A Clinical Trial of Silver Diamine Fluoride to Arrest Early Childhood Caries in Young Children

NCT04054635

Study Protocol and Statistical Analysis Plan

15 April 2019

Purpose:

To investigate the effectiveness of using silver diamine fluoride (SDF) to arrest early childhood caries in very young children randomized to different application frequency regimens. We will also study potential oral microbiome changes in children receiving SDF treatment.

Hypotheses:

1. Two applications of SDF at different frequencies will yield similar arrest rates.

2. SDF will negatively influence the population of cariogenic bacteria in the oral microbiome.

Objectives (*primary objective, †secondary objectives):

1. Determine the effectiveness of various application regimens of SDF to arrest caries*;

2. Determine potential changes to the oral microbiome in young children†; and

3. Determine the impact on early childhood oral health related quality of life†.

Methods:

Design: We propose a RCT to study the use of SDF to arrest cavitated caries lesions in primary teeth at different application regimens. Regimen 1 will be two applications of SDF four months apart, which is the protocol frequency adopted by the Winnipeg Regional Health Authority's Clinical Guideline on SDF. This frequency was used in a pilot study. Regimen 2 will be two applications of SDF six months apart (American Dental Association's [ADA] recommendation). Regimen 3 will be two applications of SDF one month apart, which is proposed in the American Academy of Pediatric Dentistry's clinical practice guideline. The ADA recently indicated that SDF should be prioritized over 5% NaFV for nonrestorative management of cavitated lesions. Thus, we will not include a control group to receive fluoride varnish as this would now be considered unethical and substandard care. However, we will attempt to follow as a comparison group those children whose parents/caregivers do not consent to SDF to manage their child's caries and only choose 5% NaFV.

Arrest of caries lesions will be determined by assessing clinical hardness, colour change, and size of lesions at baseline, at second visit, and at the final study visit. Children will be recruited and we will perform block randomization by site in order to achieve equal proportions in each regimen by clinic site of recruitment. Study visits will occur at the Children's Hospital Research Institute of Manitoba (CHRIM) or at community-based dental clinics. Following informed consent the child's parent/caregiver will complete a short questionnaire (via interview) on general and dental health, oral hygiene, dietary intake of sugars, and family demographics along with the ECOHIS to assess OHRQL. SDF will be applied on the day of recruitment to cavitated lesions involving dentin followed by 5% NaFV. Depending on which frequency regimen children are randomized to, they will return for a second visit. During this second visit, caries lesions treated with SDF at baseline will be assessed to see if caries is arrested as determined through measures of hardness, colour change, and size. At this same visit a second application of SDF will be applied to these initially treated caries lesions followed by 5% NaFV. Children and parents will return for the third and final study visit according to the schedule of their randomized grouping. Parents/caregivers will complete a follow-up questionnaire similar to the

baseline tool. Caries lesions previously treated by SDF will be assessed for clinical hardness, colour change and size to determine if they have arrested.

Population: As ECC is age specific, participants will be < 72 months of age with active caries and their parents/caregivers. The majority will be recruited from community-based dental clinics in Winnipeg (i.e., Access Downtown, Mount Carmel Clinic, and SMILE Plus Children's Dental Clinic) or who are currently on a wait list for dental surgery under general anesthesia in Winnipeg. We found that these were ideal sites for our recently completed feasibility trial of SDF. We will restrict participation to children living in the Winnipeg region or within a one hour drive of Winnipeg to minimize the risk of loss-to-follow-up. Eligibility criteria are designed to select young children who have active caries, and thus are at an increased risk of morbidity from existing caries and onset of new caries.

Inclusion Criteria: 1) Child is < 72 months of age with ECC with active caries lesions; 2) Child has ≥ 1 primary tooth with caries that is eligible to receive SDF. Eligible primary teeth must: a) have soft cavitated caries lesions extending into dentin (ICDAS 5 or 6); b) the cavitated lesions must allow for direct application of SDF. Teeth that meet any of the PUFA criteria (i.e. spontaneous pain due to caries, pulp exposure, mobility, signs of pulpal infection such as abscess, fistula, or swelling) will be excluded. However, a child would still be eligible even if they have at least one tooth that meets PUFA criteria, but other eligible teeth with caries do not.

Exclusion Criteria: 1) Child is allergic or has sensitivity to silver or other heavy metal ions; 2) Child has hereditary generalized developmental defects of enamel (e.g., amelogenesis imperfecta, dentinogenesis imperfecta); 3) Child has severe medical problems that limit participation; 4) Child requires immediate rehabilitation under general anesthesia because of severe infection or pain; 5) Antibiotic use within the last 2 weeks (for the microbiome sub-study).

Sample and Justification of Sample Size: Sample size for this pilot study has been determined in discussion with Dr. Robert Tate (collaborator, Professor & Biostatistician). Our intent is to compare arrest rates between groups and to see whether the three different regimens will yield arrest rates within a range of what we will determine to be clinically acceptable. Based on our recent pilot feasibility study of SDF with 40 children (with 239 lesions) we reported an arrest rate of approximately 96% following two applications of SDF. Results from a recent systematic review state that 80% of lesions can arrest because of SDF. We believe that a range of arrest rates from 80% to 96% yield similar beneficial outcomes in the clinical setting. Based on our pilot study, 40 children had 239 lesions (average 6 lesions/child). With our pilot sample of 239 lesions, it is possible to estimate an arrest rate with a 95% confidence interval to be accurate within ± 6.5%. With 400 lesions anticipated in our proposed recruitment sample, the 95% confidence interval for the arrest rate would be ± 5.0%. We propose three SDF regimen groups and anticipate that each group will have 22 children anticipating an average of six lesions. This would mean 396 lesions would be followed in this study. We anticipate that with 400 lesions the percent of arrest will be within ± 5% if we have 22 children in each group. To deal with potential drop-outs and loss-to-follow-up of up to 20% we will over recruit by into each group and recruit 28 per group. We anticipate that we can successfully recruit 10 children each month.

Instrumentation and Outcome Measures: Baseline and follow-up visit questionnaires will be a modified versions of those used in our SDF pilot feasibility study (developed by Dr. Margherita Fontana [collaborator] in her SDF efficacy study.The questionnaire collects child and family

demographic information, oral hygiene and use of toothpaste, dietary habits (i.e., snack foods and drinks), consumption of fluoridated water, appearance of the teeth, and symptoms (e.g., pain). The tools also include sections for the parent/caregiver to complete with their child on how the child believes their teeth look and feel and how they rated their visit and SDF treatment.

The Early Childhood Oral Health Impact Scale (ECOHIS) will be used to assess changes in OHRQL from baseline to completion of study. ECOHIS is a validated tool for use with parents/caregivers of children < 72 months of age. It consists of 13 questions grouped into two sections: 1) child impact, and 2) family impact. The child impact section includes nine questions in four areas: 1) symptoms, 2) functions, 3) psychology, and 4) self-image and social interaction. The family impact component covers two areas: 1) parental distress and 2) family function. Each question is scored from 0 to 5 [0= never, 1= hardly ever, 2= occasionally, 3 = often, 4= very often, 5= don't know]. A total score for each child is calculated by summing up response codes. The ECOHIS will allow us to calculate and compare mean ECOHIS scores at each visit and between groups. Our team has experience with analyzing ECOHIS.

Clinical outcomes assessed will include the proportion of teeth arrested (i.e., "arrest rate" = total number teeth arrested / total number of teeth treated), the proportion of children with any arrested caries, associated morbidity (dental pain and, dental abscess assessed using the PUFA index), and proportion of children requiring dental surgery under GA. The PUFA index is a score of the consequences of severely decayed teeth with visible pulpal involvement (P/p), ulceration caused by dislocated tooth fragments (U/u), fistula (F/f) and abscess (A/a). We will also record dmft and dmfs scores for each child at baseline and at subsequent study visits. The dmft and dmfs scores are cumulative counts of the total number of primary teeth or surfaces decayed, missing due to, or filled because of caries.

Caries activity will be determined according to hardness and colour of the caries lesion. Hardness is the best indicator of dentinal tissue caries activity. We will assess the hardness of caries lesions by applying light force to the caries lesion with a ball ended probe and will classify the lesion into one of three hardness categories: 1) very soft; 2) medium; or 3) very hard. Hardness is associated with arrested caries. We will record these ratings of hardness of lesions on the Clinical Record Forms at the baseline visit, second visit, and third (final) clinical visit. The Clinical Record Forms will be those used in our pilot feasibility study of SDF. The colour of caries lesions will also be assessed. Dentin colour of each caries lesion will be classified as: 1) yellow; 2) brown; or 3) black. The colour black is associated with arrested caries. The size of caries lesions will also be measured (in mm) at the baseline, second, and third clinical visits.

Problems and adverse events will be recorded reported to the University of Manitoba's ethics office.

Implementation: Research staff will regularly visit community-based dental clinics in the Winnipeg region to recruit participants. Clinical dental staff at these sites will also be briefed on the study, its objectives, and eligibility criteria so that they can inform parents/caregivers of the study and make referrals to the research team. We will also recruit participants who are on the Children's Hospital dental clinic's wait list for pediatric dental surgery. Recruitment posters will also be placed in patient waiting areas of the various dental clinics and the study advertisements will also be distributed to all dentists in the Winnipeg region via the Manitoba Dental Association's weekly email distribution list. From our past study experiences we know that we can recruit at least 10 participants each month.

Our research staff will contact interested parents/caregivers and will inform them of the study objectives, eligibility criteria, and procedures. Children will undergo a dental screening by the principle investigator or a calibrated and trained dental examiner to determine whether children meet the clinical criteria for this study by having cavitated caries lesions involving dentin (i.e. ICDAS category 5 or 6). Since ECC is more common in disadvantaged populations, we will arrange for transportation (i.e., taxis) for participants. We also anticipate that some participants will be newcomers and will require interpreters. We will arrange for WRHA interpreters when needed. Visits will occur at the principle investigator's dental suite at CHRIM or at one of the community-based clinics.

Baseline visit: Following written informed consent, children will be randomly allocated into one of three groups using sealed envelopes to ensure random allocation. Parents/caregivers will complete the baseline questionnaire administered by interviewer. Children will undergo a dental examination (without x-rays) to record the number of teeth and tooth surfaces with caries meeting ICDAS 5 or 6 criteria and the specific tooth numbers. We will record the location, size, hardness, colour, and activity status of each eligible caries lesion. We will also assess the total number of primary teeth and tooth surfaces affected by caries (i.e., dmft and dmfs). We will also determine the PUFA index. SDF will then be applied with a microbrush for one minute to each cavitated lesion meeting the eligibility criteria followed by 5% NaFV.

Second visit: Depending on the regimen children will return 4 months (Regimen 1), 6 months (Regimen 2), or 1 month (Regimen 3) later for their first follow-up visit and second application of SDF. Parents/caregivers will complete the ECOHIS tool. Prior to the second application of SDF, caries lesions that received the first application of SDF will be assessed to determine if caries is arresting. Lesions will be assessed for colour change, size, and hardness. Clinical data will be recorded including dmft, dmfs, and PUFA scores will be recorded. Following the dental assessment of the lesions under investigation, SDF will be applied to these lesions for one minute followed by 5% NaFV.

Third visit: Depending on the regimen children will return 4 months (Regimen 1), 6 months (Regimen 2), or 1 month (Regimen 3) later for their final follow-up visit. Parents/caregivers will complete a follow-up questionnaire administered by interviewer. Caries lesions that were treated with applications of SDF will be assessed to see if caries is arrested. Caries lesions will be assessed for colour change, size, and clinical hardness. We will also record dmft, dmfs, and PUFA scores. Clinical data will be recorded on the Clinical Record Form.

Clinical data from baseline and each follow-up visit will be linked with questionnaire data. Data will be entered into a REDCap database and saved on the secure server at CHRIM.

Oral Microbiome Sub-Study: SDF may inactivate cariogenic bacteria in vitro. There was only one study that conducted RNA analysis of plaque in six children before and after treatment (3 receiving SDF and 3 placebo) reporting no changes in relative abundance of cariogenic bacteria. In that study, not only was sample size a major limitation, but the lead author is a director of Advantage Arrest^{TM}. Our proposal to assess 30 children would provide statistical power and help elucidate if SDF leads to changes in the oral bacteriome and mycobiome. This will provide novel insights into SDF's mechanism of action, whether antimicrobial, remineralization, or both. Ten children from each regimen will have plaque samples collected. Samples will be obtained at baseline (prior to SDF application), at the first follow-up visit (prior to SDF application), and at the final visit. Nucleic acid isolation from plaque samples will be done using the DNeasy

PowerSoil Kit (Qiagen). It allows the isolation of genomic DNA (gDNA) from fungi and Gram (+/-) bacteria, which will be used for downstream analyses. For the 16S rRNA (bacteriome) and ITS1 rRNA (mycobiome) amplicon sequencing, isolated gDNA will be used for PCR amplification of the V4 region of the bacterial 16S rRNA gene, and for PCR amplification of the fungal Internal Transcribe Spacer 1 (ITS1) rRNA gene. gDNA will be sequenced at Génome Québec using paired-end Illumina MiSeq PE250 sequencing. Data analysis will be performed in the Chelikani lab using established methods. Briefly, demultiplexed raw sequencing results will be filtered and clustered into operational taxonomic units (OTUs) and alpha and beta diversity analyses performed using QIIME2 (Quantitative Insights into Microbial Ecology) v. 2018.11. 16S sequences will be aligned and taxonomy assigned with the HOMD database. ITS1 sequences will be aligned and taxonomy assigned with the UNITE database.

Data Analysis:

This study will estimate the success of different SDF. Descriptive statistics will be used (e.g. frequencies, proportions, and means ± standard Deviations). The "arrest rate" (primary outcome) will be calculated for the second visit and again at the third and final visit. Bivariate analyses will assess changes in clinical measures and survey data from baseline to the follow-up. McNemar's test will be used to compare the arrest rate between the second and third clinical visits and to compare dichotomous data from the baseline questionnaire with that from the follow-up questionnaire within each regimen. Chi-squared analysis will compare arrest rates between the regimen groups. Paired t-test will be used to compare normally distributed interval data from the baseline questionnaire with that from the follow-up questionnaire within regimens (Mann-Whitney test if not normally distributed). We will rely on repeated measures analysis of variance to assess changes in ECOHIS scores and other continuous data over time (i.e. baseline vs. second visit vs. final study visit) within each regimen group and to assess differences between regimen groups. Although this is a pilot RCT, we will explore potential changes in the oral microbiome of those randomized to different regimens. This will provide insights into potential mechanisms of SDF action, whether it has antimicrobial activity and influences the oral microbiome composition. A p value ≤ 0.05 will be significant.

Ethics:

An application will be submitted to the University of Manitoba's Biomedical Research Ethics Board by the June 2019. Additional approvals are being sought from the WHRA and Mount Carmel Clinic. Considering some participants will be First Nations, we will notify Nanaandawewigamig before starting this RCT, although First Nations status will not be a covariate in our data analysis. Written informed consent will be obtained from parents or legal guardians of the child. The consent form will state that parents/caregivers are free to withdraw at any time, without any effect on the child's dental treatment at the dental clinic they attend. Patients of the PI are eligible to participate. However, he will not obtain consent from parents/caregivers of his own patients. At the end of this RCT we will offer SDF to parents to manage any new caries lesions that have developed on their child's other teeth or surfaces or those lesions not eligible in this RCT (i.e., ICDAS 3 and 4).

Knowledge Translation (KT):

Study outcomes will be disseminated at conferences and in publications. Dr. Robert J. Schroth is a Canadian Institute for Health Research Embedded Clinician Researcher and is integrated into

the Winnipeg Regional Health Authority and Shared Health, providing opportunity to share findings with stakeholders responsible for oral health policy and programs. We will also work with our knowledge users (Drs. James Taylor, Alyssa Hayes, and Khalida Hai-Santiago). We will rely on established networks to share our findings. Dr. Robert J. Schroth co-leads (and Dr. Michael E. K. Moffatt is a member of) the Healthy Smile Happy Child initiative, which promotes early childhood oral health in Manitoba. Telehealth and Zoom conferencing are used for these activities. Drs. Schroth and Moffatt are part of Nanaadawewigamig's Canadian Institutes for Health Research Partners for Engagement and Knowledge Exchange, which will disseminate evidence to communities. Dr. Schroth also leads the Oral Health and the Aboriginal Child Knowledge Transfer website where findings will be disseminated (> 35,500 page views). The Canadian Dental Association's Knowledge Networks will assist with knowledge translation to inform dental professionals, stakeholders, researchers, and the public. Dr. Schroth is strategically positioned as chair of the Candian Dental Association's Committee on Clinical and Scientific Affairs, which provides another avenue to disseminate findings to inform policy and clinical guidelines on SDF.

Significance and Future Directions:

SDF may be a simple and non-invasive agent to arrest caries in children. Before SDF can be implemented in dental public health programs and Indigenous communities it is important to study which application regimen is most effective and appropriate. CHRIM funding will provide essential information on the ability for SDF to arrest ECC and will inform a future CIHR application to conduct a scaled-up RCT of SDF with high-risk children, including those from Indigenous, newcomer, rural, and disadvantaged communities.