

**USE OF CONVALESCENCE PLASMA IN THE
TREATMENT OF PATIENTS INFECTED WITH
COVID-19 VIRUS INFECTION (SARS-CoV-2)**

PROTOCOL VERSION v 1.2

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1 Background

The COVID-19 outbreak is a significant new public health threat due to rapid progression of infection with an estimated rate of severe disease that needs hospitalization and medical intervention. Early results with the use of convalescent plasma suggest that this may be a potentially useful treatment modality for COVID-19. Previous experience with Corona SARS demonstrated a therapeutic benefit of using convalescent plasma for patients with Corona SARS in Hong Kong[1]. A recent publication encourages the use of COVID19 convalescent serum for the preparation of hyper immunoglobulin to be used for passive immunization as well as treatment of early disease before the development of lower respiratory tract disease; pneumonia[2, 3].

1.1 *Investigational Agent*

- Convalescence plasma collected from “donors” who recovered from confirmed infection with COVID-19 Virus (SARS COV-2) infection who are subsequently tested negative for the presence of the virus (**Nucleic acid tests negative twice consecutively on respiratory tract samples such as sputum and nasopharyngeal swabs, sampling interval being at least 24 hours**) before plasma collection.

1.2 *Preclinical Data*

Convalescence plasma was previously used with varying success in treatment of viral respiratory epidemics and used recently in china with some success in patients with COVID-19.

1.3 Risk/Benefits

Potential risks of the investigational agents include transfusion reactions (febrile, allergic, infectious).

Potential benefit is clinical improvement in the course of the COVID-19 infection, which has a high morbidity and fatality rate.

1.4 Dose Rationale

Based on previous experiences of use of convalescence plasma in previous respiratory viral epidemics, the proposed dose of plasma to be used for each patient is 2 doses of 200 ml of blood group specific or compatible pathogen inactivated convalescence plasma according to the severity of the disease.

1.5 Trial Conduct

This study will be conducted in compliance with the protocol approved by the Institutional Review Board, and according to Good Clinical Practice standards. No deviation from the protocol will be implemented without the prior review and approval except where it may be necessary to eliminate an immediate hazard to a research subject.

1.6 Population

- Donor population will consist of adult males (>18 years of age) who had a confirmed COVID-19 infection and were subsequently tested negative for the virus. **Collection of plasma will be at least 28 days from onset of symptoms and at least 2 weeks of recovery from the disease. (Nucleic acid tests negative twice consecutively on respiratory tract samples such as sputum and nasopharyngeal swabs, sampling interval being at least 24 hours).**

Recipient population will consist of any adult patient (>16 years of age) who has confirmed COVID-19 admitted to the hospital and requires treatment. Children and pregnant women will be excluded.

Both donors and recipients need to agree to participation and sign an Informed consent.

2 Trial Objectives

To assess whether use of pathogen inactivated convalescence plasma (referred to here as plasma) may result in clinical benefit in patients with COVID-19 infection requiring treatment.

3 Trial Designs

1.7 *Primary Study Endpoints/Secondary Endpoints*

Primary endpoints: death, admission and discharge from ICU, discharge from hospital, days of hospitalization, number of days on mechanical ventilation after administration of the intervention.

Secondary endpoints: severe transfusion reactions, transfusion-transmitted infections

1.8 *Study Design/Type*

This is a prospective study.

Male donors who recovered from COVID-19 infection and subsequently were tested negative for the virus (PCR) will be approached for collection of convalescence plasma **at least 2 weeks** from recovery and negative testing.

Donors have to fulfill the criteria for eligibility for blood donation in this institution. **Repeat sputum, and blood testing for COVID-19 PCR will be performed before plasma donation. Plasma will be discarded in case of positive PCR testing.**

Plasma will be collected through the apheresis machine that is used routinely for apheresis donations in this institution. 600 mls of plasma will be collected at 1 setting. Collection may be repeated once, with the interval between the 2 donations being no less than 7 days.

Collected plasma will be virally Inactivated (Pathogen Inactivation Technique) and split in 200 ml doses. Plasma will have special labeling (ISBT 128 labeling system) and will be stored separately from plasma used routinely in the institution. It will undergo serologic and nucleic acid testing for transfusion-transmitted infections as per the standard procedure for blood donations. Plasma, which will be remaining and not used for the clinical trial may be used to produce immunoglobulin to be used in management of future patients (plasma and serum samples could be saved for determination of the neutralizing antibody titers) This would permit the study of the anti-viral effect with correlation to the administered dose of neutralizing antibodies in patients.

All patients fulfilling the inclusion criteria of being age 16 years or above, admitted to the hospital and confirmed positive for COVID-19 virus infection will be approached for participation and divided into 2 arms:

1- **1st arm** to receive convalescence plasma, in addition to standard of care therapy or specific medications used for treatment of COVID-19 through observational study (eg. Hydroxychloroquine & Zithromax).

Patients who provide informed consent will **receive 2 doses** of 200 ml each of group specific or compatible convalescence plasma. 48 hours apart. Patients will be

randomized into 2 groups. 1 group will receive 2 doses from the same donor, while the other group will receive 2 doses from 2 different donors.

Patients will be followed up clinically and through serial tests for sputum, stool, urine and blood. Patient samples could be saved for determination of viral loads pre- and post- therapy.

2- **2nd arm** will receive Medications alone without addition of convalescence Plasma.

The safety and efficacy of convalescent plasma or serum are unproven, clinical use of this product will be managed as an experimental therapy consistent with ethical safeguards informed consent, institutional approval, special labeling and a commitment to gather and report outcome data independently of the outcome of the study

1.9 Randomization

Patients who agree to receive the intervention will be randomized into 2 arms and first arm will receive required medications and 2doses of group compatible convalescence plasma from a single donor or 2 doses of plasma from 2 different donors.

2nd arm will receive only the required medication without use of convalescence plasma.

1.10 Trial Treatment

Patients who provide informed consent will receive 2 doses of 200 ml each of group compatible convalescence plasma 48 hours apart. Patients will be randomized into 2 groups. 1 group will receive 2 doses from the same donor, while the other group will receive 2 doses from 2 different donors.

1.11 Duration

Recipients will be followed during admission and for a month after discharge

1.12 Discontinuation

The trial may be discontinued in case the research team noticed an increase in the number of adverse events and serious adverse events.

This pilot study may be discontinued after recruitment of 30 patients

2 Selection and Withdrawal of Subjects

2.1 Inclusion Criteria

Donor population will consist of adult males (>18 years of age) who had a confirmed COVID-19 infection and were subsequently tested negative for the virus.

Recipient population will consist of any adult patient (>16 years of age) who has confirmed COVID-19 and requires treatment. Children and pregnant women will be excluded.

Both donors and recipients need to agree to participation and sign an informed consent.

2.2 Exclusion Criteria

Pregnant women and children below the age of 16 will be excluded from the recipients group.

Patients not confirmed to have COVID-19 would also be excluded

2.3 Subject Withdrawal

Donors and recipients may withdraw from the trial at any time. Follow up to ensure safety will be maintained with recipient consent.

2.4 Treatment of Subjects

Patients who provide informed consent will receive 2 doses of 200 ml each of group specific or compatible convalescence plasma., 48 hours apart each plus their management protocol. Patients will be randomized into 2 groups.

2.5 Medication

All medication that can be administered as “standard of care” may be used.

Or experimental medication as Hydroxychloroquine or chloroquine may be used.

2.6 Monitoring for subject compliance

The intervention will be administered under direct medical and nursing supervision. Follow up clinically and through serial investigation for the virus sputum, urine, stool and blood, chest CT. Patient samples could be saved for determination of viral loads pre- and post- therapy.

3 Assessment of Efficacy

3.1 Efficacy Parameters

Data on death, admission and discharge from ICU, days of hospitalization, number of days on mechanical ventilation after administration of the intervention will be used.

3.2 Method and Timing

Data will be recorded in real time

4 Assessment of Safety

4.1 Safety Parameters

Data on transfusion reactions, transfusion-transmitted infections will be used.

4.2 Method and Timing

Data will be recorded in real time

4.3 Adverse Event Reporting

Adverse events will be reported in compliance with the local IRB requirements and the requirements of other regulatory authorities.

4.4 Definitions

Adverse events: any unfavorable medical occurrences in subjects.^[1]_{SEP}

Serious adverse events: adverse events that result in any of the following: death, a life-threatening adverse event, emergency room visit or hospitalization.

4.5 Adverse Event Follow-up

Patients who experience adverse events will be followed until their resolution or for 6 months, whichever is sooner?

5 Data Handling and Record Keeping

Records will be kept in a confidential manner and will be only accessible to authorized individuals

6 Publication Plan

Negative or positive results will be submitted for publication in a peer-reviewed journal.

References:

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