Title:	Povidone-Iodine Oral Rinse Study: A 2-phase, Randomized Trial to Test the Effects of Povidone-iodine 0.5% as Mouthwash/Gargle on SARS-CoV-2 (COVID 19) Load as an Adjuvant Infection Control Measure in Dental Practice
Brief Title:	Povidone-Iodine Oral Rinse Study
NCT Number:	05239598
IRB Number:	849386
Version Date:	5/13/2022

Protocol

Abstract
This study is a two-arm, randomized, 2-phase study. Phase I will be double blinded clinical trial of the safety and efficacy of an antiseptic mouth rinse solution on reducing SARS-CoV-2 load in COVID 19+ adult individuals. Phase II is designed as an open label trial, and all subjects will receive the active mouthwash.

Objectives

Overall objectives
Primary Objective: is to test the efficacy of Povidone-iodine 0.5% when used as a mouth rinse on reducing SARS-CoV-2 load in the oral cavity of COVID-19+ individuals.

Primary outcome variable(s)
The primary outcome is the change in amount of SARS-CoV-2 in the oral cavity before and after intervention.

Secondary outcome variable(s)
Subjects clinical status at day 7 and the number of COVID-19 symptoms, symptoms onset and the severity of symptoms will be collected throughout Phase 2 of the study.

Background
Severe acute respiratory syndrome, or SARS is caused by a novel coronavirus termed the SARS coronavirus, or SARS-CoV-2, spreads through droplet infection produced when the infected person speaks, coughs, or sneezes, and affects people of any age. The epidemic of coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2, originating in Wuhan, China, has become a major public health challenge for not only China but also countries around the world. [1] The disease has affected vulnerable individuals, especially those with co-morbidities. [1]
The incubation period for SARS-CoV-2 is widely considered to be 2-7 days, but occasionally may last up to 10 days. Most patients identified up to now were previously healthy adults aged 25 through 70 years. [3] Dentists have been alarmed by the spread of SARS-CoV-2 in clinical facilities, where a disproportionately large number of health care workers (HCWs) have been infected in major hospitals treating infected individuals worldwide. Due to the characteristics of dental settings, the risk of cross infection can be high between patients and dental practitioners as the infection typically enters through mouth, nose, and eyes making dentistry one of the medical practices at highest risk of infection due to the frequent production of aerosols and the constant presence of saliva.
According to the World Health Organization (WHO), close contact with or short-range transmission of infectious saliva droplets is a primary mode for SARS-CoV-2, while long-distance saliva aerosol transmission is highly environment-dependent.

Dental practices, which operate indoors with a high volume of aerosol-generating procedures, are a high-risk environment if the appropriate precautions are not taken. [4] Saliva stands at the entry of the respiratory system and has been found to be SARS-CoV-2 nucleic acid positive. [5-7] Besides the lungs, salivary glands and tongue are possibly other hosts of SARS-CoV-2 due to expression of angiotensin-converting enzyme II (ACE2). Several studies have shown that ACE2 play a crucial role in the entry of the virus into the cell to cause the final infection, making the oral cavity a potential reservoir for SARS-CoV-2. [8-11] Preliminarily, these findings may explain the basic mechanism that the oral cavity is a potentially high risk for SARS-CoV-2 infectious susceptibility and provide evidence for the future prevention strategy for dental practices in areas that are potentially affected with COVID-19 and where additional effective infection control protocols are urgently needed. Current guidelines from the US Center for Disease Control (CDC), WHO, and the American Dental Association (ADA) have stressed the importance of personal hygiene measures and social distance approaches for SARS-CoV-2 prevention.

In additional, personal protective equipment (PPE) guidelines have been established to protect the skin and mucous membranes of the eyes, nose, and mouth from exposure to potentially infectious material. These infection control measures are critical for preventing the spread of community acquired disease, nevertheless additional measures are needed in dental care settings to prevent the spread of disease between providers and patients when treating patients with known infective or high-risk individuals.

These measures should be focused on reducing the viral load in the nasopharynx and oropharynx in patients who are high-risk or COVID-19 positive prior to delivering aerosol generating dental interventions. Past research studies on infections similar to COVID-19 have shown the efficacy of targeted mouthwash solutions such as chlorhexidine gluconate (CHG), polyvinylpyrrolidone iodine (PVP-I), saline solutions (SS), and hydrogen peroxide (H2O2) amongst others on reducing viral load against respiratory and oral track pathogens. [12-18] Efficacy in the reduction of viable bacteria in dental aerosols by procedural rinsing with an antiseptic mouth rinse has been demonstrated to potentially reduce the risk of cross-contamination in the dental operator. [19]. The ADA (2020) has issued interim guidelines for minimizing the risk of COVID-19 transmission from the patient to the dental professional recommending the use of a preoperative 0.2% PVP-1 mouth rinse. Theuse of PVP-1 mouth rinse has also been recognized by the Centers for Disease Control and Prevention.Challacombe et al. suggests that all patients requiring dental treatment should be administered a 9 mL of the 0.5% solution as a mouth rinse (30 s for gentle gargling). [19] However, until now, only a few in vivo, in vitro and in silico studies has been conducted to support the recommendation of mouth rinses to control the viral load and manage the risk of COVID-19 infections in the dental office and the community. Clinical trials evaluating the potential applications of existing mouth rinses is essential to gaining an understanding of the anti-SARS-COVID-19 activities of active ingredients like PVP-1. In summary, PVP-1 has the potential to be a simple, affordable and effective preventive therapy to rapidly inactivate SARS-CoV-2 and may play an adjunctive role in mitigating viral transmission beyond personal protective equipment.

Study Design

Phase*
Phase II

Design
Phase I: Study participants will complete a one-time study visit and will be asked to rinse/gargle with 10ml of the assigned mouthwash for 30 seconds. Subjects will be randomized to either rinse/gargle with Povidine-iodine 0.5% or a placebo. Phase II: Study participants will be given a 1 week supply of Povidone-iodine 0.5% mouth rinse and will be asked to rinse/gargle with 10ml for 30 seconds 4 times per day. Subjects will be contacted on Day 7 using Telemedicine, phone calls, and/or text messages to determine clinical status.

Study duration
Phase I: 1 day Phase II: 1 week

Characteristics of the Study Population

Target population
Forty (40) subjects with confirmed clinical diagnosis of COVID-19 and at least one onset clinical sign will be recruited and randomized in the study. If there are screen failures, more than 40 subjects may consent. Subjects who sign the informed consent form and are randomized and receive the study product, and subsequently withdraw, or are withdrawn or discontinued from the study, could be replaced at the investigators discretion. For example, if a subject's samples are found to be less than optimal.

Subjects enrolled by Penn Researchers
40

Key inclusion criteria
1. Able and willing to provide informed consent prior to initiation of study procedures. 2. Stated willingness to comply with all study procedures and availability for the duration of the study. 3. Male or female, aged 18 years and older. 4. Clinical diagnosis of COVID-19 infection confirmed with a positive point of care test. 5. Confirmed diagnosis within 5 days of baseline visit (within 5 days of COVID-19 test) and at least one clinical COVID-19 symptom [*Signs and symptoms of COVID-19 present at onset, but over the course of the disease, most people will experience the following: fever or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle or body aches, headache, new loss of taste of smell, sore throat, congestion or runny nose, nausea or vomiting and diarrhea.] 6. Presents with a minimum of six natural teeth. 7. Ability to rinse/gargle with study products. 8. Not using mouth rinse/gargling solutions at the time of enrollment. 9. Not taking antimicrobial medications (antibacterial, antiviral, antibiotics, including hydroxychloroquine) at time of enrollment. 10. Ability to participate in the study and come to site during Phase I of the study for collection of swabs and saliva. 11. Willing to use an acceptable method of birth control throughout duration of the study. Acceptable methods include hormonal contraceptives, barrier methods, abstinence, or other effective methods approved by the PI. 12. If continuing to Phase II of the trial, ability to continue using study products for 1 week (+ 3 days). (Participants do not have to agree to participate in Phase II in order to participate in Phase I.) 13. If continuing to Phase II of the trial, agree to receive text messages/phone calls containing questionnaires regarding compliance and use of study product, and reminders, able to complete virtual follow-up study visit for collection of outcomes data.

Key exclusion criteria
1. Individuals receiving antiviral medications 2. Pregnant or breastfeeding women (for premenopausal women of childbearing potential, pregnancy status to be confirmed through a urine pregnancy test during the study visit) 3. Inability to comply with study protocol 4. Having an allergy to any of the study mouthwash ingredients 5. Having any thyroid condition. 6. Presents with a current suspicious oral lesion at the examiners discretion, and/or currently undergoing radiation therapy for head or neck cancer, and/or has received radiation therapy to the head or neck (including radioactive iodine therapy).

Populations vulnerable to undue influence or coercion
Although not directly targeted, mentally disabled persons, economically or educationally disadvantaged person, and/or employees or students of the University of Pennsylvania will not be denied enrollment and any special protections an/or additional safeguards will be undertaken in order to protect the rights and welfare of these subjects from coercion or undue influence as appropriate.

Subject recruitment
COVID-19+ patients will be recruited to achieve 40 study subjects who enroll in and are eligible for study participation. Primary recruitment will be through the University of Pennsylvania testing sites. We will also place flyers within our hospitals and dental clinics, including our community health centers outside the school. Subjects who present a positive COVID test and at least one COVID symptom (see inclusion criteria) will be recruited. Email messages advertising using an IRB approved template the study will also be sent out to University of Pennsylvania mailing lists that include faculty, staff, and students.

Will the recruitment plan propose to use any Penn media services (communications, marketing, etc.) for outreach via social media avenues (examples include: Facebook, Twitter, blogging, texting, etc.) or does the study team plan to directly use social media to recruit for the research?
Yes

Subject compensation*
Will subjects be financially compensated for their participation?
Yes

If there is subject compensation, provide the schedule for compensation per study visit or session and total amount for entire participation, either as text or separate document

Baseline/Visit 1 can be done in one visit with confirmatory diagnosis of COVID and after inclusion/exclusion is met. If a subject is a screen failure during Phase I for any reason and is unable to be enrolled, they will receive $20. Phase I: $100 Phase II: $20 for attending the remote visit on Day 7 Subjects will be compensated through Greenphire ClinCard. If a subject does not have a social security number, he/she will be compensated via an Amazon gift card.

Study Procedures

Procedures

At the Screening/Baseline visit, the following procedures will be performed: Informed consent will be obtained; Demographic information will be obtained; Vital signs measurements will be performed (temperature, blood pressure, heart rate, height, weight); Oral health questionnaire; A clinical oral exam will be completed; Dental and Medical history will be reviewed to determine eligibility based on inclusion/exclusion criteria; A point of care COVID-19 test will be completed to determine eligibility based on inclusion/exclusion criteria; Premenopausal women of child bearing potential will complete a urine pregnancy test to confirm eligibility; Eligible subjects will be randomized to one of two treatments; Randomized subjects will rinse with 10 ml of their assigned product for 30 seconds; Swab samples (posterior dorsal tongue and nasal swabs) will be collected at Baseline (pre-rinse) and at 5, 30 and 60 minutes post-rinse; Salivary samples will be taken at Baseline (pre-rinse) and at 5, 30 and 60 minutes post-rinse; Subject who successfully complete Phase I will be invited to continue into Phase II of the clinical trial and given the product to take home to use as instructed. If continuing they may be scheduled for a remote follow-up visit on Day 7. If not continuing the subject will be exited from the clinical trial after Visit 1. Phase II Visit 2 (Day 7 +/- 3 Days): Medical history will be updated. This visit will be completed remotely via the collection of questionnaires. Subjects will be sent a link to the questionnaires via text message or email, and/or be contacted via phone or telemedicine. Questionnaires will collect outcomes data assessing their clinical status, number of COVID-19 symptoms, symptoms onset and the severity of symptoms. At this timepoint subjects will exited the study. A separate modification request will be submitted at the time a pregnancy is identified, before any follow-up on incidental pregnancy will occur. At that time, the pregnancy supplemental form, along with a description of the data and method of collection (i.e. via self-report, medical chart review, questionnaires, etc.) will be provided.

STATISTICAL CONSIDERATIONS

Statistical Hypotheses (Phase 1 ONLY)

For the study, the null hypothesis (H0): $\delta = 0$ and the alternative hypothesis (H1): $\delta \neq 0$. The type of comparison in all cases will be superiority. Our primary endpoint is the percentage reduction of SARS-Co-V-2 load at 60 minutes (post-intervention) compared to baseline between the PVP-I mouthwash versus the placebo mouthwash. The secondary endpoints are the respective percentage reductions of SARS-Co-V-2 load at both 5 and 30 minutes (post-intervention) compared to baseline between the PVP-I mouthwash versus the placebo mouthwash.

Sample Size Determination

Assumptions:

- Looking to determine the value of the difference in the percentage reduction of SARS-Co-V-2 load at 60 minutes (post-intervention) compared to baseline between the PVP-I mouthwash versus the placebo mouthwash.
- Will use a two sample t-test assuming equal variance and sample size in each of the two arms
- δ is the difference between population means at which power and sample size calculations are made.
- Null hypothesis (H0): $\delta = 0$, Alternative hypothesis (H1): $\delta \neq 0$
- Trying to determine necessary sample size to show a significant difference under the alternative hypothesis by assuming a 20% greater difference (PVP-I versus placebo) in the reduction of SARS-Co-V-2 load after 60 minutes and a corresponding standard deviation for both groups of 0.20.
- Alpha (probability of Type-I error [true null hypothesis is rejected]) of 0.05
- Power (probability of rejecting a false null hypothesis) of 0.80
- We will assume 20% dropout rate in calculating the final # of patients to be enrolled

For the desired 80% power, the necessary sample size(s) is calculated to be n=34 (17 per arm). After accounting for the aforementioned 20% dropout, 44 patients will be enrolled in the study (22 per arm). The power calculations were performed using PASS Software 20.0.3.

General Approach

Descriptive statistics will be used to compare characteristics of the two groups (PVP-I mouthwash and placebo mouthwash. Group randomization will occur prior to the study visit using block randomization with block sizes randomly chosen as 4 or 6. Categorical variables will be described by frequencies, whereas continuous variables will be described using ranges, means, medians, and inter-quartile ranges and compared between groups using either the Chi-square test for binomial proportions or the Fishers' exact test as needed. Continuous variables will be compared using either a t-test for independent groups or the Mann-Whitney for cases where normality is not a reasonable assumption. All statistical tests will be two tailed, with an alpha level of 0.05.

Note that we may not be able to adjust for anything (or the adjustments will have to be very limited in scope and breadth) due to sample size issues.

Analysis of the Primary Efficacy Endpoint(s)

As described earlier, the primary endpoint is the percentage reduction of SARS-Co-V-2 load at 60 minutes (post-intervention) compared to baseline between the PVP-I mouthwash versus the placebo mouthwash. Assuming normality is a reasonable assumption, this percentage reduction will be compared between the two mouthwash groups (PVP_I versus placebo) using a t-test. Results will be presented as means and standard deviations with corresponding 95% confidence intervals and p-values.

Note that missing data should not be a concern as the cross-sectional study is a single visit.

Analysis of the Secondary Endpoint(s)

The secondary endpoints are the percentage reduction of SARS-Co-V-2 load at both 5 and 30 minutes (post-intervention) compared to baseline between the PVP-I mouthwash versus the placebo mouthwash. Assuming normality is a reasonable assumption, these respective percentage reductions will be compared between the two mouthwash groups (PVP_I versus placebo) using a t-test. Results will be presented as means and standard deviations with corresponding 95% confidence intervals and p-values.

Note that missing data should not be a concern as the cross-sectional study is a single visit.

Safety Analyses

Safety data will be collected at all study visit through solicitation of adverse events from subjects. Safety data will also be collected throughout the duration of the study via the subject's medical records.

All subject reported and evaluator observed adverse events will be collected documented on the appropriate CRF. Only related adverse events will be reported for this research study. Expected related adverse events include gingival/mucosal irritation and allergic reaction to study products.

Baseline Descriptive Statistics

Baseline (including demographic) characteristics will be summarized by standard descriptive statistics (including mean and standard deviation for continuous variables such as age and standard percentages for categorical variables such as gender). This will be done for both the overall cohort and stratified by mouthwash solution (antiseptic versus placebo). The baseline characteristics will be compared across the two mouthwash groups using Fisher's Exact test for categorical variables and t-tests for continuous variables (also accounting for equal versus unequal variance across the groups).