Arresting dentine caries with different concentration and periodicity of silver diamine fluoride

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Knowledge Transfer Statement: The results of this study can be used by clinicians and dental public health professionals when deciding which concentrations and frequency of application of silver diamine fluoride solution should be adopted for arresting dentine caries. With consideration of caries arrest treatment with silver diamine fluoride, which is painless, simple and low cost, this information could lead to more appropriate therapeutic decisions for caries control in young children or those who lack access to affordable conventional dental care.

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Abstract

Different regimens of silver diamine fluoride (SDF) have been used to manage early childhood caries. So far, there is limited information regarding the concentrations and frequency of applications for effective caries control in primary teeth. This study aimed to compare the efficacy of two commercially available SDF solutions at pre-prepared concentrations of 38% and 12% when applied annually or biannually over 18 months in arresting dentine caries in primary teeth. This randomised double-blinded clinical trial recruited kindergarten children aged 3-4 years who had at least one tooth with dentine caries. The children were randomly allocated to receive four treatment protocols: Group 1 – annual application of 12% SDF; Group 2 – biannual application of 12% SDF; Group 3 – annual application of 38% SDF; and Group 4 – biannual application of 38% SDF. Clinical examinations at 6-month intervals were conducted to assess whether active carious lesions became arrested. Information on the children's background and oral hygiene habits was collected through a parental questionnaire at baseline and follow-up examinations. A total of 888 children with 4,220 dentine carious tooth surfaces received treatment at baseline. After 18 months, 831 children (94%) were examined. The caries arrest rates were 50%, 55%, 64% and 74% for Groups 1, 2, 3 and 4, respectively ($p<0.001$). Lesions treated with SDF biannual application had a higher chance of becoming arrested compared to those receiving SDF annual application (OR=1.33; CI95%: 1.04 – 1.71, $p=0.025$). The interaction between concentration and lesion site was statistically significant ($p<0.001$). Compared to 12% SDF, the use of 38% SDF increased a chance of becoming arrested ($p<0.05$), except lesions on occlusal surfaces. Based on the 18-month results, SDF is more effective in arresting dentin caries in the primary teeth of preschool children at 38% concentration than 12% concentration and when applied biannually rather than annually.

Introduction

Early childhood caries (ECC) is highly prevalent, especially in poor and disadvantaged children (Tinanoff and Reisine 2010, Chu et al. 1999). Epidemiological studies reported that ECC was mostly left untreated (Chu et al. 2012, Schwendicke et al. 2015). The conventional restorative approach requires sophisticated dental equipment and well-trained health personnel, especially in apprehensive young children (Chu and Lo 2007). Effective and feasible caries treatment protocols are required to address this major dental public health problem. Clinical studies have shown that the use of 38% silver diamine fluoride (SDF) is effective in preventing and also arresting caries (Chu et al. 2002, Llodra et al. 2005, Braga et al. 2009). A clinical trial demonstrated that SDF treatment was more effective (relative risk 67%) than interim restorative treatment using a glass ionomer cement (relative risk 39%) in arresting caries of primary teeth (dos Santos et al. 2012).

Different concentrations of SDF solutions are commercially available. An in-vitro study using a 40% aqueous solution of silver fluoride in Australia suggested that such a high concentration of fluoride may allow a substantial amount of fluoride to enter the systemic circulation and potentially caused dental fluorosis in young children (Gotjamanos 1997). Although this suggestion of the risk of dental fluorosis was refuted by the Health Department of Western Australia (Neesham 1997), some researchers have recommended the use of a lower concentration of SDF to minimise this risk (Yee et al. 2009). However, a one-off application of a low concentration (12%) of SDF was not effective in arresting dental caries (Yee et al. 2009). In contrast, a 30-month clinical study found that three applications of 10% SDF over three consecutive weeks was effective in arresting caries in children (Braga et al. 2009). There is no study so far to investigate the effectiveness of regular applications of low concentration of SDF in arresting caries of young children.

Rosenblatt et al. (2009) performed a review on SDF and concluded that it is a safe, effective, efficient and ‘equitable’ caries control agent for preventing and arresting dental caries. Milgrom and Chi (2011) advocated that SDF therapy is an important prevention-centred caries management strategy during critical periods in early childhood. However, more randomised, controlled clinical trials on SDF are thus needed before recommending the widespread use of this potentially useful interventional agent. At present, no study has shown whether low and high SDF concentrations are equally effective or if 6- or 12-month applications differ in the treatment outcome. The objective of this study was to compare the efficacy of two commercially available SDF solutions at pre-prepared concentrations of 38% and 12% when applied annually or biannually over 18 months in arresting dentine caries in primary teeth. The null hypothesis tested was that there was no difference in the effectiveness of SDF in caries arrest in the primary teeth of children at i) concentrations of 12% or 38% and ii) an application frequency of every 6 or 12 months.

Methods

The study was approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (IRB Reference Number: UW 09-302). The trial was registered in the Registry of Clinical Trials run by the United States National Library of Medicine (ClinicalTrials.gov Identifier: NCT02385474). Healthy preschool children aged 3-4 years who had at least one tooth with untreated active dentine caries attending the first year in 37 kindergartens were invited to join this study. Informed consent was sought from parents of each participating children. Teeth with exposed pulp or non-vital teeth were excluded in this study.

A trained dentist conducted the field examination in the kindergarten through a careful visual inspection with the aid of a CPI periodontal probe and a dental mirror with light-emitting diode intra-oral illumination. The oral hygiene status was measured using the visible plaque index (VPI). The buccal and lingual surfaces of six index teeth (55, 51, 63, 71, 75 and 83) were examined for recording the VPI scores. The tooth status (decayed, missing, filled surfaces [dmfs] score), tooth discoloration and hyper-mobility were recorded. The caries was diagnosed at the cavitation level. A lesion was recorded as active if softness was detected upon gentle probing, or if the decayed tooth was extracted or restored at the follow-up examination. If the dentine surface was hard to probing, it was classified as arrested caries (Chu et al. 2002, Llodra et al. 2005, Yee et al. 2009, Zhi et al. 2012). For caries arrest assessment, all surfaces (buccal, lingual, mesial, distal and occlusal for posterior teeth) of each tooth were assessed. The follow-up oral examinations were conducted by the same examiner at 6, 12 and 18 months. Intra-examiner agreement on the plaque and caries assessment was conducted in 10% of the children at all examinations. A parental questionnaire was administered at baseline and 18-month follow-up visits regarding their children’s oral hygiene habits, frequency of toothbrushing, use of fluoride toothpaste, dental visit behaviour, snacking habits, main caretaker, parental condition, parental educational level and family total income.

A two-factor factorial design (concentration: 12% vs. 38% and frequency: annually vs. biannually) was adopted. Participating children with dental caries were categorised as having a higher caries rate (more than 3 caries tooth surfaces) or a lower caries rate (3 or fewer caries tooth surfaces). A dental assistant who held the random allocation list prepared the materials according to the child's assigned group. The children were then allocated by a stratified randomisation method (block size of 8) using a personal computer into one of four groups as follows:

Group 1 - Topical application of 12% SDF solution every 12 months;
Group 2 - Topical application of 12% SDF solution every 6 months;
Group 3 - Topical application of 38% SDF solution every 12 months;
Group 4 - Topical application of 38% SDF solution every 6 months.

In this study, the 12% SDF solution was Cariostop 12% (Biodinâmica Química e Farmacêutica LTDA, Brazil), while the 38% SDF solution was Saforide (Toyo Seiyaku Kasei Co. Ltd., Japan). SDF was applied after the examination by an independent operator blinded to the group allocation. A normal saline solution was applied to the carious tooth surfaces of the Group 1 and 3 children during the half-yearly follow-up visits to blind the children. The examiner was blinded to the treatment group allocation of the children and the identity of the solutions throughout the study.

The results of previous clinical trials showed that around 70% of the active dentin caries became arrested after 24 months (Chu et al. 2002). An absolute difference of 10% in the caries arrest rates between treatment groups was considered to be clinically significant. The estimated sample size was based on the expected proportion of arrested caries, with the power of the study set at 80% (β=0.2) and with α=0.05 as the statistical significance level. The sample size per study group, calculated by using the software Sample Power 2.0 (SPSS Inc. Chicago, Illinois, USA), was 353 active carious tooth surfaces. Based on the results of epidemiological surveys (Chu et al. 2012, Lo et al. 2009), we estimated that the mean baseline active carious surfaces would be 3. The intraclass correlation coefficient (ICC) for dental caries data at the surface level within the individual would be approximately 0.3 (Masood et al. 2015). Following the equation for the required sample size in a multi-level study (Twisk, 2006), the estimated sample size would be at least 565 active carious surfaces and with at least 188 children being recruited for each group at baseline. The anticipated drop-out rate was approximately 15% (Duangthip et al. 2015); thus, 221 children in each group or 884 children in total needed to be recruited at baseline.

Statistical analysis

An intention-to-treat analysis was undertaken. All data were analysed using the software SPSS 23.0 for Windows (SPSS Inc., Chicago, USA). Cohen's Kappa statistics were used to assess the intra-examiner reliability in caries diagnosis, assessment of visual plaque index (VPI) at baseline and follow-up examinations. Chi-square test was used to assess the categorical data of children's demographic information (age, gender, place of birth, parental condition, main caretaker, father's and mother's education level and monthly family income level); oral health-related habits (bottle feeding before bed, stop bottle feeding age, start toothbrushing age, daily toothbrushing frequency, use of fluoride toothpaste); dental visits; caries condition (baseline ECC status, tooth position and lesion site); and adverse effects among the four treatment groups. Analysis of variance (ANOVA) was performed to assess the comparability between the treatment groups according to the baseline conditions of the children such as frequency of snack time, dmft/dmfs score, number of non-vital teeth, number of included teeth/surfaces and VPI score. The McNemar test was used to compare the changes in oral health-related habits at baseline and the follow-up examinations.

Since more than one caries lesion could be chosen from one child, the generalized estimating equations (GEE) approach was used to adjust for the clustering effect. The first level was the tooth surface while the second level was the child (subject). This analysis accounted for the correlation (clustering) between observations of multiple surfaces from the same child. Therefore, a multi-level logistic regression analysis was performed to analyse the effects of independent variables on the caries arrest rates at the 18-month examinations. Treatment group was replaced with SDF concentration (12% or 38%), frequency (annually or biannually), and interaction between concentration and frequency to evaluate the effects of these factors in the presence of other significant independent variables adjusted in the model. Based on prior knowledge, tooth position, lesion site, lesion size, plaque on lesion and overall VPI score are significant factors affecting caries arrest (Duangthip 2015). Therefore, besides the concentration and frequency of application, the above mentioned factors and their significant interaction with the assigned treatment were included as variables in the base model. Other potential variables (namely the child's demographic characteristics collected at baseline, oral health related behaviours and dental visits collected at 18 months and clinical characteristics at 18 months) with p<0.1 in the univariate analysis were selected and added to the base model. All possible subset models approach was used and these models were compared. The goodness of fit of the models was estimated by the corrected quasi-likelihood information criterion (QICC). QICC is a reverse value for goodness of fit so that the smaller the value, the better the model fit. The model with all variables being significant, and showing the lowest QICC was selected as the best-fit logistic regression model. The level of statistical significance for all tests was set at p<0.05.

Results

A total of 4,251 kindergarten children were screened and 888 eligible children were randomly allocated into four treatment groups with 222 children in each group. Among them, 419 children (48%) were regarded as having high caries rates. The mean (SD) age of the children was 3.8 (0.6) years old, and 519 (58.4%) were boys. Background information and clinical characteristics of children in the four study groups at baseline are shown in Table 1. There was no statistically significant difference in mean age, gender, place of birth, parental condition, main caretaker, father's and mother's education level, monthly family income level and oral health related behaviours among the four groups. Regarding the clinical characteristics, the mean (SD) dmft and dmfs at baseline were 3.84 (2.79) and 5.15 (4.75), respectively. The mean (SD) VPI score was 0.69 (0.20). There was no statistically significant difference in the baseline of the mean dmft and dmfs scores, number of teeth and surfaces included for treatment, number of non-vital teeth and mean VPI scores between four groups. According to the tooth position, 2,421 (57%) surfaces were in upper anterior arch, 561 surfaces (13%) were in upper posterior arch, 115 (3%) surfaces were in lower anterior arch and 1,123 (27%) surfaces were in lower posterior arch. There was no statistically significant difference in the distribution of caries surfaces according to tooth position or lesion site.

Follow-up findings

The flow of children was summarised in the CONSORT flowchart (Figure 1). The subject and surface drop-out rate were 6.4% and 5.8%, respectively. There was no statistically significant difference in subject or surface drop-out rates among four groups (χ^2 test, p>0.05). The main reason for participants leaving this study was due to changing kindergartens. All the 831 remaining children returned the parental questionnaires after the 18-month examination. There were no statistically significant differences among the four groups of children on gender, bottle feeding habit, oral health related behaviours, dental visits, mean daily snacking frequency at the 18-month examination. At 18 months, 25% of the study children were still using nursing bottles for feeding. Regarding the oral health related behaviours, 64% of them brushed their teeth twice daily or more but 2% of them did not brush their teeth. Regarding the age of starting brushing, 14% of them started brushing at age 12 month-old or younger, 23% at 13-18 month-old, 22% at 19-24 month-old and 39% after 24 month-old. After receiving SDF treatment, 5% of the children visited a dentist for dental check up. No statistically significant difference was found in baseline caries experience, number of caries teeth and surfaces included and number of non-vital teeth of children who dropped out and remained in the 18-month follow-up ($p>0.05$). Intra-examiner reliability of VPI scores and caries arrest assessment, as measured by the Cohen's Kappa statistics, were at least 0.91 at baseline and all follow-up examinations.

The oral hygiene status in mean VPI score at baseline, 6-, 12- and 18-month examination were 0.69, 0.43, 0.45 and 0.36, respectively, and no significant differences were found in VPI scores among four groups ($p>0.05$). Compared with baseline examination, there was significant improvement in all four groups from baseline to 6-month follow-up but not at 12- or 18-month examinations. At the 18-month follow-up examination, almost all of the soft lesions (99% - 100%) were presented with visible plaque while only 72% to 81% of the arrested lesions were presented with visible plaque. However, no significant interaction between plaque on lesion and the assigned treatment was found. There were significantly more soft caries surfaces than arrested caries with visible plaque ($p < 0.001$). No significant difference in caries experience (dmft and dmfs) was found among the four treatment groups at all examinations.

Effectiveness of SDF treatment

At baseline, the respective total numbers of active cavitated dentin lesions in Groups 1 to 4 were 1,051, 1,072, 1,073 and 1,024. Before adjustment of covariates, at the 18-month follow-up, the treatment effectiveness among 4,220 included caries surfaces was 50%, 55%, 64% and 74% for Groups 1 to 4, respectively (Table 2). Statistically significant differences were found in caries arrest rates between the four groups at all follow-up examinations (χ^2 test, $p<0.001$). The proportions of arrested surfaces of upper anterior teeth, upper posterior teeth, lower anterior teeth and lower posterior teeth are shown in Table 2. Besides the known black staining on carious lesions after SDF treatment, no major adverse event occurred during the 18-month study.

Logistic regression model at 18-month follow-up

For the base model, both high concentration (38% SDF) and high frequency (biannually) were associated with an increased chance to arrest caries lesion ($p<0.05$). All other variables in the base model (tooth position, lesion site, lesion size, plaque on lesion and overall VPI score) were also significantly associated with effectiveness of caries arrest ($p<0.05$). No statistically significant interaction between SDF concentration and frequency of application was found. However, the interaction between concentration and lesion site was statistically significant. This interaction was included in the base model together with the assigned treatment (concentration and frequency of application) and other variables mentioned above.

Six variables (mother's education, main care taker, tooth brushing frequency, use of bottle feeding before bed, start toothbrushing age, dental visit) with $p<0.1$ in the univariate analysis were selected as the additional independent variables. As a result, one base model plus 63 possible subset models were generated. Comparing these 64 subset logistic regression models, the best-fit model with all additional significant variables was selected (Table 3). It had lower QICC (3233) than the base model (3515). The intra-class correlation coefficient (ICC) was 0.13.

At 18 months, lesions of the children receiving biannual SDF application had a higher chance of becoming arrested compared to those receiving annual SDF application (OR=1.33; CI 95%: 1.04 – 1.71, $p=0.025$). The interaction between SDF concentration and lesion site was statistically significant ($p<0.001$). Lesions on mesial, distal, buccal and lingual surfaces that received SDF concentration at 38% had higher chance of becoming arrested than those receiving a SDF concentration at 12% ($p<0.05$). However, there is no statistically significant difference in arresting caries on occlusal surfaces by 38% SDF and 12% SDF. Lesions in the posterior teeth ($p<0.001$), large lesions ($p<0.001$) and lesions in a child with a higher VPI score ($p<0.001$) had a lower chance of becoming arrested. Similarly, lesions with visible plaque had a lower chance of becoming arrested compared to those without visible plaque ($p<0.001$). Children who started brushing at age 18 months and younger ($p=0.001$), whose mother completed primary education ($p=0.024$), or whose care takers were their own parents ($p=0.030$) had a higher chance of having arrested caries.

Discussion

This study used a 2 x 2 factorial design, and this allowed simultaneous study of two factors at two levels together with their potential interaction effect (Bria et al. 2007, Stamm 2004). Stratification was used to reduce baseline differences in disease severity and therefore reduce the potential bias to the treatment outcomes (Kingman 1984, Meier 1981). Block randomisation was used to ensure that the number of participants in each group was almost the same (Matts and Lachin 1988). In this study, the allocation ratio of 1:1:1:1 among the four treatment groups was achieved.

According to the sample size calculation, the obtained ICC in the present study (0.13) was smaller than the estimated one (0.3). In addition, the completeness of follow-up is considered very satisfactory as the subject-dropout rate was approximately 6% over 18 months, which was lower than the anticipated rate in the planning study. Therefore, the efficiency or power in the multi-level analysis could be maintained. Since staining on the treated tooth surfaces was commonly found among four SDF treatment groups, detection bias may be less likely to occur during the examination. Randomisation was performed at child (subject) level. It could not be done at the tooth surface level due to the contamination of the intervention in each child. Therefore, besides the treatment effects, information on potential confounding factors especially at the tooth surface level should be collected and analysed. Predicting the model of treatment effectiveness at the subject level would not be precise because the assessment at the subject level could not allow the predicting variables that were related to the lesion site to be investigated.

The clinical diagnosis of caries activity was based on the visual-tactile assessment of the caries lesions (Nyvad and Fejerskov 1997). A blunt CPI probe with light force was used to assess the surface condition in order to avoid damaging the caries surface and avoid missing certain parts of the surface that were not arrested. Despite the fact that a gold standard tool for caries activity assessment has not been available, the visual-tactile clinical assessment is the only validated method for assessing caries lesions in a single session (Ekstrand et al. 2009). After SDF application, the black staining layer over the arrested dentin was identified to be a hard and impermeable layer of silver phosphate (Yamaga et al. 1972), and the collagens were protected from being exposed in the arrested cavitated dentinal lesion (Mei et al. 2014). Arrested dentin caries surfaces had a significantly higher microhardness value than the soft active caries surfaces (Chu and Lo 2008). Although caries activity could also be assessed by the depth of lesions obtained from the longitudinal radiographic examinations (Lunder and von der Fehr 1996), such facilities could not be available in the epidemiological or field studies like the current study. However, the reliability of clinical assessment of dentin caries in field settings could be improved through trainings and calibrations (Chu et al. 2012). The Cohen's Kappa statistics in lesion activity and oral hygiene assessments could be maintained to be over 0.9 in this study. The negative control group was not used in this study due to the ethical issue. In this study, Group 3 (annual application of 38% SDF) was used as a positive control for comparison with other treatment groups because this treatment protocol has been proven to be effective in arresting dentine caries in the previous study (Chu et al. 2002). In the present study, the differences in treatment effectiveness by varying the concentration and frequency were studied.

The first null hypothesis that there was no difference in effectiveness between 12% and 38% SDF in arresting dentin caries in primary teeth was not supported in this study. The treatment effectiveness of 38% SDF was more effective than 12% SDF in arresting caries. Since the interaction effect between the concentration and lesion site was found to be significant, the combination of lesion site and SDF concentration should be taken into consideration when applying SDF solution for caries arrest. The second null hypothesis that there was no difference in treatment effectiveness when SDF was applied annually or biannually was also not supported by the present findings. The results of this study agreed with the findings reported by Zhi and co-workers (2012) that biannual application could significantly increase the proportion of surfaces that became arrested after 18 months at surface level. Nevertheless, this study was the first to evaluate the interaction effect between concentration and frequency on the treatment effectiveness of SDF. The interaction between the concentration of the SDF solutions and application frequency on treatment effectiveness was disproven in this study. This indicated that the treatment effectiveness of SDF was not significantly modified by the presence of both factors.

Based on the results of the present study, 38% SDF with biannual application is the most effective therapeutic regime for arresting dentin caries in preschool children. Besides SDF concentration and frequency of application, other factors such as lesion site, tooth position, VPI score, plaque on lesion, lesion size, the age of start tooth brushing, mother's education, main care taker were significantly associated with treatment effectiveness. It should be highlighted that the disturbance of dental plaque is an effective measure contributing to the control of caries progression and affecting the success rate of SDF. Once cavities have been developed, the trapping of food over these lesions made the natural cleansing and remineralisation actions of saliva almost impossible. Even a protective layer could be formed after SDF treatment (Mei et al. 2014); it might soon be dissolved, and, therefore, the lesions cannot be arrested. Therefore, further oral health education on toothbrushing should be emphasised in the kindergarten oral health programmes.

SDF at 38% contains approximately 254,000 ppm silver ions (Mei et al., 2013). Approximately 18% of orally administered silver are absorbed (Hadrup and Lam, 2014). Vasquez et al. (2012) measured the serum concentrations of silver and fluoride after oral SDF application and reported occasional SDF application should pose little toxicity risk when used in adults. Although no severe adverse effect was found in the present study during 18 months, the possibility of having toxicity in children due to silver ingestion cannot be excluded. Thus, one needs to pay attention to the safety aspect when applying high concentration silver agents to young children.

This study reported the 18-month results of SDF therapy on young children. As the application frequencies were only completed once biannually or annually, a longer period of evaluation is more desirable. In addition, it should be noted that the results of the present study were based on dentine caries lesions that became arrested. Thus, these findings may not be transferable to different types of carious lesions such as enamel carious lesions.

Due to the simplicity and non-invasive approach of SDF treatment as well as teachers' support during the examination, the caries arrest treatment could be easily carried out in most of the study children. These findings could provide evidence-based support for the further development of using SDF in dental public health programmes. However, other issues related to feasibility, cost, sustainability and patient's acceptability should also be considered when translating research to practice.

Conclusions

Based on the 18-month results of this randomised clinical trial, it can be concluded that SDF is more effective in arresting dentin caries in the primary teeth of preschool children at 38% concentration rather than 12% concentration and when applied biannually than annually.

Acknowledgements

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Figure 1 Flow Diagram of participants' progress over 18 months

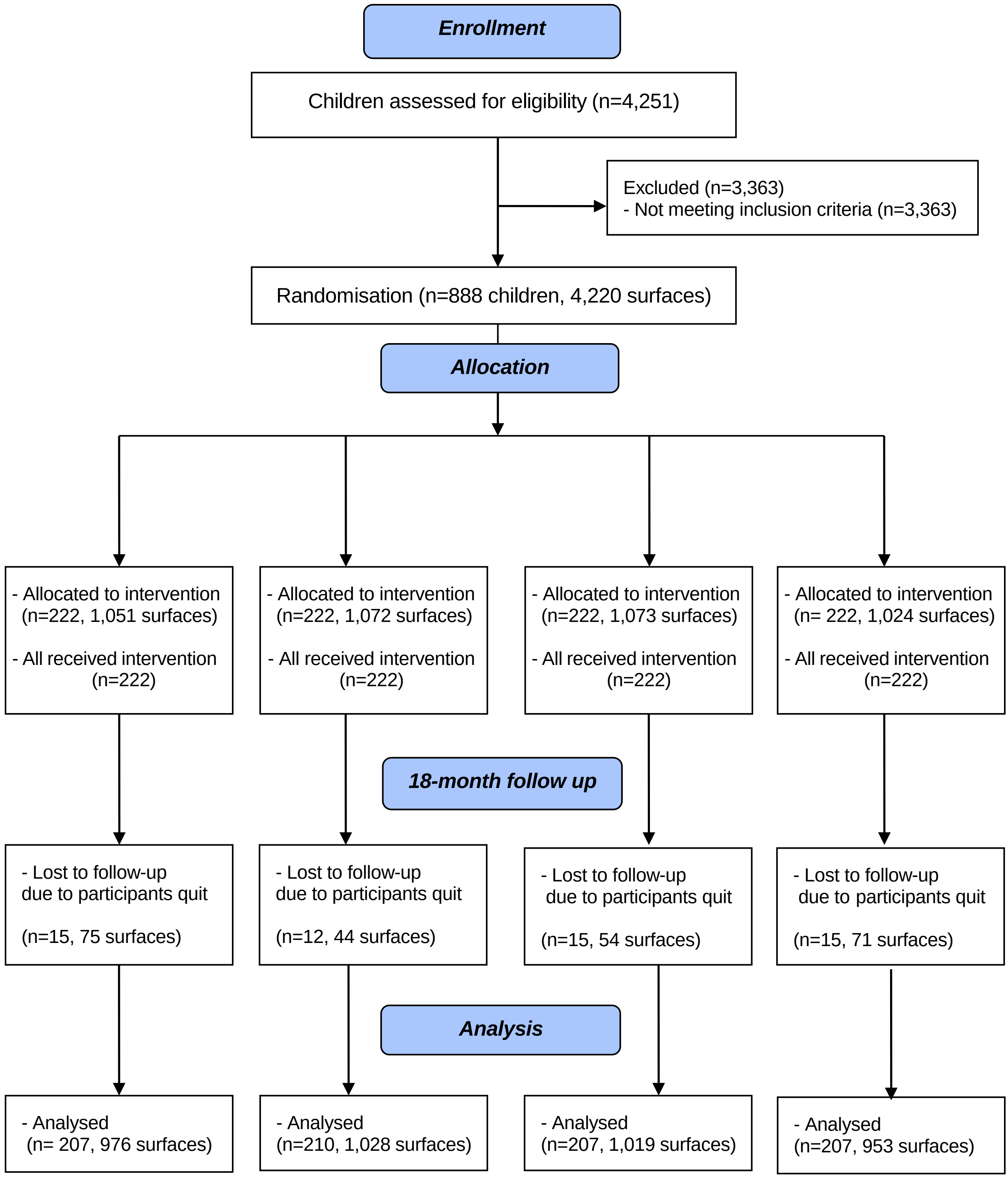

Table 1 Baseline demographic information, oral health related habits and clinical characteristics of children in the four study groups (n=888).

	Group 1 (12%, annual) (n=222)	Group 2 (12%, biannual) (n=222)	Group 3 (38%, annual) (n=222)	Group 4 (38%, biannual) (n=222)
Demographic background#				
Gender				
- Male	134 (60%)	130 (59%)	132 (60%)	123 (55%)
Main Care Taker				
- Father or mother	151 (69%)	145 (65%)	150 (68%)	145 (65%)
- Grandparents	44 (19%)	44 (20%)	40 (18%)	49 (22%)
- Maid or other people	27 (12%)	33 (15%)	32 (14%)	28 (13%)
Father's education level				
- 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				
- 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				
- 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%)
Oral health related habits#				
Toothbrushing frequency				
- Once or less daily	132 (59%)	123 (55%)	129 (58%)	122 (55%)
- Twice or more daily	90 (41%)	99 (45%)	93 (42%)	100 (45%)
Use of fluoride toothpaste	119 (54%)	119 (54%)	115 (52%)	120 (54%)
Use of bottle feeding before bed	117 (53%)	113 (51%)	127 (57%)	111 (50%)
Mean (SD) daily snacking frequency	2.37 (1.61)	2.36 (1.31)	2.24 (1.26)	2.42 (1.39)
Clinical characteristics#				
Baseline dmft	3.82 (2.72)	3.81 (2.83)	3.92 (2.91)	3.83 (2.72)
Baseline dmfs	5.00 (4.49)	5.20 (4.86)	5.41 (5.16)	5.00 (4.47)
No. of teeth included	3.65 (2.67)	3.76 (2.64)	3.71 (2.86)	3.62 (2.48)
No. of surfaces included	4.73 (4.11)	4.83 (4.13)	4.83 (4.47)	4.61 (3.71)
No. of non-vital teeth	0.05 (0.29)	0.07 (0.40)	0.11 (0.47)	0.05 (0.34)
VPI score at baseline	0.68 (0.21)	0.68 (0.19)	0.70 (0.20)	0.69 (0.20)

No statistically significant difference about children's demographic background, oral health-related habits and clinical characteristics among four groups.

Table 2 Caries arrest rates at 6-, 12- and 18-month follow-up examinations

	Group1 (12%, annual)	Group2 (12%, biannual)	Group 3 (38%, annual)	Group 4 (38%, biannual)	p-value
All surfaces					
Baseline	(n=1,051)	(n=1,072)	(n=1,073)	(n=1,024)	
6-month	337/1051 (32.1%)	346/1072 (32.3%)	471/1073 (43.9%)	449/1024 (43.8%)	p<0.001
12-month	409/1007 (40.6%)	502/1046 (48.0%)	540/1041 (51.9%)	618/987 (62.6%)	p<0.001
18-month	487/976 (49.9%)	566/1028 (55.1%)	649/1019 (63.7%)	701/953 (73.6%)	p<0.001
Upper anterior teeth					
Baseline	(n=605)	(n=612)	(n=619)	(n=585)	
6-month	213/605 (35.2%)	208/612 (34.0%)	314/619 (50.7%)	284/585 (48.5%)	p<0.001
12-month	276/587 (47.0%)	331/596 (55.5%)	367/610 (60.2%)	403/565 (71.3%)	p<0.001
18-month	335/572 (58.6%)	382/582 (65.6%)	450/599 (75.1%)	447/543 (82.3%)	p<0.001
Upper posterior teeth					
Baseline	(n=140)	(n=140)	(n=143)	(n=138)	
6-month	29/140 (20.7%)	33/140 (23.6%)	41/143 (28.7%)	56/138 (40.6%)	p=0.004
12-month	30/132 (22.7%)	44/138 (31.9%)	41/134 (30.6%)	67/133 (50.4%)	p<0.001
18-month	33/126 (26.2%)	55/138 (39.9%)	57/131 (43.5%)	74/128 (57.8%)	p<0.001
Lower anterior teeth					
Baseline	(n=33)	(n=26)	(n=29)	(n=27)	
6-month	24/33 (72.7%)	17/26 (65.4%)	22/29 (75.9%)	16/27 (59.3%)	p=0.533
12-month	23/32 (71.9%)	19/26 (73.1%)	22/29 (75.9%)	23/27 (85.2%)	p=0.208
18-month	29/32 (90.6%)	21/26 (80.8%)	28/29 (96.6%)	25/26 (96.2%)	p=0.108
Lower posterior teeth					
Baseline	(n=273)	(n=294)	(n=282)	(n=274)	
6-month	71/273 (26.0%)	88/294 (29.9%)	94/282 (33.3%)	93/274 (33.9%)	p=0.005
12-month	80/256 (31.3%)	108/286 (37.8%)	110/268 (41.0%)	125/262 (47.7%)	p=0.001
18-month	90/246 (36.6%)	108/282 (38.3%)	114/260 (43.8%)	155/256 (60.5%)	p<0.001

Table 3 The adjusted logistic regression with the best goodness of fit estimated by corrected quasi-likelihood information criterion

	Explanatory variable	Predicted probability#	Odds ratio	95% confidence interval	p-value	Pairwise comparison
Base model	Frequency				0.025	
	(1) Annually [a]	0.53				
	(2) Biannually	0.61	1.33	1.04 – 1.71		
	SDF Concentration				<0.001	
	(1) 12% [a]					
	(2) 38%		2.73	1.86 – 3.99		
	Lesion site				<0.001	
	(1) Mesial [a]					
	(2) Buccal		2.50	1.69 – 3.71		
	(3) Lingual		1.03	0.67 – 1.57		
	(4) Distal		1.53	1.14 – 2.06		
	(5) Occlusal		1.31	0.85 – 2.01		
	Lesion site * SDF Concentration				0.001	
	(1.1) Mesial * 12%	0.53 ##				
	(1.2) Mesial * 38%	0.76				(1.2) > (1.1)
	(2.1) Buccal * 12%	0.74				
	(2.2) Buccal * 38%	0.90	1.12	0.63-1.98		(2.2) > (2.1)
	(3.1) Lingual * 12%	0.54				
	(3.2) Lingual * 38%	0.75	0.92	0.91-0.49		(3.2) > (3.1)
	(4.1) Distal * 12%	0.64				
	(4.2) Distal * 38%	0.75	0.64	0.46-1.01		(4.2) > (4.1)
	(5.1) Occlusal * 12%	0.60				
	(5.2) Occlusal * 38%	0.63	0.41	0.25-0.68		
	Tooth position				<0.001	
	(1) Upper anterior [a]	0.53				(1) > (2),(4)
	(2) Upper posterior	0.22	0.25	0.17 – 0.36		(3) > (2),(4)
	(3) Lower anterior	0.77	2.88	1.06 – 7.83		
	(4) Lower posterior	0.24	0.27	0.19 – 0.40		
	Size of lesion				<0.001	
	(1) Small [a]	0.53				
	(2) Large	0.25	0.29	0.24-0.37		
	Lesion with visible plaque				<0.001	
	(1) Yes [a]	0.53				
	(2) No	0.99	82.58	35.70-191.00		
	High VPI score		0.19	0.10 – 0.37	<0.001	
	Mean VPI=0.40	0.30				
Additional significant variables	Age of start brushing				0.001	
	(1) No brushing [a]	0.53				(2),(3) > (1)
	(2) 12 months or younger	0.85	4.89	1.81-13.22		(3) > (5)
	(3) 13-18 months	0.85	4.81	1.89-12.22		
	(4) 19-24 months	0.78	3.06	1.20-7.85		
	(5) over 24 months	0.78	3.02	1.20-7.55		
	Mother' s education				0.024	
	(1) Primary education [a]	0.53				(1) > (2)
	(2) Secondary education	0.42	0.62	0.44-0.88		
	(3) Post-secondary education	0.46	0.73	0.45-1.18		
	Main care taker				0.030	
	(1) Parents [a]	0.53				NS
	(2) Grandparents	0.46	0.74	0.53-1.03		
	(3) Maid or others	0.43	0.66	0.46-0.94		

[a] Reference category, * Interaction

[#] Predicted probability of arrested caries with the mean VPI score of 0.40 (after excluding missing data) and other variables as reference category

[##] Predicted probability for Lesion site * SDF concentration was calculated using estimates for both main and interaction effects

NS - No significant multiple comparisons were identified