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Efficacy of Fluoride Varnish and Casein Phosphopeptide-Amorphous Calcium Phosphate for Remineralization of Primary Teeth: A Randomized Clinical Trial

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Key Words
Early childhood caries · Fluoride varnish · Casein phosphopeptide-amorphous calcium phosphate · Primary teeth

Abstract
Objective: We aimed to evaluate the efficacy of oral hygiene instruction, fluoride varnish and casein phosphopeptide-amorphous calcium phosphate (CPP-ACP) for remineralizing white spot lesions (WSL), and the effect of these on the dmft index in primary teeth. ***Subjects and Methods:*** In this 1-year, randomized clinical trial, 140 children aged 12–36 months with WSL in the anterior maxillary teeth were selected and randomly divided into 4 groups of 35 children each. Group 1 (control) received no preventive intervention. In group 2, there was oral hygiene and dietary counseling. In group 3, there was oral hygiene and the application of fluoride varnish at 4, 8 and 12 months after baseline. In group 4, there was oral hygiene and tooth mousse was applied by the parents twice a day over a 12-month period. At baseline and 4, 8 and 12 months after the intervention, the size of WSL in millimeters and the dmft index were recorded. One hundred and twenty-two children completed the study. Data were analyzed using the repeated-measures ANOVA test. ***Results:*** In group 1, the mean percent WSL area and dmft index values had increased significantly at 12 months after baseline ($p < 0.001$). The interventions led to significant decreases in the size of the WSL; the greatest reduction was in group 4 (63%) followed by group 3 (51%) and group 2 (10%) after 12 months. The smallest increase in the dmft index was in group 4 (0.17), followed by groups 3 (0.3) and 2 (0.42). However, there were no significant differences between the groups ($p < 0.001$). ***Conclusions:*** Oral hygiene along with four fluoride varnish applications or constant CPP-ACP during the 12-month period reduced the size of WSL in the anterior primary teeth and caused a small increase in dmft index values.

Introduction

Severe early childhood caries (SECC) is defined as ‘any signs of caries, either cavitated or noncavitated, on the smooth surface of primary teeth in children younger than 3 years’ [1]. A number of studies have documented that 9.5–32.19% of children experience SECC [2, 3].

Prolonged bottle-feeding with milk or sweet liquids during sleep can lead to enamel demineralization and the caries process. Initially, the demineralized lesions appear

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as white spot lesions (WSL) on the cervical margins of the maxillary primary incisors [4]. The early stages of decay are slow, so it is beneficial to slow or reverse enamel demineralization before the noncavitated lesion becomes a cavity [5]. Remineralization can be achieved using noninvasive methods that are effective in very young children, e.g. the use of products that contain fluoride, calcium and phosphates, combined with oral hygiene [6–11].

Enhanced oral hygiene plays a significant role in preventing SECC [6, 7]. Studies have shown that using fluoride varnish, together with oral hygiene practices and dietary counseling, leads to the remineralization of WSL [2, 5, 8] and decreases early childhood caries (ECC) [1, 9]. Fluoride acts via two main mechanisms: its bacteriostatic effect and enhanced enamel remineralization by the absorption of fluoride on the porous subsurface of the lesion area and the formation of fluoroapatite crystals [8]. Although fluoride enables enamel remineralization, the presence of calcium and phosphate ions in the supragingival plaque is also necessary to promote the process [5]. On the basis of the high levels of these ions available in milk and its derivatives, a new product has been introduced that contains a milk protein nanocomplex (casein phosphopeptide, CPP) which stabilizes amorphous calcium phosphate (ACP) and forms CPP-ACP complexes that can enter the subsurface of demineralized early enamel lesions [5] and remineralize them [10, 11].

To our knowledge, there are no clinical studies to date that compare these noninvasive preventive methods in very young children. This study compared the clinical efficacy of fluoride varnish and a CPP-ACP product in preventing the dmft index values and enabling the remineralization of WSL in the enamel of primary teeth in young children.

Subjects and Methods

The research protocol was approved by the Human Ethics Review Committee of the Faculty of Dentistry, Shiraz University of Medical Sciences, and the Iranian Registry of Clinical Trials (code: IRCT201207077402N2). For this 1-year, parallel, double-blind, randomized, controlled clinical trial, 140 children were enrolled at 4 local public health care centers in Shiraz. The inclusion criteria were: an age of between 12 and 36 months at the time of recruitment, having lived since birth in towns with a similar water fluoridation level (<0.7 ppm) and if the parents planned to reside in the same town for the 12 months after recruitment. All participants had at least 4 erupted maxillary primary incisors. WSL were present in at least 2 teeth, and none of the teeth showed signs of cavitated caries [9].

Children who did not use any oral hygiene methods, fluoride-containing products or other preventive measures at home or at dental clinics were not included in the study. Other exclusion criteria were a history of systemic disease, congenital physical or mental disability, oral or dental anomalies or disabilities, a history of drug allergies, allergies to milk protein or benzoate preservatives and no parental consent to participate in the research. The purpose and methods of the study were described for the parents and they all provided written informed consent. The parents were asked to follow the instructions given to them, to attend regular appointments with their children and to not visit or obtain care from other dentists during the study period.

The 140 children were randomized into 4 groups with 35 in each group, based on a type I error rate of $\alpha = 5\%$ and a power of $1 - \beta = 80\%$, in accordance with a study by Almeida et al. [12]. At baseline and follow-up appointments, a staff member at the health clinic selected children by means of a block randomization method with the help of a random number table. All dental examinations were conducted between June 2012 and June 2013. Recruitment started in June 2012 and was completed within 2 months.

Evaluation of WSL

Dental Examination

Two dentists (E.F. and S.D.) performed all of the dental examinations at the baseline and follow-up appointments. To ensure consistency, a pretest was done by both examiners, who first recorded WSL in 20 children and were given instructions on how to perform the examination and apply the varnish. The teeth surfaces were cleaned with a finger brush and then wiped with a cotton roll and air-dried.

At baseline, an intraoral examination was performed with a disposable mirror and head-light [4]; the location and size of WSL were recorded with a scored dental probe, and the area was then calculated and recorded. For each child, the dmft index was recorded. This index is defined as 'd' which indicates a decayed tooth, 'm' a missing tooth due to decay and 'f' a filled tooth. The classification of WSL used in this study is shown in table 1 [4, 13]. As changes in WSL size are important to assess dental caries, this size was recorded in each group at each follow-up appointment [16].

Follow-Up

The examiners and the parents were blinded as to which group each child had been randomly assigned. At each follow-up appointment, one of the examiners first measured WSL and then recorded the dmft index. One of the preventive methods was applied by the other examiner (detailed below). Follow-up appointments were scheduled for each child at 4, 8 and 12 months after the baseline examination. During follow-up, 18 children were excluded from the study (fig. 1). For groups 2, 3 and 4, in order to review the oral health instructions given to the parents, each child was seen by the dentist every 3 weeks during the first 3 months. After this 3-month period, in each group, the intervention proceeded as detailed above, and each child received a new toothbrush every 4 months. If the preventive treatment failed and any cavitated lesions were observed, the parents were referred to treatment for the caries. The patients in the control group also received oral health instructions and the application of fluoride varnish after completing the study.

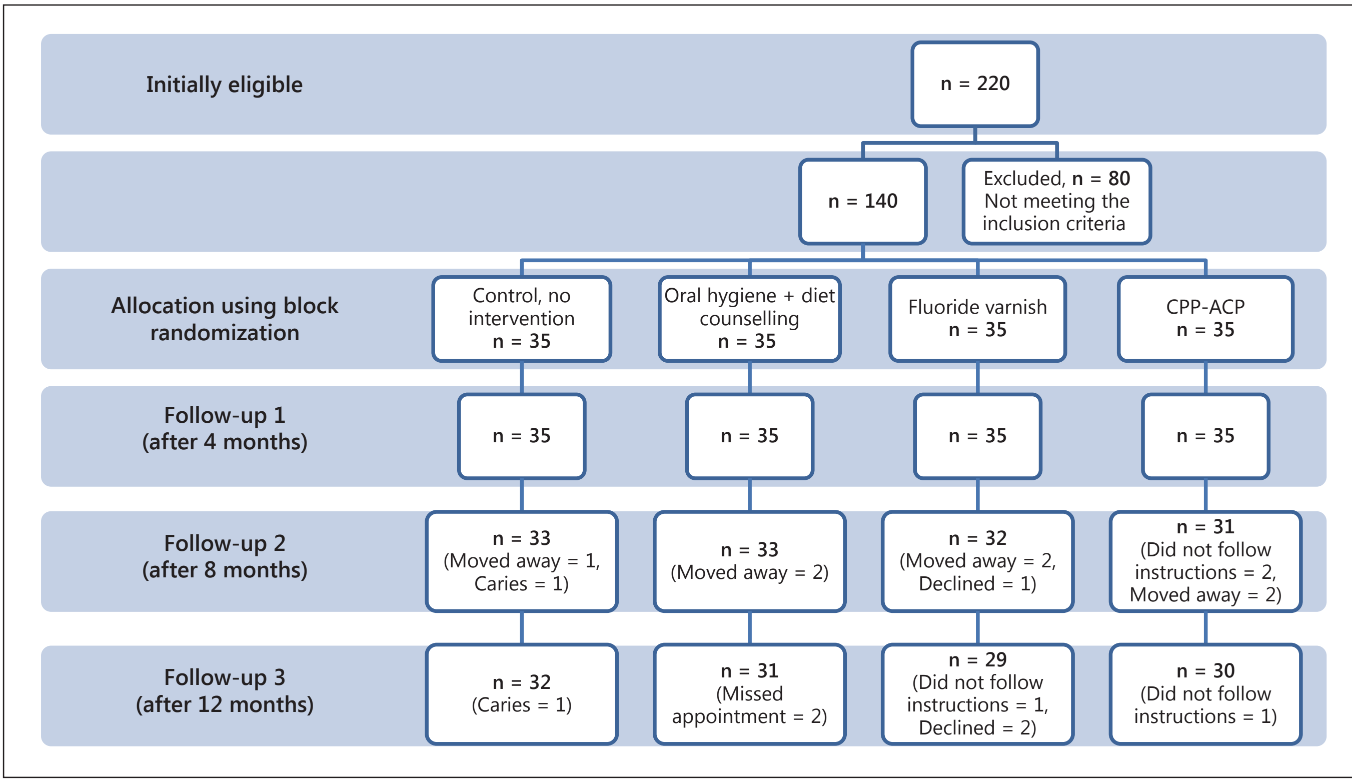


Fig. 1. Flow diagram of study participants and research methodology.

Table 1. Classification used for dental caries [4, 13]

Smooth surface	Noncavitated lesions	Cavitated lesions
Appearance/color (enamel)	Chalky/white	Chalky white with darker center
Surface	Intact	Cavitated dentin loss of tooth structure
Tactile	Normal (tactile exam usually not necessary)	Soft
Location	Usually adjacent to gingival margin	Usually adjacent to gingival margin

Experimental Groups

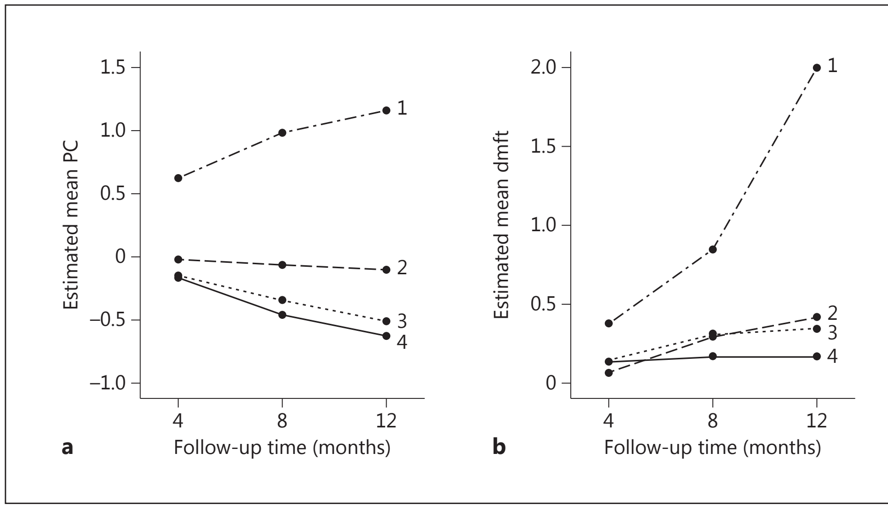
For group 1 (control), a dental examination was performed at baseline and at 4, 8 and 12 months. The parents did not receive counseling about caries prevention methods. As a placebo, a water-based, colored solution in a colored container was brushed over the teeth surfaces. The solution was tasteless and odorless, and was similar in color to the fluoride varnish used in group 3.

For group 2 (oral hygiene), at the first visit, the parents received a free gift bag containing an educational pamphlet and a finger toothbrush (Panbehriz, Busher, Iran). The pamphlet explained the factors that influence ECC and provided dietary and feeding advice to prevent SECC, instructions on oral hygiene and information about the importance of caring for primary teeth. The parents were also supplied face-to-face with the oral health instructions in the pamphlet [6]. Subsequent appointments were scheduled until the end of follow-up. At each follow-up appointment, there was motivational oral health counseling and any questions were answered.

For group 3 (oral hygiene and fluoride varnish application), the parents received counseling about oral hygiene and diet. The dentist cleaned the teeth by brushing. The teeth were then isolated with cotton rolls, and fluoride varnish containing 5% sodium fluoride (DuraShield; Sultan Healthcare, Hackensack, N.J., USA) was applied with a disposable brush to all tooth surfaces and left for 1 min. A small amount of varnish was applied on the surface of the 4 anterior primary teeth; in some children more varnish was used for more teeth. The parents were advised to not allow the child to eat rough (abrasive) foods for the rest of the day [14] and to not brush the teeth until the following day [15]. The fluoride varnish was applied every 4 months.

For group 4 (oral hygiene and tooth mousse application), the parents were given instructions on oral hygiene. One tube of tooth

Fig. 2. Percent changes in white spot lesions (**a**) and changes in the dmft index (**b**) in all experimental groups during 12 months. 1: Control group; 2: oral hygiene and dietary counseling group; 3: oral hygiene and fluoride varnish group; 4: oral hygiene and tooth mousse (CPP-ACP) group.



mousse containing CPP-ACP (GC, Tokyo, Japan) was given to the parents. They were advised to apply the mousse with a disposable swab to the entire teeth surface twice a day (in the morning and at bedtime) after the child's teeth had been brushed, and to leave the product in place for at least 3 min. The children were not to be allowed to drink or eat for 30 min, after which they could rinse their mouth. The parents were informed that the tooth mousse was a milk-derived product which was harmless if swallowed. During the study, the parents were given a new tube of tooth mousse on request.

At the first visit, immediately after the fluoride varnish or tooth mousse had been applied, the oral cavity was examined for possible side effects such as gingival inflammation. The parents were asked to wait for 30 min and then asked if they had observed any side effects. In addition, two phone numbers were given to the parents so that they could inform the dentist of any side effects at any time.

Statistical Analysis

Demographic variables were compared using the χ^2 test and one-way analysis of variance (ANOVA). The percent change (PC) in WSL area was calculated for each child at each follow-up appointment, using the formula: PC = [WSL (at follow-up) − WSL (at baseline)]/WSL (at baseline).

Multisample, repeated-measures RM-ANOVA was used to determine the PC in WSL size and dmft index in each group. One-sample, repeated-measures ANOVA with the Bonferroni correction and one-way ANOVA with the Tukey test were used for between-group and within-group comparisons, respectively. All tests were done at a $p < 0.05$ level of significance.

Results

At baseline, 140 children (mean age: 21.20 ± 6.76 months) with a total of 483 active WSL were enrolled. During follow-up, 18 children were excluded from the study (fig. 1). There were no significant differences between groups in terms of sex ratio ($p = 0.280$) or mean age ($p = 0.657$). No side effect or unexpected effects were reported or observed in groups 3 and 4.

A high level of intraexaminer reliability was achieved for the identification and measurement of WSL according to a weighted kappa statistic of 85% and an intraclass correlation of $r = 0.88$ in 20 randomly selected children.

WSL Changes in All Groups

The pattern of mean PC in WSL over time was not similar across groups (fig. 2a) or there was a significant interaction effect ($p < 0.001$).

Between-group comparisons at each time point are denoted by capital letters in the columns of table 2. For all time points, the mean PC of WSL in group 1 was significantly greater than in the other groups. For example, after 12 months, the mean of WSL area increased by 115% in group 1 and decreased by approximately 63% in group 4, 51% in group 3 and 10% in group 2 ($p < 0.001$ for all pairwise comparisons with group 1). However, there were no statistically significant differences between these other groups at 4, 8 and 12 months.

Within-group comparisons at the different follow-up times in each group are shown by lower-case letters in the rows of table 2. The mean area of WSL in group 1 increased as time increased. The mean (median) PC was 1.15 ± 1.26 (0.79%) at the end of a 12-month follow-up. The mean after 8 months ($p = 0.001$) was greater than after 4 months ($p = 0.002$), but there was no significant difference between months 8 and 12 ($p = 0.221$). In groups 3 and 4, the mean percent WSL area decreased with time. In group 2, there was little change in WSL during the

Table 2. Changes in mean WSL size in all groups during follow-up ($p < 0.05$)

Group	Follow-up			p value[1]
	4 months	8 months	12 months	
Control				
Mean ± SD	$+0.62 \pm 1.04^{A, a}$	$+0.98 \pm 1.22^{A, b}$	$+1.15 \pm 1.26^{A, b}$	<0.001
Median	0.36	0.67	0.79	
Children	35	33	32	
Oral hygiene				
Mean ± SD	$-0.02 \pm 0.41^{B, a}$	$-0.06 \pm 0.78^{B, a}$	$-0.10 \pm 1.12^{B, a}$	0.594
Median	–0.09	–0.29	–0.50	
Children	35	33	31	
Fluoride varnish				
Mean ± SD	$-0.14 \pm 0.36^{B, a}$	$-0.34 \pm 0.48^{B, b}$	$-0.51 \pm 0.56^{B, c}$	<0.001
Median	–0.27	–0.48	–0.74	
Children	35	32	29	
CPP-ACP				
Mean ± SD	$-0.17 \pm 0.38^{B, a}$	$-0.46 \pm 0.54^{B, b}$	$-0.63 \pm 0.62^{B, c}$	<0.001
Median	–0.27	–0.62	–0.81	
Children	35	31	30	
p value[2]	<0.001	<0.001	<0.001	

[1] Within-group comparison using one-sample repeated-measures ANOVA. The results of the Bonferroni test are reported as a lower-case letter in each row.
[2] Between-group comparison using one-way ANOVA. The results of the Tukey test are reported as a capital letter in each column.

study period, and no significant differences between the 3 time points ($p = 0.594$). These data show that the area of WSL increased with time in group 1, remained unchanged in group 2 and decreased in groups 3 and 4.

dmft Index in All Groups

There was a significant group-by-time interaction effect for dmft ($p < 0.001$; fig. 2b).

Between-group comparisons at each time point are denoted by capital letters in the columns of table 3.There were significant differences between groups in the mean dmft index only at the end of the study ($p < 0.001$). The mean dmft index in group 1 was higher than that in groups 2–4 (all $p < 0.001$). The dmft index after 12 months was lowest in group 4.

Within-group comparisons at the different follow-up times in each group are shown by lower-case letters in the rows of table 3. The mean dmft index in group 1 increased as time increased ($p < 0.001$). The mean dmft index after 8 and 12 months was greater than after 4 months ($p < 0.001$ and $p = 0.015$, respectively), and greater after 12 months than after 8 months ($p = 0.015$). In groups 2–4, the mean dmft index did not change significantly and re-

Table 3. The dmft index in all groups during follow-up

Group	Follow-up			p value[1]
	4 months	8 months	12 months	
Control	$0.37 \pm 1.21^{A, a}$ (n = 35)	$0.84 \pm 1.69^{A, b}$ (n = 33)	$2 \pm 2^{A, c}$ (n = 32)	<0.001
Oral hygiene	$0.06 \pm 0.25^{A, a}$ (n = 35)	$0.29 \pm 0.86^{A, a}$ (n = 33)	$0.42 \pm 0.99^{B, a}$ (n = 31)	0.055
Fluoride varnish	$0.14 \pm 0.52^{A, a}$ (n = 35)	$0.31 \pm 0.89^{A, a}$ (n = 32)	$0.3 \pm 0.90^{B, a}$ (n = 29)	0.070
CPP-ACP	$0.13 \pm 0.43^{A, a}$ (n = 35)	$0.17 \pm 0.53^{A, a}$ (n = 31)	$0.17 \pm 0.53^{B, a}$ (n = 30)	0.326
p value[2]	0.336	0.189	<0.001	

[1] Within-group comparison using one-sample repeated-measures ANOVA. The results of the Bonferroni test are reported as a lower-case letter in each row.
[2] Between-group comparison using one-way ANOVA. The results of the Tukey test are reported as a capital letter in each column.

mained relatively constant, i.e. near to zero, over time. These results suggest that each of the three interventions effectively prevented the increase in dmft value after the different follow-up periods.

Discussion

The methods of preventing dental caries and providing noninvasive intervention that favor the remineralization of decalcified lesions tested in this study showed the beneficial effects of stopping or reversing caries progression. In the control group, which did not receive preventive dental care, the surface area of WSL and the dmft index increased during the 12-month period of the study, thereby indicating that in untreated teeth, the rate of demineralization was faster than remineralization as previously reported [14]. Compared to the control group, children who received oral hygiene and dietary counseling (group 2) showed no significant increase in WSL size and dmft index; this confirmed the findings of Wagner et al. [17]. Therefore, oral health education and regular visits to the dentist are considered basic public dental health interventions intended to decrease dental caries [18].

In this study, the finding that educational pamphlets, free toothbrushes, fluoride varnish and tooth mousse were effective confirmed the results of previous studies [19, 20]. We used direct, repeated instruction to increase the awareness of parents and change their attitude toward dental care for their children [19, 21].

WSL decreased in groups 2, 3 and 4 over time; however, the percentage decrease in group 2 was smaller than in groups 3 and 4. This showed that with time, oral hygiene measures alone were effective in decreasing dental caries but were insufficient to reverse WSL or stop ECC [19].

Our results showed that four periodic applications of fluoride varnish combined with oral hygiene instruction was an effective method to reverse and decrease the WSL area and dmft index after 12 months as previously reported [14, 22]. Application of fluoride varnish is well accepted by young children, easy and safe and does not take long. It is the most common form of fluoride used to decrease dental caries [15, 22]. Fluoride is released slowly from the varnish and retards enamel softening [8]. The fluoride ion, in the presence of calcium and phosphate released by enamel demineralization or by dental plaque and saliva, produces fluorapatite, a strong deterrent to demineralization. We used four fluoride applications (because of the advantages over only two applications) on intact enamel [23, 24] where WSL form. Ferreira et al. [25] and Almeida et al. [12] reported that four fluoride varnish applications reduced WSL in the permanent teeth in school children. Another study showed that using varnish converted 81% of active enamel lesions to inactive lesions in the primary teeth after 9 months [24], a finding consistent with our results.

In this study, WSL in children who used the tooth mousse decreased with time in a linear fashion. However, the differences between groups 3 and 4 in the PC in WSL size and dmft index were not significant. The presence of fluoride and the level of calcium and phosphate ions available for remineralization are both important in the reversal of WSL. Products with high levels of ions, such as CPP-ACP, lead to increased remineralization of the subsurface enamel [7, 26].

Our results showed that the prolonged use of CPP-ACP was effective in stopping and reversing WSL in young children as previous reported [10]. These findings are evidence of the long-term benefits of using CPP-ACP [26]. This result may be due to the high level of calcium and phosphate available for remineralization. When fluoride products are used, calcium and phosphate ions may be limited, and this may, in turn, compromise the effectiveness of the fluoride-containing products in preventing ECC [5, 14]. In agreement with our findings, Zhou et al. [27] concluded that CPP-ACP is more suitable than sodium fluoride for the remineralization of primary teeth. There is evidence that the simultaneous use of CPP-ACP and fluoride is more effective than using fluoride only [28]. However, some other studies claim that these applications do not significantly reduce dental caries [29, 30]. The differences between studies may be due to differences in sampling, dental care techniques and study design [20]. In our study, we did not use other sources of fluoride because the use of products containing fluoride (e.g. dentifrices) is contraindicated for very young children [5]. In addition, because CPP-ACP was as effective as the fluoride varnish, using CPP-ACP may offer advantages in very young children since it can help reduce the risk of caries without increasing the risk of fluorosis.

The main strengths of our study were its long follow-up period (1 year), its focus on very young children and its use of noninvasive methods (fluoride and CPP-ACP in conjunction with oral health instruction) to achieve reductions in WSL size and dmft index. These straightforward, inexpensive methods can be used by dentists as well as other health center staff members. The main limitations of our study were its limited geographic setting and the possibility that some parents did not follow our recommendation correctly. Another possible limitation is that we did not fully assess all potential caries risk factors in all groups.

Conclusions

This study showed that preventive intervention methods play an important role in reducing WSL and dental caries in young children. Oral hygiene instruction alone was not sufficient to reduce WSL and dmft index values compared to interventions that use fluoride varnish and CPP-ACP. However, oral hygiene instruction together with the application of fluoride varnish and CPP-ACP was an effective method to reduce WSL size and dmft index values in primary teeth. Prolonged use of CPP-ACP decreased WSL and the dmft index values in primary teeth.

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