RESEARCH PROTOCOL

Project Title

A multicenter, single blind, randomized controlled trial of virucidal effect of Polyvinylpyrrolidone-Iodine on SARS-CoV-2 as well as safety of its application on nasopharynx & oropharynx of COVID-19 positive patients

BMRC Reg. No: 38624012021

Project Title

A multicenter, single blind, randomized controlled trial of virucidal effect of Polyvinylpyrrolidone-Iodine on SARS-CoV-2 as well as safety of its application on nasopharynx & oropharynx of COVID-19 positive patients.

Summary

Povidone Iodine (Iodine with water soluble polymer Polyvinylpyrolidone) or PVP-I is a proven and time trusted antiseptic agent having best possible (99.99%) virucidal effect in it's only 0.23% concentration, against all viruses including SARS-Co, MERS-CoV; even in SARS-COV-2 due to it's nonspecific mode of action for virus killing and having no resistance [1,2]. Corona virus is transmitted by/via respiratory droplets or aerosol, produced from sneezing or coughing of infected persons to healthy individual through mouth and nose mainly [5, 6]. The routes of entry of coronavirus in human body are mouth, nose and eye. PVP-I products for gargling the throat and spraying or washing the nose may have a preventive effect on COVID-19 and if it is proved in this study following human trial, this will be a landmark research in COVID-19 pandemic.

In line of this, PVP-I containing oro-nasal spray, proposed Bangasafe, which should be regarded as PONS (Povidone Iodine oro-nasal spray) in this protocol, has been developed and proposed to use against corona virus disease. The proposed clinical trial would assess the safety and efficacy of this virucidal PONS. This oro-nasal spray is prepared following GMP guideline, easily applied and has been found to be safe and effective. The clinical trial proposed here would be conducted in Bangladesh to specifically assess the safety and efficacy concern of this oro-nasal spray among Bangladeshi citizen. For preliminary assessment of efficacy and safety, a small scale randomized controlled trial with about 200 patients who are COVID-19 positive within last 24 hours had already been taken place in Dhaka medical college hospital and the data has been collected from May 2020 to September 2020 which were very much satisfactory [Attachment 2].

Introduction

The corona virus COVID-19 pandemic is the defining global health crisis of our time and the greatest challenge we have faced since World War Two. We have now reached the tragic milestone of two million deaths, and the human family is suffering under an almost intolerable burden of loss. The pandemic is much more than a health crisis; it's also an unprecedented socio-economic crisis. Stressing every one of the countries it touches; it has the potential to create devastating social, economic and political effects that will leave deep and longstanding scars. Every day, people are losing jobs and income, with no way of knowing when normality will return. Small island nations, heavily dependent on tourism, have empty hotels and deserted beaches. The International Labor Organization estimates that 400 million jobs could be lost

Background Information

1. Description of Povidone Iodine

PVP-I is a water-soluble iodophor (or iodine-releasing agent) that consists of a complex between iodine and a solubilizing polymer carrier, polyvinylpyrrolidone. In aqueous solution, a dynamic equilibrium occurs between free iodine (I_2), the active virucidal agent, and the PVP-I-complex.

2. Composition

The PONS contains 0.6% PVP-I as an Active Pharmaceutical Ingredients (API) in sterile de-ionized water. The molecular structure of PVP-I is as follow:

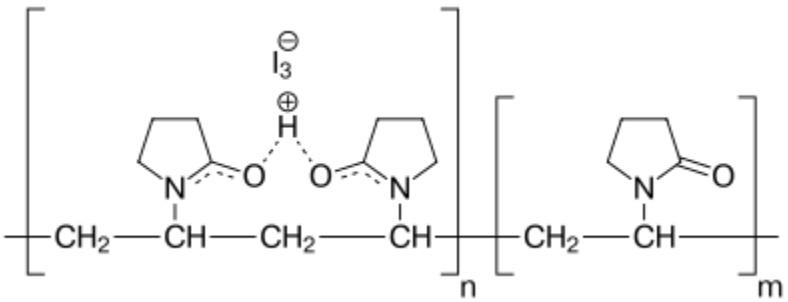

Figure: Chemical Structure of Povidone Iodine

3. Product Development, Quality Control and Quality Assurance

Following aspects of raw materials including API, manufacturing in-process steps, finished product are to be real time monitored and produced in Bangladesh Reference Institute for Chemical Measurements (BRiCM), Ministry of Science and Technology which is the nation first and only recognized national reference institute in chemical metrology.

- Raw materials characterization: Appearance, solubility, identification, nitrogen content, iodide value, loss on drying, pH, sulphated ash and available iodine.
- Solvent/diluents characterization: pH, conductivity, total organic carbon, heavy metal (Pb, As), endotoxin, microbial count.
- Product development and quality testing in several stages: pH, available iodine, iodide, UV absorbance, potency.
- Impurity profile testing: 1-Vinyl-2-pyrrolidinone, 2-Pyrrolidinone, heavy metal (Pb)
- Accelerated & real time stability study and shelf-life determination: pH, available iodine, iodide, UV absorbance Up to 3 (three) month at 25°C, 30 °C and 35 °C

4. Mode of Action

The active moiety, non PVP- bound ('free') iodine is released into solution from the PVP- I complex. PVP itself has no microbicidal activity but rather delivers the free iodine to target cell membranes. It is this free iodine that mediates the basic mechanism of action (oxidation of amino acids and nucleic acids in biological structures), which is difficult, if not impossible, to counteract. This basic mechanism of action leads to strong microbicidal activity expressed by multiple modes of action that include the disruption of microbial metabolic pathways, as well as destabilisation of the structural components of cell membranes, causing irreversible damage to the pathogen. Consumed free iodine is then replaced by PVP- bound iodine. The concentration of free iodine is the determining factor of the microbicidal action of PVP- I. In a study investigating the virucidal activity of different disinfectants, electron micrographs revealed how exposure to iodine led to degeneration of the nucleoproteins of viral particles, which was the main mechanism of action .However, disruption of surface proteins essential for the spread of enveloped viruses has also been noted. Furthermore, iodine is a scavanger of free radical oxygen species, contributing to anti-inflammatory properties. This interaction ultimately results in microbial death.

Corona virus is transmitted via respiratory droplets or aerosol, produced from sneezing or coughing of infected persons to healthy individual through mouth, nose and eye. After entry into nasopharynx and oropharynx and Eyes virus stayed there for certain period of time. Then it attached with ACE-2 receptor protein in nasopharynx and oropharynx and invade in to deeper cell s in to these areas. PONS containing 0.6 PVP-I will directly kill the virus and also keep the respective person protective layer of PVP-I for considerable time which will give an additional protection for individual user from SARS-CoV-2 virus infection.

5. Dosage and Administration

For adult (18 years and above)

Two puffs in mouth & each nostril in 3-4 hours interval not more than 4 times a day.

6. How Supplied

PONS_aqueous solution containing 0.6%PVP-I is supplied in 30ml amber color High Density Poly Ethylene (HDPE) bottle designed for pharmaceutical packaging to provide adequate protection against sun light.

Side effect

7. Contraindications

Iodine hypersensitivity

Patients with sensitivity to iodine and polyvinylpyrrolidine should not receive treatment with povidone-iodine. (ref)

Before intervention all participants will be asked about any H/O hypersensitivity of any drug or food or Iodine containing food or drug. If any participant had previous H/O hypersensitivity he/ she will be excluded from the study.

For immediate hypersensitivity (like other food and drugs) could be ascertained by manifestation of hypotension, respiratory distress, skin itching, discomfort, mucosal swelling.If any , necessary treatment will be provided to settle the patient. For delayed hypersensitivity different biochemical test , like FT3, FT4, TSH etc. will also be done.

Thyroid disease

Caution is advised when administering povidone-iodine to patients with thyroid disease.It should not be used prior to or after radioiodine scintigraphy or radioiodine treatment of thyroid carcinoma.

Children, infants

Safety and efficacy of the non-prescription use of povidone-iodine products have not been established in infants or children. Use in the pediatric population should be under the prescription of a qualified health care professional; newborn exposure is typically not recommended for umbilical care due to the possibility of inducing hypothyroidism from iodine absorption. Store out of the reach of children.

Pregnancy and Breast-feeding mother

Not recommended for pregnant and breast feeding mother. Topical use of povidone-iodine immediately prior to delivery has resulted in iodine overload in breast-feeding infants in the postpartum period, and may lead to transient hypothyroidism.

8. Instructions to the Patient

The package contains a patient information leaflet to facilitate explaining the characteristics of PONS to patients. A copy of the leaflet should be given to each patient. The advantages and disadvantages of PONS should be explained thoroughly to the patient.

9. Interaction with other drugs
Effects of other drug on Povidone Iodine as below:

Benzalkonium Chloride: The use of iodine (povidone-iodine) with benzalkonium chloride aqueous solutions may be incompatible.

Bupivacaine Liposomal/Lidocaine: Bupivacaine liposomal/Lidocaineshould not come into contact with the product containing povidone-iodine.

Collagenase: Povidone-iodine inactivates collagenase and concurrent use should be avoided.

Fibrin Sealant, Human: If povidone-iodine has been used to clean the wound area, thoroughly rinse and dry prior to application of fibrin sealant. The sealer protein and thrombin solutions of Artiss, TachoSil, and Tisseel can be denatured by povidone-iodine.

Lithium Therapy: Use with concurrent lithium therapy has been shown to exhibit additive hypothyroidic effects; therefore concurrent administration is not recommended.

10. Undesirable effects

No significant side effect is reported when recommended dose is administered at defined frequency. Mild irritation and burning sensation for few seconds to minutes may be observed. Anaphylactic reactions, anaphylactoid reactions and anaphylactic shock have been reported uncommonly with products containing Povidone-Iodine or Povidone. Excess Iodine can produce goitre and hypothyroidism or hyperthyroidism. Such effects have occasionally been seen with extensive or prolonged use of Povidone Iodine.

Research Question

- Does 0.6% PVP-I containing oronasal spray kill or reduce spread transmission of SARS-CoV-2 virus residing on nasopharynx and oropharynx of healthy person or healthy carrier before and after exposed to COVID-19 case?

- Does 0.6% PVP-I containing oronasal spray could be safely used amongst healthy individual

or healthy carrier?

Objectives of the study

a. Primary Objective

To assess the virucidal efficacy of 0.6% PVP-I against SARS-CoV-2 in nasopharynx and oropharynx in order to use:

- To prevent viral infection before exposure while visiting and treating COVID-19 patients, attending public gatherings, using public transport etc.
- To prevent viral infection after exposure to COVID-19 patients
- To reduce viral load in nasopharynx and oropharynx of COVID-19 patients which is supposed to reduce viral transmission through respiratory route

b. Secondary Objectives

- To assess the viral load in the nasopharynx and oropharynx before and after application of 0.6% PVP-I of participants of this study.
- To assess the duration of effectivity of 0.6% PVP-I on mucosal surface of participating COVID-19 patients by testing consecutive sample hourly upto 4hr .
- To estimate the shelf-life and stability of 0.6 % PONS.
- To characterize raw materials and impurities for product development and quality control/ assurance
- To measure the safety level of 0.6% PONS by biochemical analysis of participants blood & urine

Study Rationale

Povidone Iodine or PVP-I (Iodine with water soluble polymer Polyvinylpyrolidone) is a proven and time trusted antiseptic agent having best possible (99.99%) virucidal effect in 0.23% concentration. It acts against many/maximum viruses including SARS-CoV and MERS-CoV due to it's nonspecific mode of action in virus killing and shows no resistance. Baley et. al, 2020, proposed that 0.5% PVP-I could safely be used in nasal spray to kill SARS-CoV-2 virus [4, 6]. A previous study showed that 1.0% PVP-I used in gargle/mouthwash could reduce the viral titer of ≥4 log 10 by 99.99% in case of MERS-CoV infection [4]. Even in higher concentration of PVP-I (2.2% to 4.4 % liposomal preparation) was proved safer to apply as a nasal spray for antimicrobial activity [5].

Corona virus is transmitted via respiratory droplets or aerosol, produced from sneezing or coughing of infected persons to healthy individual through mouth, nose and eye. PVP-I gargle/spray used in throat and nose are shown to have board spectrum antimicrobial activity and may have preventive effect on SARS-CoV-2. Though wearing masks and social distancing can significantly reduce transmission and spread but these practice have not been universally adopted. As we are eagerly waiting for a definition treatment and an effective vaccination to contain and pervert the spread of SARS-COV-2, additional strategies are required to reduce transmission. 0.6% PONS which will directly treat the major sites of reception of transmission of SARS-Cov-2 virus may provide an additional level of protection against this virus. This study aims to evaluate virucidal efficacy of 0.6% PVP-I against SARS-CoV-2 amongst humans and its safety that is expected to contribute to save lives during this COVID-19 pandemic.

Methodology

Study design

It will be a Multicentre, Single blind, Randomized Controlled Trial.

The participant will be divided into three groups namely Group A (384 intervention group and 384 control group), Group B (20 patient) and Group C (10 healthy person).

Group A Number of participants 768 COVID-19 positive, moderately ill admitted patient who will receive intervention once (2 puff 0.6% PVP-I in each nostril and 2 puff inside mouth).

Step 1: Enrollment of the study populations by applying inclusion and exclusion criteria
Step 2: Randomization to allocate experimental and controlled group by using table of random number
Step 3: Application of 0.6% PVP-I spray to experimental group and distilled water to control group
Step 4: Follow up (waiting for 2-5 minutes)
Step 5: Collection of nasopharyngeal and oropharyngeal sawab for RT-PCR test for both group
Step 6: Observation of the patients for 30 minutes for possible early adverse effects (if any) and subsequent management (if needed).
Step 7: Analysis data collection, data processing and analysis by using SPSS software.

Group B Number of participants 20 asymptomatic to mild COVID -19 patients to whom after single time application of PVP-I oro-nasal spray, RT-PCR test will be done hourly for 4 hours in a single day (to assess the duration of effectiveness of PVP-I oronasal spray).

Step 1: Selection of 20 patients randomly with no or mild symptoms and obtain their consent for the further tests.
Step 2: Collection of 2^{nd}, 3^{rd} and 4^{th} sample from nasopharynx and oropharynx hourly
Step 3: Data collection, data processing and analysis by using SPSS software

Group C Number of participants 10 healthy individual who accept intervention 0.6% PVP-I oronasal spray 3-4 hours interval but not more than 4 times a day for 30 days.

Step 1: Selection of 10 healthy volunteers randomly who will be selected for using 0.6% PVP-I Oro-Nasal spray 2 puff inside both nostrils and mouth 3 to 4 times a day for one month.
Step 2: Collection of blood & urine of participants on day 0, 10, 20, 30 for determination of any change in biochemical marker (thyroid, kidney and liver functions will be done)
Step 3: Data collection, data processing and analysis by using SPSS software

N.B.

- Data collectors and Health Care Worker (HCW) involving in the research will be provided with standard and adequate number of all protective gears for their personal protection. Even though, if anyone become infected all the necessary treatment will be provided from the respective hospital without any expenditure.

- Viral concentration will be estimated semiquantitatively by analyzing the 'Cycle threshold value (CT value)' following RT- PCR. The CT value is a semiquantitative value that broadly categorises the concentration of viral genetic materials (NA) is in the samples. The CT value is inversely proportional to the concentration of viral genetic materials.i.e. low CT means high concentration of viral genetic materials and high CT value is the low concentration of viral genetic materials.

- BRiCM ensures Raw material & impurities characterization and determination of shelf life by performing the stability studies as follows:

Raw material & impurities characterization

- PVP-I collection from approved vendor with certificate of analysis (CoA)
- Characterization tests of PVP-I such as appearance, identification, solubility, nitrogen content, iodide value, loss on drying, pH, sulphated ash and available iodine as per BP 2019 are performed in well-equipped lab of BRiCM to review the test results with the acceptance criteria stated in the specification.
- Impurity testing of PVP-I as 1-Vinyl-2-pyrrolidinone, 2-Pyrrolidinone according to British Pharmacopeia (BP) 2019 and heavy metal (Pb) as per Association of Analytical Communities (AOAC) is carried out using HPLC, LC-MS-MS, AAS & ICPMS.
- Sterile water, the diluent of 0.6% PVP-I solution is characterized by performing the tests of pH, conductivity, total organic carbon, heavy metal (Pb, As) as per American Water Works Association (AWWA), endotoxin as per European Union (EU) 85 and microbial count as per AOAC in the well-equipped Microbiology Lab of BRiCM.
- Production of 0.6% PVP-I Oro-nasal spray solution from batch dispensing to final product packing is carried out following the norms of cGMP
- In-process quality assurance/control of the product is done at real time by performing, volume check, pH of the solution, available iodine, UV absorbance as per BP 2019 and packing integrity with necessary primary and secondary packing materials.

Stability Study & Shelf-life estimation

- Stability studies of the product are carried out at both accelerated condition as well as real time condition as per International Council for Harmonization (ICH) guidelines applicable for Stability Zone Iva.
- Stability studies at accelerated condition is carried out at 40 deg. C up to 12 months in 2 months interval and stability studies at real time condition is carried out at 25 deg. C up to two years in three months interval.
- Stability indicting parameters such as color of the solution, pH, available iodine, UV absorbance are included in both stability studies.
- Findings of both accelerated and real time stability studies are used to predict the shelf-life of the product up to two years.

Period of study

The study will be carried out during the period of May 2020 to June 2021.

Place of study

Dhaka Medical College Hospital, Kurmitola General Hospital and Kuwait Moytree Hospital including product development & quality assurance will be held at Bangladesh Reference Institute for Chemical Measurements (BRiCM)

Study Population

18 years and above aged COVID -19 positive admitted patients of COVID-19 dedicated unit of Dhaka Medical College Hospital , Kurmitola General Hospital and Kuawit Moytree Hospital will be included in this study, who are willing to participate. Written informed consent will be taken before participation in the study. A group of healthy person (10) will be randomly selected who are interested to receive intervention (PONS) 3-4 times interval but not more than 4 time a day for 30 days.

Selection Criteria

Selection of Participants : For G**roup A** and **Group B**

Inclusion Criteria

1. Hospital admitted patients tested positive COVID-19 within 24 hours in the laboratory by RT-PCR.
2. Patients with asymptomatic, mild to moderate illness of COVID-19.
3. Age group 18 year and above.
4. Consent of the patients, wish to be included in the study willingly.

N.B.

- Patient with moderate symptoms are normally get admitted in Hospital, who will be included in Group-A.
  The intervention Group-A will receive Oronasal spray containing PVP-I and control group will receive distilled water containing oronasal spray.
  As all participants of Group-A (asymptomatic, mild, moderate) are included in the study, so they will receive the same treatment (PONS)
- Asymptomatic and mild patients having co-morbid conditions are also admitted in Hospital who will be included in Group-B.
- For Group-C Participants, pre- intervention investigation will be done (FT3, FT4 TSH etc).

Exclusion Criteria

1. Patients with critical COVID-19 and moderate COVID-19 with other complication.
2. Patients having thyroid dysfunction, pregnant or lactating mother.
3. It should not be used prior to or after radioiodine scintigraphy or radioiodine treatment of thyroid carcinoma.
4. Patients allergic to iodine should be avoided
5. Have participated in other clinical study
6. Subjects with other severe acute or chronic conditions that may increase the risk of participation in the study and study treatment, or may interfere with interpretation of study results, and judged by the investigator as not suitable for participation in this clinical trial.

Selection of participants of Group- C

Inclusion Criteria

1. Healthy individual (non COVID-19)
2. Age -18 years and above (as below18 years lesser concentration of drug may be required).
3. Consent of the participants who wish to participate.

Exclusion Criteria

1. Participants who has any major comorbidity.
2. Participants having thyroid dysfunction, pregnant or lactating mother.
3. It should not be used prior to or after radioiodine scintigraphy or radioiodine treatment of thyroid carcinoma.
4. Participants allergic to iodine should be avoided
5. Have participated in other clinical study
6. Subjects with other severe acute or chronic conditions that may increase the risk of participation in the study and study treatment, or may interfere with interpretation of study results, and judged by the investigator as not suitable for participation in this clinical trial.

Sampling Technique

Random sampling procedure will be followed by using table of random numbers Admitted patients of dedicated Covid-19 hospital like KGH, KMH and DMCH will be taken after fulfilling of inclusion and exclusion criterias. Then from interested participants written informed consent will be taken. After ward randomization will be carried out to select intervention group and control group.

Sample Size

- The minimum sample size is given by:

  for a finite population $n = (Z^2 \times p \times q) / d^2$

  Where, n= sample size ,Z = Standard normal deviate usually set at 1.96 at 95% confidence If prevalence is not known, the value of prevalence will be considered as 50%.

  So, p will be 0.5.

  So, q = (1-p) = 0.50, and

  d = Desired accuracy or degree of allowable error. It is usually set as 5%(0.05).

  So, $n = \{(1.96)^2 \times 0.5 \times 0.5\} / (0.05)^2$

  Or, n = 384

N.B. Calculated sample size is equally applicable for both experimental (Intervention) and control group.

Sampling Unit

Individual study subject i.e. selected each participants will be considered as a sample unit.

Data Collection instrument and Technique

A preformed semi structured questionnaire and a check list will be used as data collection instrument. Besides medical history sheet and investigation papers of respective participants will also be used. Face to face interview will also be taken.

After receiving written permission from respective hospital authority and obtaining written informed correct data collection will be started. Study personnel at the site will enter data from source documents corresponding to a subject's visit into the protocol-specific paper CRF(Case report form). Subjects will not be identified by name in the study database or on any study documents to be collected by the principle investigator but will be identified by a site number, subject number and initials.

For paper CRFs: If a correction is made on a CRF, the study staff member will line through the incorrect data, write in the correct data and initial and date the change.

The Investigator is responsible for all information collected on subjects enrolled in this study. All data collected during the course of this study must be reviewed and verified for completeness and accuracy by the Investigator. A copy of the CRF will remain at the Investigator's site at the completion of the study (Annexure 3).

Data Processing

Everyday in later part of the evening collected data will be scrutinized thoroughly to check its consistency and cohesiveness of nearing quality to entre in draft data which will be saved in computer for future use. At the same time necessary coding, editing and cleaning of data will be done. Collected data will be preserved in master data sheet as per objectives and key variables.

All procedures for the handling and analysis of data will be conducted using good computing practices meeting FDA guidelines for the handling and analysis of data for clinical trials. In this regard latest SPSS software version will be used for statistical analysis.

Data Quality Control and Reporting

After data have been entered into the study database, a system of computerized data validation checks will be implemented and applied to the database on a regular basis. All changes to the study database will be documented.

Archival of Data

The database is safeguarded against unauthorized access by established security procedures; appropriate backup copies of the database and related software files shall be maintained. Databases are backed up by the database administrator in conjunction with any updates or changes to the database.

At critical junctures of the protocol (e.g. production of interim reports and final reports), data for analysis is locked and cleaned per established procedures.

Availability and Retention of Investigational Records

The Investigator must make study data accessible to the monitor and authorized representatives of the principle investigator. The Investigator must provide interim study report with data at every three months interval to the principle investigator. As per requirement study report and data may be provided to BMRC and DGDA. A file for each subject must be maintained that includes the signed Informed Consent form and copies of all source documentation related to that subject. The Investigator must ensure the reliability and availability of source documents from which the information on the CRF will be derived.

All study documents (patient files, signed informed consent forms, copies of CRFs, Study File Notebook, etc.) must be kept secured for a period of five years.

Data safety & Monitoring

Monitoring visits will be conducted by principle investigator, co- investigator as well as the representatives according to Guidelines for GCP. By signing this protocol, the investigator grants permission to the appropriate regulatory authorities to conduct on-site monitoring and/or auditing of all appropriate study documentation.

Subject Confidentiality

In order to maintain subject confidentiality, only a site number, subject number and subject initials will identify all study subjects on CRFs and other documentation submitted to the investigator. Additional subject confidentiality issues (if applicable) are covered in the Clinical Study Agreement.

Demographic and Baseline Characteristics

The following demographic variables at screening will be summarized by dose level: race, gender, age, height and weight.

Data Analysis

Data will be analyzed by computer using SPSS software computer program. Descriptive statistical analysis including mean, medium, mode, standard deviation, percentage, frequenc will be analyzed by SPSS. Inferential statistics including chi-square test , t-tes, F-test, Anova, Correlation etc will also be done to find out existence of any significant relationship between variables of this study. An analysis plan will also be prepared considering objectives of the study. Different data will be presented in to the frequency tables, graphs, chart according to the requirements.

Study personnel at the site will enter data from source documents corresponding to a subject's visit into the protocol-specific paper CRF(Case report form). Subjects will not be identified by name in the study database or on any study documents to be collected by the principle investigator but will be identified by a site number, subject number and initials.

For paper CRFs: If a correction is made on a CRF, the study staff member will line through the incorrect data, write in the correct data and initial and date the change.

The Investigator is responsible for all information collected on subjects enrolled in this study. All data collected during the course of this study must be reviewed and verified for completeness and accuracy by the Investigator. A copy of the CRF will remain at the Investigator's site at the completion of the study (Annexure 3).

Ethical Issues and Implication

This study will be approved by the BMRC, DGDA and the respective institution where the study will be taken place. Informed written consent of study populations will be taken. The study populations will be properly briefed about the risks and benefits of the study. None to minimum physical, psychological, cultural or financial harm of any kind is expected in the research work. If any adverse reaction on discomfort develop after applying one oro-nasal spray the individual participants will be provided with all necessary treatment without any cost in the respective hospital. The data will be coded and analyzed anonymously. The study will be conducted as per the Good Clinical Practice (GCP) and Good Laboratory Practice (GLP) guidelines applicable in Bangladesh and in accordance with the Declaration of Helsinki. All study information will be stored for twenty years and confidentiality of the study materials will be ensured. Necessary permission for data collection will be taken from respective hospital namely DMCH, KGH and KMH. Participants will have full right to participate or retract from the study at any level which will be well informed to the participants. The study will not have any ethical implication on the study subjects whatsoever. BMRC's Guidelines for Ethical Review of Projects involving Human Subjects has been carefully consulted in preparing this application for ethical clearance

Risk Management Plan

PVP-I, the active ingredient of PONS oro-nasal spray assumes no potential threat to the subjects. It substantially retains the broad spectrum germicidal activity of iodine against the commonly encountered organisms in skin and wound infections, without the undesirable features or disadvantages of iodine. PVP-I is decisively microbicidal against all 4 (four) major classes of pathogens: bacteria (gram-positive and gram-negative, as well as antibiotic-resistant strains), fungi, viruses and protozoa. PVP-I is being used widely in various dosage forms such as eye drop preparation, ointment, mouthwash in much more higher concentration (4%, 1% etc.) for several decades [2-6]. So, PONS oro-nasal spray containing comparatively very low concentration (0.6% of PVP-I) which supposed to be safed in oro-nasal application. Moreover, this oro-nasal spray is intended to be used in the selected hospitalized patients under the direct supervision of doctors &

nurses only volunteer will be healthy one who will also be remained is close supervision of physicians and researcher. Therefore, any adverse reaction risk if arises will be managed accordingly with the available facilities in respective hospital without any cost.

- If any discomfort, irritation, burning sensation occur then nasal irrigation with sterile plan water by 50 cc disposable syringe is to be given.
- If any hypersensitivity reaction occurs then anti-histamine and/or steroid is to be given

- **Clinical Laboratory Measurements**

Blood Chemistry Profile

Blood sample for Group - C participants will be collected and sent to the respective hospitals/BRICM clinical chemistry lab for determining of TSH, FT3, FT4, Serum creatinine, alanine aminotransferase (ALT/SGPT) level including urine test.

- **Facilities: (Resources, equipment, chemicals, subjects (human, animal) etc. required for the study):**

Existing facilities of Dhaka Medical College Hospital, Kurmitola General Hospital, Kuwait-Moitree Hospital and Bangladesh Reference Institute for Chemical Measurements will be utilized human subjects will be randomly selected for three hospital after getting proper written comments.

Endpoints

Primary Endpoints:

- Virucidal efficacy of 0.6% PVP-I against SARS-COV-2 virus which infect oropharyngeal and nasopharyngeal mucosa of humans.

Secondary Endpoints:

- Patient is to be safe with no significant side effect after using this oronasal spray.
- Safe if participants of the study who will use 0.6% PONS with minimum side effect (if any)

Sponsoring agency

BRiCM will be the sponsoring agency of this research work. BRiCM, said to be the producer of proposed PONS Oro-nasal Spray containing 0.6% PVP-I, is a statutory body functioning under the administrative control of the Ministry of Science and Technology. It is basically a research organization and a reference institute in the area of chemical measurements. It is neither a commercial enterprise nor a profit making organization. According to constitutional sanction the principal responsibility of BRiCM is to carry on research leading to such innovation that will add value to the government effort for ensuring welfare of the people.

Worth mentioning that, undertaking R&D program targeting to improvement of the quality of life of the people is one of the prime functions of a research laboratory like BRiCM. It is well equipped with necessary state of the art equipment, skilled manpower (scientists and logistic support staff) and adequate fund for implementation of R&D program either by itself or in collaboration with others. So, it is within the scope of BRiCM to undertake the proposed R&D, in collaboration with Dhaka Medical College Hospital, from its own budget which is provided by the government.

The proposed product cannot be considered as a commercial one and BRiCM is not the commercial producer. Rather, BRiCM takes the responsibility to develop it as a laboratory product ensuring appropriate quality as mentioned in Annexure-C (rephrased), the Methodology and Study design

Section meeting compliance requirements, especially targeting to ease the severity of the current pandemic situation in the country.

Besides, the clinical trial will be conducted in the hospitals, independent of BRiCM, under the general the guidance of BMRC, wherein, BRiCM will not have any role in decision making and the efficacy of the product will be finally determined by BMRC. Hence, funding by BRiCM for proposed PONS Oro-nasal Spray cannot give rise to the question of conflict of interest.

N.B.

The researchers and supporting persons those are directly involved in the hospital work with patient service; their effort should be awarded by honorarium, depicted in the Annexure E. Moreover, researcher and supporting stuff those who have to come in direct contact/exposure to COVID-19 patient which involve huge risk. The honorarium should be considered as source of encouragement of this novel task.

Utilization of Results

By providing information and assurance about the efficacy and safety of 0.6% PVP-I , we can inform and encourage people to use it as oronasal spray safely for prevention of COVID-19, as an adjunct to PPE and reduce transmissibility of SARS Cov-2 virus. The safe use of oronasal spray cumulatively will provide very significant impact on COVID-19 prevention inside the country as well as over global population which is expected to contribute to save lives in this COVID-19 pandemic situation.

References: Vancouver style will be followed.

Ethical approval for the study will be taken from BMRC

- **Approval / Forwarding of the Head of Department / Institute / IRB.**

Schedule of Activities (Flow Chart)

Feb 2021- June 2021

Events	February	March	April	May	June
Topic selection and submission of protocol					
Approval of protocol					
Planning and designing					
Literature review					
Preparation of questions					
Data collection field preparation					
Data processing and analysis					
Report writings and editing					
Submission of report					

NB: All stages of the main task supervision committee will be consulted.

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