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Research article

Caries arrest and lesion appearance using two different silver fluoride therapies with and without potassium iodide: 6-month results

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ABSTRACT

Objectives: to compare arrest rates and colour change in carious lesions in primary teeth using two different silver fluoride solutions with and without potassium iodide (KI).
Methods: The study was a four-armed, parallel-design randomised controlled trial and investigated four protocols for caries arrest at 6m. Children in Group 1 and Group 2 received Rivastar Silver Diammine Fluoride (SDF), and Children in Group 3 and Group 4 received an aqueous silver fluoride solution (AgF). Children in Group 2 and Group 4 received a two-step procedure where application of the AgF or SDF solution was followed by KI.
Results: At the six-month follow-up 446 (82.2%) children were re-examined. The arrest rate across the full sample was 51.4% and there were no significant differences in arrest rate by type of silver fluoride therapy. The lesion size, tooth type, surface type, presence of plaque on the carious lesion and caries increment all had an influence on caries arrest. Once clustering effects were accounted for, the use of KI was associated with a higher chance of arrest (OR 1.23; P-value 0.008) and a lower chance of the lesion darkening (OR 0.73; P-value <0.001).
Conclusions: The combination of AgF & KI was associated with the most favourable clinical outcomes in terms of caries arrest and lesion colour.
Clinical significance: The major draw-back of arrest of caries treatment with silver fluoride solutions is that it can create an appearance which may be aesthetically unacceptable. This study explores ways in which the base colour of lesions could be improved and as such provide the opportunity for better aesthetic outcomes for children afflicted with a severe burden of dental caries in their primary dentition, and in whom conventional treatment is not being provided.

1. Introduction

Children in Cambodia have a severe burden of dental caries especially affecting the primary teeth. The average 6 year old Cambodian child has 9 cavitated primary teeth and 2.7 pulpally-involved teeth [1]. If the conventional treatment approach to address these problems (eg. "drilling and filling" and extractions) was implemented, the costs would be more than the national health budget for Cambodia, and the whole dental workforce of Cambodia could still not provide all the treatment needed. And even then, such an approach would still not reduce the incident burden of disease because the conventional model of care does not address the social and behavioural drivers of the disease. In response to this situation, The Healthy Kids Cambodia (HKC) strategy uses Arrest of Caries Treatment with silver fluoride solutions to treat a large proportion of the open carious lesions among the 16,000 children in the project. In the case of HKC, Silver Fluoride treatments are viewed as the best first step to slowing down the caries progression in a population where the disease is ubiquitous and very severe. The SDF makes it possible to deploy a triage system whereby the bulk of the lesions (excluding lesions on permanent anterior teeth) are managed with SDF at the time of screening after daily tooth brushing has been implemented. Some children are referred for more advanced care (eg restorations and extractions) according to an established set of criteria [2].

Proponents of the HKC approach believe that Arrest of Caries Treatment with Silver Fluoride solutions is the strategy of choice for Cambodian children as an initial step to reducing suffering as a result of dental caries [3]. Previous studies in Cambodia have demonstrated up to 70% arrest rate with a single application of SDF [4]. While there is clear evidence that the effectiveness of such products is influenced by concentration and frequency of application [5], what is not clear is whether different products containing the same active ingredient (Silver Fluoride)

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carried in different solutions will perform with different rates of effectiveness.

The caries arrest activity of silver fluoride solutions occurs through a number of mechanisms including the fluoride enhancing mineral formation, hardening of the tooth surface, and the inhibition of the enzymes that break down tooth structure (matrix metalloproteinase inhibition) [6]. The silver and fluoride are normally carried in an alkaline solution and there are a number of different carriers that have been used. The Riva Star 38% Silver Diammine Fluoride (SDF) product is carried in an ammonium base solution which is volatile in storage and has a high pH. An experimental water-based 38% silver fluoride solution is under development (AgF) to address both the solution volatility and pH issues. The water based solution has not yet been tested in clinical trials.

The main disadvantage of treatment with Silver Fluoride solutions is that the cavitated carious lesions become a darker colour. This can result in poor aesthetics that could potentially be stigmatising or unacceptable to children and their families. For that reason, it is important to explore ways in which clinicians can achieve the most aesthetically favourable outcome. The application of potassium iodide solution after the silver fluoride has been shown to improve aesthetic outcomes in other studies [7].

It is important to consider which solution or combination of solutions will be most successful at achieving both caries arrest and patient satisfaction. This could have positive impacts on how the HKC program is perceived by schools and families who are offered treatment. The hypothesis of this investigation was that there would be no difference in caries arrest by use of two different silver fluoride solutions, and that the use of potassium iodide would reduce the chance of a lesion becoming a darker colour.

2. Methods

This was a four-armed, parallel-design randomized controlled trial that followed the recommendations for Interventional Trials (SPIRIT) 2013 Statement. The protocol can be accessed through the International Standard Randomised Controlled Trials Number Registry (ISRCTN87596444). The study recruited children from four schools who were scheduled to join the HKC strategy in the 2020–2021 academic year; this investigation facilitated early access to the program for children at each school. The four schools involved were Ang Sleng and Monirangsey primary schools in Takeo province, and Neareay and Taten primary schools in Kampot province of Cambodia. Children were randomized at school level for allocation into the four treatment groups. Randomisation was performed by the research assistant (RH) using the 'pull out of a hat' method. Those who did not meet the inclusion criteria received routine HKC treatment and management; in addition, those who were identified as needing urgent care were referred for more advanced management.

2.1. Ethical considerations

The HKC strategy had an existing ethical approval from the National Ethics Committee for Health Research to formerly observe and monitor the treatment provided including placement of SDF (Review number: 209NECHR). The present study involves a clinical protocol that varies from the standard HKC treatment regime, therefore it moves away from an observational study design and towards an experimental design. For that reason, an additional ethical review and approval was required. The experimental protocol was reviewed and approved by the Internal Research Committee of the University of Puthisastra and by the National Ethics Committee for Health Research, Ministry of Health, Cambodia. Children in the study received two applications of silver fluoride (at baseline and at the six-month follow-up) and were examined at the same time-points.

The consent process involved multiple steps due to the fact that some parents were expected to have limited literacy. The first step involved group level consent and distribution of information through the school support committee; the second step involved a written consent process whereby the parent either signed or asked the teacher to sign on their behalf. For those parents who did not fill out the consent form or communicate their consent to the teacher, a phone call was made to verify that consent had been given. Children were able to opt out at any point in time and were given a small gift of stationary regardless of their participation. In addition, the schools supported a daily handwashing and toothbrushing routine with the HKC project providing training and materials (tooth brushes, toothpaste, soap, and toothbrush holders).

The investigators declare that there is a conflict of interest in the conduct of the study because the lead investigator was commissioned as a consultant by the manufacturer of the products being tested (SDI Limited). This conflict is partly mitigated by the fact that the HKC project has been using SDF therapy since 2014 and the payment was consistent with local expectations of salary for conducting this type of work in a Cambodian environment through local agencies. This project could be considered a partnership between the dental company and the existing HKC project to improve the quality of care for participating children.

2.2. Sample size calculation

The results of previous clinical trials showed that around 70% of the active dentin caries became arrested after 24 m [8]. An absolute difference of 10% in the caries arrest rates between treatment groups was considered clinically significant. The estimated sample size was based on the expected proportion of arrested caries, with the power of the study set at 80% ($\beta = 0.2$) and with $\alpha = 0.05$ as the statistical significance level. The sample size per study group, calculated by using the G-power, was 353 active carious tooth surfaces. Based on the results of epidemiological surveys [1] it was estimated that the mean baseline active carious surfaces would be 5 after excluding those active lesions which are pulpally-involved (average of 2.7/child). The intra-class correlation coefficient (ICC) for dental caries data at the surface level within the individual would be approximately 0.3. Following the equation for the required sample size in a multilevel study, the estimated sample size would be at least 565 active carious surfaces recruited for each group at baseline.

Children were included who attended one of the target schools, who had one or more active carious lesions in primary teeth not involving the pulp, and were 11-years-old or below. Children whose parents refused consent or who refused assent themselves, those who were outside the target age-range, and those with no teeth eligible for silver fluoride treatment were excluded. Overall 421 children were included in the study, representing 4606 lesions in primary teeth that met the criteria of: (1) ICDAS code 3 or above; and (2) not associated with a pulpally involved or soon to exfoliate tooth. At the 6m follow-up 3055 lesions were examined after accounting for loss to follow-up and exfoliation of teeth (Figure 1).

2.3. Clinical procedures

Clinical examination was performed by visual inspection under torch light, with children in a supine position. Probing of cavitated lesions (ICDAS code 5 and 6 lesions) was performed using a ball ended World Health Organization CPI probe. Each child was assigned a unique identifier at baseline in order to anonymously track them throughout the trial. Data analysis was performed on a de-identified dataset only. A full-mouth, surface level charting was performed at baseline and at the six-month follow-up; data were collected on tooth status using the ICDAS index. In addition data on the colour of the cavity was collected using a standardized scale [9], and the centre of the lesion was gently probed to gain a tactile measure of hardness. Oral hygiene status was examined by observing the presence or absence of visible plaque on the carious surface.

There were two separate groups of clinicians involved the study at each time-point; one group made up of four calibrated examiners and four assistants, and a second group made up of four clinical operators and

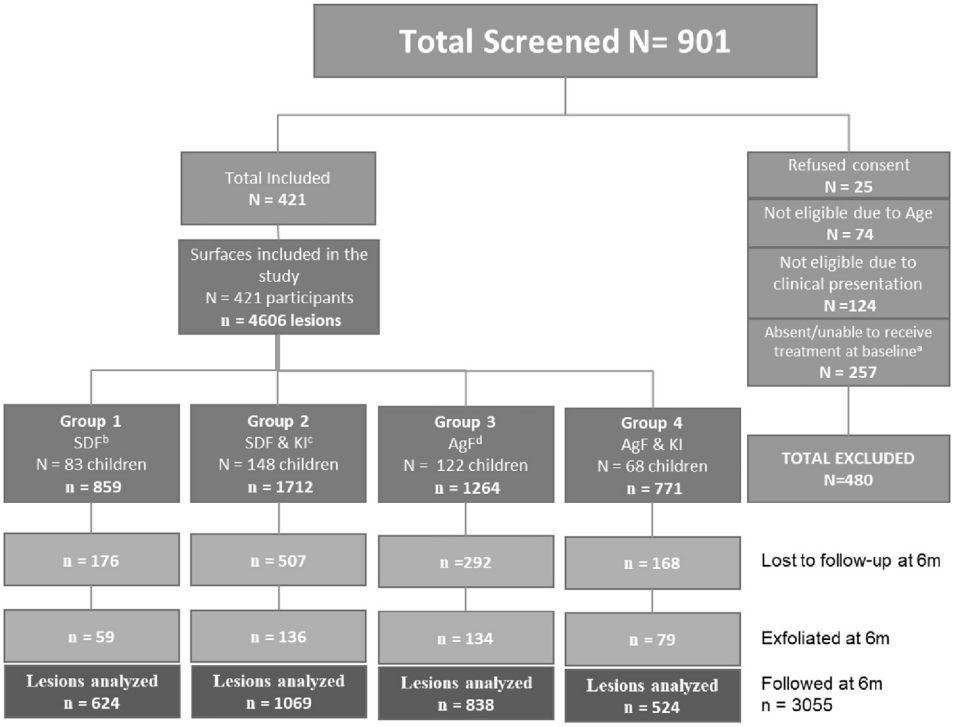

Figure 1. Recruitment of participants and flow over 6-months. [a]Time constraints meant that 257 children received Silver fluoride therapies after the initial recruitment phase at but were either not present during the initial baseline recruitment phase or time-constraints did not facilitate inclusion. [b]SDF refer to Rivastar Silver Diammine Fluoride (38%). [c]KI refers to a clinical protocol where second step of Potassium Iodide is placed. [d]AgF refers to the experimental 38% Silver Fluoride solution with an Aqueous base.

four assistants. Most of the clinicians were active at the three time-points and at each site, however logistic restraints meant that some examiners could not participate at each time point or each site. As such the number of examiners and clinicians who had been involved grew throughout the course of the trial to a total of 6 calibrated examiners and 12 clinical operators. Children were examined by different examiners at each time-point.

Children were first examined by an examiner and then received the topical silver fluoride therapy by a clinical operator. Calibrated examiners underwent a four-hour training session at baseline, 6m and 12m. The training culminated with testing to achieve an inter-examiner kappa score >0.85 for the ICDAS index, which indicates near perfect agreement. Clinical operators received a two-hour training on how to use the open source data collection tool (KoBo Collect v1.25.1; KoboToolBox, MA, USA), as well as on the appropriate placement of the AgF/SDF/KI material(s) according to group membership. Silver fluoride was applied at baseline and also immediately following the 6m follow-up examination. The clinical protocol varied according to group (Figure 1). Group 1 and Group 3 received a single step therapy with variation in the type of silver fluoride (SDF or AnF) therapy. After isolating the tooth and drying the cavity with cotton pellets, SDF or AgF was placed; moisture control was maintained for one minute. Children in Group 2 and Group 4 received a two-step procedure where silver fluoride solution was placed on the lesion (after drying) followed by Potassium Iodide (KI) until the precipitate went from yellow to white, and then clear. Moisture control was maintained for 1-minute post placement. Children in Group 1 and Group 2 received SDF, and children in Group 3 and Group 4 received AgF.

After each clinical application the child was checked twice to ensure that no adverse events had occurred; once immediately after the procedure and a second time, in the classroom the following day. At each check, children were asked to verbally indicate if they had experienced any discomfort and, if so, then intra-oral soft tissues were examined for signs of chemical burns. Adverse events were documented on a standardised adverse events form. The clinical procedure for isolation was modified to include placement of Vaseline on soft tissue in the anterior zone, after three adverse events were associated with migration of treatment solutions onto soft tissues during the treatment of anterior smooth-surface lesions, causing a superficial chemical irritation.

2.4. Data analysis

The primary outcome of interest was the arrest of the carious lesion at surface level which was based on (a) a change in size of a lesion using the ICDAS index, and (b) the hardness of a lesion. These criteria were applied differently depending on the clinical presentation of the lesion at baseline. Those lesions which were ICDAS code 3 or code 4 lesions at baseline were judged to have arrested if at the 6m follow-up they had not transitioned to a more severe ICDAS code. In the case of ICDAS code 6 lesions then the lesion had to be 'hard' rather than 'leathery' or 'soft' in order to qualify as arrested. For a lesion that was ICDAS 5 at baseline, then it would be classified as being arrested if it was hard or if it were stable in size. The outcome of colour did not form part of the arrest criteria in this study since the addition of KI in two groups is known to reduce the discoloration caused by the silver fluoride solution.

The secondary outcome of interest was the darkening of the lesion which was judged according to a colour scale incorporating categories representing 'yellow', 'light brown', 'dark brown' and 'black'. For smaller (ICDAS code 3 and code 4) lesions colour was judged by the colour of staining and shadowing surrounding the lesion while larger lesions (ICDAS code 5 and code 6) could be judged based on the colour of the dentine which was visible by direct vision. Lesions which were judged as black at baseline were excluded from the colour-change analysis. A lesion was classified as becoming darker if it transitioned into a 'darker' colour category at the 6m review. Caries increment was calculated as a measure of caries activity at individual level. Any new cavitated lesion that was present at the 6m follow-up was counted towards surface level caries increment.

Survey data were collected on the Kobo Collect app and clinical data were collected on paper and then entered into an Excel spreadsheet. Data were transferred and analysed using SPSS Version 23 (IBM Corp, NY, USA). Differences in proportions among groups were compared using a chi-square test and differences in means between groups were compared using the Kruskal-Wallis test for non-parametric data. A two-level model

was used to allow for the clustering effect of multiple lesions that might occur within one individual. The first level of the model included tooth surface variables and the second level included lesion level effects. The categorical covariates included were sociodemographic characteristics (sex and age), tooth type, lesion position, and presence of plaque on a lesion at follow-up. Caries increment was entered as an ordinal variable. Data from the present study will be subject to further analysis at later stages of the project.

3. Results

Of the 421 participants who received treatment at baseline (February 2019) 346 were re-examined at the 6-month follow-up (August 2019). At baseline there were three adverse events due to migration of treatment solutions onto soft tissues causing transient gingival irritation which resolved within days. There were no adverse events at the six-month follow-up. Table 1 presents data on attrition by group membership. There were no significant differences in follow-up by group membership although group 2 had a slightly lower follow-up rate. 5-year-old children were more likely to be lost to follow-up than children from other age-groups (P-value <0.05; χ^2).

There were significant (P-value <0.05; χ^2 test) differences in caries experience at baseline according to group membership. Those in Group 3 and Group 4 had a more severe caries experience with a higher proportion of larger carious lesions and a higher proportion of cavitation on anterior primary teeth. Lesions in group 1 had a significantly higher chance of having visible plaque present on lesions at the 6-month examination (Table 2).

There was a significant difference in the primary outcome of caries arrest (based on lesion size and hardness) by group membership (Table 3). Lesions treated with potassium iodide (Groups 2 & 4) had around one quarter lower chance of transitioning into a darker colour category (secondary outcome) compared with Groups 1 and 3. Children in Group 4 (AgF + KI) had a lower proportion of lesions which were considered 'hard' however the same treatment group had a higher proportion of lesions which were stable in size. Proximal lesions and more the severe lesions (according to ICDAS code) were less likely to remain stable in size or to become hard at 6m.

Table 4 presents data on Arrest of Caries and darkening of lesions by group membership. Group 4 (AgF + KI) had a 50% higher odds of achieving arrest when compared to Group 1 (P-value <0.05). Analysis on changes in colour was based on the 2335 (76.4%) lesions which were not already black at baseline. Those lesions in Group 2 and Group 4 had lower odds of becoming a darker shade at 6-months (P-value <0.05) compared with Groups 1 and 3.

The size of the lesion, the tooth type, the surface type, the presence of plaque in the lesion, and the caries increment all had an influence on the odds of caries arrest and colour change within a lesion (Tables 4, 5, and 6). After control for confounding and clustering effects there was no significant difference in the chance of caries arrest or change in colour by type of silver fluoride therapy (Table 5).

There was a statistically significantly higher chance of arrest when using KI (Table 6). In addition, those lesions where KI was placed had around one quarter lower chance of becoming a darker shade.

4. Discussion

The present study was a four-armed, parallel-design randomized controlled trial which examined differences in lesion arrest (based on size stability and hardness) and lesion colour following application of two different silver fluoride solutions (AgF and SDF) with and without placement of potassium iodide. It found that the combination of AgF and KI was the most favourable therapy for achieving caries arrest and avoiding and darkening of the lesion. Before further examination of the findings of the study it is appropriate to first consider the strengths and limitations of the study. Performing clinical trials in challenging environments such as exist in Cambodia can yield important information, however, balancing ethical considerations can make it difficult to maintain ideal experimental conditions. The 4 schools selected were all due to enter the Healthy Kids Cambodia project in 2020. They were randomly assigned to one of the 4 treatment groups. The individual children within those schools were not randomly assigned into the treatment groups, the caries experience was unequal, and all children at the school were given the same treatment, which means that the examiners were not blinded. This could lead to bias due to the fact that some examiners may have been tempted to score lesions differently knowing the type of treatment that was provided.

Table 1. Attrition analysis by group membership and sociodemographic characteristics.

	Baseline N (column %)	Lost N (row %)	Followed N (row %)
Group membership			
Group 1 – SDF	83 (19.7)	13 (15.7)	70 (84.3)
Group 2 – SDF & KI	148 (22.3)	33 (22.3)	115 (77.7)
Group 3 – AgF	122 (29.0)	20 (16.4)	102 (83.6)
Group 4 – AgF & KI	68 (16.2)	9 (13.2)	59 (86.8)
Sex			
Male	233 (53.0)	40 (17.9)	183 (82.1)
Female	198 (47.0)	35 (17.7)	163 (82.3)
Age-group[a]			
3-years	10 (2.4)	2 (20.0)	8 (80.0)
4-years	5 (1.2)	2 (40.0)	3 (60.0)
5-years	40 (9.5)	15 (37.5)	25 (62.5)
6-years	62 (14.7)	16 (25.8)	46 (74.2)
7-years	82 (19.5)	10 (12.2)	72 (87.8)
8-years	93 (22.1)	9 (9.7)	84 (90.3)
9-years	45 (10.7)	6 (13.3)	39 (86.7)
10-years	52 (12.4)	10 (19.2)	42 (80.8)
11-years	32 (7.6)	5 (15.6)	27 (84.4)
Total	421 (100.0)	75 (17.8)	346 (82.2)

[a] P = 0.005; χ^2 test for differences among groups within the same column.

Table 2. Clinical characteristics of participants and lesions at 6m follow-up by group membership.[b]

	Group 1 n (%)	Group 2 n (%)	Group 3 n (%)	Group 4 n (%)
Caries increment of participant Mean (SD)	5.6 (5.7)	5.8 (6.7)	6.3 (6.6)	6.2 (5.9)
Plaque visible inside lesion	354 (56.7)	481 (45.0)	403 (48.1)	239 (45.6)
Anterior tooth lesion	311 (49.8)	553 (51.7)	501 (59.8)	330 (63.0)
Surface type				
Occlusal	75 (12.0)	140 (13.1)	111 (13.2)	84 (16.0)
Proximal	384 (61.5)	652 (61.0)	540 (64.4)	298 (56.9)
Smooth surface	165 (26.4)	277 (25.9)	187 (24.3)	142 (27.1)
Baseline ICDAS code				
code 3	268 (42.9)	546 (51.1)	263 (31.4)	201 (38.4)
code 4	173 (27.7)	230 (21.5)	213 (25.4)	96 (18.3)
code 5	115 (18.4)	139 (13.0)	169 (20.2)	72 (13.7)
code 6	68 (10.9)	154 (14.4)	193 (23.0)	155 (29.6)
Sex				
Male	286 (45.8)	538 (50.3)	456 (54.4)	276 (52.7)
Female	338 (54.2)	531 (49.7)	382 (45.6)	248 (47.3)
Age-group				
3-years	42 (6.7)	0 (0.0)	78 (9.3)	0 (0.0)
4-years	39 (6.2)	11 (1.0)	0 (0.0)	0 (0.0)
5-years	91 (14.6)	191 (17.9)	241 (28.8)	173 (33.3)
6-years	116 (18.6)	191 (17.9)	241 (28.58)	173 (33.0)
7-years	125 (20.0)	329 (30.8)	206 (24.6)	132 (25.2)
8-years	132 (21.2)	157 (14.7)	173 (20.6)	155 (29.6)
9-years	22 (3.5)	89 (8.3)	87 (10.4)	3 (0.6)
10-years	43 (6.9)	85 (8.0)	18 (2.1)	1 (0.2)
11-years	14 (2.2)	16 (1.5)	35 (4.2)	3 (0.6)

[a] Group 1 = SDF; Group 2 = SDF; Group 3 = AgF; Group 4 = AgF&KI.
[b] Brackets contain column percentages unless otherwise indicated. There were statistically significant differences in clinical characteristics by group membership across all descriptors in the table; P-value =<0.01; χ^2 test or Kruskal Wallis test for differences among groups within the same row as appropriate.

Table 3. Hardness, size stability and colour of lesions at 6-month follow-up.[a]

	Hard lesions n (row %)	Size stable n (row %)	Darkening of lesion[c] n (row %)	Arrest n (row %)
Group				
Group 1	477 (76.6)[b]	399 (63.9)[b]	241 (49.1)[b]	339 (54.3)
Group 2	747 (69.9)	656 (61.4)	263 (34.3)	536 (50.1)
Group 3	589 (70.2)	568 (67.8)	303 (46.1)	444 (53.0)
Group 4	303 (57.8)	387 (73.9)	130 (31.0)	250 (47.7)
Silver therapy				
SDF	1224 (72.8)[b]	1055 (62.3)[b]	504 (40.1)	875 (51.7)
AgF	892 (65.7)	955 (70.1)	433 (40.2)	694 (51.0)
Use of KI				
Placed KI	1050 (66.4)[b]	1043 (65.5)	393 (33.1)[b]	789 (49.3)
No KI	1066 (73.1)	967 (66.1)	544 (47.4)	783 (53.6)
Lesion type				
Occlusal	264 (63.8)[b]	279 (68.0)[b]	133 (46.2)[a]	196 (47.8)[b]
Proximal	1271 (60.1)	1118 (59.7)	628 (42.4)	880 (47.0)
Smooth surface	584 (76.1)	613 (79.5)	176 (31.2)	493 (63.9)
ICDAS code				
code 3	932 (73.2)[b]	717 (56.1)[b]	468 (47.4)[a]	623 (48.7)[b]
code 4	504 (71.1)	390 (54.8)	209 (44.8)	332 (46.6)
code 5	325 (65.8)	333 (67.3)	123 (31.1)	259 (52.3)
code 6	355 (62.9)	570 (100.0)	137 (28.2)	355 (32.3)
Overall	2116 (69.2)	2010 (34.2)	937 (40.1)	1569 (51.4)

[a] Group 1 = SDF; Group 2 = SDF; Group 3 = AgF; Group 4 = AgF&KI.
[b] P= <0.001; χ^2 test for differences among groups within the same column.
[c] analysis of transition of a lesion from one colour category to a darker category was performed for lesions that were not classified as being a black colour at baseline (n = 2334).

Table 4. Logistic regression model for caries arrest rate and darkening of the lesion colour at 6m follow-up by group membership with clustering effects.

	Arrest of Caries			Darkening of the lesion		
	Odds ratio	95% CI	P-value	Odds ratio	95% CI	P-value
Group 1[a]						
Group 2	1.18	0.95–1.45	0.135	0.75	0.59–0.94	0.015
Group 3	1.07	0.86–1.35	0.545	1.02	0.81–1.30	0.844
Group 4	1.50	1.17–1.94	0.002	0.74	0.56–0.97	0.027
ICDAS code						
Code 3[a]						
Code 4	1.12	0.92–1.37	0.248	0.89	0.71–1.12	0.321
Code 5	0.91	0.73–1.13	0.384	0.69	0.54–0.881	0.002
Code 6	0.58	0.46–0.72	<0.001	0.70	0.55–0.88	0.002
Tooth type						
Anterior[a]						
Posterior	0.99	0.84–1.16	0.876	1.16	0.96–1.40	0.119
Surface type						
Occlusal[a]						
Smooth	0.49	0.375–0.641	<0.001	0.65	0.48–0.89	0.007
Proximal	0.99	0.79–1.25	0.226	0.80	0.61–1.05	0.112
Plaque in lesion						
No plaque visible[a]						
Plaque visible	1.06	0.91–1.24	0.214	1.16	0.98–1.38	0.077
Caries increment[b]	1.05	1.04–1.06	<0.001	1.00	0.99–1.02	0.077

[a] Reference category.
[b] entered as an ordinal variable, odds ratio for the increase in odds for each new surface that was cavitated between baseline and 6m follow-up.

Table 5. Logistic regression model for caries arrest and darkening of lesion colour at 6m follow-up by type of silver fluoride solution with clustering effects.

	Arrest of Caries			Darkening of the lesion		
	Odds ratio	95% CI	P-value	Odds ratio	95% CI	P-value
SDF[a]						
AgF	1.11	0.061–2.62	0.222	1.08	0.91–1.28	0.734
ICDAS code						
Code 3[a]						
Code 4	1.09	0.89–1.32	0.398	0.94	0.75–0.91	0.569
Code 5	0.87	0.70–1.09	0.225	0.71	0.56–0.91	0.006
Code 6	0.58	0.46–0.72	<0.001	0.69	0.55–0.87	0.002
Tooth type						
Anterior[a]						
Posterior	0.98	0.83–1.16	0.820	1.17	0.98–1.41	0.091
Surface type						
Occlusal[a]						
Smooth surface	0.49	0.38–0.64	<0.001	0.65	0.478–0.89	0.007
Proximal	0.98	0.78–1.24	0.879	0.81	0.62–1.06	0.123
Plaque in lesion						
No plaque visible[a]						
Plaque visible	1.05	0.90–1.23	0.510	1.18	1.01–1.41	0.036
Caries increment[b]	1.05	1.04–1.06	0.062	1.00	0.99–1.01	0.614

[a] Reference category.
[b] entered as an ordinal variable, odds ratio for the increase in odds for each new surface that was cavitated between baseline and 6m follow-up.

The weaknesses in sample selection design have been partly mitigated by appropriate statistical methods to control for clustering and differences between groups. The strengths of the study include that an adequate sample size was selected and that follow-up rates were high, which meant that this study has sufficient statistical power to examine the research questions that were posed. Another strength of the study design was the use of the ICDAS codes to quantify the stability of the size of the lesion as a criteria for arrest. Some previous studies have determined arrest based only on hardness and colour, which are difficult to calibrate. In the present study the calibrated examiners could provide an accurate measure of lesion size stability.

Children in Cambodia have a much higher rate of dental caries than that seen in other parts of the world, and so it is important to generate context specific evidence for therapies that are to be applied. When this is considered in the context of the present definition of lesion arrest (described in the methods section) then it is likely that some proportion of that lesion activity could have been accounted for by the presence of ICDAS code 4 lesions at baseline. An ICDAS code 4 lesion is defined as "an

Table 6. Logistic regression model for caries arrest and darkening of lesion colour at 6m follow-up by type of silver fluoride solution with clustering effects.

	Arrest of Caries			Darkening of the lesion		
	Odds ratio	95% CI	P-value	Odds ratio	95% CI	P-value
No KI[a]						
KI placed	1.23	1.06–1.43	0.008	0.73	0.62–0.87	<0.001
ICDAS code						
Code 3[a]						
Code 4	1.12	0.92–1.37	0.266	0.89	0.71–1.12	0.322
Code 5	0.91	0.73–1.14	0.410	0.69	0.54–0.88	0.003
Code 6	0.60	0.48–0.74	<0.001	0.70	0.55–0.88	0.002
Tooth type						
Anterior[a]						
Posterior	0.98	0.83–1.15	0.802	1.16	0.96–1.39	0.121
Surface type						
Occlusal[a]						
Smooth surface	0.49	0.38–0.64	<0.001	0.65	0.48–0.89	0.007
Proximal	0.99	0.79–1.25	0.942	0.80	0.61–1.05	0.113
Plaque in lesion						
No plaque visible[a]						
Plaque visible	1.06	0.91–1.23	<0.001	1.16	0.98–1.37	0.079
Caries increment[b]	1.05	1.04–1.06	<0.001	1.00	0.99–1.02	0.532

[a] Reference category.
[b] entered as an ordinal variable, odds ratio for the increase in odds for each new surface that was cavitated between baseline and 6m follow-up.

underlying dark shadow from dentine" and such lesions may behave in a distinct manner from biomechanical and a chemo-therapeutic point of view. ICDAS code 4 lesions have undermined enamel that might increase in size (ie progress to ICDAS 5) due to enamel breakdown, even if the body of the lesion within dentine has arrested. Regarding differences in chemo-therapeutic benefit according to lesion morphology, although the demineralised enamel on the surface of an ICDAS 4 lesion may benefit from application of silver therapies, the body of the lesions is not accessible to microbrush application. In this way, when whole groups have differences in the proportions of different lesion sizes then that can confound the arrest outcome.

Other studies have reported arrest rates of 70–80% being achieved at 12-months (after two applications of SDF). (references?) It is possible that during the first 6 months after the baseline examination, ICDAS 4 lesions progress in size due to enamel breakdown, even though the dentine caries has arrested. This hypothesis will be tested during the 12-month data collection [10]. This phenomenon might explain some of the variation in arrest rates between Groups 1 + 2 (SDF) and the Groups 3 + 4 (AgF); those in group 3 and group 4 had a more severe caries experience at baseline.

It is also important to note that for Group 4 (AgF in combination with KI), when both clustering effects and confounders were controlled for, the odds of arrest was higher compared to other groups even though the raw arrest rate was lower. It is unclear whether this could have been due to an additional anti-caries effect of KI or that it was an artefact of the systematic differences in disease presentation among groups. While dentine lesions with silver 'microwires' have been shown to have greater hardness than untreated lesions [11], it is not known how treatment with KI might modify the biomechanical properties of a lesion. Also, although there is evidence that KI might have benefits for desensitisation of dentine and occlusion of dentinal tubules [12], it is not clear how KI might perform in the dynamic system that is the caries process. Taking this into account, the differences in arrest performance by the four silver fluoride protocols should be verified after the 12-month data collection. The 6-month arrest rates observed in this study are consistent with systematic reviews and meta-analyses that have examined arrest of caries in primary teeth using single applications of silver fluoride solutions with 30% and 38% concentrations [5].

The two silver fluoride solutions showed no difference with respect to darkening the lesion, and it was clear that the KI had a statistically significant benefit in terms of avoiding darkening of the lesion. Although this benefit was observable by examiners, it is not clear what the clinical significance of this difference is, particularly for posterior teeth. Anecdotally, in those cases where the base-colour of the lesion was recorded as a lighter colour, it was common to see a speckled appearance at 6m, where the colour of different parts of the lesion varied greatly even within the same surface (Figure 2). It has been documented that the black colour of arrested lesions treated by SDF is a barrier for some parents and children who may be offered arrest of caries treatment [13, 14]; however, it is not clear whether or not the observed alterations in the appearance of the lesions with the KI treatment would be noticeable or more aesthetically pleasing to families and peers.

An earlier study found an aesthetic benefit of KI due to the avoidance of staining overlying restorative materials on root surface lesions [7].

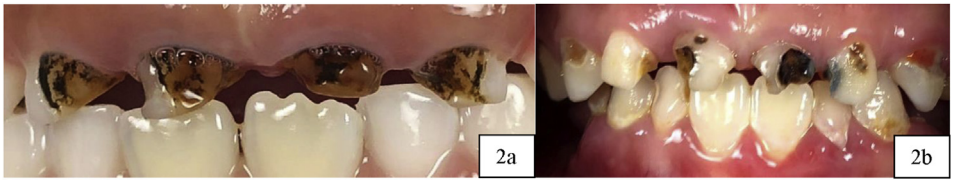

Figure 2. Variation in lesion appearance after the placement of silver fluoride solutions in combination with KI. [2a]A typical speckled appearance on anterior teeth treated with both silver fluoride solutions and a KI solution. [2b]This patient shows the variation of lesion colour that is observed within one patient where all teeth received the same treatment protocol.

This effect might be relevant for preschool children who have lesions on primary anterior teeth treated by silver fluoride that may later be restored; having a lighter base colour could be beneficial in terms of achieving a more aesthetically pleasing result when the tooth is restored. In addition to the observed reduction in staining with using KI, it was also observed that KI was associated with a higher odds of caries arrest when compared to silver fluoride therapy alone. This is further justification for placing KI on primary teeth especially if that finding could be verified at the 12-month follow-up.

5. Conclusions

This study found a difference in arrest rate according to the use of different silver fluoride solutions with and without the use of KI. There was no difference between the AgF and SDF groups. However, there was greater odds of caries arrest when KI was also applied. The discoloration of the lesions was statistically significantly less when KI was used; the use of KI solution almost halved the odds of developing a darker base colour within the cavitated lesions. The clinical relevance of this finding around colour change and aesthetic acceptability is not yet clear. Further verification is needed at the twelve-month time-point due to variations in baseline caries experience among groups.

Declarations

Author contribution statement

B. Turton: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

C. Durward: Conceived and designed the experiments.

R. Horn: Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data.

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Competing interest statement

The authors declare no conflict of interest.

Additional information

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