre-molar	19 (10)	15 (11)	34 (11)	
Molar	106 (58)	90 (67)	196 (61)	0.12
Plaque over the lesion				
Absent	37 (20)	23 (17)	60 (19)	
Present	147 (80)	111 (83)	258 (81)	0.51
Total	184 (100)	134 (100)	318 (100)	

*Missing data; dmfs: number of decayed, missing or filled surfaces (primary dentition); DMFS: number of decayed, missing or filled surfaces (permanent dentition)

surfaces of erupting molars. In this subgroup, the study hypothesis was accepted.

Since fluoride was added to toothpaste formulation, it has been difficult to distinguish between the chemical and the mechanical effects of oral hygiene measures in preventing and arresting caries lesions.[18] Previous studies assessing the effectiveness of 1.23% APF gel compared with placebo gel to treat incipient enamel lesions failed to show any superiority of the fluoridated product[9,10]. We hypothesized that this lack of difference could be attributed to the mechanical action of supervised/professional toothbrushing weekly as part of the treatment protocol adopted in these studies[9,10]. It could be argued that toothbrushing

performed once a week before fluoride gel application would have no noticeable effect on caries lesion activity; however, this possibility was previously shown by Holmen et al.[11]. In the present study, children improved their oral hygiene pattern even without professional tooth cleaning or specific oral hygiene instructions, evidenced by the significant reduction in VPI scores from baseline to the 4–6-week examinations in both groups ($p < 0.05$). This significant improvement in hygiene levels can be attributed to the Hawthorne effect[19], which is the positive behavioral changes that may occur due to the awareness of being studied. In this case, children may have improved their oral hygiene habits simply because they were participating in a survey and receiving weekly visits from dentists. Consequently, we also found similar results between placebo and fluoride groups, corroborating Ferreira et al.[9] and Bonow et al.[10]

In an attempt to isolate fluoride's chemical effect and test our hypothesis, a secondary analysis was performed. It included only the occlusal surfaces of permanent molars stratified by their eruption stage, based on the knowledge that erupting molars are more prone to plaque accumulation than molars in full occlusion.[13,20] In fact, molars under eruption

Table 2. Visible plaque index (VPI) and gingival bleeding index (GBI) at baseline and after 4-6 weeks. Mean (95% confidence interval). n = 98 patients.

Variable	Baseline	After 4–6 weeks
VPI		
Placebo	41.0 (35.8–45.3)^{Aa}	34.6 (29.4–39.8)^{Ab}
Fluoride	38.8 (34.1–43.5)^{Aa}	29.1 (24.5–33.7)^{Ab}
GBI		
Placebo	8.6 (6.9–10.4)^{Aa}	8.8 (6.7–10.9)^{Aa}
Fluoride	10.4 (8.3–12.5)^{Aa}	9.0 (6.9–11.2)^{Aa}

Different uppercase letters indicate significance in columns (between-group comparisons, Mann-Whitney test, $p < 0.05$); different lowercase letters indicate significance in rows (within-group comparisons, Wilcoxon test, $p < 0.05$).

Table 3. Association between group and lesion arrestment. n = 318 lesions.

Variable	Active lesions	Arrested lesions	Risk assessment*		
	n (%)	n (%)	OR	95%CI	p-value
Group					
Placebo	73 (40)	111 (60)	1.00		
Fluoride	50 (37)	84 (63)	1.01	0.81–1.27	0.91

*Odds ratio (OR) obtained in a logistic regression model based on generalized estimating equations. Estimates are adjusted for plaque accumulation over the lesion at baseline, surface type and tooth type.

Table 4. Association between group and lesion arrestment including occlusal caries lesions on permanent molars stratified by stage of eruption (incomplete and complete). n = 125 lesions.

Variable	Active lesions	Arrested lesions	Risk assessment*		
	n (%)	n (%)	OR	95%CI	p-value
Incomplete eruption (n = 66)					
Group					
Placebo	29 (67%)	14 (33%)	1.00		
Fluoride	9 (39%)	14 (61%)	2.85	1.23-6.61	0.01
Complete eruption (n = 59)					
Group					
Placebo	8 (26%)	23 (74%)	1.00		
Fluoride	10 (36%)	18 (64%)	1.02	0.70-1.48	0.92

*Odds ratio (OR) obtained in a logistic regression model based on generalized estimating equations. Estimates are adjusted for plaque accumulation over the lesion at baseline.

(eruption stage 1, 2, or 3) remained with large biofilm accumulation throughout the study, despite the significant reduction observed over time (reduction from 2.18 ± 0.99 to 1.42 ± 1.16, $p < 0.05$). In this subgroup of teeth, fluoride gel was more effective in arresting caries lesions (61%) than placebo gel (33%), which was not observed in molars with complete eruption. The risk assessment analysis demonstrated that the likelihood of lesion arrestment was approximately 3-fold greater in the 1.23% APF group than in the placebo group. Thus, it was found that when the mechanical removal of the biofilm is difficult and the cariogenic challenge is greater, the presence of professional fluoride in the oral environment confers a greater ability to reverse initial lesions.

In this study, we adopted a protocol initially composed of 4 applications at weekly intervals despite the findings by Jardim et al.,[21] which found no difference between 3 and 4 applications on surface microhardness of the enamel. However, considering specific individualities and the number of factors influencing the carious process, signs of lesion arrestment were not observed in most lesions at the 5-week assessment, and two more applications were performed. It is important to emphasize that this variation in the protocol (from 4 to 6 gel applications) was defined a priori by the research team to customize the treatment according to individual needs up to a number of sessions considered clinically acceptable. Even after 6 applications of 1.23% APF, 37% of the lesions (50 out of 134) remained with a clinical aspect suggestive of active lesions. We speculated that this finding might be attributed to the lack of professional cleaning of the lesion surface, considering that the short-term clinical signs of arresting non-cavitated caries lesions (shiny and smooth surface) are clearly a result of the polishing effect of toothbrushing.[11] Notwithstanding, previous studies on the effectiveness of fluoride gel did perform professional/supervised brushing and found similar rates of lesion arrestment[9,10]. These findings led us to infer that the clinical aspect of a smooth and shiny surface may take more time to be detectable. However, it is imperative to highlight that it does not mean that the fluoride uptake from the topical application is not enhancing enamel hardness and resistance to further cariogenic challenges. Further long-term studies evaluating whether non-cavitated lesions exposed to fluoride gel are less likely to progress to cavitation may contribute to this research field.

Among the strengths of this study, we could emphasize the attempt to isolate the chemical effect of fluoride gel since no mechanical removal of the biofilm was performed by prophylaxis or weekly professional/supervised brushing, as well as the fact that all dental surfaces were included, unlike previous studies that included only buccal lesions.[9,10] In addition, all clinical examinations were performed by a single calibrated examiner, and the gels were identical and manipulated with the same color, odor, taste and, consistency, allowing patients, operators and examiner to be blinded concerning the intervention group, which increases the internal validity of the study. A limitation of this study was the unbalanced number of lesions included in both groups (184 in the placebo group and 134 in the test group). It occurred because the unit of randomization was the patient, but the unit of analysis was the lesion. We recognize this as a limitation of our study; however, we decided to include all active non-cavitated lesions to assess the outcome in the whole data set. Another motivation to conduct data analysis at the lesion level was the fact that lesions behaved differently in the same patient. Models were fitted using generalized estimating equations, and estimates were adjusted for data clustering in order to overcome the problem of data dependency. Although we have accounted for clustered data in the statistical analysis, no design effect for correlated data was anticipated in the sample size calculation because our original intention was to analyze the data at the patient level. This may have affected the study power and must be recognized. Although performing a post hoc power analysis has been considered conceptually flawed and analytically misleading[22,23], we calculated the statistical power of our data and found only 8% for the whole data set, 60% for the subset of partially erupted molars, and 13% for the subset of fully erupted molars. It could be argued that the lack of tooth-cleaning before

fluoride gel application may have contributed to reducing the efficacy of the intervention. However, evidences from the 1980s show that it is not necessary to clean teeth to get the major benefit of fluoride[24,25]. It is known that the concentration of fluoride ions in biofilm fluid is the primary factor governing the de/remineralization characteristic of caries, and it is in this milieu that fluoride exerts its major anti-caries effects[26]. By being trapped in biofilms, fluoride can exert a longer-term anti-caries effect. Thus, we do not believe that this has affected the study findings. In terms of cost-benefit, it has been argued that "prophylaxis has the disadvantage of significantly elevating the costs of the traditional fluoride technique"[25]. In this sense, we believe that the application of a fluoride gel using a toothbrush could combine the benefits of topical fluoride application, surface polishing, teeth cleaning, and oral hygiene instruction. This is likely to be a highly cost-effective strategy for caries control, especially considering it does not require a traditional dental unit or a dentist. Future cost-effectiveness studies may adequately answer this question.

Conclusion

In conclusion, the benefit of fluoride gel for arresting non-cavitated caries lesions could not be identified by clinical assessment in this short-term trial. Notwithstanding, when the cariogenic challenge was greater (as on the occlusal surfaces of erupting molars), 1.23% APF gel treatment was an important tool for caries control.

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