Randomized Clinical Trial of 12% and 38% Silver Diamine Fluoride Treatment

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Abstract

This 30-mo randomized clinical trial compared the effectiveness of 2 concentrations (12% or 38%) of silver diamine fluoride (SDF) and 2 periodicity of application (once or twice a year) in arresting cavitated dentin caries in primary teeth. Children aged 3 to 4 y who had at least 1 active cavitated caries lesion were enrolled and randomly allocated into 4 groups for intervention. Group 1 had 12% SDF applied annually (every 12 mo), group 2 had 12% SDF applied semiannually (every 6 mo), group 3 had 38% SDF applied annually, and group 4 had 38% SDF applied semiannually. Clinical examinations were performed semiannually in kindergarten by a single examiner to investigate whether the SDF-treated caries became arrested. A total of 888 children with 4,220 decayed tooth surfaces received SDF application at baseline, and 799 (90.0%) children with 3,790 surfaces (89.8%) were evaluated at the 30-mo examination. The caries arrest rates were 55.2%, 58.6%, 66.9%, and 75.7% for groups 1, 2, 3, and 4, respectively ($P < 0.001$). Caries treated with 38% SDF had a higher chance of becoming arrested than those treated with 12% SDF (odds ratio [OR], 1.98; 95% confidence interval [CI], 1.51–2.60, $P < 0.001$). The interaction between frequency of SDF application and visible plaque index (VPI) score was significant ($P = 0.017$). Among those children who received annual SDF application, children with a higher VPI score had a lower chance to have their caries become arrested (OR, 0.59, 95% CI, 0.49–0.72). In conclusion, SDF at a concentration of 38% is more effective than that of 12% in arresting active caries in primary teeth. For children with poor oral hygiene, caries arrest rate of SDF treatment can be increased by increasing the frequency of application from annually to semiannually (ClinicalTrials.gov NCT02385474).

Keywords: dental caries, dentin, child, clinical studies/trials, primary teeth, silver compounds

Introduction

Early childhood caries (ECC) is one of the most prevalent chronic diseases worldwide (Kassebaum et al. 2015). Restorative interventions for young children are challenging because of their young age and uncooperative behaviors. Moreover, access to dental care is often limited due to the constraints of resources. As a result, there is a public health challenge in many communities that decayed primary teeth are mostly left untreated (Chu et al. 2012; Duangthip et al. 2017). Clinical trials provided some evidence supporting the use of silver diamine fluoride (SDF) for arresting dentin caries in preschool children (Chu et al. 2002; Duangthip et al. 2016). The US Food and Drug Administration cleared SDF for off-label use in the United States in 2015 (Horst et al. 2016). A survey in the United States found that SDF was rapidly adopted in pediatric dentistry residency training, and most of the respondents supported to incorporate it into curricula and teaching clinics (Nelson et al. 2016). Several commercially available agents containing different concentrations (12%, 30%, and 38%) of SDF are used by dentists (Gao, Zhao, et al. 2016). Since SDF at 38% contains high fluoride concentration (44,800 ppm), the use of a low-concentration (12%) SDF was introduced to minimize the risk of dental fluorosis. So far, there is limited information about the effectiveness of different combinations of concentration and application frequency of SDF in arresting dentin caries in primary teeth. Thus, we conducted a 30-mo randomized clinical trial to compare the effectiveness of 2

concentrations (12% and 38%) of SDF when applied once or twice a year in arresting dentin caries in primary teeth in pre-school children. The 18-mo results of this study suggest that SDF is more effective in arresting dentin caries at a concentration of 38% than at 12% and when applied every 6 mo than every 12 mo (Fung et al. 2016). This study reports the final results. The first null hypothesis of this study was that there was no difference in the effectiveness of SDF solution in arresting caries in primary teeth at different concentrations (12% or 38%). The second null hypothesis was that there was no difference in the effectiveness of SDF in arresting caries in primary teeth when applied at different frequencies (every 6 or 12 mo).

Materials and Methods

This study was registered in the Registry of Clinical Trials run by the US National Library of Medicine (ClinicalTrials.gov identifier: NCT02385474). Ethical approval was obtained from the institutionalized review board of the University of Hong

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A supplemental appendix to this article is available online.

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Kong. Written consent was obtained from the parents of each child. The recruitment period started in September 2009 and ended in November 2010. The last follow-up examination was in May 2013.

Trial Design and Implementation

This 30-mo study was conducted in 37 kindergartens in Hong Kong. Healthy children aged 3 to 4 y and with at least 1 soft carious lesion at the dentin level were recruited. Teeth with signs suggesting that they were nonvital were excluded. After baseline examination, eligible children were randomly allocated to 1 of the 4 treatment groups. Follow-up examinations were performed every 6 mo by the same trained examiner who was blinded to the treatment group allocation. A community periodontal index (CPI) probe and a disposable dental mirror attached to an intraoral LED light handle were used in the examinations. Oral hygiene status of the children was recorded using the visible plaque index (VPI) (Ainamo and Bay 1975). The presence or absence of visible plaque on the buccal and the lingual surfaces of 6 index teeth (55, 51, 63, 71, 75, and 83) was recorded. VPI score was calculated as a percentage of the number of surfaces with plaque to the total number of surfaces examined. Caries experience was measured using the decayed, missing, and filled teeth (dmft) index. At tooth surface level, the size of lesion was classified as small (less than half of the mesial or distal surface or less than one-third of the buccal, lingual, or occlusal surface) or large. For lesion activity assessment, a caries lesion was diagnosed as arrested if its surface was smooth and hard on probing. A lesion was recorded as active if it was soft on probing (Chu et al. 2002). A lesion that was later restored or in a tooth later extracted due to caries was categorized as not arrested because the lesion had led to surgical intervention. The intraexaminer reliability of caries diagnosis and oral hygiene assessment was evaluated through reexamining a 10% random sample of children on the same day. At baseline and the 30-mo examinations, parents of the study children were asked to fill in a questionnaire about their child's demographic background, including sex, age, birthplace, main caretaker, father's and mother's education level, family structure, and family income. Information about dental health-related habits, including bottle feeding, daily tooth-brushing frequency, supervised brushing, use of fluoride toothpaste, daily frequency of sugary snacking, and dental checkup experience, was collected. Parents were informed to report to the principal investigator if their child had acute or systemic illness associated with the SDF treatment.

After screening at baseline, a dental assistant enrolled the participant children. Before randomization, the children were put into 2 strata according to the number of carious tooth surfaces they had (1 to 3 surfaces and >3 surfaces) to achieve balance of the disease severity among groups (Duangthip et al. 2016). A list of random allocation numbers was generated by computer using a stratified randomization method based on the aforementioned disease severity level with a block size of 8. The assistant who performed the random allocation of study children also prepared the treatment materials. The bottles of

the SDF solutions were wrapped with aluminum foil and coded. An independent dentist who was blind to the children's group allocation applied SDF or placebo on the caries lesion. For groups 1 and 3, normal saline was applied as placebo at the semiannual visits to blind the study children. The 4 treatment groups were as follows:

Group 1: 12% SDF applied every 12 mo

Group 2: 12% SDF applied every 6 mo

Group 3: 38% SDF applied every 12 mo

Group 4: 38% SDF applied every 6 mo

Sample-Size Calculation

The sample size was estimated based on 1) caries arrest rate of 70% (Gao, Zhang, et al. 2016), 2) a 10% absolute difference in caries arrest rate would be clinically significant, 3) statistical power of 80%, and 4) statistical significance level at 0.05. The required sample size calculated by using the software Sample Power 2.0 (SPSS, Inc.) was 353 caries lesions/group. The anticipated intraclass correlation coefficient (ICC) was 0.3 (Masood et al. 2015) and mean number of surfaces with caries at baseline per child was 3. Following the equation for a multi-level study (Twisk 2006), 565 caries lesions in 188 children/group would be required. With an anticipated 15% dropout rate, 221 children/group were needed at baseline.

Statistical Analyses

Data were analyzed using the software SPSS 23.0 for Windows for statistical analysis (SPSS, Inc.) by retaining subjects' allocation to treatment groups according to randomization regardless of the intervention they received. Complete case analysis was used without imputation of missing data (Moher et al. 2010). Kappa statistics was adopted to evaluate intraexaminer reliability in caries diagnosis and assessment of oral hygiene. Chi-square test and 1-way analysis of variance (ANOVA) were used to compare the baseline information of study children between groups. The changes in oral health-related habits at baseline and 30-mo examinations were assessed using the McNemar test. The generalized estimating equations (GEE) approach was employed to adjust the effect of correlation since multiple lesions could be included in a child. A GEE model with logit link and 2-level clusters (surface level and subject level) was performed to investigate the effects of variables on caries arrest at the 30-mo examination at tooth surface level. Treatment group allocation was replaced with concentration (12% or 38%) and application frequency (annual or semiannual) of SDF and their interactions to evaluate the treatment effects of these factors in the presence of other significant variables adjusted in the model. Three baseline variables (tooth position, tooth surface, and size of lesion) and 2 variables at the follow-up examination (plaque on lesion and VPI score) can significantly affect the outcomes of caries arrest treatment (Fung et al. 2016). The possible modification effects of the above-mentioned variables with the treatment group were also examined. Therefore, besides the concentration and frequency

Table 1. Children's Demographic Background, Clinical Characteristics, and Dental Health–Related Habits at Baseline.

Group	Group 1 (12% SDF, Annual)	Group 2 (12% SDF, Semiannual)	Group 3 (38% SDF, Annual)	Group 4 (38% SDF, Semiannual)	P Value
Demographic background					
Sex: male	134 (60)	130 (59)	132 (60)	123 (55)	0.735
Place of birth: Hong Kong	214 (96)	208 (94)	213 (96)	207 (93)	0.335
Family structure: both parents	209 (95)	210 (96)	209 (95)	212 (96)	0.784
Main caretaker					0.920
Father or mother	151 (68)	145 (65)	150 (68)	145 (65)	
Grandparents	44 (20)	44 (20)	40 (18)	49 (22)	
Maid or other people	27 (12)	33 (15)	32 (14)	28 (13)	
Father's education level					0.923
Primary education	35 (17)	37 (17)	32 (15)	36 (17)	
Secondary education	145 (68)	140 (66)	143 (67)	135 (64)	
Postsecondary education	32 (15)	36 (17)	38 (18)	41 (19)	
Mother's education level					0.752
Primary education	37 (17)	34 (16)	38 (17)	42 (19)	
Secondary education	161 (73)	152 (70)	149 (68)	147 (67)	
Postsecondary education	22 (10)	30 (14)	31 (14)	30 (14)	
Monthly family income					0.752
Below HK\$10,000	80 (37)	80 (37)	80 (38)	84 (41)	
HK\$10,001–\$20,000	78 (37)	66 (31)	74 (35)	65 (31)	
Above HK\$20,000	56 (26)	69 (32)	57 (27)	59 (28)	
Clinical characteristics					
Mean (SD) dmft score	3.82 (2.72)	3.81 (2.83)	3.92 (2.91)	3.83 (2.72)	0.970
Mean (SD) VPI score	0.68 (0.21)	0.68 (0.19)	0.70 (0.20)	0.69 (0.20)	0.695
Severity of dental caries					0.983
Having 1 to 3 carious lesions	114 (51)	117 (53)	118 (53)	117 (53)	
Having >3 carious lesions	108 (49)	105 (47)	104 (47)	105 (47)	
Dental health–related habits					
Current bottle feeding	117 (53)	113 (51)	127 (57)	111 (50)	0.432
Daily frequency of snacking, mean (SD)	2.37 (1.61)	2.36 (1.31)	2.24 (1.26)	2.42 (1.39)	0.600
Daily frequency of toothbrushing					0.880
Twice a day	90 (40)	99 (45)	93 (42)	100 (45)	
Once a day	88 (40)	78 (35)	84 (38)	85 (38)	
Less than once a day	44 (20)	45 (20)	45 (20)	37 (17)	
Use of fluoride toothpaste	119 (54)	119 (54)	115 (52)	120 (54)	0.999
Supervised toothbrushing	182 (82)	188 (85)	176 (79)	181 (82)	0.530

Values are presented as number (%) unless otherwise indicated.

dmft, decayed, missing, and filling teeth index; SD, standard deviation; SDF, silver diamine fluoride; VPI, visible plaque index.

of application, the 5 covariates and their significant interaction with the assigned treatment were included in the base model. Other confounding factors with $P < 0.1$ in the bivariate logistic regression were chosen and entered into the base model. The corrected quasi-likelihood information criterion (QICC) of all potential subset models was compared. The multivariable logistic regression model with all variables being statistically significant and demonstrating the smallest QICC was presented as the best-fit model. The significance level for all statistical tests was set at 0.05.

Results

A total of 888 kindergarten children (519 boys, 369 girls) with 222 study children in each treatment group were recruited in this trial. At baseline, their mean (standard deviation [SD]) age was 3.8 (0.6) y. Their mean (SD) decayed, missing, and filled teeth/surfaces (dmft/dmfs) score were 3.84 (2.79) and 5.15 (4.75), respectively. Their mean (SD) number of carious teeth

and surfaces were 3.69 (2.67) and 4.75 (4.11), respectively. The number of active caries lesions in groups 1, 2, 3, and 4 was 1,051, 1,072, 1,073 and 1,024, respectively. Approximately, two-thirds (60.1%) of the carious lesions were in anterior teeth (i.e., incisors and canines). The carious lesions were located in mesial (29.2%), occlusal (29.0%), buccal (18.2%), distal (13.7%), and lingual (10.0%) surfaces. Plaque was found on the surface of nearly all lesions. Parents of all the study children returned their questionnaires. There were no significant differences among the children in the 4 study groups regarding their clinical features, demographic background, and oral health–related behaviors (χ^2 test and ANOVA with $P > 0.05$) (Table 1).

At the 30-mo examination, 799 children (465 boys, 58.2%) with 3,790 lesions were evaluated, giving an overall tooth surface level dropout rate of 10% (Fig.). The subject-level dropout rates were 12%, 9%, 9%, and 12% in groups 1, 2, 3, and 4, respectively (χ^2 test, $P > 0.05$). Moving to another kindergarten was the reason for leaving this study. There were no statistically

Figure. Flowchart of study children's progress over 30 mo. SDF, silver diamine fluoride.

significant differences in the demographic background, dental health-related behaviors, clinical characteristics, and caries experiences between children who were examined at baseline and remained at the 30-mo examination ($P > 0.05$). The κ values of the duplicate examinations of lesion activity were 0.91 and 0.95 at the baseline and 30-mo examination, respectively. Those of presence of visible plaque (0.92 and 0.92) were similarly high.

Effectiveness of SDF in Arresting Caries

At the 30-mo examination, the mean (SD) numbers of tooth surfaces with arrested caries were 2.59 (2.94), 2.85 (2.91), 3.20 (3.71), and 3.49 (3.27) for groups 1, 2, 3 and 4, respectively (ANOVA, $P = 0.030$; post hoc Bonferroni test: group 1 < group 4,

$P = 0.032$). At surface level, the caries arrest rates for groups 1, 2, 3, and 4 were 55.2%, 58.6%, 66.9%, and 75.7%, respectively (Table 2). There were statistically significant differences in caries arrest rates among the 4 groups at the 24- and the 30-mo examinations (χ^2 test, $P < 0.001$). The caries arrest rates of upper anterior, upper posterior, and lower posterior teeth were significantly different among the 4 groups (χ^2 test, $P < 0.001$).

At the 30-mo evaluation, all distributed questionnaires were returned and an improvement in oral health-related habits between the baseline and 30-mo follow-up was found in all 4 groups of children (McNemar, $P < 0.05$). No significant differences were found among the 4 groups regarding children's background and dental health-related habits ($P > 0.05$) in the Appendix Table.

Logistic Regression Model of Caries Arrest at Surface Level at the 30-mo Follow-up

Besides the assigned treatment group variables (concentration and application frequency), other variables, including lesion size, tooth position, lesion site, VPI score at 30 mo, and plaque on lesion at 30 mo, were significantly ($P < 0.05$) associated with caries arrest at surface level (0 = not arrested, 1 = arrested). No statistically significant interaction between frequency of application and concentration of SDF was detected. However, the interaction between frequency of application and 30-mo VPI score was significant. Thus, this interaction term was added to the base model.

Additional potential variables with $P < 0.1$ in the bivariate analysis (family income, father's and mother's education, caretaker, and experience of dental visit) were also added to the base model (Table 3). Therefore, 32 possible models (31 subset models plus 1 base model) were computed. All additional variables with $P < 0.1$ were not statistically significant in the 31 subset models. The base model with all significant variables gave the smallest QICC (3,030) and was the best-fit logistic regression model, as shown in Table 4. The clustering effect was significant with an ICC of 0.227.

After 30 mo, lesions treated with 38% SDF had a higher chance to become arrested than those treated with 12% SDF (odds ratio [OR], 1.98; 95% confidence interval [CI], 1.51–2.60). The interaction between 30-mo VPI score and frequency of application was statistically significant ($P = 0.017$). For

Table 2. Tooth Surface Level Caries Arrest Rates at 24- and 30-mo Examinations According to Study Group.

Group	Group 1 (12% SDF, Annual), n/N (%)	Group 2 (12% SDF, Semiannual), n/N (%)	Group 3 (38% SDF, Annual), n/N (%)	Group 4 (38% SDF, Semiannual), n/N (%)	P Value
All surfaces					
Baseline	(n = 1,051)	(n = 1,072)	(n = 1,073)	(n = 1,024)	
24 mo	504/937 (53.8)	591/999 (59.2)	620/971 (63.9)	698/912 (76.5)	<0.001
30 mo	512/927 (55.2)	578/987 (58.6)	650/971 (66.9)	685/905 (75.7)	<0.001
Upper anterior teeth					
Baseline	(n = 605)	(n = 612)	(n = 619)	(n = 585)	
24 mo	353/545 (64.8)	404/569 (71.0)	422/572 (73.8)	446/518 (86.1)	<0.001
30 mo	352/535 (65.8)	399/559 (71.4)	442/572 (77.3)	441/515 (85.6)	<0.001
Upper posterior teeth					
Baseline	(n = 140)	(n = 140)	(n = 143)	(n = 138)	
24 mo	34/122 (27.9)	51/133 (38.3)	49/125 (39.2)	71/122 (58.2)	<0.001
30 mo	39/122 (32.0)	49/133 (36.8)	52/125 (41.6)	69/121 (57)	<0.001
Lower anterior teeth					
Baseline	(n = 33)	(n = 26)	(n = 29)	(n = 27)	
24 mo	27/30 (90.0)	19/24 (79.2)	26/28 (92.9)	25/26 (96.2)	0.142
30 mo	27/30 (90.0)	19/24 (79.2)	26/28 (92.9)	22/24 (91.7)	0.268
Lower posterior teeth					
Baseline	(n = 273)	(n = 294)	(n = 282)	(n = 274)	
24 mo	90/240 (37.5)	117/273 (42.9)	123/246 (50.0)	156/246 (63.4)	<0.001
30 mo	94/240 (39.2)	111/271 (41.0)	130/246 (52.8)	153/245 (62.4)	<0.001

SDF, silver diamine fluoride.

illustration, carious lesions in children with a high VPI score (say, mean VPI score $[0.45] + 1 \text{ SD } [0.20] = 0.65$) and received annual SDF application had a lower chance to become arrested than those in children with the mean VPI score (OR, 0.59; 95% CI, 0.49–0.72). Large caries lesions—those in occlusal surfaces, those in posterior teeth, and those covered with visible plaque—had a comparatively lower chance to become arrested ($P < 0.001$). Apart from the black staining on the arrested caries lesions, the present study did not find any major long-term or permanent adverse effects.

Discussion

This 30-mo randomized clinical trial was satisfactorily completed, and the dropout rate at caries lesion level was lower than anticipated (10% vs. 15%). Moreover, the observed ICC for caries arrest within subject was also lower than the expected value (0.23 vs. 0.30). Therefore, the power of the study in the multilevel analysis was higher than planned. The intraexaminer agreement was good as the κ values in the duplicate examinations were at least 0.91 at baseline and follow-up examinations. The strengths of the present study include large sample size, low dropout rate, good intraexaminer reliability, and relatively long (30-mo) follow-up period. In the data analysis, several alternatives had been proposed to handle missing data. However, there was no empirical evidence to guide the data analysis for those who were lost to follow-up (Alshurafa et al. 2012). Thus, complete case analysis was adopted. Due to ethical reasons, there was no negative control group.

Based on the 30-mo results, the null hypotheses of this clinical trial were rejected. It was found that 38% SDF was more effective than 12% SDF in arresting caries in primary teeth.

These findings are in line with those from laboratory studies (Mei et al. 2012, 2014). Hence, use of high-concentration (38%) SDF is recommended due to its higher caries arrest effectiveness. The caries arrest rates of 38% SDF were 66.9% for annual application and 75.7% for semiannual application. These results are comparable to that of a systematic review reporting that the overall caries arrest rate of 38% SDF was 65.9% (Gao, Zhang, et al. 2016). Increasing the frequency of application from once to twice a year would increase the caries arrest rate by about 15%. Furthermore, increasing the frequency of SDF application can raise the caries arrest rate in children with poor oral hygiene. Despite this, in places where many young children have untreated ECC (Duangthip et al. 2017), annual application of SDF solution would be a practical and effective strategy for ECC management. Besides the primary analysis about the effectiveness of the assigned SDF treatment, the exploratory or secondary analysis investigating other significant variables on the caries arrest outcomes was also presented. This study found that good oral hygiene and absence of plaque on lesions are paramount for the success of caries arrest treatment by SDF. This finding concurs with that of a previous study (Duangthip et al. 2016). The application of SDF on cavitated lesions was not sufficient to prevent the development of new caries over the 30-mo period in the participant children who probably were at high caries risk, as reflected by their high mean baseline dmfs score. Other preventive measures such as hands-on training in plaque control and topical fluorides should be used to complement caries arrest treatment in the management of ECC.

This study found a significant interaction between frequency of SDF application and child's oral hygiene status. It is difficult to halt caries progression in children with heavy

Table 3. Bivariate Logistic Regression Using GEE Model with Logit Link and Two-Level Clusters (Surface Level and Subject Level).

Explanatory Variables	Unadjusted Odds Ratio	95% Confidence Interval	P Value
Demographic background			
Sex (reference: Female)			0.873
Male	1.02	0.81 to 1.28	
Place of birth (reference: others)			0.140
Hong Kong	0.66	0.38 to 1.15	
Family structure (reference: single parent)			0.158
Both parent	1.53	0.85 to 2.74	
Main caretaker (reference: domestic helper)			0.014
Parent	1.45	1.05 to 2.00	
Grandparent	1.04	0.71 to 1.52	
Father's education level (reference: tertiary)			0.040
Secondary	1.39	1.02 to 1.89	
Primary	1.63	1.09 to 2.41	
Mother's education level (reference: tertiary)			0.072
Secondary	1.20	0.86 to 1.67	
Primary	1.62	1.06 to 2.48	
Monthly family income (reference: above HK\$20,000)			0.086
HK\$10,000–\$20,000	1.23	0.93 to 1.64	
Below HK\$10,000	1.37	1.03 to 1.81	
Clinical parameters at baseline			
dmft score	0.98	0.94 to 1.02	0.247
Severity of dental caries (reference: >3 carious lesions)			0.784
Having 1 to 3 carious lesions	1.03	0.82 to 1.30	
Lesion site (reference: mesial)			<0.001
Buccal	1.19	0.96 to 1.47	
Lingual	0.83	0.66 to 1.03	
Distal	0.84	0.70 to 1.00	
Occlusal	0.32	0.26 to 0.38	
Tooth position (reference: upper anterior)			<0.001
Upper posterior	0.24	0.19 to 0.31	
Lower anterior	2.93	1.18 to 7.27	
Lower posterior	0.33	0.26 to 0.41	
Size of lesion (reference: small)			<0.001
Large	0.63	0.54 to 0.73	
Clinical parameter at 30 mo			
VPI score	0.392	0.22 to 0.69	0.001
Presence of plaque on lesion (reference: yes)			<0.001
No	11.17	6.35 to 19.65	
Dental health–related habits at 30 mo			
Current bottle feeding (reference: yes)			0.413
No	1.13	0.85 to 1.50	
Daily frequency of snacking	0.96	0.87 to 1.06	0.417
Daily frequency of toothbrushing (reference: twice a day)			0.350
Once a day	1.13	0.88 to 1.45	
Less than once a day	0.75	0.42 to 1.33	
Use of fluoride toothpaste (reference: yes)			0.603
No	1.10	0.78 to 1.54	
Supervised toothbrushing (reference: yes)			0.637
No	1.06	0.84 to 1.33	
Having dental visit after start of study (reference: yes)			<0.001
No	2.35	1.72 to 3.19	
SDF treatment			
Concentration of SDF (reference: 12% SDF)			<0.001
38% SDF	1.70	1.36 to 2.12	
Frequency of SDF application (reference: annual)			0.008
Semiannual	1.35	1.08 to 1.69	

dmft, decayed, missing, and filled teeth index; SDF, silver diamine fluoride; VPI, visible plaque index.

Table 4. Multivariable Logistic Regression Model with the Best Goodness of Fit Estimated by Corrected Quasi-Likelihood Information Criterion.

Explanatory Variables	Predicted Probability ^a	Adjusted Odds Ratio	95% Confidence Interval	P Value	Pairwise Comparison
SDF concentration				<0.001	
(1) 12% ^b	0.85				
(2) 38%	0.92	1.98	1.51 to 2.60		
Frequency of application				0.194	
(1) Annual ^b					
(2) Semiannual		0.64	0.32 to 1.26		
Lesion site				<0.001	
(1) Mesial ^b	0.85				
(2) Buccal	0.88	1.32	0.99 to 1.77		(2) > (5)
(3) Lingual	0.84	0.93	0.67 to 1.28		
(4) Distal	0.86	1.08	0.85 to 1.36		(4) > (5)
(5) Occlusal	0.78	0.63	0.45 to 0.88		
Tooth position				<0.001	
(1) Upper anterior ^b	0.85				(1) > (2), (4)
(2) Upper posterior	0.52	0.19	0.13 to 0.28		
(3) Lower anterior	0.95	3.32	0.99 to 11.16		(3) > (2), (4)
(4) Lower posterior	0.67	0.36	0.24 to 0.53		(4) > (2)
Size of lesion				<0.001	
(1) Small ^b	0.85				
(2) Large	0.70	0.42	0.34 to 0.51		
Lesion with visible plaque at 30 mo				<0.001	
(1) Yes ^b	0.85				
(2) No	0.99	13.02	7.56 to 22.44		
VPI score at 30 mo		0.07	0.03 to 0.19	<0.001	
Frequency of application × VPI score				0.017	
(1) Annual ^b					
(2) Semiannual		5.14	1.33 to 19.80		
Illustrations of interaction effect between frequency of application and VPI score using the estimates from both main and interaction effects					
I. Annual × mean VPI score	0.85 ^c				
II. Semiannual × mean VPI score	0.88 ^c	1.33	1.02 to 1.74		
III. Annual × high VPI score ^d	0.29 ^c	0.59	0.49 to 0.72		
IV. Semiannual × high VPI score ^d	0.74 ^c	1.09	0.53 to 2.25		

SDF, silver diamine fluoride; VPI, visible plaque index.

^aPredicted probability of arrested caries evaluated with VPI score at mean level of 0.45 (after excluding missing data) and other variables set at the reference category.^bReference category.^cPredicted probability of arrested caries evaluated with other variables set at the reference category.^dHigh VPI score = mean VPI score (0.45) + 1 SD (0.20) = 0.65.

plaque. Clinicians should recall their child patients with unsatisfactory oral hygiene every 6 mo, and another SDF application would be necessary. Besides the above-mentioned factors, in this study, the effectiveness of caries arrest by SDF was site specific. The SDF treatments were more effective in arresting caries on smooth surfaces of anterior teeth. These results are consistent with those of a previous study (Zhi et al. 2012).

The success of an oral health care program in preschool children can be influenced by social determinants such as poverty (Braun et al. 2016). In the present study, the bivariate regression analysis showed a significant impact of father's education. However, the multivariate regression analysis showed the absence of this significance, possibly due to a potential mediating role of other variables such as plaque scores. In deprived communities, where poor oral hygiene is common, an effective plaque control program should be developed to enhance the caries arrest rates.

Besides the black staining on the arrested lesions, the present study did not find any major long-term or permanent adverse effects. A pharmacokinetic study found that 2.37 mg SDF was the largest applied dose for 3 decayed primary teeth, which is far below the acute toxic dose by more than 400 times (Vasquez et al. 2012). Furthermore, topical SDF application on teeth is just an exposure only once or twice a year. Therefore, the safety concern of excessive fluoride exposure should be insignificant. This study supports the previous reviews that SDF is an effective, efficient, and safe caries therapeutic agent for caries control in young children (Rosenblatt et al. 2009; Duangthip et al. 2015). When generalizing the findings of this study, one should consider that the participants in this study were preschool children with cavitated dentin carious lesions, and the study site was in Hong Kong, where the water supply is fluoridated at 0.5 ppm. In addition, parental acceptance of the staining of caries lesions after SDF application can vary significantly in different communities.

Conclusion

Based on the 30-mo results of this study, 38% SDF solution is more effective in arresting dentin caries of primary teeth among preschool children compared to 12% SDF. Interaction between frequency of SDF application and oral hygiene status can be significant. Children's oral hygiene should be taken into account when choosing the periodicity of SDF application. In children with poor oral hygiene, semiannual application of SDF is more effective than annual application in arresting dentin caries.

Author Contributions

M.H.T. Fung, contributed to conception, design, data acquisition, analysis, and interpretation, drafted and critically revised the manuscript; D. Duangthip, contributed to data acquisition, analysis, and interpretation, drafted and critically revised the manuscript; M.C.M. Wong, E.C.M. Lo, C.H. Chu, contributed to conception, design, data acquisition, analysis, and interpretation, critically revised the manuscript. All authors gave final approval and agree to be accountable for all aspects of the work.

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