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Arresting early childhood caries using silver and fluoride products – A randomised trial

Sherry Shiqian Gao, Kitty Jieyi Chen, Duangporn Duangthip, May Chun Mei Wong, Edward Chin Man Lo, Chun Hung Chu *

Faculty of Dentistry, The University of Hong Kong, Hong Kong, China

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ABSTRACT

Objective: The aim of this randomised non-inferiority clinical trial was to compare the effectiveness of semi-annual (every six months) applications of 25 % silver nitrate ($AgNO_3$) solution followed by 5 % sodium fluoride (NaF) varnish to semi-annual applications of 38 % silver diamine fluoride (SDF) solution in arresting early childhood caries (ECC).

Methods: Three-year-old children with active cavitated carious lesions were recruited and randomly assigned to two intervention groups. Children in Group A received semi-annual applications of 25 % $AgNO_3$ solution followed by 5 % NaF varnish on carious lesions. Children in Group B received semi-annual applications of 38 % SDF solution followed by a placebo varnish. One trained dentist assessed ECC status at baseline and in all follow-up examinations. An independent operator performed the interventions. The dentist, the children, and their caretakers were blinded to the intervention allocation. Data were analysed using a non-inferiority test. Group A's non-inferiority would be accepted if the lower limit of the 95 % confidence interval (CI) for the difference in the mean number of arrested decayed surfaces (ds) was greater than −0.5.

Results: At baseline, 1,070 children were recruited, and 535 children were assigned to each group. After 30 months, the mean arrested ds in Groups A (n = 447) and B (n = 433) were 3.7 ± 3.6 and 3.6 ± 3.7, respectively (p = 0.694). The difference in the mean arrested ds between the two groups was 0.088 (95 % CI: -0.351 to 0.526).

Conclusion: Semi-annual application of 25 % $AgNO_3$ followed by 5 % NaF is at least as effective as the semi-annual application of 38 % SDF in arresting ECC.

Clinical significance: Silver and fluoride products are effective in arresting caries. As a simple, non-invasive, and inexpensive strategy, it can be used in young children, elderly adults, and people with special needs.

1. Introduction

Early childhood caries (ECC) is defined as the presence of one or more decayed, missing (due to caries), or filled tooth surfaces in the primary teeth of a child younger than six years old [1]. It remains a major health problem affecting a considerable number of young children worldwide, although dental care technology has improved in recent decades. The prevalence of ECC in the United States (US) increased during the periods 1988–1994 and 1999–2004, during which approximately half of US children had ECC before entering kindergarten [2]. In China, approximately two thirds of preschool children had untreated caries [3]. A recent review found that the prevalence of ECC in Southeast Asian countries varied from 70 % to 90 %, and most decayed teeth remained untreated [4]. Untreated dental caries can progress into pulp and cause pain and infection. Poor primary dentition not only influences children's oral health, but can also affect their chewing ability, nutrition absorption, cognitive development, growth, and quality of life [5]. Conventional restorative treatment for ECC in young children is challenging because of their uncooperative behaviour [6]. However, the presence of ECC is related with children's socioeconomic background [7]. In the US, 24 % of children, most of whom were from low-income families, experienced 80 % of all ECC [8]. Therefore, conventional treatment for advanced ECC can be unaffordable or inaccessible for children from disadvantaged communities [9]. Simple and inexpensive alternative strategies are necessary to manage ECC in young children.

Laboratory studies found that fluoride is effective in enhancing the

* Corresponding author at: 3B26, Prince Philip Dental Hospital, 34 Hospital Road, Hong Kong, China.
E-mail address: chchu@hku.hk (C.H. Chu).

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remineralisation of enamel and dentine tissues, whereas silver has an antibacterial effect [10]. Therefore, products containing fluoride and silver can be effective in managing dental caries [11]. One such product is silver diamine fluoride (SDF), which can inhibit dentine demineralization and prevent collagen degradation [12,13]. Systematic reviews found that the caries arresting rate of SDF for primary teeth was approximately 80 % [14,15]. SDF is available in some countries, such as the US, Japan, and Brazil. However, it remains unapproved for use in many others.

Sodium fluoride (NaF) varnish can stop the progression of enamel lesions and is commonly used to prevent dental caries [15]. However, 5 % NaF varnish was not as effective as 38 % SDF solution in arresting dentine caries [16]. Silver nitrate ($AgNO_3$) was used to manage dental caries because of its disinfectant properties [11]. Therefore, Duffin proposed the combined use of 25 % $AgNO_3$ solution followed by 5 % NaF varnish as a non-invasive treatment for managing ECC in young children [17]. A laboratory study reported the remineralisation of caries after treatment with 25 % $AgNO_3$ solution and 5 % NaF varnish [18]. However, no clinical trial in the literature has investigated the effectiveness of using 25 % $AgNO_3$ solution and 5 % NaF varnish in combination to arrest ECC.

Because 38 % SDF solution has proven effective in managing ECC in young children [14], this study used a non-inferiority design when using 38 % SDF in the active control group. The study's aim was to compare the effectiveness of the semi-annual (every six months) application of two sets of silver and fluoride products (i.e., 25 % $AgNO_3$ + 5 % NaF and 38 % SDF) in arresting ECC.

2. Materials and methods

2.1. Trial design

This is a non-inferiority, double-blind, active-controlled, randomised clinical trial. We obtained ethical approval for the study from the Institutional Review Board of the University and the Hospital Authority (No.: UW 13-569); this study was registered at ClinicalTrials.gov (No.: NCT02019160). The trial protocol was published in 2015 [19]. The reporting of this study followed the Consolidated Standards of Reporting Trials (CONSORT) guidelines [20].

2.2. Participant recruitment and randomised allocation

Twenty-nine local kindergartens were contacted, and all of them agreed to join this study. The kindergarten staff helped to distribute an invitation letter and consent form to the parents of children attending the first year of kindergarten. Children aged 3–4 who were generally healthy, had parental consent, and had at least one untreated active dentine carious lesion were recruited for this trial. The exclusion criteria were children who 1) had severe oral problems other than dental caries, 2) had major systemic diseases and/or a history of long-term medication use, and 3) were uncooperative during dental examinations. The baseline eligibility screening was conducted in the kindergartens. Eligible children were assigned to two intervention groups using a stratified randomisation procedure to balance the baseline caries status between two groups. First, the children were classified into two strata according to their caries experience: stratum 1 included children with 1–3 decayed, missing, and filled tooth surfaces (dmfs), and stratum 2 included children with more than 3 dmfs. Then, children in each stratum were allocated to intervention groups using computer-generated random numbers with a block size of 8. The computer-generated random numbers were generated by an independent statistician and delivered to an independent assistant. The assistant performed the randomised allocation procedure in the field. The examiner, participating children, and their parents were blinded to the intervention allocation.

2.3. Clinical examination

A dentist was trained to use the diagnostic criteria and indices adopted in this study by an experienced epidemiologist. The same dentist performed all dental examinations in the kindergartens, including baseline and all follow-up examinations (i.e. 6-month, 12 month, 18-month, 24-month and 30 month). The dentist used ball-ended Community Periodontal Index probes (Ash/Dentsply, Addlestone, UK), disposable dental mirrors, and intra-oral illuminations (Kudos Crown Limited, Hong Kong, China) to conduct the examinations. Teeth that showed symptoms such as discoloration, pulp exposure, and abscess or fistula were considered nonvital and excluded. Each tooth surface was assessed for the presence of dental caries. Caries was diagnosed at cavitation level. The activity of each carious lesion was also recorded. If a carious lesion was soft upon probing with a light force, it was classified as active. A carious lesion was considered arrested if hardness was detected upon probing [16,21,22]. Visible plaque index (VPI) was used to assess the participants' oral hygiene status. The presence of visible plaque on the buccal and lingual surfaces of six indexed teeth (55, 51, 63, 71, 75 and 83) was recorded [22]. We randomly selected 10 % of the children for duplicate examinations to assess intra-examiner reliability.

2.4. Interventions

There were two intervention groups in this study: Group A, which received 25 % $AgNO_3$ solution (Gordon Labs, CA, USA) followed by 5 % NaF varnish (Duraphat Varnish, Colgate-Palmolive, NY, USA), and Group B, which received 38 % SDF solution (Saforide, Toyo Seiyaku Kasei Co., Osaka, Japan) followed by placebo varnish (Vaseline, Unilever, NJ, USA). Treatments were only applied on the carious lesions. According to the assigned intervention group, an independent operator used a microbrush to apply the appropriate solution and varnish on each carious lesion. Each application to the carious lesion lasted approximately five seconds. The children were not to eat or drink for 30 min after the interventions. The same operator performed the baseline interventions and 6-month, 12-month, 18-month, 24-month and 30-month follow-ups after the clinical examination in the kindergartens.

2.5. Questionnaire

A modified validated questionnaire [9,23,24] was used at baseline to study the children's oral health-related behaviours (e.g. bottle-feeding and tooth brushing habits) and socioeconomic backgrounds (e.g. birthplace, parental status, parental educational level, family income, main caretaker). Information on each child's oral health-related behaviours at the 30-month follow-up was collected using another parental questionnaire; the content included bottle-feeding before sleeping, snacking habits, daily tooth brushing habits, assisted tooth brushing, and use of fluoride toothpaste.

2.6. Statistical methods

In this study, we considered a mean number of arrested decayed surfaces (ds) between two intervention groups of -0.5 to be clinically negligible, which was set as the non-inferiority margin. Assuming the true difference was 0, the standard deviation of the mean was 2.5, the effect size was 0.25, and the statistical power was 90 %; therefore, 856 children were required for statistical analysis (G*Power version 3.1.7, Kiel, Germany). We anticipated the overall dropout rate to be 20 %. Therefore, we required 1,070 participants, with 535 in each intervention group.

Two independent assistants input the data separately. After cleaning, the data were analysed using the Statistical Package for the Social Sciences 24.0 (SPSS Inc., Chicago, US). This study used the intention-to-treat (ITT) approach. Missing data were input by the last observation

carried forward (LOCF) method. The primary outcome measure was the status of the carious lesions (active or arrested) at the 30-month follow-up examination. The mean number of arrested ds was calculated in two groups. The non-inferiority of Group A compared with Group B would be acceptable if the lower limit of the 95 % confidence interval (CI) for the difference of mean number of arrested ds was greater than -0.5 (non-inferiority margin). Independent t-tests were performed to compare the mean number of active ds, the dmfs scores, the mean number of arrested ds, the numbers of newly developed dmfs, and VPI scores between Group A and B. Chi-square tests were used to compare the two groups' caries arresting rates, oral health-related habits, and socioeconomic backgrounds. Intra-examiner agreement on caries diagnoses was assessed using Cohen's Kappa statistics. The level of statistical significance was set at 0.05 for all tests.

Generalized estimating equations (GEE) with a logit link and two-level clusters (subject level and tooth-surface level) were adopted to investigate the effects of the intervention, related clinical parameters, oral health-related behaviours, and socioeconomic backgrounds on caries arrest after adjusting for the effect of the correlation between variables. The status of the carious lesion (arrested or not arrested) was

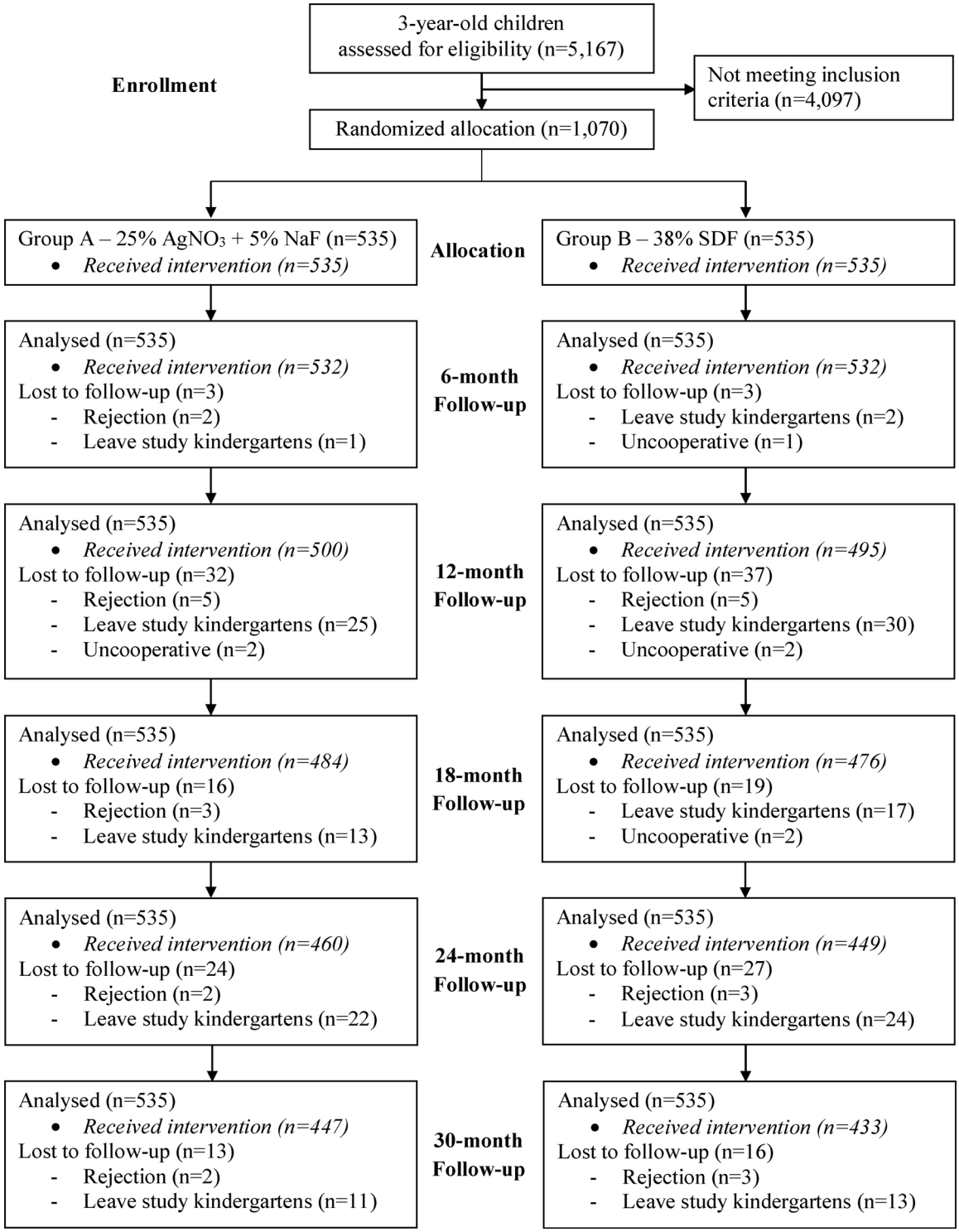

Fig. 1. Flow diagram of this trial.

the dependent variable in this logistic regression analysis. The GEE model for a bivariate logistic regression was used to analyse each independent variable. Those independent variables with p-values less than 0.05 were included to form a base model. Independent variables with p-values higher than 0.05 but less than 0.2 were entered into the subset models. Multivariable logistic regressions were conducted on the base and subset models. The model with the smallest Corrected Quasi-likelihood under Independence Model Criterion (QICC) was presented as the best-fit model for reporting. Inner-variable analysis was conducted using the Bonferroni test for pairwise comparison.

3. Results

At baseline, 1,070 children were recruited, with 535 children in each group (Fig. 1). The baseline mean dmfs scores of Groups A and B were 5.87 ± 6.26 and 5.96 ± 6.11, respectively (p = 0.828) (Table 1). No significant difference was found in oral health-related behaviours or socioeconomic backgrounds between the two groups at baseline (Appendix A). The dropout rate after 30 months was 16 % (88/535) and 19 % (102/535) in Groups A and B, respectively (p = 0.263). Withdrawing from the participating kindergartens was the main reason that the children dropped out of the study (Fig. 1). Clinical results of Groups A and B at each follow-up were presented in Table 1 including the children's mean number of dmfs, arrested ds, newly developed dmfs, caries arresting rate, and VPI scores. The Cohen's Kappa values for the duplicated examinations were higher than 0.9 in all examinations.

Table 1
Mean decayed, missing and filled surfaces (dmfs), active decayed surfaces (ds), arrested ds, caries arresting rate, new dmfs and visible plaque index of the two intervention groups at baseline and follow-up examinations.

	Variables	Group A 25 % $AgNO_3$ + 5% NaF	Group B 38 % SDF	p-value
Baseline	dmfs	5.87 ± 6.26	5.96 ± 6.11	0.828
	active ds	5.18 ± 4.64	5.18 ± 4.72	1.000
	visible plaque index	62.8 %±17.6 %	60.9 %±18.1 %	0.092
6-month follow-up	dmfs	6.58 ± 6.56	6.64 ± 6.43	0.869
	arrested ds	2.14 ± 2.53	2.00 ± 2.51	0.370
	caries arresting rate	41.3 %	38.7 %	0.048
	new dmfs	0.71 ± 1.24	0.68 ± 1.16	0.741
	visible plaque index	54.7 %±15.6 %	53.2 %±15.6 %	0.108
12-month follow-up	dmfs	7.45 ± 7.10	7.45 ± 6.88	0.993
	arrested ds	3.23 ± 3.37	3.10 ± 3.41	0.534
	caries arresting rate	62.4 %	60.0 %	0.069
	new dmfs	0.86 ± 1.58	0.80 ± 1.29	0.484
	visible plaque index	55.0 %±17.3 %	52.4 %±17.9 %	0.015
18-month follow-up	dmfs	8.36 ± 7.57	8.28 ± 7.57	0.856
	arrested ds	3.32 ± 3.42	3.23 ± 3.47	0.664
	caries arresting rate	64.1 %	62.4 %	0.202
	new dmfs	0.96 ± 1.59	0.83 ± 1.91	0.251
	visible plaque index	54.1 %±16.9 %	53.8 %±16.9 %	0.733
24-month follow-up	dmfs	9.14 ± 7.80	8.93 ± 7.84	0.653
	arrested ds	3.55 ± 3.59	3.44 ± 3.59	0.622
	caries arresting rate	68.6 %	66.5 %	0.092
	new dmfs	0.80 ± 1.36	0.69 ± 1.24	0.167
	visible plaque index	51.3 %±18.2 %	50.4 %±17.7 %	0.413
30-month follow-up	dmfs	9.75 ± 7.90	9.55 ± 8.04	0.682
	arrested ds	3.65 ± 3.62	3.56 ± 3.69	0.694
	caries arresting rate	70.6 %	68.9 %	0.163
	new dmfs	0.82 ± 1.45	0.89 ± 1.60	0.508
	visible plaque index	56.2 %±18.7 %	57.1 %±18.6 %	0.479

At the 30-month examination, the mean number of arrested ds in Groups A and B were 3.65 ± 3.62 and 3.56 ± 3.69, respectively (p = 0.694) (Table 1). The estimated difference in the mean number of arrested ds between the two groups was 0.088 (95 % CI: -0.351 to 0.526). Arrested carious lesions were stained black. No other significant side effects were observed by the examiner or reported by the parents.

The results of logistic regression for individual variables revealed that the number of baseline dmfs, newly developed dmfs at the 30-month follow-up, the tooth and surface locations of the carious lesion, and daily snack intake were associated with the caries status at tooth surface level (Table 2). Potentially significant variables (p-values higher than 0.05 but lower than 0.2) were the intervention group, VPI score at the 30-month follow-up, and the age at which the child stopped bottle feeding. Because the intervention group is the major factor under investigated in this study, it was automatically put in the base model. Thus, four possible models (one base model plus three subset models) were computed for the multi-variable logistic regression analysis. Base model was the best-fit model among the four potential models because its QICC (4051.143) was the smallest (Table 3).

Arresting of caries outcome was significantly negatively associated with the number of newly developed dmfs (odds ratio: 0.835, p < 0.001) at the 30-month follow-up. The tooth and surface location of the carious lesion were significantly related with caries activity (p < 0.001). Carious lesions in the anterior teeth or on the buccal surfaces were more likely to be arrested. The caries of children who had daily snack intake behaviour were less likely to be arrested (p = 0.003).

4. Discussion

This study found that 25 % $AgNO_3$ solution followed by 5 % NaF varnish is as effective as 38 % SDF solution in arresting ECC. Both treatments are simple, inexpensive, and non-invasive; thus, they can be used to manage ECC, especially when the conventional restorative treatments are not available or affordable. It is even more convenient to use 38 % SDF than 25 % $AgNO_3$ plus 5 % NaF to arrest ECC because the 38 % SDF application consists of only one step. Nevertheless, for some places where 38 % SDF solution is not yet available, such as some European countries, 25 % $AgNO_3$ solution followed by 5 % NaF varnish can be an alternative strategy for managing ECC.

In this trial, we adopted a non-inferiority design, which investigates whether one treatment is at least as effective as an existing treatment [25]. This addressed ethical concerns because it enabled the control group to receive effective treatment. This study used an ITT analysis, which is recommended by the CONSORT guidelines [20]. We included all children who had been randomised into the two groups at baseline for data analysis, regardless of their adherence to the assigned intervention or subsequent withdrawal from the trial. Our results reflect a practical scenario because the ITT analysis included noncompliance, such as dropouts and protocol deviation. It therefore provides a relatively conservative estimation of treatment effectiveness [26]. In this study, missing data were input by the LOCF method. Previous clinical studies have reported that the caries arresting rate increased over follow-ups when the interventions were repeated annually or semi-annually [21,22,27]. Thus, inputting the missing data by the LOCF method (usually worse than the true value) in this trial prevented the overestimation of the treatment outcome. We used the hardness of the carious lesion as a diagnostic criterion to determine whether a lesion was active or arrested. Laboratory studies have shown that the

Table 2
Bivariate logistic (arrested = 1; active = 0) regression using the generalized estimating equations model with a logit link and two-level clusters (subject level and tooth-surface level) for individual factor.

Explanatory variables	Odds ratio	95 % Confidence Interval	p-value
Clinical parameters			
Intervention group (ref: 38 % SDF)			0.103
- 25 % $AgNO_3$ + 5 % NaF	1.168	0.969–1.409	
Baseline dmfs	0.986	0.974–0.998	0.020
30-month new dmfs	0.923	0.877–0.970	0.002
30-month VPI score	0.907	0.815–1.008	0.070
Tooth location (ref: lower posterior tooth)			<0.001
- Upper anterior tooth	6.547	5.331–8.041	
- Upper posterior tooth	1.498	1.189–1.887	
- Lower anterior tooth	23.374	11.169–48.916	
Surface location (ref: occlusal surface)			<0.001
- Buccal surface	8.774	6.906–11.149	
- Mesial surface	6.212	4.960–7.780	
- Distal surface	4.126	3.194–5.331	
- Lingual surface	6.542	5.420–7.898	
Oral health-related habits			
Age stopped bottle-feeding (ref: after 24 months)			0.056
- Breast feeding only	1.515	1.111–2.065	
- 1 to 12 months	0.839	0.479–1.470	
- 13 to 24 months	1.054	0.828–1.341	
Current bottle-feeding before sleeping (ref: no)			0.248
- Yes	0.823	0.591–1.146	
Daily snack intake (ref: no)			0.003
- Yes	0.392	0.214–0.720	
Age of start tooth-brushing (ref: after 24 months)			0.959
- 1 to 12 months	1.052	0.744–1.487	
- 13 to 24 months	1.011	0.832–1.230	
Daily tooth-brushing (ref: twice per day or more)			0.691
- Less than once per day	0.804	0.307–2.104	
- Once per day	0.905	0.699–1.171	
Assisted tooth-brushing (ref: no)			0.746
- Yes	0.967	0.790–1.183	
Use of fluoride toothpaste (ref: no)			0.674
- Yes	1.067	0.788–1.447	
Socioeconomic backgrounds			
Sex (ref: female)			0.606
- Male	1.051	0.870–1.270	
Birthplace (ref: mainland)			0.218
- Hong Kong	0.809	0.578–1.133	
Parental status (ref: single parent)			0.817
- Both parents	1.057	0.661–1.691	
Monthly family income (ref: HK$ 40,001 or above)			0.333
- HK$ 20,000 or less	1.254	0.923–1.705	
- HK$ 20,001–40,000	1.254	0.900–1.749	
Father's education level (ref: higher education)			0.809
- Mandatory education	1.026	0.835–1.260	
Mother's education level (ref: higher education)			0.668
- Mandatory education	1.044	0.856–1.274	
Main caretaker (ref: maid)			0.404
- Parents	0.964	0.593–1.565	
- Relatives	0.826	0.494–1.381	

ref, reference group; SDF, silver diamine fluoride; $AgNO_3$, silver nitrate; NaF, sodium fluoride; dmfs, decayed, missing (due to caries) and filled surfaces; VPI, visible plaque index; HK$, Hong Kong dollars.

Table 3
Multivariable logistic (arrested = 1; active = 0) regression model with the best estimated fit by quasi-likelihood information criterion.

Explanatory variables	Odds ratio	95 % CI	p-value	Pairwise comparison
Intervention group			0.888	
(1) 25 % $AgNO_3$ + 5% NaF	0.983	0.773–1.250		
(2) 38 % SDF (ref)				
Baseline dmfs	0.990	0.975–1.006	0.240	
30-month new dmfs	0.835	0.793–0.890	<0.001	
Tooth location			<0.001	(3)>(1)>(2), (4)
(1) Upper anterior tooth	4.351	3.095–6.116		
(2) Upper posterior tooth	1.265	0.961–1.665		
(3) Lower anterior tooth	49.655	15.640–157.646		
(4) Lower posterior tooth (ref)				
Tooth surface location			<0.001	(1),(2),(3), (4)>(5)
(1) Buccal surface	3.518	2.586–4.785		(1)>(4)
(2) Mesial surface	2.828	2.129–3.756		
(3) Distal surface	2.409	1.770–3.278		
(4) Lingual surface	1.887	1.344–2.648		
(5) Occlusal surface (ref)				
Daily snack intake			0.003	
(1) Yes	0.392	0.212–0.726		
(2) No (ref)				

ref, reference group; $AgNO_3$, silver nitrate; NaF, sodium fluoride; SDF, silver diamine fluoride; dmfs, decayed, missing (due to caries) and filled surfaces.

microhardness of an arrested lesion increases because a highly remineralised zone rich in calcium forms [13,28]. Therefore, the hardness of the carious lesion can be a reliable measure for determining the lesion's activity level; it has been adopted in cariology studies worldwide [29].

The results of this non-inferiority trial indicated that, during the entire follow-up period, 25 % $AgNO_3$ solution followed by 5 % NaF varnish was not worse than 38 % SDF solution in arresting ECC based on the number of arrested ds and caries arresting rate. In addition, there was no significant difference between the two intervention groups in terms of other clinical parameters, such as the dmfs index, newly developed dmfs, and VPI scores during the follow-up examinations. The results of logistic regressions also supported that the intervention group was not significantly related to arresting of caries outcome. Therefore, the effectiveness of 25 % $AgNO_3$ solution followed by 5 % NaF varnish is generally comparable to that of 38 % SDF solution in managing ECC. This study found that the tooth and surface location of the carious lesion was related to the silver and fluoride treatment outcome. Carious lesions on the anterior teeth and on the buccal surface were more likely to be arrested than those on other locations. These findings were consistent with other clinical studies [22,27]. In this trial, the protocol for silver and fluoride treatment application did not consist of moisture control because we wanted to simplify the treatment application and improve young children's compliance. A lack of moisture control may lead to treatment dilution and reduce solution contact time on the posterior teeth and the lingual and occlusal surfaces. This may subsequently influence the treatment effectiveness. In addition, we found that the development of new dental caries and daily snack intake were related to the caries activity (active or arrested). Snack intake behaviour and the increment of dental caries may indicate those children have relatively high levels of cariogenic bacteria [30]. High oral cariogenic bacteria levels can lead to demineralisation of dental hard tissues and inhibit the remineralisation process [31], which can result in an unfavourable caries arresting outcome. Therefore, developing good dietary habits and preventing further ECC development is essential to achieve a better treatment outcome when using silver and fluoride products.

This study had several limitations. First, the interval between dental examinations was six months. Therefore, we cannot provide the exact time when the carious lesions became arrested. Second, because we used the LOCF method to input missing data, the caries arresting effectiveness reported in this study might be lower than the true number. In addition, because this study was conducted in an outreach setting with

compromised equipment, the caries arresting effectiveness of using silver and fluoride products could be higher in a clinical setting.

5. Conclusion

In conclusion, the semi-annual application of 25 % $AgNO_3$ solution followed by 5 % NaF varnish is at least as effective as the semi-annual application of 38 % SDF solution in arresting ECC. The child's caries risk and snack intake habits, along with the location of the carious lesion, are related to the outcome of the caries arrest. Both silver and fluoride treatment protocols were simple, inexpensive, and non-invasive. Using silver and fluoride can be a promising strategy for managing ECC in young children.

CRediT authorship contribution statement

Sherry Shiqian Gao: Formal analysis, Investigation, Writing - original draft. **Kitty Jieyi Chen:** Investigation, Resources. **Duangporn Duangthip:** Validation, Resources. **May Chun Mei Wong:** Software, Formal analysis, Data curation. **Edward Chin Man Lo:** Conceptualization, Writing - review & editing, Supervision. **Chun Hung Chu:** Conceptualization, Methodology, Writing - review & editing, Supervision, Project administration, Funding acquisition.

Declaration of Competing Interest

The authors declared no potential conflicts of interest with respect to the authorship and/ or publication of this article.

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Appendix A

Children's oral health-related habits and socioeconomic background at baseline

Factor		Group A 25 % $AgNO_3$ + 5 % NaF	Group B 38 % SDF	p-value
Sex	Male	295 (55.1 %)	294 (55.0 %)	0.951
	Female	240 (44.9 %)	241 (45.0 %)	
Birthplace	Hong Kong	487 (91.9 %)	484 (91.1 %)	0.666
	Mainland	43 (8.1 %)	47 (8.9 %)	
Parental status	Both parents	508 (95.0 %)	513 (96.2 %)	0.302
	Single parent	27 (5.0 %)	20 (3.8 %)	
Monthly family income ($HK)	20,000 or less	300 (56.7 %)	315 (59.4 %)	0.159
	20,001–40,000	178 (33.6 %)	152 (28.7 %)	
	40,001 or above	51 (9.6 %)	63 (11.9 %)	
Father's education level	Mandatory	137 (26.7 %)	160 (30.9 %)	0.138
	Higher education	376 (73.3 %)	358 (69.1 %)	
Mother's education level	Mandatory	171 (32.2 %)	183 (34.4 %)	0.448
	Higher education	360 (67.8 %)	349 (65.6 %)	
Main caretaker	Parents	397 (74.2 %)	413 (77.5 %)	0.395
	Other relatives	109 (20.4 %)	98 (18.4 %)	
	Maid	29 (5.4 %)	22 (4.1 %)	
Age of stop bottle-feeding	Breast-feeding	36 (6.7 %)	35 (6.5 %)	0.969
	1 to 12 months	15 (2.8 %)	14 (2.6 %)	
	13 to 24 months	108 (20.2 %)	103 (19.3 %)	
	After 24 months	375 (70.2 %)	383 (71.6 %)	
Age of start tooth-brushing	1 to 12 months	59 (11.0 %)	56 (10.5 %)	0.246
	13 to 24 months	230 (43.0 %)	257 (48.0 %)	
	After 24 months	246 (46.0 %)	222 (41.5 %)	

$AgNO_3$, silver nitrate; NaF, sodium fluoride; SDF, silver diamine fluoride; $HK, Hong Kong Dollar.

References

[1] American Academy of Pediatric Dentistry, Definition of Early Childhood Caries (ECC), 2008 (Accessed 22 April 2020), http://www.aapd.org/assets/1/7/D_ECC.pdf/.
[2] B.A. Dye, S. Tan, V. Smith, B.G. Lewis, L.K. Barker, G. Thornton-Evans, P.I. Eke, E. D. Beltrán-Aguilar, Trends in oral health status: united States, 1988-1994 and 1999-2004, Vital Health Stat, Ser 11, Nat. Health Surv. 248 (2007) 1–92.
[3] M.Y. Li, Q.H. Zhi, Y. Zhou, R.M. Qiu, H.C. Lin, Impact of early childhood caries on oral health-related quality of life of preschool children, Eur. J. Paediatr. Dent. 16 (2015) 65–72.
[4] D. Duangthip, S.S. Gao, E.C.M. Lo, C.H. Chu, Early childhood caries among 5- to 6-year-old children in Southeast Asia, Int. Dent. J. 67 (2017) 98–106, https://doi.org/10.1111/idj.12261.
[5] A. Sheiham, Dental caries affects body weight, growth and quality of life in pre-school children, Br. Dent. J. 201 (2006) 625–626, https://doi.org/10.1038/sj.bdj.4814259.
[6] M.K.M. Yamada, Y. Tanabe, T. Sano, T. Noda, Cooperation during dental treatment: the children's fear survey schedule in Japanese children, Int. J. Paediatr. Dent. 12 (2002) 404–409, https://doi.org/10.1046/j.1365-263X.2002.00399.x.
[7] S.S. Gao, D. Duangthip, E.C.M. Lo, C.H. Chu, Risk factors of early childhood caries among young children in Hong Kong: a cross-sectional study, J. Clin. Pediatr. Dent. 42 (2018) 367–372, https://doi.org/10.17796/1053-4625-42.5.8.
[8] M.E. Nunn, T. Dietrich, H.K. Singh, M.M. Henshaw, N.R. Kressin, Prevalence of early childhood caries among very young urban Boston children compared with US children, J. Public Health Dent. 69 (2009) 156–162, https://doi.org/10.1111/j.1752-7325.2008.00116.x.
[9] C.H. Chu, P.L. Ho, E.C.M. Lo, Oral health status and behaviours of preschool children in Hong Kong, BMC Public Health 12 (2012) 767, https://doi.org/10.1186/1471-2458-12-767.
[10] M.L. Mei, C.H. Chu, K.H. Low, C.M. Che, E.C.M. Lo, Caries arresting effect of silver diamine fluoride on dentine carious lesion with S. mutans and L. acidophilus dual-species cariogenic biofilm, Med. Oral Patol. Oral Cir. Bucal 18 (2013) e824–e831, https://doi.org/10.4317/medoral.18831.
[11] S.S. Gao, I.S. Zhao, S. Duffin, D. Duangthip, E.C.M. Lo, C.H. Chu, Revitalising silver nitrate for caries management, Int. J. Environ. Res. Public Health 15 (2018) 80, https://doi.org/10.3390/ijerph15010080.
[12] M.L. Mei, C.H. Chu, E.C.M. Lo, L.P. Samaranayake, Fluoride and silver concentrations of silver diammine fluoride solutions for dental use, Int. J. Paediatr. Dent. 23 (2013) 279–285, https://doi.org/10.1111/ipd.12005.

[13] M.L. Mei, L. Ito, Y. Cao, E.C.M. Lo, Q.L. Li, C.H. Chu, An ex vivo study of arrested primary teeth caries with silver diamine fluoride therapy, J. Dent. 42 (2014) 395–402, https://doi.org/10.1016/j.jdent.2013.12.007.
[14] S.S. Gao, I.S. Zhao, N. Hiraishi, D. Duangthip, M.L. Mei, E.C.M. Lo, C.H. Chu, Clinical trials of silver diamine fluoride in arresting caries among children: a systematic review, JDR Clin. Transl. Res. 1 (2016) 201–210, https://doi.org/10.1177/2380084416661474.
[15] S.S. Gao, S. Zhang, M.L. Mei, E.C.M. Lo, C.H. Chu, Caries remineralisation and arresting effect in children by professionally applied fluoride treatment–a systematic review, BMC Oral Health 16 (2016) 12, https://doi.org/10.1186/s12903-016-0171-6.
[16] C.H. Chu, E.C.M. Lo, H.C. Lin, Effectiveness of silver diamine fluoride and sodium fluoride varnish in arresting dentin caries in Chinese pre-school children, J. Dent. Res. 81 (2002) 767–770, https://doi.org/10.1177/0810767.
[17] S. Duffin, Back to the future: the medical management of caries introduction, J. Calif. Dent. Assoc. 40 (2012) 852–858.
[18] I.S. Zhao, M.L. Mei, Q.L. Li, E.C.M. Lo, C.H. Chu, Arresting simulated dentine caries with adjunctive application of silver nitrate solution and sodium fluoride varnish: an in vitro study, Int. Dent. J. 67 (2017) 206–214, https://doi.org/10.1111/idj.12291.
[19] C.H. Chu, S.S. Gao, S.K. Li, M.C.M. Wong, E.C.M. Lo, 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 (2015) 426, https://doi.org/10.1186/s13063-015-0960-2.
[20] D. Moher, K.F. Schulz, D.G. Altman, The CONSORT statement: revised recommendations for improving the quality of reports of parallel group randomized trials, BMC Med. Res. Methodol. 1 (2001) 2, https://doi.org/10.1186/1471-2288-1-2.
[21] D. Duangthip, C.H. Chu, E.C.M. Lo, A randomized clinical trial on arresting dentine caries in preschool children by topical fluorides - 18 month results, J. Dent. 44 (2016) 57–63, https://doi.org/10.1016/j.jdent.2015.05.006.
[22] M.H.T. Fung, D. Duangthip, M.C.M. Wong, E.C.M. Lo, C.H. Chu, Randomized clinical trial of 12% and 38% silver diamine fluoride treatment, J. Dent. Res. 97 (2018) 171–178, https://doi.org/10.1177/0022034517728496.
[23] K.J. Chen, S.S. Gao, D. Duangthip, S.K.Y. Li, E.C.M. Lo, C.H. Chu, Dental caries status and its associated factors among 5-year-old Hong Kong children: a cross-sectional study, BMC Oral Health 17 (2017) 121, https://doi.org/10.1186/s12903-017-0413-2.
[24] C.H. Chu, D. Fung, E.C.M. Lo, Dental caries status of preschool children in Hong Kong, Br. Dent. J. 187 (1999) 616–620, https://doi.org/10.1038/sj.bdj.4800347.
[25] E. Walker, A.S. Nowacki, Understanding equivalence and noninferiority testing, J. Gen. Intern. Med. 26 (2011) 192–196, https://doi.org/10.1007/s11606-010-1513-8.
[26] S.K. Gupta, Intention-to-treat concept: a review, Perspect. Clin. Res. 2 (2011) 109, https://doi.org/10.4103/2229-3485.83221.
[27] Q.H. Zhi, E.C.M. Lo, H.C. Lin, Randomized clinical trial on effectiveness of silver diamine fluoride and glass ionomer in arresting dentine caries in preschool children, J. Dent. 40 (2012) 962–967, https://doi.org/10.1016/j.jdent.2012.08.002.
[28] C.H. Chu, E.C.M. Lo, Microhardness of dentine in primary teeth after topical fluoride applications, J. Dent. 36 (2008) 387–391, https://doi.org/10.1016/j.jdent.2008.02.013.
[29] M.M. Braga, F.M. Mendes, K.R. Ekstrand, Detection activity assessment and diagnosis of dental caries lesions, Dent. Clin. North Am. 54 (2010) 479–493, https://doi.org/10.1016/j.cden.2010.03.006.
[30] P.K. Meurman, K. Pienihäkkinen, Factors associated with caries increment: a longitudinal study from 18 months to 5 years of age, Caries Res. 44 (2010) 519–524, https://doi.org/10.1159/000320717.
[31] J. Hicks, F. Garcia-Godoy, C. Flaitz, Biological factors in dental caries: role of saliva and dental plaque in the dynamic process of demineralization and remineralization (part 1), J. Clin. Pediatr. Dent. 28 (2004) 47–52, https://doi.org/10.17796/jcpd.28.1.yg6m443046k50u20.