Randomized clinical trial of 12% and 38% silver diamine fluoride treatment

Fung MHT, Duangthip D, Wong MCM, Lo ECM, Chu CH

Faculty of Dentistry, The University of Hong Kong

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Corresponding to : CHU Chun Hung

3/F Prince Philip Dental Hospital

34 Hospital Road

Hong Kong

Tel : +852 2859 0287

Fax: +852 2858 2532

E-mail: chchu@hku.hk

Abstract

This 30-month randomized clinical trial compared the effectiveness of two concentrations (12% or 38%) of silver diamine fluoride (SDF) and two periodicity of application (once or twice a year) in arresting cavitated dentin caries in primary teeth. Children aged 3-4 years who had at least one active cavitated caries lesion were enrolled and randomly allocated into four groups for intervention. Group 1 - 12% SDF applied annually (every 12 months); Group 2 - 12% SDF applied semi-annually (every 6 months); Group 3 - 38% SDF applied annually; and Group 4 - 38% SDF applied semi-annually. Clinical examinations were performed semi-annually 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-month 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 (OR=1.98; 95% 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 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 semi-annually.

This study was registered in the Registry of Clinical Trials run by the United States National Library of Medicine (NCT02385474).

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 behaviours. 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 U.S. Food and Drug Administration cleared SDF for off-label use in the United States in 2015 (Horst et al. 2016). A survey in the USA 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 et al. 2016b). 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 30month randomized clinical trial to compare the effectiveness of two concentrations (12% and 38%) of SDF when applied once or twice a year in arresting dentin caries in primary teeth in preschool children. The 18-month 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 months than every 12 months (Fung et al. 2016). This paper reported 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 months).

Materials and Methods

This study was registered in the Registry of Clinical Trials run by the United States National Library of Medicine (ClinicalTrials.gov identifier: NCT02385474). Ethical approval was obtained from the Institutionalized Review Board of the University of Hong Kong. Written

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

Trial design and implementation

This 30-month study was conducted in 37 kindergartens in Hong Kong. Healthy children aged 3-4 years and with at least one soft carious lesion at dentin level were recruited. Tooth with signs suggesting that it was non-vital was excluded. After baseline examination, eligible children were randomly allocated to one of the four treatment groups. Follow-up examinations were performed every six months by the same trained examiner who was blinded to the treatment group allocation. A CPI probe and a disposable dental mirror attached to an intra-oral 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 six 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 dmfs index. At tooth surface level, the size of lesion was classified as 'small' (<half of the mesial or distal surface; or <1/3 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). 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 intra-examiner reliability of caries diagnosis and oral hygiene assessment was evaluated through re-examining a 10% random sample of children on the same day. At baseline and the 30-month 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 toothbrushing frequency, supervised brushing , use of fluoride toothpaste, daily frequency of sugary snacking and dental check-up 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 two strata according to the number of carious tooth surfaces they had (1-3 surfaces and >3 surfaces) in order 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 eight. The assistant who performed the random allocation of study children also prepared the treatment materials. The bottles of the SDF solutions were wrapped with aluminium 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 semi-annual visits to blind the study children. The four treatment groups were as follows:

Group 1: 12% SDF applied every 12 months;
Group 2: 12% SDF applied every 6 months;
Group 3: 38% SDF applied every 12 months;
Group 4: 38% SDF applied every 6 months.

Sample size calculation

The sample size was estimated based on: (i) caries arrest rate of 70% (Gao et al. 2016a), (ii) a 10% absolute difference in caries arrest rate would be clinically significant, (iii) statistical power of 80%, and (iv) statistical significance level at 0.05. The required sample size calculated by using the software Sample Power 2.0 (SPSS, Inc., Chicago, USA) was 353 caries lesions/group. The anticipated intra-class 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 multilevel study (Twisk, 2006), 565 caries lesions in 188 children/group would be required. With a 15% drop-out rate, 221 children/group was needed at baseline.

Statistical analyses

Data was analysed using the software SPSS 23.0 for Windows for statistical analysis (SPSS Inc., Chicago, USA) 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 intra-examiner reliability in caries diagnosis and assessment of oral hygiene. Chi-square test and one-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-month examinations were assessed using 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 two-level clusters (surface level and subject level) was performed to investigate the effects of variables on caries arrest at the 30-month examination at tooth surface level. Treatment group allocation was replaced with concentration (12% or 38%) and application frequency (annual or semi-annual) 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 two 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 of application, the five 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 were 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 significant 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 age (SD) was 3.8 (0.6) years. Their mean (SD) dmft and 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 were 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 four study groups regarding their clinical features, demographic background, oral health related behaviours (χ^2 test and ANOVA with $p>0.05$) (Table 1).

At the 30-month examination, 799 children (465 boys, 58.2%) with 3,790 lesions were evaluated, giving an overall tooth surface level dropout rate of 10% (Figure 1). 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 significant differences in the demographic background, dental health related behaviours, clinical characteristics and caries experiences between children who were examined at baseline and remained at the 30-month examination ($p>0.05$). The kappa values of the duplicate examinations of lesion activity were 0.91 and 0.95 at the baseline and 30-month 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-month 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 four groups at the 24- and the 30-month examinations (χ^2 test, $p<0.001$). The caries arrest rates of upper anterior, upper posterior, and lower posterior teeth were significantly different among four groups (χ^2 test, $p<0.001$).

At the 30-month evaluation, all distributed questionnaires were returned and an improvement in oral health-related habits between the baseline and 30-month follow-up was found in all four groups of children (McNemar, $p<0.05$). No significant differences were found among the four study groups regarding the children's brushing and snacking habits, and experience of dental visits (χ^2 test, $p>0.05$).

Logistic regression model of caries arrest at surface level at the 30-month 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-month and plaque on lesion at 30-month were found to be 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-month 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 found to be not statistically significant in the 31 subset models. The base model with all significant variables gave the smallest QICC (3030) 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 months, lesions treated with 38% SDF had 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-month VPI score and frequency of application was statistically significant ($p=0.017$). For illustration, carious lesions in children with a high VPI score (let say, mean VPI score (0.45) + 1SD (0.20) = 0.65) and received annual SDF application had lower chance to become arrested than those in children with the mean VPI score (OR=0.59; 95% CI: 0.49-0.72). However, there was no significant difference between the chance of being arrested among the carious lesions in children with a high VPI score receiving semi-annual SDF application (OR=1.09, 95% CI: 0.53-2.25), compared to those in children with mean VPI score receiving annual application. Large caries lesions, those in occlusal surfaces, those in posterior teeth, and those covered with visible plaque had 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-month randomized clinical trial was satisfactory 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 multi-level analysis was higher than planned. The intra-examiner agreement was good as the kappa values in the duplicate examinations were at least 0.91 at baseline and follow-up examinations. The strength of the present study include large sample size, low dropout rate, good intra-examiner reliability and relatively long (30-

month) 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 loss 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-month results, the null hypotheses of this clinical trial were rejected. 38%SDF was more effective than 12%SDF in arresting caries in primary teeth. These findings are in line with that 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 semi-annual application. These results are comparable to that of a systematic review reporting the overall caries arrest rate of 38% SDF was 65.9 % (Gao et al. 2016a). 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 suffer from 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 lesion 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-month 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 the caries progression in children with heavy plaque. Clinicians should recall their child patients with unsatisfactory oral hygiene every 6 months 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 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, 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 three 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-month results of this study, 38% SDF solution is more effective in arresting dentin caries of primary teeth among preschool children, when 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, semi-annual application of SDF is more effective than annual application in arresting dentin caries.

Conflicts of interest

The authors declare no potential conflicts of interest.

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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, semi-annual)	Group 3 (38% SDF, annual)	Group 4 (38% SDF, semi-annual)	*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 parent	209 (95%)	210 (96%)	209 (95%)	212 (96%)	*0.784*
Main Care Taker					*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%)	
- Post-secondary 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%)	
- Post-secondary 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 dmft score	3.82 (2.72)	3.81 (2.83)	3.92 (2.91)	3.83 (2.72)	*0.970*
Mean 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 1-3 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	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 toothbushing	182 (82%)	188 (85%)	176 (79%)	181 (82%)	*0.530*

Table 2 Tooth surface level caries arrest rates at 24- and 30-month examinations according to study group.

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

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

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	1.51-2.60		
Frequency of application				0.194	
(1) Annual[b]					
(2) Semi-annual		0.64	0.32-1.26		
Lesion site				<0.001	
(1) Mesial[b]	0.85				
(2) Buccal	0.88	1.32	0.99-1.77		(2) > (5)
(3) Lingual	0.84	0.93	0.67-1.28		
(4) Distal	0.86	1.08	0.85-1.36		(4) > (5)
(5) Occlusal	0.78	0.63	0.45-0.88		
Tooth position				<0.001	
(1) Upper anterior[b]	0.85				(1) > (2),(4)
(2) Upper posterior	0.52	0.19	0.13-0.28		
(3) Lower anterior	0.95	3.32	0.99-11.16		(3) > (2),(4)
(4) Lower posterior	0.67	0.36	0.24-0.53		(4) > (2)
Size of lesion				<0.001	
(1) Small[b]	0.85				
(2) Large	0.70	0.42	0.34-0.51		
Lesion with visible plaque at 30-month				<0.001	
(1) Yes[b]	0.85				
(2) No	0.99	13.02	7.56-22.44		
VPI score at 30-month		0.07	0.03-0.19	<0.001	
Frequency of application * VPI score				0.017	
(1) Annual[b]					
(2) Semi-annual		5.14	1.33-19.80		
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. Semi-annual * Mean VPI score	0.88[c]	1.33	1.02-1.74		
iii. Annual * High VPI score[d]	0.29[c]	0.59	0.49-0.72		
iv. Semi-annual * High VPI score[d]	0.74[c]	1.09	0.53-2.25		

[a] Predicted 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

[b] Reference category, * Interaction

[c] Predicted probability of arrested caries evaluated with other variables set at the reference category

[d] High VPI score = Mean VPI score (0.45) + 1SD (0.20) = 0.65