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Government of India
Directorate General Health Services
Central Drugs Standard Control Organisation

Date: 17-04-2020

NOTICE

Sub: Clinical trial of convalescent plasma in COVID-19 patients- Regarding

It is to informed that in light of public interest the proposal of ICMR for conducting the said trial has been reviewed through the Subject Expert Committee (SEC) in its meeting held on 13-04-2020 under accelerated approval process in light of the current prevailing situation of COVID-19 and based on the recommendation of the committee, CDSCO has conveyed it's No objection for conduct of the clinical trial subject to certain amendments in the protocol and various conditions under the New Drugs and Clinical Trial Rules 2019.ICMR have also given a list of institutes to CDSCO which have shown interest in the conduct of said trial. Copy of amended protocol is enclosed.

While deliberating the clinical trial protocols of other applicants for conduct of clinical trial with convalescent plasma in COVID-19 patients, the SEC in the said meeting opined that ICMR has developed a protocol for a controlled clinical trial with convalescent plasma in moderate COVID-19 patients which has been reviewed by the committee and the same may also be considered by the applicants as appropriate.

In view of the above, any person/Institute/organisation interested in conduct of trial of convalescent plasma as per the protocol developed by ICMR and approved by CDSCO, may do so in consultation with ICMR and accordingly the applicant may approach ICMR for conduct of the clinical trial.

Enclosed: Copy of Protocol

V.G.S

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A Phase II, Open Label, Randomized Controlled Trial to Assess the Safety and Efficacy of Convalescent Plasma to Limit COVID-19 Associated Complications in Moderate Disease.

Introduction

The novel coronavirus disease (COVID-19), which began in Wuhan, China, in December 2019, has been declared to be a pandemic by the World Health Organization (WHO).[1] Caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), COVID-19 has resulted in 1,781,127 cases and 108,994 deaths globally (till 12th April, 2020), affecting 199 countries and 2 international conveyances.[2] In India, it has caused 8,356 confirmed cases, 716 recoveries, and 273 deaths from COVID-19 (till 12th April, 2020).[3]

The clinical manifestations of COVID-19 range from fever, cough, fatigue, sore throat, shortness of breath and less common symptoms such as headache, nausea and diarrhea.[4,5] The most common abnormalities in vital signs are increased temperature and tachypnea. The most common radiological findings are bilateral pulmonary infiltrates, ground glass opacities and consolidation. The most common findings associated with severe disease are older age, d-dimer levels greater, higher SOFA score, elevated IL-6, increased Lactate Dehydrogenase, hyperferritinemia and lymphopenia on admission.[6,7] The most common complications are sepsis, respiratory failure, acute respiratory distress syndrome (ARDS), cardiac injury and acute kidney injury.

Although not completely understood, multiple pathophysiological mechanisms have been hypothesized for the cause of mortality in COVID-19.[8] The plausible mechanisms of respiratory failure are hyperinflammation due to cytokine storm causing ARDS.[9] Another plausible mechanism of respiratory failure is occlusion and micro-thrombosis in small pulmonary vessels.[10]

Secondary hemophagocytic lymphohistiocytosis (sHLH) is a hyperinflammatory condition characterized by hypercytokinemia with multi-organ failure.[11] sHLH is usually triggered by viral infections and sepsis.[12] Infections account for 6-28% of causes triggering sHLH.[12–14] Severe COVID resembles sHLH characterized by cardinal features like fever, cytopenia, hyperferritinemia and increased Interleukins.[9]

Significantly abnormal coagulation parameters were noted in people who succumbed to COVID-19, with higher levels of D-dimer and fibrin degradation products (FDP), and lower levels of the fibrinogen and AT levels.[15] Increased levels of D-dimer are commonly reported in one third of patients with severe illness.[16] Occlusion and micro-thrombosis formation in pulmonary small vessels in such patients have also been reported.[10] The endothelial cell dysfunction, induced by infection, results in excess thrombin generation and fibrinolysis shutdown in patients with infection.[17,18] In addition, hypoxia stimulates thrombosis through not only increasing blood viscosity, but also a hypoxia-inducible transcription factor-dependent signaling pathway.[19]

According to another hypothesis, COVID-19 attacks the 1-beta chain of hemoglobin to dissociate the iron to form the porphyrin. This will cause reduced ability of the lungs to effectively exchange Oxygen and Carbon Dioxide. This inability causes inflammation in lungs causing ground glass opacities on radiological imaging.[20]

Convalescent Plasma in COVID-19

Currently, there are no approved treatments for COVID-19. The management plan is supportive care with supplemental oxygen and mechanical ventilation.[21] Multiple trials are being done across the globe to assess the efficacy of various treatment strategies. WHO initiated the SOLIDARITY trial in several countries to compare the effectiveness of the following regimens against COVID-19: Remdesivir, Lopinavir/Ritonavir, Lopinavir/Ritonavir with interferon beta, and hydroxychloroquine.[22] In a clinical trial, Lopinavir/Ritonavir did not demonstrate any benefit over Standard of care.[23] US FDA has recently approved Convalescent Plasma from patients recovered from COVID 19 for the treatment of severe or life threatening COVID-19 infections.[24]

In a small case series, five critically ill COVID-19 patients with ARDS were treated with convalescent plasma containing neutralizing antibodies. Infusion of plasma was followed by improvement in clinical status in all five patients, with no deaths and the study reported that three patients were discharged, whilst two continued to be stable on mechanical ventilation.[25] In another small case series of four patients, including one pregnant woman, it was seen that all four recovered eventually.[26]

In another feasibility study of convalescent plasma therapy, 10 severely ill patients were transfused with 200 ml of convalescent plasma.[27] It was well tolerated with significant increase in neutralizing antibodies and disappearance of viremia in 7 days. Clinical symptoms rapidly improved in 3 days.

Historically, it has been used in viral diseases such as poliomyelitis, measles, mumps and influenza before vaccines became available.[28–32] A meta-analysis of 1703 patients with H_1N_1 influenza during the Spanish Flu of 1918 suggested that patients who received convalescent plasma had lower mortality.[33] Conversely, in a double blind, randomized, placebo-controlled trial, convalescent plasma was not found to be superior to placebo in patients infected with Influenza A.[34–36] Furthermore, 84 patients with Ebola virus disease who were transfused with convalescent plasma without known levels of neutralizing antibodies did not have a survival benefit.[37] Convalescent plasma was also studied during the previous coronavirus outbreak of SARS in 2002 -2004. In a retrospective study of 80 patients by Cheng et al, it was observed that patients who received convalescent plasma before day 14 of illness had better outcomes, defined as early hospital discharge, compared to patients who received it after day 14 of illness (15.6% vs 58.3%; $P<0.001$).[38] Considering the lack of efficacious treatments for COVID 19 and the epidemic situation with high mortality rate, US FDA has approved convalescent plasma for COVID-19 for clinical trials, expanded access and single patient emergency investigational new drugs (IND).[39]

Majority of the adverse effects associated with plasma transfusion are non-lethal; medically treatable adverse effects commonly associated with transfusion of plasma include TRALI; transfusion associated circulatory overload (TACO); allergic/anaphylactic reactions;

transfusion related transmission of infections (TTI); febrile non-hemolytic transfusion reactions (FNHTR); hemolytic transfusion reactions (HTR); and rarely RBC allo-immunization.[40] Another theoretical risk of using convalescent plasma includes antibody dependent enhancement of infection.[41]

Hypothesis and Objectives

We hypothesize that the use of convalescent plasma will improve the clinical outcomes in patients with moderate COVID-19 infection.

We designed this phase II, open label, randomized clinical trial with the primary objective to assess the safety and efficacy of the therapy in the second stage.

Efficacy Objective: To assess the efficacy of convalescent plasma to limit complications in COVID-19 patients.

Safety Objective: To evaluate the safety of treatment with anti SARS-CoV-2 plasma in patients with COVID-19.

Methods

Study Design

Multi-center, two-arm, prospective, Phase II, open label, randomized controlled trial.

Study Population

Hospitalized COVID-19 patients fulfilling the inclusion and exclusion criteria, and admitted for care at COVID-19 management facilities in India will be eligible for inclusion in the trial.

Inclusion Criteria

1. Patients admitted with RT-PCR confirmed COVID-19 illness.
2. Age > 18 years
3. Written informed consent
4. Has any of the two
    a. PaO2/ FiO2 <300
    b. Respiratory Rate > 24/min and SaO2 $\leq$ 93% on room air

Exclusion criteria

1. Pregnant women
2. Breastfeeding women

3. Known hypersensitivity to blood products
4. Receipt of Pooled Immunoglobulin in last 30 days
5. Critically ill patients:
    a. P/F ratio <200 (moderate - severe ARDS)
    b. Shock (Requiring Vasopressor to maintain a MAP >= 65mmHg or MAP below 65)
6. Participating in any other clinical trial
7. Clinical status precluding infusion of blood products

Assessment of donor for eligibility

COVID-19 convalescent plasma will be collected from recovered individuals if they are eligible to donate blood. Considerations for assessment of donor for eligibility are outlined in the section on convalescent plasma.

Sample Size

For sample size calculation, we considered that given the standard of care, 18% of patients would succumb to COVID-19 infections.[5] We considered a relative effectiveness of 50% for sample size calculations. We calculated sample size using the PASS v11.0 software.[42]

Group sample sizes of 226 in the intervention group and 226 in the control group achieve 80% power to detect an absolute difference of -0.09 between the group proportions. The proportion of participants meeting the primary outcome in group one (the treatment group) is assumed to be 0.18 under the null hypothesis and 0.09 under the alternative hypothesis. The proportion of participants in group two (the control group) who meet the primary outcome is assumed to be 0.18 based on current evidence.[5] The test statistic used is the two-sided Z test with pooled variance. The significance level of the test was targeted at 0.05, with a power of 0.8.

Primary Outcomes

The primary outcome is a composite measure of the avoidance of -

1. Progression to severe ARDS (P/F ratio <100) and
2. All-cause Mortality at 28 days

Secondary Outcomes

1. Time to symptom resolution
    a. Fever
    b. Shortness of Breath
    c. Fatigue
2. Hospital length of stay
3. Change in SOFA pre and post transfusion
4. Duration of respiratory support required
    a. Duration of Invasive Mechanical Ventilation
    b. Duration of Non-Invasive

5. Radiological improvement
6. Adverse events (AE) associated with transfusion
7. To measure the change in RNA levels (Ct values) of SARS-CoV-2 from RT-PCR [Time Frame: Days 0, 1, 3, and 7 after transfusion]
8. Correlation between Viral neutralization titer and Elisa antibody Assay
9. Correlation between titers in donor plasma and IgG titer on transfusion
10. Levels of bio-markers pre and post transfusion
11. Need of Vasopressor use
12. Pre and post transfusion antibody titers

Other Exploratory Endpoints

1. Cumulative incidence of serious adverse events during the study period: transfusion reaction (fever, rash), transfusion related acute lung injury (TRALI), transfusion associated circulatory overload (TACO), transfusion related infection
2. Rates and duration of SARS-CoV-2 PCR positivity (RT-PCR) from days 0 and if further available.

Analysis Plan

Baseline data about the demography, clinical presentations, ongoing medical therapy, and clinical history of participants in both arms will be collected and compared. Response to convalescent plasma will be coded as a binary outcome – based on whether the composite primary end point is met or not. Adverse events associated with infusion of convalescent plasma will also be descriptively summarized and compared with the adverse events experienced by participants receiving standard of care.

The objective response rate, defined as the proportion of participants successfully meeting the primary end points, will also be reported, along with a two-sided 95% confidence interval calculated using the Clopper-Pearson method.[45] This will be compared between the intervention and control groups.

Participants who drop off from the treatment arm prior to evaluation of post-intervention response will be considered as non-responders, regardless of the discontinuation reasons, and will be included in the intention to treat analysis. Comparison between group response rates will be analyzed and reported.

Study Procedures:

	Screen	**Baseline**	**Intervention (Convalescent Plasma infusion)**	**Follow-up**				
Day	**-1 to 0**	**0**	**0**	**1**	**3**	**7**	**14**	**28**
Pre-Intervention Screening								
Eligibility screening and Informed Consent	x							

Demographic and Medical history	x							
SARS-CoV-2 RT-PCR test for eligibility	x							
Pregnancy test	x							
ABO	x							
Study Intervention								
Symptom checking	x	x	x	x	x	x	x	x
Randomization	x							
Convalescent Plasma Infusion			x					
Vital signs	x	x	xxxx[1]	x	x	x	x	x
Physical examination	x		x	x		x		x
Concomitant medications		x	x					
Adverse event monitoring			x	x	x	x	x	x
Lab Investigations								
CBC and CMP		x		x		x	x	
SARS-CoV-2 RT-PCR		x			x	x	x	
SARS-CoV-2 antibody		x		x	x	x	x	
Blood for testing and archiving		x		x	x	x	x	
Imaging		x		x				x
Others	As clinically indicated							

1 Vital signs need to be tested immediately prior to infusion, within 15 minutes after initiation of infusion, at the completion of infusion and within 1 hour of end of infusion

Convalescent plasma:

Eligibility of Donor

Potential donors will include the following[39]:

- Prior diagnosis of COVID-19 documented by a laboratory test and
- Complete resolution of symptoms and at least one negative lab test for COVID-19 at least 28 days prior to donation (as per NBTC guidelines after COVID -19 pandemic for donor selection). If plasma is collected prior to 28 days after full recovery from illness, then confirmation of the resolution of the infection should be obtained through demonstration of two non-reactive Nucleic Acid Tests (NAT) for SARS-CoV-2 performed at an interval of at least 24 hours on nasopharyngeal swabs.
- These individuals will be contacted telephonically and explained the details of the study and their extent of participation. They will be encouraged to visit the main blood bank for further evaluation towards eligibility for blood donation. If requested, they will be provided transport for the same.

Recruitment of Donor

At the time of discharge, all recovered COVID-19 patients will be counselled. They will be motivated towards donation of convalescent plasma after 28 days of symptom free period and its probable beneficial effects in the management of COVID-19 patients. Such patients will be briefed in detail regarding their extent of participation in the study. Later on, these individuals will be contacted telephonically on Post discharge Day 25. They will be encouraged to visit the Blood Bank for further evaluation towards eligibility for blood donation. If need arises, the participant will be provided conveyance for facilitating transport.

Donor eligibility criteria

The following eligibility criteria will be applied towards potential donors:

1. Only males and nulliparous female donors of weight > 55 kgs will be included.

2. Donor eligibility criteria for whole blood donation as per the departmental SOP will be followed in accordance to the Drugs & Cosmetics Act 1940 and rules 1945 therein (as amended till March 2020).[44] Donor will be screened, followed by brief physical examination.

3. Donors not fit to donate blood based on the history and examination will be deferred and excluded from plasma donor pool for a time period specified by country regulation & departmental SOPs.

4. In addition to the aforementioned donor eligibility criteria, two EDTA samples (5 ml each) and one plain sample (5 ml) will be drawn for the following pre-donation tests as required for convalescent plasmapheresis (CPP).

    - Blood group and antibody screening – Antibody screen positive donors will be deferred.
    - Complete blood count including Hb, Hct, Platelet count, Total and differential leucocyte count. Donors with Hb>12.5g/dl, platelet count >1,50,000 per microliter of blood and TLC within normal limits will be accepted.
    - Screening for HIV, HBV and HCV by serology and NAT. Donor negative by both the tests will be included.
    - Screening for syphilis and malaria by serology. Negative donors will be included
    - Total serum protein. Donors with total serum protein > 6gm/dl will be accepted (as per Drugs and Cosmetics (Second Amendment) Rules, 2020)
    - Presence of IgG and IgM antibodies to COVID-19 by rapid test as per manufacturers instruction. Donors negative for these will be deferred.

- Titration of anti-COVID-19 (both IgG and IgM) antibodies and SARS-CoV-2 neutralizing antibodies may be done depending on availability of facilities at the time of testing. (Desired titers for IgG antibodies >1024 or neutralizing antibodies >40) doubling dilution of donor serum will be done and titration will be done using ELISA. If not done at the time of plasma collection the donor samples will be stored in aliquots at <-80° C to be tested at a later date.
- Molecular test for COVID-19 either from nasopharyngeal swab specimens or blood may be done depending on availability of tests. Donors positive will be deferred.

Plasmapheresis of donors

Donors will be explained the procedure of plasma donation and the adverse events associated with the process. Among the consenting donors and based on the results, accepted donors will be asked to return on a specified date for plasma donation.

Plasma collection will be done by centrifugal separation using any of the apheresis equipment available at the facility. Volume collected will not exceed 500 ml per sitting (as per Drugs and Cosmetics (Second Amendment) Rules, 2020). Throughout the procedure the extracorporeal volume of blood will never exceed >15% of the total blood volume of the donor. Donor adverse events will be managed as per departmental SOP for Apheresis donations.

A unique donor identification number will be provided to the collected unit as per departmental SOP and the unit will be stored as per departmental SOP or issued for patient use. The collected plasma will be divided into smaller packs of 200 ml each for easy storage and transfusion. The plasma will be stored at <-40 degree Celsius.

No pooling of plasma from different donors will be done.

Successful plasma donors will be requested to repeat the donation. If the donor agrees for a repeat donation, such donation will be scheduled after at least 2 weeks of the first plasma donation. If there was a loss of red cells at the time of first donation owing to any procedural problems or otherwise the donor will be deferred for a period of 3 or 4 months for male or female donors respectively. All the donor selection guidelines described above will apply to repeat donation as well.

In repeated plasmapheresis:

1. Total serum protein will be tested before the third procedure if done within four weeks and it should be 6 gm/dl.
2. The quantity of plasma separated from the blood of donor will not exceed 500 ml per sitting and once in a fortnight or shall not exceed 1000 ml per month.

Infusion of Blood Products

For infusion of plasma existing SOP of the wards w.r.t transfusion of FFP should be followed with special care to monitor these patients during and post-24 hours of transfusion. All such transfusions have to be done using blood transfusion sets. The clinician will send a request for plasma component specifically mentioning the diagnosis and that convalescent plasma is required. An ABO compatible plasma bag of approx. 200ml will be issued maintaining all the blood bank records after thawing at 37 degree Celsius. the first plasma transfusion may be followed by one or two additional doses of 200 mL at 24 hours interval according to disease severity and tolerance of the infusions. The second plasma unit will preferably be from a different donor depending on the availability of another ABO compatible plasma unit or else plasma unit from the same donor will be issued.

Safety Assessments and Reporting

Definition of adverse events[45,46]

- Donor-related adverse events: They were divided into local reactions and systemic reactions. AEs were classified according to severity into mild, moderate, and severe and according to etiology in a donor into hypotensive reactions, citrate reactions, hematomas, loss of consciousness, seizures, and allergy.

- Kit/ Equipment-related adverse events: These are secondary to improper disposable sets. These are hemolysis, thrombus formation, air embolism, leakage, infection, improper mounting of the kits etc.

- Recipient related adverse events: A transfusion-related adverse reaction is a response or effect in a patient temporally associated with the administration of blood or blood components. Majority of the non-lethal and medically treatable adverse effects commonly associated with transfusion of plasma include transfusion related acute lung injury (TRALI); transfusion associated circulatory overload (TACO); allergic/anaphylactic reactions; transfusion related transmission of infections (TTI); febrile non-hemolytic transfusion reactions (FNHTR); hemolytic transfusion reactions (HTR); and rarely RBC allo-immunization

Details of Standard of care

The Ministry of Health and Welfare has issued detailed guidelines for the management of sCOVID-19 based on varying grades of severity.[47] For the management of ARDS or sepsis, the respective guidelines issued by ARDSNet and Surviving Sepsis campaign will be followed. Other institutional protocols for supportive management will be implemented.

Logistics of Investigational Products

Indicative list of supplies/logistics necessary to conduct this study.

Sl No	Item name
1	Anti-A
2	Anti-B
3	Anti-D
4	Antibody screen
5	Complete blood count
6	Serology (HIV, HBV, HCV, Syphilis & malaria)
7	NAT test (HIV, HBV & HCV)
8	Rapid IgG and IgM tests for COVID-19
9	IgM ELISA
10	IgG ELISA
11	Plasmapheresis disposable kit
12	Transfer bags
13	EDTA vials
14	Plain vials
15	20ml syringes
16	PPE kits
17	ELISA reader and washer
18	BBR-cum-freezer
19	Biosafety cabinet type 2
20	Donor Transport
21	Staff (technician / research associate)

Safety Assessments and Reporting

Definition of adverse event

An Adverse Event/Experience [AE] is any untoward medical occurrence in a participant undergoing TPE, is one which does not necessarily have a causal relationship with the TPE procedure. It can be any unfavorable and unintended sign, symptom, or disease, which is temporally associated with the use of convalescent plasma, whether or not considered to be causally related to convalescent plasma.

A Serious Adverse Event [SAE] is any untoward medical occurrence, at any point during convalescent plasma, results in:

- Death
- A life-threatening condition. This means any event in which the participant is at risk of death; it does not refer to a condition, which, with increasing severity, may result in death.
- Significant disability

Other medically significant outcomes, which may not result in any of the above, but may jeopardize the well-being of the participant, requiring greater degrees of medical or surgical interventions to prevent one of the outcomes listed above.

Data Management

Data Management Responsibilities

The Investigators will be responsible for assuring completeness, accuracy and timely collection of data. Case Record Forms (CRFs) should support the data entered in the electronic data capture system. They will be signed and dated by the person filling out the forms, and the investigator reviewing the same. Data will be reviewed by the Investigator and co-signed. Data management will be undertaken by ICMR-National Institute of Epidemiology.

Data Capture Methods

Paper CRFs will be used to collect data. The data will then be entered on an electronic system. A data entry system with electronic tracking, password restricted access, audit trail, with time and date stamps on data entry and edits, will be developed.

Types of Data

Data source would include, but are not limited to, participant CRFs, Informed Consent Forms (ICFs), participant medical records, laboratory reports, ECG tracings, x-rays or other radiologic scans, radiologist's reports, any biopsy or microbiology reports, ultrasound photographs, progress notes, pharmacy records, and any other similar reports or records of procedures performed during the subject's participation in the study, which is deemed to hold informational value by the investigator.

Access to Source Data/Documents

All data source documents, including clinical reports and records necessary for the evaluation and reconstruction of the clinical trial, will be stored securely, with a focus on ensuring the patient's confidentiality.

Record Retention

The investigator will be responsible for retaining all essential documents as outlined in the GCP Guidelines for a period of at least 5 years. All stored records will be kept confidential as outlined by applicable law.

Ethical Principles and Informed Consent

Informed Consent Process

If participants are compos mentis, they will provide their informed consent, and sign the document prior to any procedures being done specifically for the study. The signature of a legally authorized representative (LAR) of the potential participant will be obtained for adults who are impaired and unable to provide informed consent. In the case of adults whose ability to consent is uncertain, capacity to consent will be evaluated by the Investigator(s).

The participants or their representatives may withdraw consent at any time throughout the course of the trial. The welfare and rights of the participants will be protected by providing them assurance that their medical care will not be impaired if they refuse to participate in the trial. The experimental nature of the treatment will also be emphasized to the participants or their consenting LARs.

A copy of the informed consent/assent document will be given to the participants or their family members/LAR for their records. The completion of the signing of the informed consent form will be noted in the participants' medical records by the trial physicians.

Participant Confidentiality

All records and CRFs will be kept confidential, with access only to study staff, monitors, other authorized representatives who may inspect any documents which are required to be maintained by the investigator. Paper forms will be stored in locked cabinets and computer entered data will be maintained on password protected, access restricted computers.

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