Effect of PVP-I Nasal Sprays vs Normal Saline Nasal Sprays on SARS-CoV-2 Nasopharyngeal Titers

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Background Summary

Human transmission of SARS-CoV-2 (COVID-19) occurs primarily through droplet spread into the nose and mouth. Arresting COVID-19 replication after infection of the nasal tissues specifically would decrease the duration and severity of infection in COVID-19-exposed patients, and may significantly impact COVID human to human transmission. Povidone-iodine (PVP-I) solution is a widely available, inexpensive antiseptic medication, used in the surgical theater to reduce the incidence of surgical wounds and intranasally to reduce MRSA colonization. However, the role of PVP-I in the treatment of nasal infections is limited. Interestingly, prior in vitro studies have demonstrated dilute PVP-I solutions, in concentrations as low at 0.23%, produce a ≥ 4 log10 decrease (inactivation of ≥ 99.99%) in SARS and MERS virus titers within 15 seconds.[1,2] Both viruses share high structural overlap with COVID-19. A study of 29 patients with recalcitrant sinusitis found reduced bacterial growth with good safety profile after use of 0.08% PVP-I nasal rinses.[3] PVP-I nasal sprays of up to 4.4% concentration have also been used on healthy volunteers without adverse effects or nasal tissue damage.[4] In Wuhan, China, PVP-I was recently used empirically by healthcare providers devoid of COVID-19 protection, given its ease of use, and potential for mitigating infection. Given this encouraging background, and current world events, we propose testing dilute PVP-I sprays as a topical treatment to directly ablate COVID infection within the nasal cavity.

Specific aims

1. To determine if PVP-I nasal sprays reduce viral shedding in the nasopharynx and nasal cavity
    a. Hypothesis 1: PVP-I nasal sprays will reduce viral shedding in the nasopharynx and nasal cavity as determined by PCR testing when compared to control groups
2. To determine if PVP-I nasal sprays affect the severity and time to resolution of signs and symptoms of COVID-19
    a. Hypothesis 2a: PVP-I nasal sprays will not change the severity or time to resolution of systemic signs and symptoms (such as fever, fatigue) when compared to control groups
    b. Hypothesis 2b: PVP-I nasal sprays will reduce the duration of anosmia symptoms when compared to control groups
3. To determine adverse effects of PVP-I nasal sprays
    a. Hypothesis 3: PVP-I nasal sprays will not be associated with a greater rate of adverse effects as compared to the control groups

Methods

Overview of study design

This is a prospective, double-blind, placebo controlled, randomized control trial of COVID-19 positive patients that has three study arms.

Arms:

(1) 2% povidone iodine nasal spray – two sprays to each nare four times a day for 5 days

(2) 0.5% povidone iodine nasal spray – two sprays to each nare four times a day for 5 days

(3) Control – Dyed normal saline (0.9% NaCl) spray – two sprays to each nare four times a day for 5 days

Study population: COVID-19 positive inpatients and outpatients

Inclusion criteria:

1. >/= 18 years ago
2. Diagnosis of COVID-19 by lab test within 5 days of study participation

Exclusion criteria:

1. Allergy to "iodine," shellfish, or food dye
2. Receiving intranasal steroids
3. Sinus surgery within 30 days of beginning the study
4. Intubated at the time of enrollment
5. Pregnancy
6. Participation in other COVID-19 studies - to be determined on a case by case basis

Measurements/Outcomes

The primary outcome measure is the viral load on nasopharyngeal swab determined by quantitative PCR testing. A baseline sample (Day 1) will be obtained prior to first administration of the sprays. Subsequent samples will be collected at 4 hours after first administration and on day 5 after initiating nasal sprays.

Intake questionnaire – dates of symptom onset, comorbid conditions, specific questions regarding taste and smell disturbances

Patient reported symptoms (completed on Day 3 and Day 5) – fever, fatigue, change or loss of sense of smell, change or loss of sense of taste, nasal congestion, sore throat, etc

Adverse effects questionnaire (completed on Day 3 and 5) – Nasal burning/pain, headaches, ear pain, sneezing, nose bleeds, rash

University of Pennsylvania Smell Identification Test (completed on day 1 and day 30) – to assess smell recovery in COVID-19 patients

Statistics

T-test or ANOVA to compare difference in mean viral load between groups. Chi-square to assess for differences in signs, symptoms, adverse effects.

Sample size: 45 subjects (15 subjects per study arm)

Study Procedures - Outpatient

Recruitment strategy

In terms of advertising to the general public, we will send out flyers for general distribution on social media (e.g., Facebook, Nextdoor, etc) that will allow interested persons in the general public to contact our team. Our social media advertising strategy is being developed in conjunction with StudyPages, a clinical trial recruitment company recommended by the Stanford Research Participation Program. Moderation of Facebook and other social media posts will be conducted as outlined in a separate

attached document and includes daily monitoring of comments and hiding/deletion of protected health information. Prospective participants can opt to have their contact information sent to the team.

Potential subjects who have expressed interest in being contacted about research studies will be contacted by phone by one of the investigators. The study will be described, patients will have the opportunity to ask questions, and if they wish to proceed, they will be given details on their first in person study visit.

Prospective participants that have undergone telephone screening will come to the clinic parking lot at 801 Welch Rd or the Galvez lot at the designated date and time. At this in person study visit, the study will be reviewed again and the consent form signed if the patient still wishes to proceed. Randomization will take place. This will count as Day 1 of the study.

Active Phase

Given the known COVID-19 positive status, we are putting in place the following procedure for in person study visits. For first study visits scheduled on a Saturday, subjects will drive to the 801 Welch Rd parking lot which is the parking lot associated with the Department of Otolaryngology's clinics. We have approval from the department chair and clinic leadership to use the parking lot. Participants will remain in their vehicle with the window rolled down for necessary study procedures. Return visits on day 5 will be scheduled for times either before 8 am or after 5 pm. Privacy will be ensured in several ways. First, the parking lot is behind the building and thus not visible from the main road. Second, we will be using moveable plastic barriers during study procedures to protect privacy. Lastly by having subjects only come in outside normal clinic hours (Saturday or pre/post-clinic), this will minimize the presence of other persons.

We have also received approval from Julie Morris who is the Operations Manager of the Galvez research lot to utilize the tent space or the parking lot space at this site for study procedures. Weekday study procedures will take place at this site (270 Galvez Street).

Participants will complete the first questionnaire and take the University of Pennsylvania Smell Identification Test (UPSIT) on the day of enrollment. This is a multiple-choice scratch and sniff test that is self-administered. A baseline nasopharyngeal sample will be taken. Next the first dose of the nasal spray will be given. Subjects will have the option to stay or return for the four hour sample collection timepoint. Four hours later, a member of the research team will obtain the 4-hour post-administration nasal sample. Subjects will then return home. Participants will be given (physical or electronic) a gift card for $25 at the end of the day.

Participants will continue to self-administer the spray as instructed while at home. They will also take daily symptom questionnaires administered through REDCap. Participants will return for a drive-through nasal swab at 801 Welch Rd or at the Galvez lot on Day 5.

On day 30, participants will complete an UPSIT, self-administered smell test, which will be given to patients with a self-addressed, pre-paid envelope to return.

Close Out

The study medication will be discontinued on Day 5. The second gift card ($25) will be mailed either through the postal service or through email to participants approximately 30 days after the first study visit upon completion of the final UPSIT.

Specimen Handling

Each sample will be labelled with a subject's unique record ID number. These samples will be processed in the Stanford clinical virology lab (permission has been obtained from Dr. Benjamin Pinsky) and results associated with a given record ID number in REDCap.

Payment/Reimbursement

Participants will be given a total of $50 in gift cards if they complete the study. They will receive a $25 gift card at the end of the first in person study visit. If they complete the remaining in person visits on Days 5, they will be mailed (either via postal service or email) the second $25 gift card along with the final smell test.

Safety of proposed treatment arms

A small quantity of food dye is commonly used on mucosa membranes in the head and neck in routine clinical practice for instance to assess for fistula or to assess swallow function.[5] It has also been used in numerous prior research studies assessing the distribution of drug delivery methods in the nasal cavity.[6] There is no added risk to including this in the control group saline solution.

PVP-I solutions are routinely used as mouth washes with minimal absorption through the mucus membranes.[7] Additionally, iodine solutions are used in the nose for MRSA decolonization and have been used long term in nursing home residents.[8] Furthermore, prior studies have used concentrations as high as 4.4% in nasal spray form for extended periods in healthy volunteers without adverse effects.[4] In our clinical practice, 10% PVP-I is used in the mouth and nose as a surgical prep prior to procedures in the operating room. Additionally, some of our patients with chronic sinus disease have been instructed to use high volume (240 mL) nasal rinses of PVP-I for several months without observed adverse effects or objective changes on nasal endoscopy.

With long term use of iodine containing compounds, there is a theoretical risk of excessive iodine absorption which could affect the thyroid gland. However, given the short duration of our study, the cumulative exposure will remain far lower than in many common medical procedures.

0.5% PVP-I contains 5 mg/mL and 2% PVP-I contains 20 mg/mL. The estimated volume delivered by two nasal sprays to each nare in a single administration is 0.33 mL.[9]

0.33 ml/dose x 4 doses/day x 7 days = 37.2 mL of solution administered.

At a 0.5% PVP-I concentration, the total amount of iodine administered is 186 milligrams. At 2.0% PVP-I, the total amount of iodine administered is 744 milligrams or 0.744 grams. The most common medical procedure in which patients are exposed to iodine are computed tomography (CT) scans which use iodinated contrast. The average dose per scan is estimated to be 15-37 **grams** of iodine[10] which is an order of magnitude greater exposure to iodine than what is proposed in this study.

Participant study timeline

Day 0	Enrollment, intake questionnaire, baseline NP swab, first dose of sprays, 4-hour post NP swab, UPSIT
Day 1	Continue sprays
Day 2	Continue sprays, symptom questionnaire, adverse symptoms and compliance questionnaire
Day 3	Continue sprays, daily questionnaire
Day 4	Final day of sprays, NP swab, daily questionnaire, adverse symptoms and compliance questionnaire
Day 6-29	No study procedures
Day 30	Repeat UPSIT

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