The Effect of Silver Diamine Fluoride on Oral Microbial Load

BY

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THESIS
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<th>Description</th>
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<tr>
<td>AAPD</td>
<td>American Academy of Pediatric Dentistry</td>
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<tr>
<td>APF</td>
<td>Acidulated phosphate fluoride</td>
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<tr>
<td>ASA</td>
<td>American Society of Anesthesiologists</td>
</tr>
<tr>
<td>ATP</td>
<td>Adenosine Tri-Phosphate</td>
</tr>
<tr>
<td>CAT</td>
<td>Caries risk assessment tool</td>
</tr>
<tr>
<td>DMFT</td>
<td>Decayed Missing and Filled Teeth</td>
</tr>
<tr>
<td>ECC</td>
<td>Early Childhood Caries</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>HIPAA</td>
<td>Health Insurance Portability and Accountability Act</td>
</tr>
<tr>
<td>IRB</td>
<td>Institutional Review Board</td>
</tr>
<tr>
<td>LAR</td>
<td>Legally Authorized Representative</td>
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<tr>
<td>MS</td>
<td>Mutans Streptococci</td>
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<tr>
<td>NHANES</td>
<td>National Health and Nutrition Examination Survey</td>
</tr>
<tr>
<td>OPRS</td>
<td>Office for the Protection of Research Subjects</td>
</tr>
<tr>
<td>PHI</td>
<td>Protected Health Information</td>
</tr>
<tr>
<td>PI</td>
<td>Principal Investigator</td>
</tr>
<tr>
<td>RLUs</td>
<td>Relative Light Units</td>
</tr>
<tr>
<td>SDF</td>
<td>Silver Diamine Fluoride</td>
</tr>
<tr>
<td>UIC</td>
<td>University of Illinois at Chicago</td>
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</table>
1. INTRODUCTION

1.1 Background Information

Caries is one of the most prevalent diseases in childhood, negatively impacting quality of life, particularly for children living in poverty. Many efforts have been focused on caries risk assessment and prevention strategies in children. High oral bacteria counts are associated with increased caries risk. An atraumatic restorative or medical approach for young children can slow the progression of caries so the arrested decayed tooth exfoliates prior to causing oral pain. Silver Diamine Fluoride (SDF) is a new and non-invasive caries-arresting and desensitizing agent. Several clinical trials and laboratory studies indicate that SDF has been proven to inhibit carious processes, aiding in the prevention of secondary caries, and reducing dental hypersensitivity. The ideal frequency of SDF application and its effect on the carious microbial level is unknown.

In the available literature, a statistically significant correlation has been reported between bioluminescence adenosine triphosphate (ATP) scores and overall oral bacterial counts, oral streptococci counts, and counts of Mutans Streptococci (MS). ATP bioluminescence is routinely used for the detection of bacterial contamination. ATP bioluminescence is a promising tool for quantifying caries risk in pediatric patients. In this study, bioluminescence technology is utilized to assess the effect of three month SDF ATP score of plaque bacteria. This can be a useful tool for patient education and disease prevention.
1.2 **Purpose of the Study**

This is a prospective, longitudinal pre- and post- intervention study that aims to evaluate the effectiveness of 38% SDF on oral microbial load in comparison to 5% sodium fluoride varnish (gold standard treatment) in pediatric patients with extensive caries.

The objectives of the study are:

- To evaluate and compare the numeric oral bacterial ATP score at initial and 3 month recall dental visits, between a control group receiving only 5 percent sodium fluoride varnish application and oral hygiene instructions vs. studied group receiving 38% SDF and oral hygiene instructions in children between 2 and 6 years of age.
- To assess and compare, between the two studied groups, a number of clinical variables including: visible plaque, regular tooth brushing, daily flossing, and dmft in pediatric patients receiving treatment.
- To establish whether 38% SDF is a more suitable alternative to 5% sodium fluoride varnish in reducing oral microbial load in pediatric patients not able to cooperate for dental treatment under conventional measures.

1.3 **Hypothesis of the Study**

The Null Hypothesis of the study is:

- There is no difference in the effectiveness of 38% SDF and 5% sodium fluoride varnish on reducing oral microbial load at three months follow up.
2. REVIEW OF LITERATURE

This section reviews early childhood caries, indications for the use of SDF and fluoride, as well as ATP bioluminescence testing to gain understanding of the clinical background of the gap in the literature and the need of the current study. Similar research trials aiming to find the antibacterial effect of SDF are identified and discussed.

2.1 Early Childhood Caries

Dental caries, or cavities, as it is colloquially known, is “a localized chemical dissolution of dental hard tissues that is caused by acidic by-products of the metabolic processes of the biofilm covering an affected tooth surface”. It has also been described as a diet-bacteria induced disease with relatively slow progression over time. The etiology of caries is multifactorial. Caries risk predictors lie in the oral microflora, diet, and host. Cariogenic plaque consists of highly organized colonies of cariogenic bacteria, especially MS, which metabolize the dietary carbohydrates into weak acids, responsible for the demineralization of the hard tooth structures and the advancement of the process.

Dental caries is a common chronic disease that causes pain and disability across all age groups. If left untreated, dental caries has an impact on risk of future caries, pain, infections, expensive emergency room visits and hospital admissions, delayed growth and development, and missed days from school and work. The American Academy of Pediatric Dentistry defines the disease of ECC as the presence of one or more decayed (noncavitated or cavitated lesions),
missing (due to caries), or filled tooth surfaces in any primary tooth in a child 71 months of age or younger. Treatment of decayed teeth in children can be expensive where general anesthesia (GA) may be necessary to ensure quality dental care for the young child.

The National Health and Nutrition Examination Survey (NHANES) is an ongoing survey of representative samples of the civilian, non-institutionalized U.S. population gathered information on persons aged ≥2 years. The most recent NHANES survey for the period 2015-2016 confirmed that caries levels remain prevalent in poor and near poor U.S. preschool children. Approximately 18% of children aged 2–5 years had experienced dental caries in primary teeth in 2015–2016 (Figure 1). Dental caries among children aged 6–11 was nearly 45%. Caries prevalence was highest for Hispanic youth (52%) compared with non-Hispanic black (44%), non-Hispanic Asian (43%), and non-Hispanic white children (39%) aged 2–19 (Figure 2).
Figure 1. Prevalence of total dental caries and untreated dental caries in primary or permanent teeth among youth aged 2-19 years, by age: United States, 2015-2016. Source: NCHS, National Health and Nutrition Examination Survey, 2015-2016

Figure 2. Prevalence of total dental caries and untreated dental caries in primary or permanent teeth among youth aged 2-19 years, by race and Hispanic origin: United States, 2015-2016. Source: NCHS, National Health and Nutrition Examination Survey, 2015-2016
2.2 **Oral Health Care for the Young Child**

Prevention of oral disease can be enhanced through the increased delivery of clinical and community preventive services. Professional dental care is essential in order to maintain oral health. The American Academy of Pediatric Dentistry (AAPD) advocates the importance establishing a dental home at the time of the eruption of the first tooth and no later than 12 months of age, and continue through adolescence and adulthood. At the comprehensive oral evaluation in the initial exam appointment, the oral health provider assesses the patient’s general health and growth, extra-oral and intra-oral health of the soft and hard tissue, oral hygiene and periodontal health, dental growth and development, caries risk assessment, and the behavior of the child. Additional tests such as radiographs, photographs and pulp vitality testing may be needed based on the intra- and extra-oral findings. In addition to the comprehensive examination, the patient typically receives a prophylaxis and topical fluoride treatment as well as anticipatory guidance. Anticipatory guidance topics include: oral hygiene, dietary habits, injury prevention, nonnutritive habits, and speech/language development. Caries risk assessment is a critical factor in developing a preventive plan tailored to the patient’s needs, optimizing protective factors such as fluoride exposure and oral hygiene, and minimizing causative factors such as cariogenic microbial burden and plaque accumulation. Brushing twice a day with fluoridated toothpaste and frequent fluoride varnish application may reduce the risk of the progression of a carious lesion or developing a new dental carious lesion.
The American Academy of Pediatric Dentistry (AAPD) endorses biannual (recall) visits to receive periodic oral examination, dental prophylaxis and topical fluoride application as a preventive method that benefits children with moderate risk for caries: 2.26% fluoride varnish (5% sodium fluoride varnish), 1.23% fluoride (APF) gel, a prescription-strength, home-use 0.5% fluoride gel or paste, or 0.09% fluoride mouth-rinse for patients 6 years or older. Only 2.26% fluoride varnish is recommended for children younger than 6 years and is more efficacious on primary teeth when applied at least twice a year.\textsuperscript{10,11} However for children who exhibit higher risk of developing caries, the AAPD recommends recall appointments at a frequency greater than every six months. This allows increased microbial monitoring, antimicrobial therapy reapplication, and professional fluoride therapy application. Other fluoride compounds, such as silver diamine fluoride, may be more effective than sodium fluoride for topical applications.

2.3 **Fluoride**

Fluoridated toothpaste is the most common form of fluoride delivery.\textsuperscript{2} Professionally applied fluoride (varnishes and gels) is effective in caries prevention, according to two published Cochrane reviews.\textsuperscript{12,13} Fluoride restores lost mineral content during the active caries process through mineralization and making the hard tissues more resistant to demineralization in future pH drops.\textsuperscript{14} Calcium fluoride deposited on a tooth surface is not readily soluble and can act as a fluoride reservoir. This lowers the critical pH value of demineralization from
approximately 5.5 to 4.5. Fluoride also inhibits plaque metabolism, changes plaque composition, affects plaque formation, and reduces plaque bacteria’s ability to produce acid from carbohydrates.\textsuperscript{15}

Fluoride affects bacterial metabolism through different mechanisms. It can act directly to inhibit enolase, a glycolytic enzyme. It can directly inhibit heme-based peroxidases, by binding to heme. Fluoride also enhances membrane permeability to protons, compromising the functioning of F-ATPases in exporting protons, thereby inducing cytoplasmic acidification and acid inhibition of glycolytic enzymes. Fluoride acts to reduce the acid tolerance of bacteria. It is most effective at acidic pH values. In the acidic conditions of cariogenic plaque, fluoride completely arrests glycolysis by intact cells of Streptococcus mutans.\textsuperscript{16}

2.4 **Silver Diamine Fluoride**

2.4.1 **History and Uses**

SDF is a novel caries-arresting and desensitizing agent that has been used in Japan since the 1970s. It has also been used to treat dental caries for many years in Argentina, Australia, Brazil, and China. Since the 1940s, silver compounds have been used for caries prevention, cavity sterilization, and dentin desensitizer.\textsuperscript{2} Since 1969, SDF has been used to arrest caries of primary teeth, prevent pit and fissure caries of erupting permanent molars, prevent root caries in elderly patients, treat tooth hypersensitivity, and to sterilize infected root canals.\textsuperscript{5} The Food and Drug Administration (FDA) cleared SDF for the United
States market in August 2014 to treat dental sensitivity, and it has been available for off-label use to arrest and prevent dental caries since April 2015.\textsuperscript{14}

The safe, simple, non-invasive nature of SDF application, along with its clinical efficacy, have garnered it significant attention in dentistry, especially among the pediatric caregiver population. Topical application of SDF has been shown to be effective in arresting active caries in primary teeth. The AAPD supports the use of 38\% SDF for the arrest of cavitated caries lesions in primary teeth.\textsuperscript{17} Studies have shown that SDF has a better caries inhibitory effect than no treatment, and a better caries arresting effect than fluoride varnish.\textsuperscript{18} The ideal frequency of SDF application is unknown. Suggestions for application frequency have ranged from annual application, twice per year application, and three times per year application.\textsuperscript{19} The effectiveness of SDF has been shown to decrease over time, while another study has shown that SDF effectiveness is increased in six month applications compared to annual applications.\textsuperscript{20-21} SDF comes in different concentrations, though it was shown that 38\% SDF (which contains 44,800 p.p.m. fluoride)\textsuperscript{5} showed a more beneficial effect than 12\% SDF when applied semi-annually rather than annually. However, good oral hygiene and absence of plaque on lesions are critical for successful caries arrest by SDF.\textsuperscript{22}

There has been much debate about the efficacy of SDF in arresting dental caries. However, there have been several clinical trials and laboratory studies indicating that SDF has been proven to inhibit carious processes, aiding in the prevention of secondary caries, and reducing dental hypersensitivity.
2.4.2 **Mechanism**

SDF is composed of three major components: the silver acts as an antimicrobial, the fluoride promotes remineralization, and the ammonia stabilizes high concentrations in solution.\(^{23}\) The exact role and actions of silver compounds is unclear, but there are several different proposed mechanisms of action. SDF reduces the solubility of enamel against chemical acid challenge, which facilitates enamel remineralization.\(^{19}\) SDF also inhibits demineralization, conserves collagen from degradation, increases microhardness of dentine lesions, and has an antibacterial effect on oral biofilms.\(^2\)

There are three steps resulting from the application of SDF to teeth: the formation of calcium fluoride and silver phosphate, the subsequent dissociation of calcium and fluoride, and the formation of fluorapatite.\(^{24}\) The alkaline nature of SDF along with calcium fluoride, which is formed upon reaction with tooth tissue, makes tooth tissue less soluble allowing it to serve as a fluoride reservoir in future caries challenge.\(^{25}\)

When SDF is applied to a decayed surface, a squamous layer of silver-protein conjugates forms, increasing resistance to acid dissolution and enzymatic digestion. Hydroxyapatite and fluorapatite form on the exposed organic matrix, increasing the hardness and mineral density of the lesion. Proteins responsible for breaking down the exposed dentin organic matrix (matrix metalloproteinases, cathepsins, and bacterial collagenases) are inhibited by SDF.\(^{23}\) SDF promotes calcium absorption and inhibits calcium dissolution from enamel.\(^5\)
2.4.3 Antibacterial Activity

SDF is a bactericidal agent. The silver ions in SDF have antibacterial action against cariogenic strains of *S. mutans* and *Actinomyces naeslundii*, which are regarded as major etiological agents of dental caries. Silver ions react with the phosphorus components and sulfur-containing proteins of the bacterial cell wall, causing destruction of the outer bacterial cell membrane and extrusion of the cytoplasm. Silver ions also react with intra-cytoplasmic sulfur-containing enzymes, which inhibits bacterial metabolism. Silver ions also bind with phosphorus-containing DNA molecules. This antibacterial activity (destruction of cell wall structure, denaturation of cytoplasmic enzyme, and inhibition of DNA replication) inhibits the colonization of bacteria on tooth surfaces, also known as the biofilm. SDF has sustained antimicrobial effects in addition to an immediate one. Upon re-acidification by new bacteria, the deposited silver in dead bacteria acts as a reservoir and is re-activated to kill the new bacteria. Dentin surfaces treated with SDF had significantly less growth of *S. mutans* and *A. naeslundii* than those without SDF treatment. In a 2017 study by Horst et al, SDF application resulted in no changes in the relative abundance of bacteria associated with dental caries, suggesting that the microbial mechanism of caries arrest by SDF is indiscriminate inhibition of all bacteria in a caries lesion, rather than particularly cariogenic bacteria.
2.4.4 Safety and Side Effects

The significant adverse effect of SDF is the black staining of carious tissue resulting from the formation of metallic silver from silver compounds. The most frequently reported perceived barrier to the use of SDF was the concern of parental acceptance due to the staining, though the level of parental acceptance of staining was higher for posterior teeth than for anterior teeth. The safety concern of excessive fluoride exposure is insignificant. A study found that 2.37 mg SDF was the largest applied dose for 3 decayed primary teeth, which is far below the acute toxic dose by more than 400 times. The risk of developing minor side effects, such as gum swelling and oral pain, after SDF application is very low.

2.5 Adenosine Triphosphate (ATP) Bioluminescence

ATP bioluminescence is a phenomenon related to the production and emission of light by a living organism that utilizes ATP. It is routinely used for the detection of bacterial contamination. ATP bioluminescence relies on the luciferase-catalyzed ATP-dependent oxidation of luciferin. Luciferin and luciferase produce light when activated by ATP, a metabolic by-product of living bacteria. ATP can then be quantified using a bioluminometer which measures the light output, in relative light units (RLUs). This allows the identification of oral bacterial load and biofilm activity levels. The specific reaction is as follows:

$$ATP + \text{ luciferin} + O_2 \xrightarrow{\text{luciferase}} {\text{AMP + PP}_i + \text{oxyluciferin} + \text{CO}_2 + \text{light}}$$
ATP-driven bioluminescence derived from oral specimens has a strong statistical association with bacterial number in plaque and saliva specimens quantified using standard microbiological plating methods. These include numbers for oral streptococci and S. mutans, the pathogen most responsible for dental caries. Bioluminescence assays measuring ATP are highly correlated with plaque mass and bacterial cell number found in dental plaque. ATP-driven bioluminescence can be used translationally to determine the efficacy of interventional therapies. The hand-held CariScreen device is a ATP meter designed for use in dental clinics (Figure 3). It is simple to use and predictive of total numbers of oral bacteria in dental specimens.³

Figure 3. Handheld CariScreen Device
3. MATERIALS AND METHODS

3.1 Overview

Institutional Review Board (IRB) approval was attained for this study from UIC (Appendix A). Participants for this study were recruited from the pool of patients attending the Pediatric Dentistry Department of the College of Dentistry (COD), University of Illinois at Chicago (UIC). Inclusion and exclusion criteria were specified separately for the selected patients. Informed consent from the parents/guardians were obtained and signed. By design, the study is a prospective, longitudinal pre- and post-intervention study utilizing parental preference for participant allocation into either the SDF group or fluoride group. A total of 50 participants (25 in each group) were recruited, with 18 lost to follow up, making for a total of 32 patients with follow up. The dosage of SDF did not approach the 5 mg/kg probable toxic dose for fluoride or the 380 mg/kg lethal dose for silver.30 One designated operator, the PI, conducted all SDF applications, fluoride applications, and oral swabs to all subjects. The PI recorded the patients’ tooth brushing habits, flossing habits, visible plaque, and dmft. The PI underwent training with respect to the use of CariScreen. All data was coded and captured on specifically designed for the purposes of the study evaluation forms. The data, gathered through all study forms was transferred into Microsoft® Excel 2016 and the statistical analysis was carried out with IBM SPSS Statistics.
3.2 Study Site, Participants and Enrollment Process

3.2.1 Study Site

This study was conducted at the UIC, COD, Pediatric Post-Graduate Dental Clinic. The site selection was based on the high volume of patients that are treated under GA and would benefit from interim therapy during the wait for GA.

3.2.2 Operator

One designated and trained operator, a pediatric dental resident, administered all oral swabs, SDF applications, and fluoride applications for the purposes of this study. The training consisted of close review of the manufacturer guide for swabbing and application techniques, and studying the step-by-step procedure guide.

3.2.3 Study Subjects

Study subjects were recruited from the UIC Post-graduate Pediatric Dental Clinic. Subjects were pre-screened by the PI through the axiUm® electronic health record system, screened through a comprehensive oral examination, and selected based on need for restorative treatment under general anesthesia. Inclusion and exclusion criteria were specified for the purposes of this study. The target number for the study sample size was 50 subjects, to account for anticipated dropout.
3.2.4 *Inclusion Criteria*

The inclusion criteria for the participants are summarized in Table 1 and were as follows:

1) Males and females, between the ages of 2 and 6 years old. The selected age group reflects the majority of patients with fully formed primary dentition and planned to receive treatment under general anesthesia at UIC.

2) In accordance to the widely recognized health status classification of the American Society of Anesthesiology (ASA), the participants were categorized as ASA I (completely healthy without any physical or mental illness) for inclusion in this trial.

3) Subjects were chosen from those planned for comprehensive dental care under GA. This decision was made based off of amount of restorative needs indicated, and uncooperative behavior for conventional dental treatment without advanced behavior management modalities. The evaluation of the patient compliance was based on the Frankl Behavior Rating Scale. Patients who demonstrated Frankl scores 1 or 2 (uncooperative) were included in the study. The Frankl rating was determined at the initial examination or prior operative treatment.

4) Subjects were chosen from those known to be cooperative for obtaining a swab sample as part of the ATP meter test.
5) Subjects were chosen from those known to be cooperative to allow SDF or fluoride application.

6) Subjects were not taking or did not have any antibiotic medication within 10 days of data collection.

7) Subjects did not have fixed orthodontic or any other oral appliances.

8) English speaking literacy of the parent/guardian and the patient was required. The study documentation, including the combined parental permission and informational form, were available only in English language.

3.2.5 **Exclusion Criteria:**

The list of the exclusion criteria for this study included:

1) Children younger than 2 years of age and older than 6 years of age were excluded from the study, as they may not be ideal candidates for general anesthesia.

2) Patients with medical status categorized as ASA II to VI. Patients with significant medical history are excluded from study enrollment as the priority of their medical condition may limit their availability for participation.

3) Patients presenting with an adult other than the parent or legal guardian.

4) Patients with orthodontic or other oral appliances.

5) Patients too uncooperative to obtain swab sample as part of the ATP meter test.
6) Patients taking or have had an antibiotic medication in the past 10 days.

7) Patients allergic to silver.

8) Patients with history of ulcerative gingivitis or stomatitis (to prevent reversible short-term irritation)

9) Non-English-speaking parents/guardians and patients as they cannot adequately understand research study materials and consent forms.

**Table I: Summary of Inclusion and Exclusion Criteria**

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
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<tbody>
<tr>
<td>Patient</td>
<td>Patient</td>
</tr>
<tr>
<td>• Medically Fit (ASA* I)</td>
<td>• Medically Compromised (ASA*II to VI)</td>
</tr>
<tr>
<td>• Age range: 2 to 6 years of age</td>
<td>• Younger than 2 or older than 6 years of age</td>
</tr>
<tr>
<td>• Cooperative for SDF/fluoride application and oral swab</td>
<td>• Uncooperative for SDF/fluoride application and oral swab</td>
</tr>
<tr>
<td>• Obtained informed consent</td>
<td>• Informed consent not obtained</td>
</tr>
<tr>
<td>• English literacy</td>
<td>• Non-English speakers</td>
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<tr>
<td></td>
<td>• Silver allergy</td>
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<tr>
<td></td>
<td>• Ulcerative gingivitis or stomatitis</td>
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<td></td>
<td>• Antibiotic medication in the last 10 days</td>
</tr>
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<td></td>
<td>• Orthodontic appliance</td>
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*American Society of Anesthesiologists (ASA)*

3.3 **Subject Enrollment**

Study participants were selected from the pool of patients attending the Pediatric Dentistry Department of the COD at UIC. The study aimed to enroll 30 subjects (to achieve a power of 96%), but recruit 50 subjects in anticipation of participant dropout. The PI reviewed the daily schedule of the PG Pediatric
Dental Clinic on the electronic health-record (EHR) system at UIC (axiUm) and accessed the past notes of the booked patients to search for potential study participants according to the specified inclusion criteria. Thus, a list of potential participants with their EHR patient numbers was generated.

The standard of care delivered for every new patient at the UIC college of Dentistry, Pediatric Dentistry postgraduate clinic includes the following during the initial visit: the assigned Pediatric Dentistry Resident provider will perform a comprehensive dental exam, complete medical and dental history, caries risk assessment, and extra-oral and intra-oral exam. The caries-risk assessment tool (CAT) is a practical tool that was developed by the American Academy of Pediatric Dentists, and assists in assessing the level of risk for caries. To use the CAT, the resident gathers information regarding oral hygiene practices, feeding practices, fluoride exposure, dental anatomy, and primary and secondary etiology for periodontal disease. Anticipatory guidance is discussed with the parent including oral hygiene instructions to the parent and patient on proper brushing and flossing techniques. Thereafter and during that same initial visit, the Pediatric Dentistry Resident will take indicated intraoral radiographs as outlined by the AAPD guidelines if the patient cooperated. Based on the intraoral findings, radiograph interpretation, and the child’s cooperation, the Pediatric Dentistry Resident developed the comprehensive treatment plan and recommended to the parent the behavior management techniques indicated to deliver quality dental care: non-pharmacological behavior technique (i.e. tell-show-do, modeling, distraction) vs. pharmacological behavior technique (nitrous
oxide, moderate sedation, or general anesthesia). Afterwards, the patient will receive a dental prophylaxis as well as a 5% topical sodium fluoride varnish application. All of the above procedures are typically covered by dental insurances companies and plans. In addition to the above procedure completed at the initial visit, the resident will recommend SDF application to the parents of patients who were determined to be treated under general anesthesia and with visible carious lesions to help arrest dental caries and avoid the carious lesions from becoming larger over the course of waiting for the dental treatment under GA, which may result in dental pain or dental infection if left without treatment.

The AAPD recommends 3 month recall dental visits for patients with high caries risk vs. 6 month recall dental visits for patients with low and moderate recall visits. Young and medically compromised patients with extensive dental needs who lack cooperation will be scheduled to be treated under general anesthesia and considered to be high risk for dental caries due to their age, medical condition and/or the extent of their dental caries. The current waiting time for a patient at the Postdoctoral clinic to receive comprehensive dental care under general anesthesia is approximately one year. Patients treatment planned to receive their comprehensive dental care under GA are added to a waitlist and tracked daily by the general anesthesia coordinator staff member.

Study-eligible patients and their parent/guardians were approached by the PI upon completion of their comprehensive oral examination, but prior to their dental prophylaxis and fluoride application. A brief verbal description of the study and a parental permission form was given to them. The form offered detailed
information on the SDF used in the study and a clear explanation of all advantages and disadvantages of the proposed treatment. It also provided a description of the study participation process and associated risks and benefits. Those patients and parents/guardians that were interested in research participation were asked to complete and sign the consent (parental permission, Appendix D) form of the study. Time for consideration before enrollment was provided within the limit of the dental appointment duration and was no less than 30 minutes. The parent/guardian then signed the Study Parental Permission Form in order to document their agreement with the terms and conditions of the study.

Patients who did not meet the study's inclusion criteria or for whom an informed parental permission (consent) could not have been obtained were not enrolled in the study and were advised to continue their dental care as previously planned.

With regard to reimbursement from dental insurance companies the American Dental Association (ADA) has established a set of standardized coding for dental procedures. The SDF application is a dental procedure that many dental insurances do not typically cover and has an associated cost of $41 that the parents need to pay if they are interested in receiving the SDF application. Some parents opt out of the SDF application, possibly due to the out of pocket cost associated with it. Those opting in to the SDF application received the follow up application at no additional expense. None of the subjects received any
financial incentives and the cost of the dental treatment plan remained the same regardless of participation in the study.

All study patients were placed on three month recall appointments. During the 3 month recall appointment, the Pediatric Dentistry Resident repeated the steps done at the initial exam: update the medical and dental history, assess the patient for caries, complete a comprehensive oral examination, take radiographs if indicated, give the anticipatory guidance including oral hygiene instructions, and apply SDF or 5% sodium fluoride varnish.

3.4 Armamentarium

Delivery of SDF required 38% SDF, microbrush, cotton gauze, and petroleum jelly. Delivery of fluoride required 5% sodium fluoride varnish, cotton gauze, and brush applicator. The ATP bioluminescence swab requires the CariScreen meter. Most of the supplies are available through many manufacturers. The specific manufacturers listed below have been chosen based on availability in the Pediatric Dental Department, UIC.

3.4.1 SDF

Elevate® is the manufacturer of Advantage Arrest® which is 38% SDF. SDF is indicated as a desensitizing agent, and off label as a caries arresting agent. SDF can safely be used in children without a silver allergy. The median lethal dose of silver is 380 mg/kg.
3.4.2  **Fluoride**

The manufacturer of Vanish®, which is 5% sodium fluoride varnish (2.26% fluoride), is 3M®. The manufacturer claims indications for use as a desensitizing agent, and off label as a remineralizing agent. Fluoride can safely be used for children. The probable toxic dose is 5 mg/kg.

3.4.3  **ATP Bioluminescence**

The CariScreen protocol involves carefully swabbing the mid-lingual surface of the lower anterior teeth. One firm swipe is required, without contact from the gingiva or any soft tissue. The swab is placed back in its tube, and the snap valve is broken by bending the bulb forward and backward. The bulb must then be squeezed to expel all liquid down the swab shaft. The tube is gently agitated for 5-10 seconds prior to inserting the swab into the CariScreen Meter, which will provide the result in RLUs from 1-9999 (Figure 4).

![ATP Bioluminescence Swab Procedure](image)

*Figure 4. Step-by-step procedure of ATP bioluminescence swab*

3.5  **Procedure**

Prior to completing the dental prophylaxis, the PI carried out the ATP bioluminescence swab test as outlined by the CariScreen collection protocol.
ATP scores were determined immediately after that swab was collected and documented in the data excel sheet. Thereafter, the Pediatric Dentistry Resident completed the dental prophylaxis and applied the SDF on the dental carious lesions of patients receiving the SDF applications. Patients not receiving SDF applications had only the 5% sodium fluoride varnish applied to their dentition. Oral hygiene and dietary instructions were consistent with AAPD recommendations. Standardized oral hygiene instructions included: twice daily parental brushing of child’s teeth with fluoridated toothpaste, and daily flossing. Dietary advice included: drinking tap water and milk during the day, no milk or sugar sweetened beverages at night, and limiting juice to a daily intake of 4-6 ounces.

Information was recorded into an Excel file (see Figure 5) at the initial exam and at three month follow up:

<table>
<thead>
<tr>
<th>Subject ID#</th>
<th>SDF or Fluoride</th>
<th>ATP bioluminescence score</th>
<th>Ethnicity</th>
<th>Sex</th>
<th>Age</th>
<th>Tooth brushing</th>
<th>Floss</th>
<th>Plaque</th>
</tr>
</thead>
<tbody>
<tr>
<td>@ Initial</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>@3 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>@ Initial</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>@3 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>@ Initial</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>@3 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 5. Data Capture Form
At the three month recall exam appointment, each participating parent/patient was given a copy of the original consent/permission, and study procedures were briefly reviewed. The parent was reminded of their participation in the study.

If the child became eligible for general anesthesia treatment prior to research completion (six months), the child would be excluded from the remaining research procedures in order to receive their definitive treatment. This did not occur during the duration of the study.

The investigator who collected the data is a current dental provider at the UIC, College of Dentistry Post-doctoral pediatric clinic and has access to the patients’ electronic health records (axiUm) and is IRB trained for this study. The investigator was trained prior to the start of the study. The training included studying the CariScreen ATP Meter manufacturer’s instructions and watching official video tutorials on the use of the device.

### 3.6 Chairside Steps of SDF Application

1. Visible plaque removed prior to SDF application
2. Petroleum jelly applied with a cotton applicator to adjacent gingival to prevent transient staining.
3. Teeth dried with air syringe or cotton gauze, whichever was feasible
4. Microbrush dipped into SDF drop until saturated
5. Microbrush applied to carious lesions and allowed to be absorbed.
3.7 **Chairside Steps of Fluoride Application**

1. Visible plaque removed prior to fluoride application
2. Teeth dried with cotton gauze
3. Fluoride varnish applied using a brush applicator

3.8 **Statistical Analysis**

Data gathered through all study forms were transferred into Microsoft Excel Spreadsheet (*Microsoft Inc., Redmond, WA, USA*). The data file was stored on a password-protected computer. The Excel data file was then transferred to the IBM SPSS statistical software program for statistical analysis. All data were assigned a numerical value in order to complete statistical analysis.

A prospective power analysis was carried out using numeric results for the Two-Sample T-Test allowing unequal variance. According to the power calculation, group sample sizes of 15 and 15 achieved 96% power to reject the null hypothesis of equal means.

The data analysis consisted of univariate descriptive statistics including frequency, mean, median, and standard deviation to describe demographic information. Bivariate statistics including independent t-test and Mann Whitney-U were used to analyze ATP bioluminescence scores. A p-value of <0.05 was used to determine statistical significance for the Mann Whitney-U and t-tests.
3.9 **Indications, risks, and benefits**

This study imposed minimum risk to participants and there were no anticipated problems or adverse reactions. The research had these mild risks: the discomfort of swabbing the child’s teeth for the ATP bioluminescence, the metallic/bitter taste of SDF, and the risk of loss of privacy of protected health information by including that information in a research project. All patients received the standard of care: comprehensive exams, caries risk assessment, and anticipatory guidance including oral hygiene instructions and diet counseling as well as fluoride application.

The SDF product was used off label as a caries-arresting agent, but it has been shown to be effective in arresting active caries in primary teeth. The maximum of 0.05 ml per patient per session was applied using an applicator on the teeth, following the manufacturer’s instruction. It benefitted those patients placed on the wait list to be treated under general anesthesia given the extended wait time to be treated.

The benefits of the study are mostly to the increase of general knowledge, helping us better understand whether SDF application interventions or topical fluoride application are helpful, feasible, and more important in reducing the levels of strep mutans, and, subsequently, the child’s risk of caries. To the best of our knowledge, the proposed study design is unique and has not been utilized in past research.
4. RESULTS

4.1 Number of Subjects

The data collection period was approximately 6 months. At the end of data collection, a total of 50 subjects were recruited to participate in the study, 32 subjects returned for follow up, and 18 subjects were lost to follow up. 17 subjects received SDF and 15 subjects received fluoride. Only one subject had not previously been to a dentist, while the remaining 31 subjects had been to a dentist and were referred for behavior. They had no history of any dental treatment. No adverse events were recorded.

4.2 Demographic Characteristics of Subjects

Table II summarizes the demographic characteristics of the study participants. The average age of the subjects was 3.76 years old for the SDF group and 3.87 years old for the fluoride group. The average age of all subjects was 3.81 years old, with an even age distribution. 9% of subjects were 2 years old, 25% were 3 years old, 47% were 4 years old, 13% were 5 years old, and 6% were 6 years old. The SDF treatment group had 12 male and 5 female subjects. The fluoride treatment group had 7 male and 8 female subjects. Total number of male and female participants was 59.4% and 40.6% respectively. Reported race information for all subjects in descending order is Hispanic (43.8%), Caucasian (28.1%), African American (25%), and Asian (3.1%). There was no statistical significance in age, gender, or race as p>0.05 for all demographic characteristics between SDF and fluoride groups.
TABLE II: SUBJECT DEMOGRAPHICS

<table>
<thead>
<tr>
<th></th>
<th>SDF n=17</th>
<th>SEM</th>
<th>Fluoride n=15</th>
<th>SD</th>
<th>Total N=32</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (mean in years)</strong></td>
<td>3.76</td>
<td>0.24</td>
<td>3.87</td>
<td>.27</td>
<td>3.81</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>12 (71%)</td>
<td></td>
<td>M=7 (47%)</td>
<td></td>
<td>M=19 (59%)</td>
</tr>
<tr>
<td>F</td>
<td>5 (29%)</td>
<td></td>
<td>F=8 (53%)</td>
<td></td>
<td>F=13 (41%)</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>7 (41%)</td>
<td></td>
<td>Hispanic=7 (47%)</td>
<td></td>
<td>Hispanic=14 (44%)</td>
</tr>
<tr>
<td>Caucasian</td>
<td>7 (41%)</td>
<td></td>
<td>Caucasian=7 (41%)</td>
<td></td>
<td>Caucasian=9 (28%)</td>
</tr>
<tr>
<td>African American</td>
<td>3 (18%)</td>
<td></td>
<td>African American=5 (33%)</td>
<td></td>
<td>African American=8 (25%)</td>
</tr>
<tr>
<td>Asian</td>
<td>1 (7%)</td>
<td></td>
<td>Asian=1 (7%)</td>
<td></td>
<td>Asian=1 (3%)</td>
</tr>
</tbody>
</table>

4.3 ATP Bioluminescence Scores

The mean initial ATP bioluminescence score was 8812 (standard deviation = 861). The mean recall ATP bioluminescence score was 7385 (standard deviation = 2237).

For the SDF group, the mean initial ATP bioluminescence score was 8780 (standard deviation = 1019), ranging from 6327 to 9862. The mean recall ATP bioluminescence score was 6398 (standard deviation = 1857), ranging from 2780 to 8927.

For the fluoride group, the mean initial ATP bioluminescence score was 8850 (standard deviation = 675), ranging from 7756 to 9746. The mean recall ATP bioluminescence score was 8505 (standard deviation = 2147), ranging from 2221 to 9907.
According to independent samples t-test, among both groups, the initial ATP bioluminescence score was lower by 70 RLUs in the SDF group. This was not found to be statistically significant (p = 0.82, t = -0.225, df = 30).

According to independent samples t-test, among both groups, the recall ATP bioluminescence score was lower by 2107 RLUs in the SDF group. This was found to be statistically significant (p = 0.01, t = -2.98, df = 30).

TABLE III: MEAN ATP BIOLUMINESCENCE SCORES

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Initial n=17</th>
<th>SD</th>
<th>Recall n=15</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>8812</td>
<td>861</td>
<td>7385</td>
<td>2237</td>
</tr>
<tr>
<td>SDF</td>
<td>8780</td>
<td>1019</td>
<td>6398</td>
<td>1857</td>
</tr>
<tr>
<td>Minimum</td>
<td>6327</td>
<td>9862</td>
<td>2780</td>
<td>8927</td>
</tr>
<tr>
<td>Maximum</td>
<td>8850</td>
<td>675</td>
<td>8505</td>
<td>1147</td>
</tr>
</tbody>
</table>

According to independent samples t-test, among both groups, the initial ATP bioluminescence score was lower by 70 RLUs in the SDF group. This was not found to be statistically significant (p = 0.82, t = -0.225, df = 30).

According to independent samples t-test, among both groups, the recall ATP bioluminescence score was lower by 2107 RLUs in the SDF group. This was found to be statistically significant (p = 0.01, t = -2.98, df = 30).

TABLE IV: MEAN DIFFERENCE OF ATP BIOLUMINESCENCE SCORES BETWEEN TREATMENT GROUPS

<table>
<thead>
<tr>
<th>ATP Bioluminescence Scores</th>
<th>Mean difference</th>
<th>t</th>
<th>df</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial</td>
<td>-70</td>
<td>-0.23</td>
<td>30</td>
<td>0.82</td>
</tr>
<tr>
<td>Recall</td>
<td>-2107</td>
<td>-2.98</td>
<td>30</td>
<td>0.01</td>
</tr>
</tbody>
</table>
At recall visit, treatment was significantly correlated with ATP bioluminescence score (p = 0.00). The $R^2$ value was 0.39, which means that knowing the treatment (SDF or fluoride) predicts 39% of the variability of the recall ATP bioluminescence score.

**TABLE V: CORRELATION OF RECALL ATP BIOLUMINESCENCE SCORES**

<table>
<thead>
<tr>
<th>Recall ATP Bioluminescence Scores</th>
<th>R</th>
<th>$R^2$</th>
<th>df</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment Group</td>
<td>0.62</td>
<td>0.39</td>
<td>30</td>
<td>0.00</td>
</tr>
<tr>
<td>Plaque at Recall</td>
<td>0.37</td>
<td>0.13</td>
<td>30</td>
<td>0.04</td>
</tr>
</tbody>
</table>

There was no statistically significant difference among both treatment groups in regards to the remaining variables: regular tooth brushing, dmft, and visible plaque.

4.4 **Oral Hygiene**

At recall visit, visible plaque was directly correlated with ATP bioluminescence score (p = 0.04) (Table IV). The $R^2$ value was 0.13, which means that presence of plaque predicts 13% of the variability of the recall ATP bioluminescence score.

Presence or absence of plaque, along with medicament selection, had significant effects on the recall ATP bioluminescence score. However, treatment
selection (Beta = -0.51) had a larger effect than plaque (Beta = -0.40) on the recall ATP bioluminescence score.

**TABLE VI: EFFECT ON CHANGE OF ATP BIOLUMINESCENCE SCORES BY PLAQUE AT RECALL AND TREATMENT GROUP**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Beta</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment Group</td>
<td>-0.4</td>
<td>-3.52</td>
<td>0.00</td>
</tr>
<tr>
<td>Plaque at Recall</td>
<td>-0.51</td>
<td>-2.66</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Within the SDF group, the reduction of ATP score was not correlated with the presence of plaque (Table VI). Within the fluoride group, the reduction of ATP score was inversely related to the presence of plaque (p = 0.04).

**TABLE VII: CORRELATION OF CHANGE OF ATP BIOLUMINESCENCE SCORES AND PLAQUE AT RECALL WITHIN EACH TREATMENT GROUP**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>R (correlation with plaque)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>SDF</td>
<td>-0.38</td>
<td>0.13</td>
</tr>
<tr>
<td>Fluoride</td>
<td>-0.54</td>
<td>0.04</td>
</tr>
</tbody>
</table>
At initial visit, four subjects did not have visible plaque, while 28 subjects had visible plaque. At recall visit, 10 subjects did not have visible plaque, and 22 subjects had visible plaque (Table VII). At initial visit, 28 subjects did not regularly brush with fluoridated toothpaste, and four subjects regularly brushed with fluoridated toothpaste. At recall visit, five subjects did not regularly brush with fluoridated toothpaste, and 27 subjects regularly brushed with fluoridated toothpaste. Tooth brushing, at both initial and recall visits, was not correlated with either treatment group.

### TABLE VIII: ORAL HYGIENE INDICATORS

<table>
<thead>
<tr>
<th>Oral Hygiene Indicators</th>
<th>Initial</th>
<th>Recall</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>SDF</td>
</tr>
<tr>
<td>Brush</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Plaque</td>
<td>28</td>
<td>15</td>
</tr>
<tr>
<td>Floss</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

At both initial and recall visits, only one subject reported daily flossing, and only one subject had not previously seen a dentist. Due to these low numbers, these variables were omitted from further statistical analysis.

4.5 dmft

For the SDF group, the mean dmft score was 11.8. For the fluoride group, the mean dmft score was 10.5. There was no change in dmft throughout the study.
Overall, there was no statistically significant correlation between dmft and age, or between dmft and ATP bioluminescence scores (both initial and recall). However, the fluoride group dmft scores were inversely related to the reduction in ATP bioluminescence scores (p = 0.04). The SDF group dmft scores were not related to the reduction in ATP bioluminescence scores.

**TABLE IX: MEAN dmft SCORES BY TREATMENT GROUP**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>dmft</th>
</tr>
</thead>
<tbody>
<tr>
<td>SDF</td>
<td>11.8</td>
</tr>
<tr>
<td>Fluoride</td>
<td>10.5</td>
</tr>
</tbody>
</table>

**TABLE X: CORRELATION OF CHANGE OF ATP BIOLUMINESCEENCE SCORES AND dmft WITHIN EACH TREATMENT GROUP**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>R (correlation with dmft)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>SDF</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Fluoride</td>
<td>-0.54</td>
<td>0.04</td>
</tr>
</tbody>
</table>
5. DISCUSSION

5.1 SDF vs. Fluoride

The null hypothesis is that there is no difference between the two groups, SDF and fluoride, in oral microbial load as measured by ATP bioluminescence. The null hypothesis is rejected, since there is a statistically significant difference. The recall ATP bioluminescence score was significantly lower in the SDF group. It is believed that this finding can be attributed to the stronger intrinsic antibacterial activity of SDF versus fluoride. Additionally, it is believed that SDF has a more potent and sustained effect, partly due to the zombie phenomenon. There was no statistically significant difference among treatment groups for initial ATP bioluminescence score. This finding strengthens the study and final results. The two groups were the same at baseline and different at follow-up. It is reasonable to conclude that the difference is attributable to SDF.

Both groups were similar at baseline on all potential confounders (age, sex, and ethnicity). Further statistical analysis was performed to rule out confounding variables attributing to the significant difference in ATP bioluminescence score. Of all of the variables, plaque was also found to have a statistically significant effect on ATP bioluminescence score at the recall appointment. Additionally, plaque was found to be inversely correlated with the reduction of ATP bioluminescence score of the fluoride group.

This study mainly focuses on the oral microflora, due to its significant contribution to the development of caries. According to the AAPD, MS levels and
the age a child becomes colonized with cariogenic flora are valuable in assessing caries risk, especially in preschool children. Individuals with active caries have higher numbers of MS and lactobacilli in their saliva and plaque than individuals without caries. Young children with high levels of MS have more severe caries in their primary dentition than older children. All of these factors suggest significant value in reducing the oral microbial load to lower a child’s risk of developing caries. While this study does not directly measure cariogenic streptococci such as MS, the ATP bioluminescence does reflect overall oral microbial load, an indirect indicator of caries risk. Total oral bacteria, as measured by ATP bioluminescence, has a strong statistical correlation with cariogenic streptococci. Total microbial load is an indirect indicator of caries risk. Our study shows beneficial effects in reducing oral microbial load due to the SDF intervention compared to the fluoride intervention.

5.2 Oral Hygiene

Most patients initially presented with poor oral hygiene, visible plaque, and irregular tooth brushing. At the recall visits, reported tooth brushing frequency improved for both treatment groups. Visible plaque decreased at recall visits, though the decrease was not directly related to the increased tooth brushing. This suggests that oral hygiene instruction may have had a positive effect on oral hygiene.

Within the SDF group, the reduction in ATP bioluminescence score was not correlated with visible plaque at recall, meaning that the ATP
bioluminescence score reduced regardless of plaque presence. Plaque in the SDF group may have acted as a reservoir for silver, causing an increase in reduction of ATP bioluminescence scores.

Within the fluoride group, the reduction in ATP bioluminescence score was inversely related with visible plaque at recall. Presence of plaque in the fluoride group was associated with a smaller reduction in ATP bioluminescence score.

The rising popularity of SDF focuses on its anti-caries effect, but it is worthwhile to consider its desensitization effect. This can lead to reduced sensitivity and reduced pain, which can result in improved oral hygiene measures and improved oral health related quality of life.

5.3 The Score of dmft

Overall, among both groups, dmft was not correlated with reduction of ATP bioluminescence scores. Further analysis revealed that within the fluoride group, as dmft score increased, the reduction of ATP bioluminescence score decreased (see Table IX). ATP bioluminescence scores in the SDF group, on the contrary, proved insensitive to dmft. This may show that SDF has stronger intrinsic antibacterial activity than fluoride, and that its effect on bacteria is not hindered by a larger bacterial load. The depth of lesions was not recorded, as it would be difficult with the selected patient population and cooperation levels.
5.4 **Comparison to Past Studies**

Currently, there are no studies available that use ATP bioluminescence to evaluate antibacterial activity of SDF as compared to fluoride varnish. This study does support the antibacterial activity of SDF found in previous studies, such as the 2012 study by *Chu et al.*\(^{27}\) The 2009 study by *Fazilat et al.* suggested using ATP bioluminescence to assess antibacterial interventions, which is what was accomplished in this study.\(^3\)

5.5 **Study Strengths**

To date, this is the only study directly comparing the antibacterial effect of 38% SDF vs. 5% sodium fluoride varnish as measured by ATP bioluminescence. This study contributes new information to the literature in using ATP bioluminescence as a tool for measuring oral microbial load.

Another strength was that the study designated a single operator, an experienced pediatric dental specialist, to perform all steps. This ensured consistency in swabbing, and in SDF and fluoride application. There was no need to calibrate multiple investigators. This strengthens the validity of the study.

Finally, all subjects were from the same, high-risk caries population. Mean dmft, tooth brushing habits, flossing habits, and visible plaque did not significantly differ between treatment groups. This minimized confounding variables.
5.6 **Study Limitations**

One limitation of the study is the lack of variation in clinical setting. All data collection for this study was conducted in the Department of Pediatric Dentistry at the University of Illinois at Chicago (UIC). Our findings may be true for similar patient populations and cannot be applied to all clinical settings. Patient population, caries risk, parental expectations and patient behavior can vary based on the type of dental setting. This particular dental clinic is one of the largest providers of Medicaid dental services in the state of Illinois and a majority of the patients receiving services have Medicaid insurance. Caries risk and extent of dental decay is typically greater in this particular population compared to a typical private practice or fee-for-service dental clinic.

Another study limitation is that it relied on parental reporting of the following variables: tooth brushing and flossing. Visual inspection of oral hygiene (as determined by plaque) did not improve in the same manner as reported tooth brushing did.

The study also lacked a true control group receiving no treatment. Instead, the control group was selected to receive sodium fluoride varnish, as this is the standard of care.

To minimize the aforementioned limiting factors, the protocol was detailed and all attempts were made to adhere to these guidelines as best as possible.
5.7 **Future Studies**

Future studies are needed to compare oral bacterial load as measured by both ATP bioluminescence and microbial lab testing. Additionally, the utilization of a plaque index would allow for more descriptive analysis of oral hygiene. These methods may be more difficult for uncooperative patients, but may be useful among more cooperative patients. Finally, it would be useful to perform a similar study, but with a more diverse patient population, so that individuals of all caries-risk levels are represented.
6. **STUDY CONCLUSIONS**

The following conclusions can be made based on the results of this study:

- The 38% SDF is more effective than 5% sodium fluoride varnish in reducing oral bacterial load, measured with ATP bioluminescence after three months.
CITED LITERATURE


APPENDIX A

UNIVERSITY OF ILLINOIS
AT CHICAGO

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Office of the Vice Chancellor for Research (MC 672)
203 Administrative Office Building
1737 West Polk Street
Chicago, Illinois 60612-7227

Approval Notice
Initial Review (Response To Modifications)

August 10, 2017

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Phone: (312) 996-7532 / Fax: (312) 413-8006

RE: Protocol # 2017-0341
“A Prospective Clinical Trial Evaluating the Oral Microbial Load in Relation to Silver Diamine Fluoride Applications at Three and Six Months”

Dear Dr. Mikati:

Your Initial Review (Response To Modifications) was reviewed and approved by the Expedited review process on August 10, 2017. You may now begin your research.

Please note the following information about your approved research protocol:

The consent document was updated to provide UIC-required language, and a stamped version will be provided for use. If you wish to make additional changes to this document, an amendment should be submitted to the IRB.

Protocol Approval Period:
August 10, 2017 - August 10, 2018

Approved Subject Enrollment #: 100

Additional Determinations for Research Involving Minors: The Board determined that this research satisfies 45CFR 46.404 and 21CFR 50.51, research not involving greater than minimal risk. Therefore, in accordance with 45CFR 46.408 and 21CFR 50.55, the IRB determined that only one parent’s/legal guardian’s permission/signature is needed. Wards of the State may not be enrolled unless the IRB grants specific approval and assures inclusion of additional protections in the research required under 45CFR 46.409 and 21CFR 50.56. If you wish to enroll Wards of the State contact OPRS and refer to the tip sheet.

Performance Sites: UIC
Sponsor: None
Research Protocol(s):

a) A Prospective Clinical Trial Evaluating the Oral Microbial Load in Relation to Silver Diamine Fluoride Applications at Three and Six Months, PI: Rami Mikati; Version 1, Date

Phone: 312-996-1711 http://www.uic.edu/depts/ovcr/oprs/ FAX: 312-413-2929
March 10, 2017

**Device:** Silver Diamine Fluoride (510(k) #: K102973)

**Assent:**

a) Waiver of Child Assent granted under 45 CFR 46.408(a)

**Parental Permission:**

a) Combined parental permission and HIPAA authorization; Version 3.1, 08/10/2017
b) Waiver of informed consent (parental permission) granted [45 CFR 46.110(d)] for the identification of potential subjects in the recruitment phase of the research

**HIPAA Authorization:**

a) Review Preparatory to Research acknowledged [45 CFR 164.512(j)(1)(ii)]

Your research meets the criteria for expedited review as defined in 45 CFR 46.110(b)(1) under the following specific categories:

1. Clinical studies of drugs and medical devices only when condition (a) or (b) is met.
   a) Research on drugs for which an investigational new drug application (21 CFR Part 312) is not required. (Note: Research on marketed drugs that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review.
   b) Research on medical devices for which (i) an investigational device exemption application (21 CFR Part 812) is not required; or (ii) the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.

2. Prospective collection of biological specimens for research purposes by noninvasive means. Examples: (a) hair and nail clippings in a nondisfiguring manner, (b) deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction; (c) permanent teeth if routine patient care indicates a need for extraction; (d) excreta and external secretions (including sweat); (e) unstimulated saliva collected either in an unstimulated fashion or stimulated by chewing gum base or wax by applying a dilute citric solution to the tongue; (f) placenta removed at delivery; (g) amniotic fluid obtained at the time of rupture of the membrane prior to or during labor; (h) supragingival and subgingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques; (i) mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings; (j) sputum collected after saline mist nebulization.

3. Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for nonresearch purposes (such as medical treatment or diagnosis).

**Please note the Review History of this submission:**

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<tr>
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Please remember to:
Use your research protocol number (2017-0341) on any documents or correspondence with the IRB concerning your research protocol.

Review and comply with all requirements on the guidance, "UIC Investigator Responsibilities, Protection of Human Research Subjects" (http://tigger.uic.edu/depts/ovcr/research/protocolreview/irb/policies/0924.pdf)

Please note that the UIC IRB has the prerogative and authority to ask further questions, seek additional information, require further modifications, or monitor the conduct of your research and the consent process.

Please be aware that if the scope of work in the grant/project changes, the protocol must be amended and approved by the UIC IRB before the initiation of the change.

We wish you the best as you conduct your research. If you have any questions or need further help, please contact OPRS at (312) 996-1711 or me at (312) 413-3788. Please send any correspondence about this protocol to OPRS at 203 AOB, M/C 672.

Sincerely,

Rachel Olech, B.A., CIP
Assistant Director, IRB # 3
Office for the Protection of Research Subjects

Enclosure (Document available for download in OPRS Live):

1. Parental Permission(s):
   a) Combined parental permission and HIPAA authorization: Version 3.1, 08/10/2017

cc: Marcio De Fonseca, Pediatric Dentistry, M/C 850
    Sahar Alrayyes, Faculty Sponsor, Pediatric Dentistry, M/C 850
University of Illinois at Chicago
Research Information and Parental Permission for Participation in Biomedical Research
“A Prospective Clinical Trial Evaluating the Oral Microbial Load in Relation to Silver Diamine Fluoride Applications at Three and Six Months”

Your child is being asked to participate in a research study. Researchers are required to provide a consent form such as this one to tell you about the research, to explain that taking part is voluntary, to describe the risks and benefits of participation, and to help you to make an informed decision. You should feel free to ask the researchers any questions you may have.

Principal Investigator Name and Title: Rami Mikati, DDS, Pediatric Dental Resident Department and Institution: Pediatric Dentistry, UIC College of Dentistry Address and Contact Information: 801 S Paulina St (MC 830), Chicago IL 60612, 312-996-7532 Emergency Contact Name and Information: Dr. Salhar Akayyes, 312-996-7532

Conflict of Interest
Your health care provider may be an investigator on this research protocol, and as an investigator, is interested in both your clinical welfare and in the conduct of this study. Before entering this study or at any time during the research, you may ask for a second opinion about your child’s care from a clinician who is not associated with this project. Your child is not obligated to participate in any research project offered by your clinician. Your child’s participation in this research study is voluntary and you do not have to participate. The decision to not participate will not affect your child’s clinical care now or in the future.

Why am I being asked?

Your child is being asked to be a subject in a research study about how the amount of oral bacteria of children changes in response to oral hygiene instructions and/or application of silver diamine fluoride. This study is conducted by Rami Mikati of the Pediatric Dentistry Department at the University of Illinois at Chicago (UIC) and held at UIC Pediatric Dental Clinic.

Your child has been asked to participate in the research because they have been identified by their provider as being healthy, between the ages of 2-6 years old, having dental cavities needing treatment requiring general anesthesia (and thus being placed on the general anesthesia waitlist).

Your child’s participation in this research is voluntary. Your decision whether or not to participate will not affect your child’s current or future dealings with the University of Illinois at
Chicago. If you decide to participate, you are free to withdraw your child at any time without affecting that relationship.

Approximately 100 subjects may be involved in this research at UIC.

What is the purpose of this research?

This research is being done to better understand whether SDF application on dental cavities, in addition to the gold standard practice of oral hygiene instructions and fluoride varnish, reduces oral microbial load, measured using ATP bioluminescence, and to what degree it reduces it over three month application intervals.

What procedures are involved?

This research will be performed at UIC College of Dentistry, Department of Pediatric Dentistry.

You will need to come to the study site two more times over the next six months. The next visit will be in three months, and the last visit will be in six months.

Each of those visits will take about 30 minutes.

The study procedures consist of:

1. Using a cotton swab, collect a plaque sample from your child before his/her dental cleaning, which will be tested for any bacteria that causes cavities. A technology called ATP bioluminescence will be used for this test, which will be done chairside, with immediate results, and minimal to no discomfort. The ATP bioluminescence swab is not routinely done in dental clinics, but will be used for this research.

2. If you choose not to receive the SDF application, your child will receive the fluoride varnish only.

3. Report whether your child received fluoride varnish application alone or along with a SDF application on dental cavities during his/her initial exam, 3 month recall visit and 6 month recall visit.

4. Repeat steps 1 and 2 after three and six months from the initial visit.

5. We will collect all this data using your child’s dental chart number to keep the data together. When the study is finished, we will remove your child’s dental chart number from all research materials.

6. A maximum of 100 children may be involved in this research at the UIC.

What are the potential risks and discomforts?

The research has these mild risks: the discomfort of swabbing the child’s teeth for the ATP bioluminescence, and the risk of loss of privacy of protected health information by including that information in a research project. All patients will receive the standard of care receiving
comprehensive exams, caries risk assessment, anticipatory guidance including oral hygiene instructions and diet counseling as well as fluoride application.

Will I be told about new information that may affect my decision to participate?

During the course of the study, you will be informed of any significant new research findings (either good or bad), such as changes in the risks or benefits resulting from participation in the research or new alternatives to participation, that might cause you to change your mind about continuing in the study. If new information is provided to you, your consent to continue participating in this study may be re-obtained.

Are there benefits to taking part in the research?

There are no direct benefits to subjects for their participation in this research.

The only benefit to your child for participating in the research is that dentists might be better able to help other people like your child avoid getting tooth decay, or might have fewer cavities because of what we learn from this study and what effect SDF has on bacterial levels in the mouth.

What other options are there?

You have the option to refuse to allow your child to participate in this research. Your child will still receive their dental exam, dental cleaning and fluoride varnish application alone or along with silver diamine fluoride application even if you choose not to participate.

What about privacy and confidentiality?

The people who will know that your child is a research subject are members of the research team, and, if appropriate, your child’s dental personnel at the clinic. No information about your child during the research will be disclosed to others without your written permission, except:

- if necessary to protect your child’s rights or welfare (for example, if your child is injured and need emergency care or when the UIC Institutional Review Board monitors the research or consent process); or
- if required by law.

Study information which identifies you and the consent form signed by you will be looked at and/or copied for examining the research by:

- UIC Office for the Protection of Research Subjects, State of Illinois Auditors

A possible risk of the research is that your child’s participation in the research or information about your child and their health might become known to individuals outside the research. Personal information, research data, and related records will be stored as coded data. Your child will be given an identifier number linked to their dental electronic health record number where that list will be kept in a locked drawer and a locked office of the Principle Investigator. The list will be destroyed at the end of the study to avoid any loss of privacy.

Parental Permission for A Prospective Clinical Trial Evaluating the Oral Microbial Load in Relation to Silver Diamine Fluoride Applications at Three Month Intervals, Version 3.1, 8/10/17  Page | 3 of 6
When the results of the research are published or discussed in conferences, no information will be included that would reveal your child’s identity.

Will health information about you be created, used or shared with others during this study?

State and federal laws, including the Health Insurance Portability and Accountability Act (HIPAA), require researchers to protect your health information. This section of this form describes how researchers, with your authorization (permission), may use and release (disclose or share) your protected health information in this research study. By signing this form you are authorizing Dr. Rami Mikati and his research team to create, get, use, store, and share protected health information that identifies your child for the purposes of this research.

The health information includes all information created and/or collected during the research as described within this consent form and/or any health information in your child’s medical record that is needed for the research and that specifically includes medical record number.

During the conduct of the research, the researchers may use or share your health information:

- With each other and with other researchers involved with the study;
- With law enforcement or other agencies, when required by law;
- With representatives of government agencies (i.e., Food and Drug Administration), review boards including the University of Illinois at Chicago Institutional Review Board, the University of Illinois Medical Center and its representatives, and other persons who watch over the safety, effectiveness, and conduct of research.

How will your health information be protected?

The researchers and Dr. Sahar Alrayyes agree to protect your health information and will only share this information as described within this research consent/authorization form.

When your health information is given to people outside of the research study, those agencies that receive your health information may not be required by federal privacy laws (such as the Privacy Rule) to protect it. They may also share your information with others without your permission, if permitted by laws that they have to follow.

What are the costs for participating in this research?

There will be no additional cost to participate in the study. Covered by insurance: one topical fluoride varnish application and one dental cleaning. Not covered by insurance (will be written off and not billed at the three month recall visit): SDF applications, additional dental cleanings and fluoride varnish applications. Please note that the initial SDF application is not covered by insurance and will not be written off. Only the second SDF application will be written off.

Will I be reimbursed for any of my expenses or paid for my participation in this research?

Parental Permission for A Prospective Clinical Trial Evaluating the Oral Microbial Load in Relation to Silver Diamine Fluoride Applications at Three Month Intervals, Version 3.1, 8/10/17
You will not be offered payment for being in this study.

Can I withdraw or be removed from the study?

If you decide for your child to participate, you are free to withdraw your permission and discontinue participation at any time without affecting your child’s future care at UIC.

Your Authorization for release of your child’s health information for this research study expires at the end of the study, but can be canceled sooner if you decide to withdraw your permission.

You may change your mind and cancel this Authorization at any time. To cancel this Authorization, you must write to: Dr. Rami Mikati, MC 850, Department of Pediatric Dentistry, 801 S. Paulina, Chicago, IL 60612.

If you cancel this Authorization, your child may no longer be allowed to take part in the research study. Even if you cancel this Authorization, the researchers may still use and disclose health information from your child that they have already obtained as necessary to maintain the integrity and reliability of the research and to report any adverse (bad) effects that may have happened to your child.

Who should I contact if I have questions?

Contact the researchers Dr. Rami Mikati, Dr. Sahar Alrayyes, Dr. Evelina Kratunova, or Dr. Christine Wu at (312) 996-7531 if you have any questions about this study or your child’s part in it,
- if you have any questions about this study or your part in it,
- if you feel you have had a research-related injury (or a bad reaction to the study treatment), and/or
- if you have questions, concerns or complaints about the research.

What are my rights as a research subject?

If you have questions about your rights as a research subject or concerns, complaints, or to offer input you may call the Office for the Protection of Research Subjects (OPRS) at 312-996-1711 or 1-866-789-6215 (toll-free) or e-mail OPRS at uicirb@uic.edu.

If you have questions or concerns regarding your child’s privacy rights under HIPAA, you should contact the University of Illinois at Chicago Privacy Officer at Ph: (312) 996-2271.

Remember:

Your child’s participation in this research is voluntary. Your decision whether or not to have your child participate will not affect their current or future relations with the University. If you decide to have your child participate, you are free to withdraw them at any time without affecting that relationship.

Parental Permission for A Prospective Clinical Trial Evaluating the Oral Microbial Load in Relation to Silver Diamine Fluoride Applications at Three Month Intervals, Version 3.1, 8/10/17
Right to Refuse to Sign this Authorization

You do not have to sign this Consent/Authorization. However, because your child’s health information is required for research participation, your child cannot be in this research study if you do not sign this form. If you decide not to sign this Consent/Authorization form, it will only mean your child cannot take part in this research. Not signing this form will not affect your child’s non-research related treatment, payment or enrollment in any health plans or your child’s eligibility for other medical benefits.

If you have not already received a copy of the Notice of Privacy Practices, you should ask for one.

Your signature below indicates that you are providing both consent to have your child participate in the research study and authorization for the researcher to use and share your child’s health information for the research.

Signature of Parent / Guardian or Legally Authorized Representative of Subject

Date (must be same as Subject’s)

Printed name of Parent / Guardian or Legally Authorized Representative of Subject

Describe relationship to subject including the legal authority this individual has to act on behalf of the subject. (Check one below)

☐ Parent
☐ Medical Power of attorney/representative
☐ Legal guardian
☐ Health care surrogate
☐ Other, specify

__________________________________________

Parental Permission for A Prospective Clinical Trial Evaluating the Oral Microbial Load in Relation to Silver Diamine Fluoride Applications at Three Month Intervals, Version 3.1, 8/10/17
VITA

Rami F. Mikati, D.D.S.

Education:

2016 – Present  University of Illinois at Chicago – College of Dentistry
Pediatric Dentistry Residency, PGY2
Masters in Oral Sciences
Projected Completion: June 2018

2012 – 2016  The Ohio State University – College of Dentistry
Doctor of Dental Surgery

2009 – 2011  Kent State University
Major: Biological Sciences
Master of Arts

2005 – 2009  Case Western Reserve University
Major: Economics. Minor: French
Bachelor of Arts

Board Examinations:

NBDE Part I – Pass
NDBE Part II – Pass

Licensure:

CDCA Licensure Exam – Pass
Illinois State Dental License
Illinois State Controlled Substance License

Work Experiences:

2016 – 2018  University of Illinois at Chicago
PGY-2 Pediatric Dental Resident
Program emphasizes behavioral management, sedation, medically compromised individuals, hospital protocols, four-handed dentistry, and orthodontics
Chicago, IL
**Presentations:**

2018  A Prospective Clinical Trial Evaluating the Oral Microbial Load in Relation to Silver Diamine Fluoride Application at Three Months
*Presented at the American Academy of Pediatric Dentistry Conference, Honolulu, HI*

2018  A Prospective Clinical Trial Evaluating the Oral Microbial Load in Relation to Silver Diamine Fluoride Application at Three Months
*Presented at the UIC Clinic and Research Day, Chicago, IL*

2017  Effectiveness of Silver Diamine Fluoride in Caries Arrest in Primary Teeth and Reduction of Oral Microbial Load
*Presented at the UIC Clinic and Research Day, Chicago IL*

2016  The Natural History and Stability of Acquisition of the Oral Microbiome from Infancy to Adolescence
*Presented at the OSU Clinic and Research Day, Columbus, OH*

2015  Understanding Consumption of Sugar-Sweetened Beverages by Adolescents with Dental Caries
*Presented at the OSU Clinic and Research Day, Columbus, OH*

**Research:**

20016 - 2018  A Prospective Clinical Trial Evaluating the Oral Microbial Load in Relation to Silver Diamine Fluoride Application at Three Months
Mentor: Sahar Alrayyes, DDS, MS
University of Illinois at Chicago Department of Pediatric Dentistry
Chicago, IL

2015 – 2016  The Natural History and Stability of Acquisition of the Oral Microbiome from Infancy to Adolescence
Mentor: Ann Griffen, PhD, DDS
The Ohio State University College of Dentistry
Columbus, OH

2014 - 2015  Understanding Consumption of Sugar-Sweetened Beverages by Adolescents with Dental Caries
Mentor: Ann Griffen, PhD, DDS
The Ohio State University College of Dentistry
Columbus, OH
**Honors and Awards:**

2015-2016  Dr. Harold E. and Faith B. Barlow Dental Scholarship  
2013,2015  Ohio Dental Association Foundation Scholarship  
2013-2016  OSU College of Dentistry Dean’s Honor List  
2011      Golden Key International Honor Society  
2009      Case Western Reserve University MLK Jr. Essay Contest, 1st place  
2006-2009  Case Western Reserve University Dean’s Honor List  

**Affiliations:**

2016 – Present  Illinois Society for Pediatric Dentists (ISPD)  
2016 – Present  American Academy of Pediatric Dentistry (AAPD)  

**Additional Language Proficiencies:**

Arabic  
French