ORIGINAL REPORT: PHASE III RANDOMIZED CLINICAL TRIAL

Randomized Trial of Silver Nitrate with Sodium Fluoride for Caries Arrest

S.S. Gao[1], D. Duangthip[1], M.C.M. Wong[1], E.C.M. Lo[1], and C.H. Chu[1]

Abstract: ***Objectives:*** *The aim of this noninferiority double-blind randomized clinical trial was to compare the effectiveness of the topical semiannual application of a 25% silver nitrate ($AgNO_3$) solution followed by a 5% sodium fluoride (NaF) varnish with that of a 38% silver diamine fluoride (SDF) solution in arresting caries among preschool children.*

Methods: *Healthy 3-y-old children with active dentine carious lesions were randomly allocated to 2 groups via computer-generated random numbers. Lesions in group A received applications of a 25% $AgNO_3$ solution followed by a 5% NaF varnish semiannually (every 6 mo). Lesions in group B received semiannual applications of a 38% SDF solution followed by a placebo varnish. A trained examiner recorded the status of caries and oral hygiene at baseline and during follow-up examinations. The examiner, children, and their caretakers were blinded to the intervention allocation. This study adopted an intention-to-treat analysis. A noninferiority test was conducted for the data analysis. Group A's noninferiority was accepted if the lower limit of the 95% CI for the difference in the mean number of arrested surfaces was >–0.5.*

Results: *A total of 1,070 children were recruited at baseline, with 535 children in each group. After 18 mo, the mean ± SD number of arrested surfaces was 3.3 ± 3.4 in group A (n = 484) and 3.2 ± 3.5 in group B (n = 476; P = 0.664). The difference in the mean number of arrested surfaces between the groups was 0.092 (95% CI, –0.322 to 0.505). Apart from black staining on the arrested lesions, no other significant side effect was observed.*

Conclusion: *A semiannual application of 25% $AgNO_3$ followed by 5% NaF is no worse than a 38% SDF in arresting dentine caries among preschool children over 18 mo. The Hong Kong Research Grants Council (GRF 17107315) funded this trial, which was registered at ClinicalTrials.gov (NCT02019160).*

Knowledge Transfer Statement: *This randomized clinical trial found that silver nitrate solution followed by sodium fluoride varnish is effective in arresting dentine caries among preschool children. As silver nitrate followed by sodium fluoride is a noninvasive and simple protocol, it can be an alternative strategy to manage dental caries among young children, especially in countries where silver diamine fluoride is not available.*

Keywords: decay, preschool, diamine, children, primary teeth, noninferiority

Introduction

Dental caries in primary teeth is a major health issue affecting many young children worldwide. The prevalence of dental caries among 2- to 5-y-old children in the United States increased from 24.2% (1988 to 1994) to 27.9% (1999 to 2004; Dye et al. 2007). More than 70% of preschool children in most Southeast Asian countries suffer from dental caries (Duangthip et al. 2017). Dental caries causes pain and infection.

DOI: 10.1177/2380084418818482. [1]Faculty of Dentistry, The University of Hong Kong, Hong Kong, China. Corresponding author: C.H. Chu, Faculty of Dentistry, The University of Hong Kong, 3B53A, Prince Philip Dental Hospital, 34 Hospital Road, Hong Kong, China. Email: chchu@hku.hk.

A supplemental appendix to this article is available online.

Poor dentition not only influences children's oral health but also can affect their nutrition intake, growth, cognitive development, and quality of life (Sheiham 2006). Restorative treatment for young children may be challenging because they are often uncooperative to clinical procedures (Yamada et al. 2002). Moreover, conventional treatment for advanced caries is neither accessible nor affordable for many children, particularly those from disadvantaged communities (Chu et al. 2012).

Clinical studies reported that the application of a silver diamine fluoride (SDF) solution can arrest active dentine caries in the primary teeth of young children (Chu et al. 2002; Duangthip et al. 2016; Fung et al. 2016). The caries arresting rate (CAR) is approximately 80% (Gao, Zhang, et al. 2016). Although SDF has been used in Australia, the United States, Canada, and some countries in Asia and Latin America, it is still not available in many countries. Sodium fluoride (NaF) varnish is effective in treating early enamel lesions (Gao, Zhang, et al. 2016). However, it is not effective in arresting active dentine caries (Chu et al. 2002). A laboratory study found that an application of a 25% silver nitrate ($AgNO_3$) solution followed by a 5% NaF varnish can inhibit the demineralization of dentine (Zhao et al. 2017). Duffin (2012) used this protocol to treat the caries of children and found that most carious lesions were arrested after treatment. We performed a literature search within the MEDLINE database (PubMed) on April 1, 2018, and found no publication of a clinical trial studying the effectiveness of $AgNO_3$ and NaF in arresting caries.

A recent systematic review concluded that the application of a 38% SDF solution is effective in arresting caries in the primary teeth of young children (Gao, Zhao, et al. 2016). Because it is not ethical to conduct a clinical trial where children do not receive treatment or are given placebos, this study adopted a noninferiority design with the application of SDF as the control. The aim of this noninferiority randomized clinical trial was to compare the effectiveness of an adjunctive application of a 25% $AgNO_3$ solution followed by a 5% NaF varnish with that of a 38% SDF solution in arresting dentine caries among young children when applied twice a year.

Materials and Methods

Trial Design

This study was a noninferiority double-blind randomized clinical trial. The noninferiority margin was set at −0.5 for the difference in the mean number of arrested surfaces (MASs) between groups, which was considered clinically negligible (effect size, 0.25; SD, 2.5; true difference, 0; Chu et al. 2015). The sample size calculation was performed with G*Power 3.1.7 (Franz Faul; Universität Kiel), and the statistical power was set at 90%. The result revealed that 856 children were required. The dropout rate was anticipated to be 20%. Therefore, 1,070 participants needed to be recruited at baseline, with 535 in each intervention group. The study received approval from the Institutional Review Board of the University of Hong Kong and Hospital Authority Hong Kong West Cluster (UW 13-569) and was registered at ClinicalTrials.gov (NCT02019160).

Participant Recruitment and Randomized Allocation

An invitation letter and consent form were sent to the parents of kindergarten children. The inclusion criteria were that children 1) were generally healthy and received parental consent, 2) were attending the first year of kindergarten and were aged 3 to 4 y, and 3) had at least 1 untreated active dentine carious lesion. Children who were uncooperative during the dental examination process, had severe oral diseases other than dental caries, had major systemic diseases, and/or were under long-term medication were excluded. The baseline screening was conducted in the children's kindergarten classrooms. A stratified block randomization method was adopted in this study. To balance the baseline caries status between the intervention groups, the children were first classified into 2 strata by the number of decayed, missing, and filled tooth surfaces (dmfs; 1 to 3 or >3 tooth surfaces). Then, they were allocated to 1 of the 2 intervention groups according to computer-generated random numbers with a block size of 8. An independent assistant conducted the random allocation procedure. The examiner, study children, and their caretakers were blinded to the treatment allocation. Treatment was provided by an independent operator after the clinical examination.

Clinical Examination

A trained examiner conducted clinical examinations using a ball-ended Community Periodontal Index probe (Ash/Dentsply) and a disposable dental mirror attached to a handle with a light-emitting diode for intraoral illumination (MirrorLite; Kudos Crown Limited). Teeth that were considered nonvital—specifically, those that had pulp exposure, abscess/fistula, or generalized tooth discoloration related to tooth nonvitality—were excluded. Each tooth surface was assessed, and caries was diagnosed at the cavitation level (Chu et al. 2002; Duangthip et al. 2016; Fung et al. 2016). A carious lesion was recorded as active if softness was detected upon probing with a light force. If the lesion was hard upon probing, it was classified as arrested (Chu et al. 2002; Duangthip et al. 2016; Fung et al. 2016). Only the carious lesions detected in the baseline examination were included for evaluation in the follow-up examinations. Oral hygiene was measured with the visible plaque index (VPI) on the buccal and lingual surfaces of 6 teeth (teeth 55, 51, 63, 71, 75, and 83; Fung et al. 2016). The VPI score was the percentage of tooth surfaces examined that had visible plaque on the surface. Prior to the study, a dentist was trained to use the indices and diagnostic criteria adopted in this study, and the assessment of caries (active and arrested) was calibrated with an experienced epidemiologist. The same examiner

performed all baseline and follow-up examinations in the kindergarten classrooms. Intraexaminer reliability was evaluated through conducting duplicate examinations on 10% of the children, selected randomly.

Interventions

The 2 intervention groups were as follows:

- *Group A*—semiannual application (every 6 mo) of a 25% $AgNO_3$ solution (Gordon Labs) followed by a 5% NaF varnish (Duraphat Varnish; Colgate-Palmolive)
- *Group B*—semiannual application of a 38% SDF solution (Saforide; Toyo Seiyaku Kasei Co.) followed by a placebo varnish (Vaseline; Unilever)

The operator used a microbrush to apply the appropriate solution (SDF or $AgNO_3$) for approximately 5 s on each carious lesion according to the child's assigned intervention group. The operator then used another microbrush to apply the appropriate varnish (Vaseline or NaF) on the lesion. The kindergarten teachers were instructed not to let the children eat or drink for 30 min after the fluoride therapy. Interventions were performed at baseline and 6-, 12-, and 18-mo follow-ups.

Questionnaire

A validated questionnaire used in previous studies (Chu et al. 1999; Chu et al. 2012; Chen et al. 2017) was used to collect the children's oral health–related behaviors (bottle-feeding and toothbrushing history) and socioeconomic backgrounds (birthplace, family income, parental educational level, main caretaker) at baseline. Information on each child's oral health–related behaviors (e.g., current bottle-feeding before sleeping, daily snack intake, daily toothbrushing, assisted toothbrushing, use of fluoride toothpaste, and dental treatment experience) was collected through a parental questionnaire at the 18-mo follow-up.

Statistical Methods

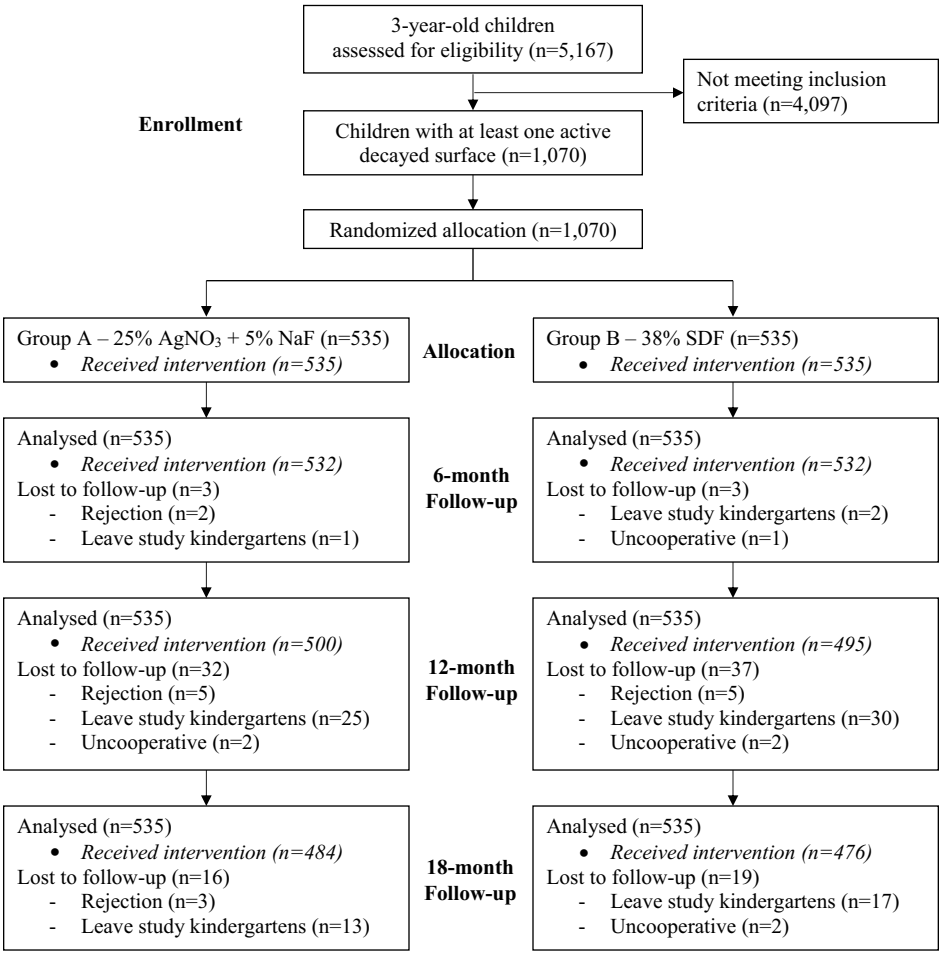
The outcome measure was the status of the carious lesion (active or arrested) at follow-up examinations. Data were analyzed with Stata 13.1 (William Gould) and SPSS 24.0 (SPSS Inc.). An intention-to-treat (ITT) analysis was performed. Missing cases were tested for randomness by using Little's "missing completely at random" test, which tests the hypothesis that one's data are missing completely at random—an assumption that must be satisfied before replacing missing values through various imputation techniques. The "last observation carried forward" method was adopted for inputting the missing data. With the noninferiority margin set to −0.5 (group A minus group B), the noninferiority of group A versus group B could be claimed if the lower limit of the 95% CI for the difference of the MASs was >−0.5. An independent *t* test was performed to compare dmfs scores, the number of active decayed surfaces at baseline, the number of newly developed dmfs, the MASs, and the VPI scores between the groups at 6-mo, 12-mo, and 18-mo follow-ups. CAR was calculated as the total number of arrested surfaces at follow-up divided by the total number of active decayed surfaces at baseline. The chi-square test was used to compare CAR, baseline oral health–related habits, and socioeconomic backgrounds between group A and group B. Intraexaminer agreement in caries diagnoses was assessed with Cohen's kappa statistics. The level of statistical significance for all tests was set at 0.05.

Because a child involved in the study could have multiple carious lesions, generalized estimating equations (GEEs) with a logit link and 2-level clusters (subject and tooth surface) were adopted to investigate the effects of the intervention, related clinical parameters (baseline dmfs score, number of newly developed dmfs at 18 mo, VPI score at 18 mo, tooth and surface of the carious lesions), oral health–related habits, and socioeconomic backgrounds on caries arrest. The dependent variable in this logistic regression was at the surface level—specifically, the status of the carious lesion (arrested or not arrested). The GEE model for a bivariate logistic regression was used to analyze each independent variable. Independent variables with a *P* value <0.05 were included to form a base model. Independent variables with a *P* value <0.2 but >0.05 were entered into the subset models. Multivariable logistic regressions were conducted on the subset models. A model with the smallest quasi-likelihood information criterion was presented as the best-fit model for reporting. The Bonferroni test for pairwise comparison was conducted for inner-variable analysis.

Results

A total of 1,070 children were recruited, with 535 children in each intervention group (Fig.). The baseline dmfs scores of groups A and B were 5.87 ± 6.26 and 5.96 ± 6.11 (mean ± SD), respectively (*P* = 0.828; Table 1). No significant difference was found in oral health–related habits or socioeconomic backgrounds between the groups at baseline (Appendix 1). The dropout rate after 18 mo was 9.5% (51 of 535) in group A and 11.0% (59 of 535) in group B (*P* = 0.421). Leaving the study's kindergartens was the main reason why children dropped out (Fig.). Little's "missing completely at random" test showed a chi-square distance of 5.0 with 6 degrees of freedom and a *P* value of 0.544. Missing data were completely random in this study because the *P* value was >0.05. The kappa values for the duplicated examinations of caries status were >0.9 for all examinations. During the follow-up examinations at 6 mo, 12 mo, and 18 mo, no significant differences were found between groups A and B regarding the children's mean dmfs scores, MASs, CARs, number of newly developed dmfs, or VPI scores, except for the CAR at 6-mo follow-up and the VPI scores at the 12-mo follow-up. Group A presented a higher CAR (41.3%) than group B (38.7%) at 6-mo examination. The mean 12-mo VPI

Figure. Flow diagram of this trial. $AgNO_3$, silver nitrate; NaF, sodium fluoride; SDF, silver diamine fluoride.



scores for groups A and B were 55.0% ± 17.3% and 52.4% ± 17.9%, respectively. The absolute difference was 2.6% (95% CI, 0.5% to 4.7%), which was considered clinically insignificant.

At the 18-mo examination, the MASs of groups A and B were 3.32 ± 3.42 and 3.23 ± 3.47, respectively ($P = 0.664$; Table 1). The estimated difference in MASs between the groups was 0.092 (95% CI, –0.322 to 0.505). Arrested lesions were stained black. The examiner did not observe any other significant side effects. No report of any systemic disease was received from the parents.

Multilevel Logistic Regression of Confounding Factors on Caries Arrest

The results of bivariate logistic regression with GEEs for individual variables revealed that the following were associated with the surface-level caries status: number of newly developed dmfs, VPI score, tooth and surface locations of the carious lesion, current bottle-feeding before sleeping, dental treatment performed during the study period, and the child's family income (Table 2). Potentially significant variables with P values <0.2 were assisted toothbrushing and parental status. Thus, 4 possible models (1 base model plus 3 subset models) were computed for a multivariable logistic regression. Among the 4 models, the base model presented the smallest quasi-likelihood information criterion (5,050.025) and thus was the best-fit model (Table 3).

Caries arrest was negatively related to the number of newly developed dmfs (odds ratio, 0.937; $P = 0.017$) and the VPI score (odds ratio, 0.990; $P = 0.002$) at the 18-mo follow-up. The tooth location and surface location of the carious lesion were significantly associated with the caries status ($P < 0.001$). Lesions in the mandibular anterior teeth presented a higher chance of being arrested than those in other teeth. In addition, lesions on the buccal surfaces had the highest chance to become arrested. Children who had no dental treatment during the study and those whose families had monthly incomes lower than HK$20,000 had a higher chance of having their caries arrested (Table 3).

Discussion

Silver has antibacterial properties, and fluoride promotes the remineralization of carious lesion (Gao et al. 2018). These may be the basic mechanisms of the caries-arresting effect of SDF. The hardness of the lesion surface is commonly used as a diagnostic criterion

Table 1.
Mean dmfs, Active Decayed Surfaces, MASs, CAR, New dmfs, and Oral Hygiene Status of the Intervention Groups at Baseline and Follow-up.

Variable	Group A[a]	Group B[b]	*P* Value
Baseline			
dmfs	5.9 (6.3)	6.0 (6.1)	0.828
Active decayed surfaces	5.2 (4.6)	5.2 (4.7)	>0.999
VPI, %	62.8 (17.6)	60.9 (18.1)	0.092
6 mo			
dmfs	6.6 (6.6)	6.6 (6.4)	0.869
MAS	2.1 (2.5)	2.0 (2.5)	0.370
CAR, %	41.3	38.7	0.048
New dmfs	0.7 (1.2)	0.7 (1.2)	0.741
VPI, %	54.7 (15.6)	53.2 (15.6)	0.108
12 mo			
dmfs	7.5 (7.1)	7.5 (6.9)	0.993
MAS	3.2 (3.4)	3.1 (3.4)	0.534
CAR, %	62.4	60.0	0.069
New dmfs	0.9 (1.6)	0.8 (1.3)	0.484
VPI, %	55.0 (17.3)	52.4 (17.9)	0.015
18 mo			
dmfs	8.4 (7.6)	8.3 (7.6)	0.856
MAS	3.3 (3.4)	3.2 (3.5)	0.664
CAR, %	64.1	62.4	0.202
New dmfs	1.0 (1.6)	0.8 (1.9)	0.251
VPI, %	54.1 (17.0)	53.8 (16.9)	0.733

Values are presented as mean (SD) or %.
CAR, caries arresting rate; dmfs, decayed, missing (due to caries), and filled surfaces; MAS, mean arrested surface; VPI, visible plaque index.
[a]25% silver nitrate + 5% sodium fluoride.
[b]38% silver diamine fluoride.

for arrested caries (Braga et al. 2010). Previous studies revealed an increase in microhardness with a highly remineralized zone rich in calcium and phosphate in the arrested lesions (Chu and Lo 2008; Mei et al. 2014). Applying a 25% $AgNO_3$ solution followed by a 5% NaF varnish follows the same principle for caries arrest. A laboratory study indicated that this method could remineralize inter- and intratubular demineralized dentine and prevent the exposure of collagen fibers on dentine surfaces (Zhao et al. 2017). A US community dental care program for children reported that this method could arrest active caries in almost all carious lesions (Duffin 2012). The present double-blind randomized clinical trial revealed that applying a 25% $AgNO_3$ solution followed by a 5% NaF varnish was no worse than applying a 38% SDF in arresting dentine caries among preschool children. $AgNO_3$ solution and NaF varnish are readily available in many countries; hence, they may be used to arrest caries when SDF is not available. Moreover, the cost of SDF (Saforide; approximately US$10 per 1 mL) is higher than $AgNO_3$ (Gordon Labs;

Table 2.
Bivariate Logistic Regression Based on the Generalized Estimating Equation Model with a Logit Link and 2-Level Clusters for Individual Factors.

Explanatory Variable[a]	Odds Ratio	95% CI	*P* Value
Clinical parameters			
Intervention group (38% SDF): 25% $AgNO_3$ + 5% NaF	1.171	0.986 to 1.391	0.072
Baseline dmfs	0.996	0.986 to 1.007	0.505
18-mo new dmfs	0.954	0.914 to 0.996	0.031
18-mo VPI score	0.994	0.989 to 0.999	0.018
Tooth location (lower posterior tooth)			<0.001
Upper anterior tooth	6.463	5.294 to 7.890	
Upper posterior tooth	1.905	1.504 to 2.413	
Lower anterior tooth	26.008	13.890 to 48.700	
Surface location (occlusal surface)			<0.001
Buccal surface	10.388	8.099 to 13.324	
Mesial surface	5.671	4.565 to 7.046	
Distal surface	4.527	3.477 to 5.893	
Lingual surface	5.180	4.314 to 6.220	
Oral health–related behaviors			
Age stopped bottle-feeding (after 24 mo)			0.566
Breast feeding only	1.178	0.873 to 1.590	
1 to 12 mo	0.980	0.594 to 1.616	
13 to 24 mo	1.131	0.903 to 1.417	
Current bottle-feeding before sleeping (no): yes	0.789	0.633 to 0.983	0.035
Daily snack intake (no): yes	0.799	0.442 to 1.446	0.459
Age of start tooth-brushing (after 24 mo)			0.869
1 to 12 mo	1.079	0.788 to 1.478	
13 to 24 mo	1.033	0.863 to 1.237	
Daily toothbrushing (twice per day or more)			0.496
Less than once per day	1.422	0.709 to 2.851	
Once per day	1.079	0.876 to 1.329	
Assisted toothbrushing (no): yes	0.882	0.734 to 1.061	0.182
Use of fluoride toothpaste (no): yes	1.157	0.901 to 1.486	0.253
Dental treatment after start of study (no): yes	0.636	0.514 to 0.787	<0.001

(continued)

Table 2.
(continued)

Explanatory Variable[a]	Odds Ratio	95% CI	*P* Value
Socioeconomic backgrounds			
Sex (female): male	1.050	0.882 to 1.249	0.584
Birthplace (mainland): Hong Kong	0.874	0.648 to 1.178	0.376
Parental status (single parent): both parents	0.722	0.463 to 1.127	0.152
Monthly family income, HK$ (≥40,001)			0.029
≤$20,000	1.472	1.094 to 1.981	
$20,001 to $40,000	1.300	0.946 to 1.786	
Father's education level (higher education): mandatory education	1.019	0.842 to 1.234	0.844
Mother's education level (higher education): mandatory education	1.104	0.920 to 1.324	0.289
Main caretaker (maid)			0.456
Parents	1.040	0.685 to 1.580	
Relatives	0.907	0.580 to 1.420	

Arrested = 1; active = 0. Subject level and tooth surface level.
$AgNO_3$, silver nitrate; dmfs, decayed, missing (due to caries), and filled surfaces; HK$, Hong Kong dollars; NaF, sodium fluoride; SDF, silver diamine fluoride; VPI, visible plaque index.
[a]Reference group in parentheses.

approximately US$4 per 1 mL) and NaF (Duraphat; approximately US$4 per 1 mL). Both treatment protocols aim to stabilize the carious lesion by arresting caries. They do not restore the cavity. Oral hygiene is difficult to maintain due to damage and loss of tooth structure. It can also cause drifting of teeth and space loss.

A noninferiority trial was adopted in this study. It tests whether a new treatment is less effective than a positive control treatment already in use (Walker and Nowacki 2011). Adopting a noninferiority trial in a study design offers several advantages. First, it addresses ethical concerns about placebo-controlled trials because participants in the positive-controlled group also receive effective treatment during the clinical trial. Second, it is more favorable to compare the new treatment with a currently available standard treatment to prove its effectiveness (Hahn 2012). Third, noninferiority trials have considerably larger sample sizes than do placebo-controlled trials, which enhances the study's reliability (Snapinn 2000). However, the large sample size required can be an obstacle in implementing a noninferiority clinical study. In the clinical trial, recruiting >1,000 preschool children with untreated cavitated caries for long-term follow-up is challenging. In this study, >5,000 children were screened to identify the required 1,070 children. In places with small populations, this can be an insurmountable difficulty when it comes to implementing a noninferiority trial. A multicenter clinical trial can be a solution, but the cost will increase significantly.

This clinical trial used an ITT analysis to avoid misleading artifacts, such as nonrandom participant dropouts from the study. ITT includes all children who were randomized into the 2 intervention groups at baseline for data processing, regardless of their adherence to the assigned treatment group or subsequent withdrawal from this study. The CONSORT guidelines (Consolidated Standards of Reporting Trials) for reporting randomized clinical trials recommend this method (Moher et al. 2001). ITT analysis reflects a practical scenario, as it includes noncompliance and dropouts and admits protocol deviation. Moreover, ITT analysis preserves the sample size to maintain statistical power. As all noncompliance and dropouts are included in the analysis, an ITT analysis can always provide a relatively conservative estimate of treatment effectiveness (Gupta 2011). It is noteworthy that a full application of ITT analysis requires complete outcome data for all participants. The presence of missing data and adherence to a 6-mo treatment protocol can impose difficulties in completing an ITT analysis. This is a limitation of this study. Furthermore, the "last observation carried forward" method was adopted for inputting missing data. Hence, the missing values were replaced with the last available measurement, which might not be the true outcome at 18 mo. Clinical studies indicated that CARs increased over follow-up periods when the fluoride application (SDF and NaF) was repeated annually or semiannually (Zhi et al. 2012; Duangthip

Table 3.
Multivariable Logistic Regression Model with the Best Estimated Fit by Quasi-likelihood Information Criterion.

Explanatory Variable	Odds Ratio	95% CI	*P* Value
Intervention group			0.416
25% $AgNO_3$ + 5% NaF	1.091	0.885 to 1.344	
38% SDF[a]	—	—	
18-mo new dmfs	0.937	0.888 to 0.988	0.017
18-mo VPI score	0.990	0.984 to 0.996	0.002
Tooth location[b]			<0.001
Upper anterior	4.566	3.383 to 6.164	
Upper posterior	1.677	1.284 to 2.190	
Lower anterior	33.805	16.092 to 71.017	
Lower posterior[a]	—	—	
Tooth surface location[c]			<0.001
Buccal	4.375	3.236 to 5.915	
Mesial	2.027	1.518 to 2.706	
Distal	1.957	1.386 to 2.764	
Lingual	1.742	1.322 to 2.297	
Occlusal[a]	—	—	
Monthly family income,[d] HK$			0.041
≤20,000	1.580	1.087 to 2.297	
20,001 to 40,000	1.358	0.911 to 2.026	
≥40,001[a]	—	—	
Current bottle-feeding before sleeping			
Yes	0.779	0.601 to 1.011	0.060
No[a]	—	—	
Dental treatment after start of study			0.006
Yes	0.689	0.527 to 0.901	
No[a]	—	—	

Arrested = 1; active = 0.
$AgNO_3$, silver nitrate; dmfs, decayed, missing (due to caries) and filled surfaces; HK$, Hong Kong dollars; NaF, sodium fluoride; SDF, silver diamine fluoride; VPI, visible plaque index.
[a]Reference group.
[b]Pairwise comparison: lower anterior > upper anterior > upper posterior > lower posterior.
[c]Pairwise comparison: buccal > mesial, distal, lingual > occlusal.
[d]Pairwise comparison: ≤20,000 > ≥40,001.

et al. 2016; Fung et al. 2017). Thus, inputting the missing values by using the "last observation carried forward" method in this study could have prevented the overestimation of treatment effectiveness.

The results of the noninferiority test suggested that a 25% $AgNO_3$ solution followed by a 5% NaF varnish was not worse than a 38% SDF for the caries-arresting effectiveness among kindergarten children. The results from the multivariable logistic regression analysis indicated that the factor intervention group ($AgNO_3$ + NaF vs SDF) did not affect caries arrest, whereas other confounding

factors, such as the number of newly developed dmfs, the VPI score, and the tooth and surface locations of the carious lesion, may influence the outcome. Caries on the anterior teeth are more likely to be arrested than caries on the mandibular posterior teeth. This finding was consistent with previous studies (Zhi et al. 2012; Fung et al. 2016). Another important finding is that caries on the buccal surface had a higher chance of becoming arrested when compared with that on the occlusal surface—perhaps because lesions on exposed smooth surfaces are easier to clean during toothbrushing than are those in pits and fissures. Furthermore, the children's oral hygiene statuses (VPI scores) and their caries incidence (new dmfs found at 18-mo follow-up) were negatively related to successful treatment outcomes. Thus, maintaining good oral hygiene and lowering caries risk are crucial for caries arrest.

Conclusion

In conclusion, a semiannual application of a 25% $AgNO_3$ solution followed by a 5% NaF varnish was no worse than a 38% SDF in arresting dentine caries among preschool children over 18 mo. The child's oral hygiene and caries risk, with the location of the carious lesion, influence the outcome of caries arrest.

Author Contributions

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

Acknowledgments

This research is funded by the General Research Fund (17107315) of the University Grant Council, Hong Kong. The authors thank Samantha Li for her statistical advice. They also thank the kindergarten teachers, children, and parents for their support in this study. The authors declare no potential conflicts of interest with respect to the authorship and/or publication of this article.

ORCID iD

C.H. Chu https://orcid.org/0000-0002-8167-0430

References

Braga MM, Mendes FM, Ekstrand KR. 2010. Detection activity assessment and diagnosis of dental caries lesions. Dent Clin North Am. 54(3):479–493.

Chen KJ, Gao SS, Duangthip D, Li SKY, Lo ECM, Chu CH. 2017. Dental caries status and its associated factors among 5-year-old Hong Kong children: a cross-sectional study. BMC Oral Health. 17(1):121.

Chu CH, Fung D, Lo EC. 1999. Dental caries status of preschool children in Hong Kong. Br Dent J. 187(11):616–620.

Chu CH, Gao SS, Li SK, Wong MC, Lo EC. 2015. The effectiveness of the biannual application of silver nitrate solution followed by sodium fluoride varnish in arresting early childhood caries in preschool children: study protocol for a randomised controlled trial. Trials. 16:426.

Chu CH, Ho PL, Lo EC. 2012. Oral health status and behaviours of preschool children in Hong Kong. BMC Public Health. 12:767.

Chu CH, Lo EC. 2008. Microhardness of dentine in primary teeth after topical fluoride applications. J Dent. 36(6):387–391.

Chu CH, Lo EC, Lin H. 2002. Effectiveness of silver diamine fluoride and sodium fluoride varnish in arresting dentin caries in Chinese pre-school children. J Dent Res. 81(11):767–770.

Duangthip D, Chu CH, Lo EC. 2016. A randomized clinical trial on arresting dentine caries in preschool children by topical fluorides—18 month results. J Dent. 44:57–63.

Duangthip D, Gao SS, Lo EC, Chu CH. 2017. Early childhood caries among 5- to 6-year-old children in Southeast Asia. Int Dent J. 67(2):98–106.

Duffin S. 2012. Back to the future: the medical management of caries introduction. J Calif Dent Assoc. 40(11):852–858.

Dye BA, Tan S, Smith V, Lewis BG, Barker LK, Thornton-Evans G, Eke PI, Beltrán-Aguilar ED, Horowitz AM, Li CH. 2007. Trends in oral health status: United States, 1988–1994 and 1999–2004. Vital Health Stat. 11(248):1–92.

Fung MHT, Duangthip D, Wong MCM, Lo ECM, Chu CH. 2016. Arresting dentine caries with different concentration and periodicity of silver diamine fluoride. JDR Clin Transl Res. 1(2):143–152.

Fung MHT, Duangthip D, Wong MCM, Lo ECM, Chu CH. 2017. Randomized clinical trial of 12% and 38% silver diamine fluoride treatment. J Dent Res. 97(2):171–178.

Gao SS, Zhao IS, Hiraishi N, Duangthip D, Mei ML, Lo ECM, Chu CH. 2016. Clinical trials of silver diamine fluoride in arresting caries among children: a systematic review. JDR Clin Transl Res. 1(3):201–210.

Gao SS, Zhang S, Mei ML, Lo EC, Chu CH. 2016. Caries remineralisation and arresting effect in children by professionally applied fluoride treatment—a systematic review. BMC Oral Health. 16:12.

Gao SS, Zhao IS, Duffin S, Duangthip D, Lo ECM, Chu CH. 2018. Revitalising silver nitrate for caries management. Int J Environ Res Public Health. 15(1):E80.

Gupta SK. 2011. Intention-to-treat concept: a review. Perspect Clin Res. 2(3):109–12.

Hahn S. 2012. Understanding noninferiority trials. Korean J Pediatr. 55(11):403–407.

Mei ML, Ito L, Cao Y, Lo ECM, Li QL, Chu CH. 2014. An ex vivo study of arrested primary teeth caries with silver diamine fluoride therapy. J Dent. 42(4):395–402.

Moher D, Schulz KF, Altman DG; CONSORT. 2001. The CONSORT statement: revised recommendations for improving the quality of reports of parallel group randomized trials. BMC Med Res Methodol. 1:2.

Sheiham A. 2006. Dental caries affects body weight, growth and quality of life in pre-school children. Br Dent J. 201(10):625–626.

Snapinn SM. 2000. Noninferiority trials. Curr Control Trials Cardiovasc Med. 1(1):19–21.

Walker E, Nowacki AS. 2011. Understanding equivalence and noninferiority testing. J Gen Intern Med. 26(2):192–196.

Yamada MKM, Tanabe Y, Sano T, Noda T. 2002. Cooperation during dental treatment: the Children's Fear Survey Schedule in Japanese children. Int J Paediatr Dent. 12(6):404–409.

Zhao IS, Mei ML, Li QL, Lo ECM, Chu CH. 2017. Arresting simulated dentine caries with adjunctive application of silver nitrate solution and sodium fluoride varnish: an in vitro study. Int Dent J. 67:206–214.

Zhi QH, Lo EC, Lin HC. 2012. Randomized clinical trial on effectiveness of silver diamine fluoride and glass ionomer in arresting dentine caries in preschool children. J Dent. 40(11):962–967.