Final Comprehensive Project Report

Project Identifier Information
a. Grant Number: R40 MC 17163-02
b. Project Title: Combination Therapy PVP-Iodine and Fluoride Varnish to Reduce Early Childhood Caries in High Risk Children
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I. Introduction
Early childhood caries (ECC) is a transmissible bacterial disease resulting in the demineralization and destruction of the primary teeth. The disease process can begin at the time of tooth eruption and is evident as early as 12 months of age (Milgrom, Riedy et al. 2000). The Surgeon General’s report of 2000 noted that “dental caries (tooth decay) is the single most common chronic childhood disease...[and] there are striking disparities in dental disease by income. Poor children suffer twice as much dental caries as their more affluent peers...” (DHHS 2000). The prevalence of ECC among children in the U.S. ranges from 11% to 72% with the higher rates found among ethnic minorities and disadvantaged children (Berkowitz 2003).

Native American children have the highest rates of tooth decay of all children in the U.S. The 1999 Oral Health Survey of American Indians and Alaska Native Dental Patients: Findings, Regional Differences and National Comparison report provides data on the oral health of 2,663 children ages 2 to 5 years (see adjacent figure excerpted from the report). The report notes 79% of the children had experienced tooth decay and 68% had untreated decay at the time of the survey. These rates are more than 4 times the national average for preschool-age children reported by the NHANES III survey. American Indian preschool-age children in the Phoenix and Navajo areas had the highest rates of tooth decay. The average number dmfs for children living in these areas were 18.3 and 19.0, respectively, compared to an average dft of 1.17 and dfs of 2.58 for children 2-5 years of age in NHANES 1999-2004 data (Dye, Tan et al. 2007).

Fluoride varnish (FV) applied topically to the teeth is being used for ECC prevention in very young children and is being incorporated into the standard of care of pediatric well-child preventive healthcare visits. There is strong evidence that FV is effective for many children (Marinho, Higgins et al. 2002) but insufficient to prevent and arrest the progression of tooth decay among high-risk ethnic and minority children. Studies of Canadian Aboriginal (Lawrence, Binguis et al. 2008) and Native American children (Holve 2008) report that fluoride varnish reduced the number of affected tooth surfaces by 24% and 35% respectively; however, the proportion of children with ECC and the extent of decay remained unacceptably high. Topical fluoride is not enough to protect the oral health of high-risk children.
Studies with adults and children have suggested that PVP-Iodine (Betadine) applied to teeth surfaces can reduce oral pathogens and may prevent new caries development.

This randomized controlled clinical trial addresses the prevention of dental caries (tooth decay) among toddlers of the Navajo Nation using a combination of fluoride varnish and an antimicrobial agent, PVP-Iodine, both being applied to tooth surfaces during the 9-24 months pediatric well-child visits.

**Hypothesis:** The combination preventative therapy of fluoride varnish plus PVP-Iodine is more effective in reducing the incidence of tooth decay in high-risk young children than fluoride varnish alone.

**II. Review of the literature**

Fluoride varnish is the mainstay of preventive treatment yet it is only partially effective. They are more effective than the fluoride foams and gels that are still in use (American-Dental-Association-Council-on-Scientific-Affairs 2006; Khattak, Conry et al. 2005). Varnishes are helpful because they are low-tech, inexpensive, and child-friendly. Fluorides main function is in the remineralization of the teeth surfaces that have been demineralized by oral pathogens. Repeated application of fluoride varnish is needed to achieve its beneficial effects to reverse and arrest the tooth decay process. The twice-yearly regimen prescribed by nearly all dentists and incorporated into Medicaid programs reduces new tooth decay in the primary teeth by 33% (Marinho, Higgins et al. 2002). Increasing the frequency of application has not resulted in major reductions in tooth decay progression in children at high risk for decay (Seppä 1991). Fluoride varnish has been successfully incorporated into the content of well-child pediatric visits and is a promising way to reach many young children with the recommended minimum dose of two applications per year (Diggle 2002; Grant, Roberts et al. 2007; Holve 2008; Hujoel, Isokangas et al. 1994; Quinonez, Stearns et al. 2006). However, the benefits of twice-yearly fluoride for young children at risk for severe caries have limits and enhance preventative strategies are needed.

An antimicrobial in addition to fluoride varnish is a potential strategy to control the development of tooth decay. There are two main biological arguments for adding a broad spectrum topical antimicrobial to measures to prevent and control tooth decay. First, children with high rates of tooth decay are much more heavily colonized with pathogenic organisms than children who experience less tooth decay (Aas, Griffen et al. 2008; Featherstone 2000; Marchant, Brailsford et al. 2001; Marsh, Featherstone et al. 1989; Milgrom, Riedy et al. 2000; Tanner, Milgrom et al. 2002; Zhan, Featherstone et al. 2006). A primary pathogen is *Streptococcus mutans* and while this appears to be true, the researchers cited above have found other species are also associated with tooth decay. A broad-spectrum antimicrobial, such as PVP-Iodine, is effective against a wide range of pathogens associated with dental caries. Second and in favor of PVP-Iodine specifically, PVP-Iodine is known to impact the ability of *S. mutans* to bind to tooth surfaces by disrupting the expression and production of glucosyltransferase (Tam, Shemesh et al. 2006). PVP-Iodine also has potent antifungal effects, suggesting that overgrowth of such pathogens should not be a concern (Sweetman 2009).

Topical treatment with PVP-Iodine is safe. Topical PVP-Iodine (also called povidone iodine or Betadine) is approved by the FDA for topical use on the skin in pediatric population and has been widely available for decades. PVP-Iodine is tolerated by most people; less than 0.4% of individuals experience contact dermatitis from exposure to PVP-Iodine (Lachapelle 2005). In the proposed protocol, PVP-Iodine will be applied to teeth surfaces; mucosal exposure will be minimal. No previous study has shown that long-term effect of intraoral use of PVP-Iodine alters the microbial ecology in the mouth detrimentally.

Studies show PVP-Iodine reduced oral pathogens and prevented new caries development. Three decades ago, in vitro studies demonstrated the bactericidal properties of iodine (I2) (Tanzer, Slege et al. 1977) and I2 in combination with sodium fluoride (Caufield 1981; Caufield and Wannemuehler 1982) on *S. mutans*. Several studies have examined the effect of PVP-Iodine with children. Two studies
examined chemotherapeutic suppression of oral *S. mutans* levels in children who required dental surgery due to severe early childhood caries (ECC). Zhan et al. (2006) studied 21 children, 2-6 years of age, who received restorative surgery under general anesthesia. Ten children were assigned to receive PVP-Iodine and 11 were controls (saline). Following dental surgery, 2 mL of either PVP-Iodine or saline was applied to the dentition using a cotton swab, followed by 1% sodium fluoride gel (both groups). Saliva samples were collected by swab immediately before surgery and 1-hour, 3-weeks and 3-months post dental surgery. *S. mutans* levels in the PVP-Iodine group were significantly reduced at all three time period; *S. mutans* levels in the saline group were significantly reduced only at 1-hour post surgery. In another investigation, 77 children with severe ECC had povidone iodine applied once to their teeth immediately after oral surgery (Berkowitz, Koo *et al.* 2009). The study reported a significant reduction in salivary *S. mutans* level collected at 30, 60, and 90 days post surgery.

Pilot studies have shown PVP-Iodine can prevent new caries in children with severe ECC. In the first study, 31 toddlers at high risk were treated with either topical PVP iodine or a placebo every 2 months and observed. The outcome measure was the survival of teeth without tooth decay. Within 155 days, 0% (15) of the children in the iodine group and 31% (5 of 16) in the control group experienced new tooth decay. Within one year, 48% of children in the control group experienced caries, while the children in the iodine group developed no new decay (Lopez, Berkowitz *et al.* 1999). No adverse events were reported. In a second larger study of a similar design with 83 toddlers, 91% of the treated children remained caries free after 12 months, compared to 54% of the controls (Lopez, Berkowitz *et al.* 2002). No adverse events were reported. Amin et al. (Amin, Harrison *et al.* 2004) studied the effect of PVP-Iodine on *S. mutans* levels and the incidence of new caries in 25 children 2-7 years of age with severe ECC. PVP-Iodine was applied to teeth following dental rehabilitation under general anesthesia. Children in the experimental group (*n* = 13) had PVP-Iodine applied 3 times at 2-month intervals; controls (*n* = 12) did not receive iodine treatment. *S. mutans* counts decreased significantly from baseline to six months for all children. At one year post treatment, 5 of the 8 children in the control condition had new lesions compared to 2 of 11 children in the experimental group (*p*=.06).

### III. Study Design and Methods

This was an 18-month, two-group, double-blind, randomized controlled clinical trial. Children will receive either: (1) topical PVP-Iodine solution (10% Povidone Iodine) followed by topical fluoride varnish (5% sodium fluoride) or (2) a topical placebo solution followed by topical fluoride varnish (i.e. fluoride varnish alone). The dental treatments will be given as part of well-child preventive health care visits at ages 6 through 24 months; up to 4 applications total. The primary outcome will be the presence and extent of dental caries identified by dental exam at age 24-30 months.

**Setting and Participants:** The study was being conducted at the Gallup Indian Medical Center (GIMC) in New Mexico which serves the Navajo Nation primarily. Participants would have been children ages 4 to 6 months (at enrollment) who attend the medical center’s pediatric clinic. A total of 350 parents and their children were to be recruited for this study.

GIMC is a large hospital in Gallup, New Mexico, on the border of the Navajo Reservation. It has a full range of inpatient clinical specialties and outpatient clinics. The majority of patients are from the Navajo Nation communities within a 30-50 miles radius of the clinic. With 11 pediatricians and 1 nurse practitioner, GIMC serves an estimated 2,500 children ages birth to 3 years and delivers approximately 700 newborns a year. The Dental Department has one pediatric dentist and seven general dentists on staff, all treat young children.

**Inclusion/Exclusion Criteria:** All children age 4 to 6 months who were patients of the Gallup Indian Medical Center Pediatric clinic and in general good health were eligible to enroll in the study. Children
would be excluded if they have allergies to sodium fluoride varnish or iodine or have uncorrected cleft palate defects.

**Recruitment & Enrollment:** Families would have been informed about the study by community announcements and study flyers posted in the pediatric clinic. Recruitment flyers would have been made available to parents at the time of clinic check in. Health care providers would have promoted the study and refer interested parents to the study recruiter. Families would have enrolled their child in the study when the child is 4 to 6 months of age but prior to completing the 6-month well-child visit.

**Randomization and Blinding:** Children would have been randomized to one of the two treatment conditions at the time of enrollment. Randomization were done in blocks of 20-30 to ensure roughly equal treatment groups.

**PVP-Iodine/Placebo and Fluoride Varnish Application Schedule:** Children would have received PVP-Iodine plus FV or placebo solution plus FV applications during their pediatric clinic's well-child preventive care schedule for ages 6 through 24 months: at the 6-, 9-, 15 to 18-, and 24-month visits.

**Data Collection Schedule:** A dental examination would have been conducted after the final preventative treatment and between the ages of 24 and 30 months. A baseline dental exam would not have been necessary because the children would have been only 4 to 6 months of age at enrollment and tooth decay was not expected. Other study procedures and data that were to be collected over the course of the study included: written informed consent (at enrollment), contact information (e.g., address, telephone number of the primary household and nearby friend or relative at enrollment, and each visit), a brief medical history of the child (at enrollment) and a questionnaire about parents’ oral health beliefs, child oral health quality of life, parent and child home hygiene practices, additional fluoride exposures (e.g., source of drinking water, child dental home and dental treatments).

**IV. Findings**

This research project provided a unique opportunity to collaborate with the Navajo Nation, one of the largest Native American tribes in the US, to evaluate a primary preventative intervention in reducing tooth decay among young children. The project would have been the first randomized clinical trial in the US to use the combination PVP-Iodine and fluoride varnish to prevent tooth decay in high risk young children. The project had the potential to produce huge impact in a population where the tooth decay rate in young children is among the highest in the nation.

Collaboration with the Navajo Nation, as with other Native American tribes, was a privilege and required the project to abide to rules and regulations set forth by the Tribal government. We worked with the Navajo Nation Human Research Review Board (NNHRRB) and completed the first 5 of 12 phases which include IRB equivalence approval and permission to implement the study. We obtained the required Letter of Support from the Navajo Nation Health Advisory Board Resolution and GIMC administrator. A Navajo Nation Project Advisory Committee was formed, which helped refine the study questionnaire and oral health education material as directed by the NNHRRB. This process took longer than planned which delayed the study by several months.

Unfortunately, unanticipated challenges again arose when the IRB application was submitted to the University of Washington. The UW IRB screener requested that the PI seek consultation from the FDA regarding the need for an Investigational New Drug (IND) application for the use of Iodine and Fluoride Varnish for the prevention of dental caries. At the time (and still currently), Iodine is approved for use as an antiseptic, antibacterial, and fluoride varnish is approved as an enamel desensitizer device but neither is approved for the indication of preventing dental caries, which this research project was to attempt to prove.
The Food and Drug Administration advised that the PI must go through the Investigational New Drug application process and, in consultation with the FDA, provide the basic science, pharmacodynamics, and product safety literature or preliminary studies per FDA’s request based on the study design. The Investigational New Drug application process was arduously long and significantly delayed the progress of the study. Furthermore, in discussion, the FDA suggested that preliminary study on safety of PVP-Iodine use in the oral cavity of young children be made available and included in the Investigational New Drug application. Funding for the original design did not include an Investigational New Drug application component or conduct of preliminary studies.

The mid-term report specified these challenges. The PI had numerous discussions with the project officer include proposal to modify the study design and aims. However, the grantee concluded that it was not possible for the study to be completed in a timely manner and within the budget allotted. The PI proposed alternative modified study design and aims were not accepted. Ultimately, the grantee decided to withdraw funding and ended the study at the conclusion of Y2 of the study before recruitment occurred. As such, there are no results to report.

Lessons learned:
Navigating through the Tribal rules, regulations, and Navajo Nation IRB requirements were arduous and required patience and positive forward thinking. The process highly resembles the CBPR model where buy-in and supports/resolutions from the local and regional communities “chapter houses” and health boards, GIMC administration support must be sought and documented to demonstrate buy-in at all levels of the Navajo Nation system at the study site. We underestimated that time it takes to navigate through the Navajo system. More time should have been allotted to accomplish this task.

The IRB process at times, such as in this case, can be extremely rigorous in the review of applications that use drugs in “off-label” indications capacity for research. It would be helpful to submit IRB application and obtain IRB consultation regarding drugs used in a study protocol early in the process even before funding is known. However, the challenge with this is having the resources available to do this work.

Investigational New Drug application is a long and arduous process that requires adequate resources to pursue. The IND application process is a step wise process that takes time and includes Pre-IND application consultation, Pre-IND meetings and conference calls to discuss the science and the drugs, obtaining the necessary scientific documentations the FDA wants to be included in the IND application, IND submission conference call to ensure all FDA requests for information are met. The IND application seeks detail laboratory, animal or human studies addressing toxicity, safety, pharmacokinetics, drug interactions, etc. Studies that have the potential need for IND must include these components in the research proposal including adequate budget to carry out the IND application. However, given the limited amount of funds awarded for research projects, it may fall on the institution to invest in such applications.