16th July 2020

Dear Sir/Madam,

Official Title: Povidone-Iodine vs Essential Oils vs Tap Water Gargling for COVID-19 Patients
NCT No: NCT04410159
Date of document: 1st May 2020

I am writing to provide the study protocol, information sheet and consent form of the abovesaid study. The documents have been approved by the Ethical Review Board.

Thank you

NA Mohamed

STUDY PROTOCOL

An Open Labelled, Randomised Controlled Trial Of Povidone-Iodine Vs Essential Oils Vs Tap Water Gargle For Covid-19 Patients: A Pilot Study

Executive summary

SARS-CoV-2 is transmitted via respiratory droplets from infected person and via contaminated surfaces. Hand hygiene, wearing mask, social distancing and environmental disinfection are important to prevent the virus spread. Gargling had been reported to have significant roles in the prevention and treatment of respiratory tract infection. However, the evidences are not strong enough to support its role in treatment and prevention of COVID-19. Therefore, the purpose of this study is to assess the ability of regular gargling to eliminate SARS-CoV-2 in the oropharynx and nasopharynx. This 4-arms interventional study compares the effect of gargling with

i) povidone-iodine
ii) essential oil
iii) tap water
iv) **control (no intervention)

Findings from this study will provide new insight on the importance of gargling in the prevention of COVID-19 and other respiratory tract infections.

Material and Methods

Study design

This 4-arms open labelled, randomized, parallel, pilot, interventional study compares the effect of gargling with povidone-iodine, and essential oils among COVID-19 patients.

Sample size and population

Sample size: at least 5 per arm

Patients will be randomly assigned to one of the groups as below:

1. Gargle with povidone-iodine (Group A)
2. Gargle with essential oil (Group B)
4. Gargle with tap water (Group C)
3. No intervention (Group D)

Inclusion criteria

1) adult aged 18 years and above
2) able to understand instructions
3) Stage 1 COVID-19
4) < 5 days of illness (DOI)

Exclusion criteria

1. Less than 18 years old
2. Unable to understand instructions
3. Unable to gargle due to any possible reason (physical/psychological)
4. Stage 2,3 COVID-19
5. Respiratory symptoms or fever on admission
6. Abnormal chest radiograph or computed tomography (CT) findings on admission
7. those started on treatment for COVID-19 or COVID-19 complication
8. Significant comorbidities

9. Those reinfected with SARS-CoV-2
10. Abnormal thyroid function test (for Group A)
11. Allergy to any of the active ingredients.

Experimental plan

After written consent taken, all groups will be briefed regarding the study protocol separately.

- Group A will be briefed on the correct procedures of gargling with Betadine®. The participants will be instructed to take 10ml of PVP-I, tilt their heads backward and gargle for 30 seconds, three times per day for 7 days

- Group B will be briefed on the correct technique of gargling with Listerine®. The participants will be instructed to take 20ml of essential oils, tilt their heads backward and gargle for 30 seconds, three times per day for 7 days

- Group C will be briefed on the correct technique of gargling with tap water. The participants will be instructed to take 100ml tap water, tilt their heads backward and gargle for 30 seconds, three times per day for 7 days

- Group D will be briefed about the involvement in this study. They will be managed according to standard protocol of the hospital with no additional intervention.

Primary Endpoint

- RT PCR result of naso & oropharyngeal swab at day 6

Secondary endpoints

- RT PCR result of naso & oropharyngeal swab at day 12
- Disease progression (signs and symptoms)
- Laboratory and radiological progression

Monitoring

1. Oropharygeal and nasopharyngeal swabs will be taken at day 4 and 6 post intervention. The swabs will be subjected for detection of SARS-CoV-2 by real time RT-PCR.
2. Patients will be given a chart for them to record their gargling practice and symptoms (if any) during the intervention period (7 days)
3. Clinical data collection sheet will be provided to attending clinicians. The required information includes demographic data, daily vital signs, serial absolute lymphocytic count, CRP, chest radiograph and symptoms. Clinical monitoring will be done for 12 days

Data Analysis

Statistical analysis will be performed using the IBM SPSS Statistics (v24.0) for descriptive and inferential statistics, such as the Fisher-Freeman-Halton exact test to determine associations between gargling groups and COVID-19 swab results.

Potential Risks

Povidone iodine:

Although measurable systemic absorption may occur with the long-term use of PVP-I, its clinical manifestation as thyroid dysfunction is not very common. Previous studies reported PVP-I mouthwash used four times daily for a short

period (2 weeks) or once-daily for a prolonged period (24 weeks) did not affect thyroid function1.
**Only those with normal thyroid function test will be enrolled in this study.

Essential oils:
Concerns have been raised about long term safety of ethanol in the formulation.The solution comprises of 4 essential oils (eucalyptol, menthol, thymol and methyl salicylate)

Benefits

Povidone iodine (Betadine) had been proven effective against viruses eg coronavirus (MERS, SARS, human CoV), influenza and bacteria. It has also proven effective against novel coronavirus (SARS-CoV2) in a recent in vitro study.

Listerine had also been proven effective against influenza and herpes virus. It is widely available in the market with fair price.

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Justification for the route of administration, dosage, dosage regimen, and treatment period

Route of administration, dosage and regimen are according to manufacturers' recommendations.

This trial will be conducted in compliance with study protocol and manufacturers' recommendation.

Stopping and Discontinuation Criteria

Respondents are allowed to stop or discontinue due to:
- Own decision
- Development of adverse effect
- Progression of disease to Stage 3

INFORMATION SHEET FOR SUBJECT/PATIENT

STUDY TITLE:

An Open Labelled, Randomised Controlled Trial Of Povidone-Iodine Vs Essential Oils Vs Tap Water Gargle For Covid-19 Patients: A Pilot Study

INTRODUCTION

We are conducting a research regarding effect of gargling among COVID-19 patients. Gargling had been reported to have significant roles in the prevention and treatment of respiratory tract infection. However, the evidences are not strong enough to support its role in treatment and prevention of COVID-19. Therefore, the purpose of this study is to assess the ability of regular gargling to eliminate the virus.

WHAT WOULD THIS INVOLVE?

You will be asked to gargle frequently during your hospital stay (see INSTRUCTION). Additional nasopharyageal swab will be taken at day 5 and 7 of intervention. You also need to fill in a form regarding frequency of gargling and symptoms of COVID-19 (if any).

THE BENEFITS

Research conducted will contribute to the development of science and medicine. Findings from this study will provide information on the effectiveness of gargling among COVID-19 patients. If the result is favourable, gargling will be recommended as part of management strategies for COVID-19.

RISKS AND DISCOMFORTS

It is possible that you may develop an allergic reaction to the gargle solution. If you experience any symptoms you may choose either to continue or terminate your participation in this study.

CONFIDENTIALITY

The results of the data obtained will be reported in a collected manner with no reference to specific individual. Hence, the data from each individual will remain confidential. As a subject/patient/parent, you have the right to know the results for you only.

DID I HAVE TO TAKE PART?

The participation in this study is voluntary. If you prefer not to take part, you do not have to give a reason and your doctor will not be upset and your decision will not affect the treatment given. You may also withdraw at any point in time during the study.

PAYMENT AND COMPENSATION

You do not have to pay for participating in this study and no payment available for participating in this study.

For futher enquiries, please do not hesitate to contact me, Dr Nurul Azmawati binti Mohamed at drnurul@usim.edu.my or 012-9646276. We will answer your questions appropriately.

INFORMATION SHEET FOR CONTROL GROUP

STUDY TITLE:

An Open Labelled, Randomised Controlled Trial Of Povidone-Iodine Vs Essential Oils Vs Tap Water Gargle For Covid-19 Patients: A Pilot Study

INTRODUCTION

We are conducting a research regarding effect of gargling among COVID-19 patients. Gargling had been reported to have significant roles in the prevention and treatment of respiratory tract infection. However, the evidences are not strong enough to support its role in treatment and prevention of COVID-19. Therefore, the purpose of this study is to assess the ability of regular gargling to eliminate the virus.

WHAT WOULD THIS INVOLVE?

As you are in the control group, **you do not have to do anything**. We would like to compare your viral load and clinical progression with those in the intervention group. Therefore, additional **nasopharyageal swab** will be taken at **day 5 and 7** of intervention. You also need to fill in a **daily chart** regarding symptoms of COVID-19 (if any).

THE BENEFITS

Research conducted will contribute to the development of science and medicine. Findings from this study will provide information on the effectiveness of gargling among COVID-19 patients. If the result is favourable, gargling will be recommended as part of management strategies for COVID-19.

RISKS AND DISCOMFORTS

As you are in the control group, there is no risk on gargling, but there is risk of pain during nasopharyngeal swab. The procedure is similar to that you have gone through before.

CONFIDENTIALITY

The results of the data obtained will be reported in a collected manner with no reference to specific individual. Hence, the data from each individual will remain confidential. As a subject/patient/parent, you have the right to know the results for you only.

DID I HAVE TO TAKE PART?

The participation in this study is voluntary. If you prefer not to take part, you do not have to give a reason and your doctor will not be upset and your decision will not affect the treatment given. You may also withdraw at any point in time during the study.

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For futher enquiries, please do not hesitate to contact me, Dr Nurul Azmawati binti Mohamed at drnurul@usim.edu.my or 012-9646276. We will answer your questions appropriately.

CONSENT FORM

TITLE OF THE PROJECT

AN OPEN LABELLED, RANDOMIZED, CLINICAL TRIAL OF POVIDONE-IODINE VS ESSENTIAL OILS VS TAP WATER FOR COVID19 PATIENTS

I,……
(IC number)……..
address……
……
……
have read the information on the research project stated above and have also been given explanation by the person in charge about the purpose of this document. I have been adequately informed about the purpose, set-up, course and risk of the study. At any time during and after my participation to the study, I am aware that the investigator is responsible for providing me any additional information about the study. I also have the right to know about the results of the research.
I **AGREE/DISAGREE** to participate in this research project.

…….
Signature
Date:
Phone number:

…… ……..
……..
Name of researcher/representative: Signature Date
NRIC:

…… ……..
……..
Name of witness: Signature Date
NRIC: