EVALUATION OF THE RESPONSE OF CARIES LESIONS IN DENTIN AFTER APPLICATION OF SILVER DIAMINE FLUORIDE GEL: A CASE SERIES

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Primary Objective. To determine the response of dental caries lesions (caries arrest) into the dentin in primary teeth at one year of follow-up where 38% silver diamine fluoride gel is applied.

Secondary Objective. To assess parent satisfaction with treatment with 38% silver diamine fluoride.

Methods.
Registration and Ethics: IRB approval will be obtained from the Institutional Review Board (IRB) of the National University of the Altiplano, Puno, Peru and the study will be registered as a case series. Note, there are no experimental treatments. All of the products are cleared by the US FDA as medical devices. There is no intent to report these data to the US FDA or alter the indication for either SDF or the varnish.

Study Design: Prospective single center case series. Cases will not be consecutive.

Setting: Faculty of Health Sciences, Professional School of Dentistry, National University of the Altiplano, Puno, Peru

Principal Investigators: Principal Professor Tania Padilla Caceres and Dr. Jorge L. Castillo. Additional investigators: Emeritus Professor Peter Milgrom, Research Associate Professor Lloyd Mancl, and Clinical Professor Marilynn Rothen (University of Washington). Dr. Mancl will serve as the project biostatistician.

Participants: Children 3-4 years old at enrollment. To be eligible a child will need to have at least one active dental caries lesion with dentin exposure (d_{2-3}). Children will be excluded if they are unable to cooperate with the clinical activities. Children will be examined and treated at baseline and 5 months and examined up at one year (± 1 mo). Parents will complete a demographic questionnaire (age and sex of child, parent rating of the health and teeth of gums of the child) which will also include satisfaction with treatment (based on Huebner et al., 2020) after the completion of the initial treatment at baseline.

If a child has an acute problem requiring a tooth extraction or a d_4 lesions involving the pulp, the child will be referred to Dr. Tania Padilla Caceres for treatment at no cost to the family. Families will receive a telephone number where they can contact the study coordinator.

Recruitment and Preventing Loss to Follow-up: The children will be recruited from five schools (Centro Educativo Inicial) in Puno, Peru. A consent form will be sent home by

the teacher to the parents in the child's school agenda and return the form to the School: 98% percent of consent forms are expected to be returned in this manner. If parents do not return the form, they will be approached at School when they pick up their child. Parents will give informed consent. All children in the School, irrespective of whether they are enrolled, will receive a t-shirt with the study logo and a tube of fluoridated toothpaste and a toothbrush at each visit after screening and initial treatment.

Initial/Baseline Examination: The exams will be conducted following National Institute of Dental and Craniofacial Research Early Childhood Caries Collaborative criteria (Warren et al. 2015) and will performed using a mouth mirror with artificial light. Neither dental explorers nor radiographs will be used. The teeth will be dry brushed and dried with cotton gauze before the exam. There will be three examiners. Ms. Rothen will serve as the gold standard examiner and will train and calibrate Dr. Tania Padilla Caceres and one additional local examiner. Examiners will participate in a exercise with 10 or more children who have both active and arrested lesions who are enrolled in the study. ICC is expected to be 70% or greater.

Intervention: All eligible teeth with enamel or dentin lesions (d_{1-3}) will be treated. Teeth will be dry brushed to remove debris. 1-2 drops 38% Silver fluoride gel (Advantage Silver Dental Arrest Gel, Elevate Oral Care, LLC, W Palm Beach FL) applied by trained dental personnel from a multi-use bottle with microbrush, agitated to ensure coverage, and then excess dabbed away with cotton. The treated teeth will then be covered with 2.5% NaF varnish (Fluorimax, Elevate Oral Care, LLC) applied by microbrush to mask the taste of the silver diamine fluoride and provide additional prevention benefit. Ms. Rothen will teach the clinical personnel the procedure for application of both the gel and varnish. Treatments will be at enrollment and 5-6 months.

Post Intervention Considerations: No restrictions on eating or drinking after treatment. The parents will contact Dr. Padilla Caceres to call if their child has any problem post treatment.

Outcome: Primary outcome will be whether the lesion is arrested (Nyvad et al. 1999, Chu et al. 2022). In larger lesions the call will be made based on the majority of the surface area of the lesion. Children will be examined by one of three examiners, who will have been calibrated in a separate exercise with 10 or more children who have both active and arrested lesions. Professor Padilla Caceres, Ms. Marilynn Rothen, and one other individual from the University will be the examiners. Each examiner will have an recoder to record the findings. Secondary outcomes will be the caries increment (d_{2-4}mfs) and the rate of new caries lesions at 6-month and 1-year follow-up. The exams will be conducted following National Institute of Dental and Craniofacial Research Early Childhood Caries Collaborative criteria (Warren et al. 2015) and will performed using a mouth mirror with artificial light. Neither dental explorers nor radiographs will be used.

Secondary Measure: A short parent questionnaire will be created in English based upon the work of Huebner et al., 2020 and then translated into Spanish and pretested. The

questionnaire will be put in the child's school agenda to be sent home for completion about two weeks after the initial treatment.

Data Collection and Quality Control: The data from the exams and treatment record will be recorded on paper forms and copied. Copies of the forms will be kept at the dental school in a locked file. Original forms will be carried to Seattle for transfer to a computer database. Similarly questionnaire data will be entered on paper. The database will be administered by the project biostatistician and password protected.

Sample Size: The sample size was determined to ensure estimates for the rate of caries lesion arrest at 5-month and 1-year follow-up have high precision, based a ½ width of a 95% confidence interval.

The caries arrest rate is expected to be as high as 50% by 6-months of follow-up and as high as 70% by the 1-year follow-up. In a prior study on caries arrest in preschool children (Milgrom et al 2018) the average caries arrest rate was 72% and the within child correlation between caries lesion arrest was 0.44. In a prior caries prevention trial for young Peruvian children (Chi, 2016) the mean number of carious surfaces (standard deviation) in 4-year-olds was 14 (9). In a randomized clinical trial of fluoride varnish in the Federated States of Micronesia the mean number of carious lesions (standard deviation) was 19 (17) in 4-year-olds and the within child correlation between new caries lesions was 0.29.

For the sample size determination, we have assumed on average of at least 10 treated caries surfaces on average per child with a coefficient of variation of 0.64 (9/14), a within-child correlation of 0.45 and a caries lesion arrest rate of 50% to 70%. Based on a sample size of 200 children precision to estimate the rate of caries arrest is at least ±6.3% (Table 1). To accommodate up to 15% attrition, 235 children will be enrolled.

Table. Precision to estimate rate of caries arrest based on 200 children[1]

Average number of treated caries lesion per child	Rate of caries arrest	Correlation between caries lesion arrest outcomes within a child	
		0.30	0.45
10	50%	±5.3%	±6.3%
	70%	±4.8%	±5.7%
20	50%	±5.1%	±6.1%
	70%	±4.7%	±5.6%

[1]Precision is based on ½ of a 95% confidence interval for the average caries lesion arrest rate and a design effect based on the average number of treated caries lesion per child of 10 to 20 surfaces with a coefficient of variation of 0.64 (9/14) and a within child correlation of 0.30 and 0.45 (Eldridge et al, 2006).

Data Analysis: The primary outcome will be caries lesion arrest and measured by the average proportion of treated surfaces with arrested lesions at 5-month and 1-year follow-up. Bias-corrected bootstrap 95% confidence intervals using 10,000 replications

will be computed for the average proportion of caries lesion arrest at 6-month and 1-year follow-up (Davison and Hinkley 2009; Canty and Ripley 2017).

Log-linear regression, implemented using generalized estimating equation (GEE) methods and robust standard errors, will be used as a confirmatory analysis, estimating the rate of caries lesion arrest at 6-month and 1-year follow-up (Hardin and Hilbe 2003). The outcome variable will be the number of arrested lesions (tooth-level outcome), and the number of treated surfaces will be accounted for by including the logarithm of the number of treated surfaces as an offset term in the log-linear regression model (Diggle et al 2002).

Secondary outcomes will be the caries increment ($d_{2\text{-}3}$mfs) and the rate of new caries lesions at 5-month and 1-year follow-up. The average caries increment and 95% confidence interval for the average will be computed at 5-month and 1-year follow-up. If the caries increment distribution is very skewed, the median and bias-corrected bootstrap 95% confidence interval for the median will be reported instead. Log-linear regression using GEE methods will be used to estimate the rate of new caries lesions at 5-month and 1-year follow-up. The unit of analysis will be the tooth and the outcome will be the number of new caries lesions per tooth. The logarithm of the surface risk time will be entered into the regression model as an offset.

Additional analyses will estimate caries lesion arrest and the rate of new caries lesions by participant characteristics (e.g., age and sex). All analyses will be based on the intention-to-treat principle. If the attrition rate by 1-year is >10%, either multiple imputation or methods for ignorable responses will be used to account for the missing data (Shafter 2005). In the case of non-ignorable non-response, we will use augmented inverse probability of censoring weighted estimating equations to perform a sensitivity analysis to examine how the estimated intervention effect varies over a range of plausible values for potential predictors of the attrition (Rotnitzky et al. 1998). A 95% confidence level and two-sided 5% significance level will be used for estimation and statistical inference. Statistical analyses will be performed with R (R Core Team 2020).

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