ASIAN JOURNAL OF PHARMACEUTICAL AND CLINICAL RESEARCH

INNOVARE ACADEMIC SCIENCES
Knowledge to Innovation

Vol 14, Issue 2, 2021

Online - 2455-3891
Print - 0974-2441

Review Article

CONVALESCENT PLASMA THERAPY FOR COVID-19 PATIENTS: REGULATORY GUIDANCE ON COLLECTION, TESTING, PROCESSING, STORAGE, DISTRIBUTION, AND CLINICAL TRIALS

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Received: 25 September 2020, Revised and Accepted: 27 November 2020

ABSTRACT

Convalescent plasma can be transfused to patients suffering from the same infection or for preparing immunoglobulin concentrates. Plasma obtained from recovered patients can be a valuable alternative during the COVID-19 pandemic for supporting its treatment within a randomized or case-control clinical trials or observational studies of plasma transfusion and for preparing plasma-derived biological products. WHO Blood Regulators Network highlighted that a systematic approach for collecting convalescent plasma from patients recovered from COVID-19 could provide a useful intervention. Structured clinical trials can be used to assess safety and effectiveness of convalescent plasma. The convalescent plasma therapy is still in the experimental stage and is currently not included in the interim clinical guidelines of WHO. However, an emergency investigational new drug application (eIND) process has been induced to ensure the availability of COVID-19 convalescent plasma to the patients with severe or life-threatening COVID-19 conditions. USFDA is regularly amending its guidance as new results, and best practices are emerging. The write-up provides an overview of convalescent plasma, from a regulatory considerations viewpoint, systematic workflow protocol, and a cross-section of clinical trials underway.

Keywords: Passive immunization, Transfusion safety, Convalescent plasma, COVID-19, Plasmapheresis.

 DOI: http://dx.doi.org/10.22159/ajpcr.2021v14i2.39803. Journal homepage: https://innovareacademics.in/journals/index.php/ajpcr

INTRODUCTION

Plasma therapy emerged as a valuable approach for pathogen immunotherapy for acute infectious diseases, since the therapeutic effects of diphtheria antitoxin plasma in 1B91 were reported by Behring and Kitasato. In severe and critically ill patients of an emerging infection, the disease progression was rapid. During the starting phase, the target organs were damaged directly by the pathogens leading to severe immunopathological damage. These pathogens can be effectively and directly neutralized by passive immune antibodies reducing damage to the target organs and further blocking subsequent immunopathological damages [1].

Prevention and treatment of human infectious diseases by passive immunization started in the late 19th century. The possible use of whole convalescent blood and convalescent plasma for treating contagious diseases come into the spotlight during the Ebola virus outbreak in West Africa as it was the only therapeutic approach available in some cases due to the unavailability of drugs, vaccines, or other specific treatments [2,3]. Initially, the COVID-19 outbreak resulted in a high mortality rate due to a lack of effective and particular treatments. The non-availability of effective therapy for the COVID-19 pandemic has resulted in more than 1,160,000 deaths till October 27, 2020 worldwide. As mortality rate is an important parameter that concerns the public, clinical treatments that can decrease the fatality rate of critical cases virtually are urgently required to avoid public panic.

Researchers and scientists are continually searching for various treatment alternatives for developing vaccines and medicines to fight this life-threatening disease. Convalescent blood products can be a better alternative in the prophylaxis/treatment of some infectious diseases both as the single therapy when a specific treatment is not available and also in association with other drugs/preventive measures [4-7]. There are many potential convalescent plasma donors and critically ill patients requiring convalescent plasma treatment in hospital. Nevertheless, there are various arguments for considering the implementation of a large-scale convalescent plasma transfusion program [1].

CONVALESCENT PLASMA

Convalescent plasma refers to plasma obtained from a patient who has recovered from an infection. During the disease, the patient's immune system escalates an attack on the invading virus, and the body develops antibodies [8,9]. These antibodies are suspended in the circulating blood and can be separated from one of the components of blood – the plasma [10]. Notably, convalescent plasma was found to be effective against the Spanish flu pandemic in 1918. At that time, convalescent plasma was used by the U.S. military to treat flu patients. More recently, WHO approved it as an empiric treatment against Ebola virus infections in 2015, and it was deployed with success against the SARS (severe acute respiratory syndrome) in 2002–2003 and middle east respiratory syndrome in 2012 as well [10-13].

In the context of COVID-19, FDA guidance has been issued that provides recommendations to health care personnel and investigators for the administration of investigational convalescent plasma obtained from individuals recovered from COVID-19 during the public health emergency. The guidance illustrates recommendations on the following aspects: (i) Pathways for the use of investigational COVID-19 convalescent plasma, (ii) eligibility of patient (iii) collection of COVID-19 convalescent plasma, including eligibility and qualifications of donor, (iv) labeling of convalescent plasma, and (v) efficient record keeping [14].

Approaches for utilization of COVID-19 convalescent plasma

Since COVID-19 convalescent plasma is awaiting approval by the FDA, it is being used as an investigational drug. In these circumstances, health care personnel should follow one of the pathways detailed in Table 1. USFDA itself does not collect/provide COVID-19 convalescent plasma, but the product can be procured from an FDA registered blood establishment maintained by health care providers or acute care facilities [14].

Procedure for obtaining a single patient emergency IND

The request can be made by the provider at different time period during a day according to Eastern Standard Time (EST) as follows:

(i) For the requests between 8 am EST and 8 pm EST (Mon-Sun), the requesting physician may submit Form 3926 downloaded from https://www.fda.gov/media/98616/ by email to CBER_eIND_Covid-19@FDA.HHS.gov. FDA will respond within four h for the eIND requests submitted through email during this time frame. The completed form should include:
- A short clinical background of the patient including the reason for the request for investigational convalescent plasma treatment with the purpose to meet the requirements mentioned in 21 CFR 312.305 and 312.310.
- Name of the blood establishment collecting COVID-19 convalescent plasma.
- The provider should fill the form electronically, if possible.
- Providers should ensure maximum completeness of the form, and the FDA will contact the provider if the need arises.
- The FDA will review the request and, upon validation, send the requesting physician a confirmatory email (including the emergency IND number).

(ii) For requests between 8 am EST and 8 pm EST when the provider cannot complete and submit the form FDA 3926 due to mitigating circumstances, the provider can contact the FDA's Office of Emergency Operations to seek verbal authorization.

(iii) In case of a medical emergency, for the requests made between 8 pm and 8 am, the convalescent plasma provider should necessarily obtain verbal authorization of the Food Drug and Administration office of Emergency Operations. If verbal consent is disposed of, the requesting physician must agree to submit an expanded access application (Form FDA 3926) within the time frame of 15 working days in accordance with section {21 CFR 312.310(d)(2)}.

Patient eligibility

For expediting the requests for eINDs to use COVID-19 convalescent plasma for treating severe patients, the patient eligibility criteria should be in accordance with the National Expanded Access Treatment Protocol. These include [14,16]:

- Age of ≥18 years.
- Laboratory confirmed COVID-19 report.
- Severe or immediately life-threatening COVID-19, as mentioned in Table 2.
- Informed consent is given by the patient or healthcare proxy.
- The blood type of patient. Convalescent plasma must be ABO compatible with the recipient's blood type.

Collection of COVID-19 convalescent plasma

It is mandatory for the acute care facilities and health care providers intending to use COVID-19 convalescent plasma, in the eIND submission, to mention that the COVID-19 convalescent plasma will be procured from an FDA-registered blood establishment that abides by the donor eligibility criteria and donor qualifications in the collection of plasma from donors as detailed below:

Donor eligibility

a. Plasma can be collected from the individuals meeting all donor eligibility requirements according to 21 CFR 630.10, 21 CFR 630.15. The additional donor eligibility requirements for plasma collection by plasmapheresis can be found in 21 CFR 630.15 (b). Donated plasma should be tested for all the applicable transfusion-transmitted infections (21 CFR 610.40), and the donation must be satisfactory (21 CFR 630.30) [8].

b. The following qualifications should be met by the donor [14,20-22]:
- Confirmation of COVID-19 by a laboratory test either by a diagnostic test during illness OR by the presence of SARS-CoV-2

Table 1: Pathways available for administering or studying the use of COVID-19 convalescent plasma [14]

Pathways	Procedure/Protocol	Section
Clinical trials	To consider the application of convalescent plasma for a clinical trial, a request should be submitted by the investigators to FDA for the investigational purposes under the conventional IND regulatory pathway. Center for Biologics Evaluation and Research (CBER's) Office of Blood Research and Review is responsible for dealing with investigators and reviewing these requests promptly. INDs can be submitted through email to CBERDCC_eMailSub@fda.hhs.gov during the current COVID-19 pandemic situation.	21 CFR Part 312
Expanded access	For those patients with severe or immediately life-threatening COVID-19 disease who are ineligible or who are unable to take part in randomized clinical trials, an IND application for expanded access can be an option for using COVID-19 convalescent plasma. For opening an expanded access protocol so that COVID-19 convalescent plasma can be made available across the country, the FDA has worked with multiple federal partners and academia. This investigational product can be accessed by the involvement of acute care facilities in an investigational expanded access protocol under an IND that already exists [15].	21 CFR 312.305
Single patient emergency IND	Even though involvement in clinical trials or an expanded access program is pathways for patients to procure convalescent plasma, for several reasons, it may not be promptly available to all patients in potential need. Hence, during this public health emergency due to the COVID-19 pandemic, when clinical trials are undergoing, and a national expanded access protocol is available, USFDA is also encouraging availability of COVID-19 convalescent plasma to patients with severe or immediately life-threatening COVID-19 infections through submission of the request for a single patient emergency IND (eIND) for the individual patient from the patient's physician. This pathway permits the utilization of an investigational drug for treating a particular patient under the supervision of a licensed physician upon FDA approval, if all the applicable eligibility criteria are fulfilled. However, under these conditions, an authorized physician should send a request for the eIND {see 21 CFR 312.310(b)} for administering COVID-19 convalescent plasma to an individual patient.	21 CFR 312.310

Table 2: Conditions defining severe and life-threatening COVID-19 [14-19]

Disease	Severe disease	Life-threatening disease
Conditions	Shortness of breath (dyspnea)	Respiratory failure
	Respiratory frequency ≥30 min	Septic shock
	The ratio of partial pressure of arterial oxygen to the inspired oxygen should be <300	Multiple organ dysfunction or failure
	Blood oxygen saturation ≤ 93%	----
	More than 50% of lung infiltrates within 24–48 h	----

antibodies after recovery (if initially diagnostic testing was not performed when COVID-19 was suspected).
- The donor should be completely symptom-free at least 14 days before plasma donation. Notably, a negative result for COVID-19 by a diagnostic test is insufficient to meet the donor eligibility [23].
- The donor can be either male or female. For females, the donor should not be pregnant or has negative report for human leukocyte antigen (HLA) antibodies.
- The body weight for male donors should be > 50 kg and > 45 kg for females.
- At least 1 week since last glucocorticoid usage.
- More than 2 weeks since the last blood donation.
- Establish SARS-CoV-2 neutralizing antibody titers.

The neutralizing antibody titers should be at least 1:160 [24]. A titer of 1:80 is admissible if another matched unit is not accessible. In case, neutralizing antibody titers cannot be measured, a retention sample from the donated convalescent plasma must be stored for later determination. However, storing samples for single patient eINDs is not recommended.

For the registered and licensed blood establishments already authorized for plasma collection for transfusion need not seek an additional license or procure their own IND for collection and preparation of COVID-19 convalescent plasma for the investigational purpose provided they

1. Follow their SOPs for plasma collection and all applicable regulations, and
2. Collect plasma from individuals meeting the donor qualifications detailed above. Once prepared, the COVID-19 convalescent plasma may be distributed for investigational use. Blood establishments do not need to seek an alternative pathway or exception under section 21 CFR 640.120(a) to collect the COVID-19 convalescent plasma.

Labeling

The labeling requirements recommendations are:

a. The label of COVID-19 convalescent plasma container must mention the statement, "Caution: New Drug--Limited by Federal (or US) law to investigational use." {21 CFR 312.6(a)}. In addition, the requirements in 21 CFR 606.121 for the container label applies, along with inclusion of a note for the circular of information (on use of plasma).
b. FDA recommends the use of a uniform container label for COVID-19 convalescent plasma. Specifically, the uniform labeling of blood and blood components using ISBT 128 has been recommended.
c. The shelf-life and storage guidelines on the label for COVID-19 convalescent plasma should be the same as for other plasma products. For example, fresh frozen COVID-19 convalescent plasma should be frozen within eight hour after collection, stored at ≤18°C, and labeled with a shelf-life of one year from date of collection [14,22].

Recordkeeping

The records for the COVID-19 convalescent plasma unit(s) administered to the COVID-19 patient (21 CFR 312.62) must be maintained by health care provider. These records should include the unique identification number of the plasma units [22].

AUTHORISATION OF CONVALESCENT PLASMA COLLECTION, TESTING, PROCESSING, STORAGE, AND DISTRIBUTION

The blood establishments meeting the criteria for donation, collection, processing, and testing are authorized by competent authority to proceed unless the National regulatory authority enforces more stringent requirements or their existing authorization already covers the activities for plasma transfusion, including convalescent plasma [25]. This facilitates the rapid creation of national inventories of COVID-19 convalescent plasma.

Blood establishments that have adopted measures for gathering outcome data to ensure safety and quality can be authorized for convalescent plasma distribution [21].

Collection, processing, and storage

Instead of whole blood, plasmapheresis is preferred to improve the yield of convalescent plasma. Apheresis is an automated technology in which whole blood is continuously centrifuged into its components (namely, red blood cells, platelets, and plasma), followed by a selective collection of the desired blood component returning remaining components to the donor. This highly efficient procedure generates around 400–800 ml of plasma from a single apheresis donation. In general, donors donate plasma by plasmapheresis, but if such facilities are not available, whole blood can be collected, followed by plasma separation in the blood establishment [26]. For those repeating donation, an average donation gap of 2 weeks is advised.

Plasma obtained by plasmapheresis should be divided into 2–3 separate units (3 × 200 ml) before freezing. The units are frozen within 24 h of collection and quarantined until reports are obtained from standard blood donor testing for transfusion-transmitted infections. Final products should be appropriately labeled as COVID-19 convalescent plasma/blood and appropriately stored. Pathogen reduction should be done if it is normally followed in the blood establishment and care should be taken not to introduce pathogen. Any serious adverse reactions in the donor should be notified to the competent authority without delay [21,27,28].

Testing of donated plasma

In addition to the general quality-control tests and the test for blood-borne diseases, the blood samples need to be tested for:

(1) Nucleic acid testing for SARS-CoV-2;
(2) 160-fold dilution for the qualitative test of SARS-CoV-2 specific lgG and lgM detection; or 320-fold dilution for the qualitative test of whole antibody detection. If possible, keep aside >3 mL of plasma for the viral neutralization experiments.

While comparing virus neutralization titer and luminescent lgG antibody quantitative detection, it was found that the present SARS-CoV-2 specific lgG antibody detection does not fully demonstrate the actual virus neutralization capability of the plasma. Therefore, the virus neutralization test was suggested as the first choice, or determines the overall antibody level with the 320-fold dilution of the plasma [29]. It is recommended that neutralizing antibody titers should optimally be more than 1:320, but lower thresholds might also be clinically effective. When the measured neutralizing activity in the collected plasma is found to be low, the plasma can be fractionated and used for other clinical applications.

Ideally, a test for the existence of the anti-SARS-CoV-2 antibody should be accomplished through neutralizing antibody testing before using convalescent plasma. In case of emergency, where convalescent plasma is transfused without antibody testing, a sample should be stored and tested later. If an appropriate correlation can be demonstrated between neutralizing activity and Elisa antibody testing, it can replace the neutralizing antibody test. Therefore, it is suggested that additional samples of the donated plasma should be archived for reference studies. Thus 10 × 0.5 mL frozen aliquots from plasma samples can be withdrawn at the time of donation. In the case of repeated donations, plasma should be collected from donors showing higher titers rather than the ones with lower titers, based on the collection capacity [21,27].

Distribution of COVID-19 convalescent plasma

Blood establishments can distribute convalescent plasma to a hospital, on the request, when the specific patient

- Has laboratory-confirmed COVID-19,
- Has been hospitalized either due to acute illness or risk of acute illness,
- Has accorded informed consent.

It is advisable to inform the potential recipient(s) about the uncertainty in the efficacy of convalescent plasma therapy in treating COVID-19 to

avoid promoting unsubstantiated expectations. The recipient may be a part of a clinical trial or monitored use. This helps in making informed decisions regarding treatment by the prospective recipients.

Blood services should provide convalescent plasma with the highest antibody titers available. Furthermore, the dose of transfused plasma should be adjusted based on its neutralizing antibody titer and the volume of plasma of the recipient. Convalescent plasma in an approved randomized or case-controlled clinical trial should be distributed as per the protocol of that trial and, where necessary, in compliance with national legislation [21,30,31]. To ensure safety, quality, and amend improvements in the collection, testing, processing, and storage protocols, the hospitals should furnish defined clinical outcomes to the supplier blood establishment [32]. The information to be included in the outcome data should entail:

1. Gender, co-morbidities, age range (20–29, 30–39, etc.),
2. Transfusion time point (days from the onset of disease)
3. Volume, number, and antibody titer of the transfused plasma unit
4. Clinical treatment given to the patient in parallel (other than supportive care)
5. Clinical symptoms and laboratory parameters according to the progression of disease at the following time points (i) before the transfusion, (ii) more than 5 days after transfusion, and (iii) at discharge (if the patient survives)
6. Length of hospitalization (if the patient survives).
7. Any adverse reactions or events potentially linked to the transfusion.

The outcome data in the above format should be reported to the supplying blood establishments and, through them, to the national database to establish a comprehensive scenario at the national level. The data from controlled clinical trials should be first evaluated according to a pre-defined analytical strategy in the clinical trial protocol and published as early as possible. The minimum outcome data should also be reported to the national database to allow meta-analysis in a larger dataset later on. Severe adverse reactions or events possibly linked to the transfusion should be notified by the hospitals to the supplying blood establishments and after that to the competent authority without delay. This reporting is essential whether the plasma has been transfused in an observational study or a controlled clinical trial [21].

PROCEDURE FOR CONVALESCENT PLASMA THERAPY PHASE

Consecutively critically ill patients admitted to the intensive care unit, or other areas of the hospital should be selected based on the following criteria [33]:

Inclusion criteria

Same as discussed for patient eligibility

Exclusion criteria

1. Negative Reverse transcription-polymerase chain reaction (RT-PCR) of respiratory secretion samples.
2. Reported history of a hypersensitive reaction to blood products or plasma.
3. Clinical situation where in administering 500 ml i.v. volume may be harmful to the patient (e.g., actively decompensated congestive heart failure).
4. Severe multi-organ failure, hemodynamic instability.
5. Other documented uncontrolled infection.
6. Patient is expected to survive for <48 h.
7. Severe DIC (disseminated i.v. coagulation) needing factor replacement, fresh frozen plasma (FFP), and cryoprecipitate.

Informed consent

The treating physician and/or the protocol coordinator will describe the purpose of this intervention and its possible benefits and risks to the patient or donor (or to his/her surrogate decision-maker). They will obtain the following consent forms in and as appropriate [33].

For the collection of convalescent plasma

1. Informed consent for COVID-19 RT-PCR and COVID-19 serologic testing for the donors.
2. Informed consent for donation of convalescent plasma from those with elevated anti-SARS-CoV-2 titers as described below.

For the Convalescent plasma therapy phase

A. Consent for enrollment in the convalescent plasma therapy phase
B. Protocol procedures for the convalescent plasma collection phase
    1. Eligible candidates for convalescent plasma donation (as per the inclusion and exclusion criteria above) will be tested for anti- SARS-CoV-2 serology. Subjects who are seropositive will be further screened for SARS-CoV-2 RT-PCR.
    2. Subjects with an anti-SARS-CoV-2 titer of either more than or equal to 1:80 and negative rRT-PCR conformation of COVID-19 infection will be selected for qualification for donating plasma according to the standard criteria following the WHO guidelines assessing donor acceptability for donating blood.
    3. Individuals fulfilling all the criteria for the plasma donation will be called for donation.

Apheresis may be used to collect plasma (500–600 ml on the basis of weight), as suitable for every donor [34]. The collection will be made by trained personnel of blood bank working as per the standard operating procedures in certified laboratories. The frozen plasma is stored at appropriate temperature in the blood bank after reported negative for a series of serological tests in accordance to the international guidelines [20,33,35].

Infusion plan

The general dosage of convalescent plasma therapy is ~400 ml for one infusion or ~200 ml per infusion for multiple infusions. The intervention consists of administering 2 units of convalescent plasma. Both the units of plasma (200–250 ml) should be infused over 2 h maintaining a gap of 1 h between the two units. Plasma transfusion will be done as per the standard policies recommended for administering blood products [33,36].

Clinical cointerventions

The clinical team exercises independent control of patient management other than convalescent plasma therapy and will not be influenced by the intervention team. Co-interventions such as administration of hydroxychloroquine, Kaletra or darunavir/cobicistat, azithromycin, tocilizumab, corticosteroids, ribavirin, and interferon will be recorded on the patient report sheets. The frequency of clinical and laboratory assessment follow-up is done at baseline, followed by day 1, 3, 5, 7, 14, and after 28 days after administration of convalescent plasma [33].

Outcome measures

These may be classified as clinical and laboratory outcomes, as mentioned in Table 3.

Safety measures

Under conditions of an acute transfusion reaction, the transfusion should be stopped immediately and must be reported immediately to the blood bank, the principal investigator and the study management committee. All the serious adverse events related to the convalescent plasma should be recorded [16,33,38].

CLINICAL USE OF THE CONVALESCENT PLASMA

Indication

(1) Severe or critically ill COVID-19 patients tested positive in respiratory tract test;
(2) The COVID-19 patients who are not severe or critically ill, but in a state of immunity suppression; or have low CT (cycle threshold) values in the virus nucleic acid testing but with a rapid disease progression in the lungs [36].

Table 3: Outcome measures of convalescent plasma therapy [30,33,37]

Clinical outcomes	Laboratory outcomes
Sequential organ failure assessment score on day 1, 3, 5, 7, 14, and 28	Virological clearance at day 7, 14, 21
Ventilator free days	CT values for SARS-CoV-2 PCR positivity (RT-PCR) at days 0, 7, 21 when available
ICU mortality and LOS	Determining anti-SARS-CoV-2 titers at day 0 and thereafter
Hospital mortality and LOS	-----
Multi-organ failure	-----

Contraindication

1. Allergy history of plasma, sodium citrate, and methylene blue;
2. For patients with a history of autoimmune system diseases or selective lgA deficiency, the application of convalescent plasma should be evaluated cautiously by clinicians [36,39-42].

Convalescent plasma trial for COVID-19 in India

Central Drugs Standard Control Organization (CDSCO) of India has entrusted permission to the Indian Council of Medical Research (ICMR) for the clinical trial of convalescent plasma for COVID-19 therapeutics. A list of institutes interested in conducting clinical trials has been submitted by the ICMR. The trial shall be conducted as an open-label, randomized, controlled Phase II study to assess the safety and efficacy of convalescent plasma in patients with moderate COVID-19 disease. Encouraging results were obtained in a small case involving five critically ill COVID-19 patients with acute respiratory distress syndrome (ARDS). Infusion of convalescent plasma containing neutralizing antibodies led to substantial clinical improvement in all patients without any deaths [43]. In another group of four patients that included one pregnant woman, convalescent plasma transfusion led to complete recovery eventually [44,45].

In the light of public interest, the ICMR's proposal for conducting a trial was reviewed by the Subject Expert Committee in its meeting held on 13 April under the accelerated approval process owing to the prevailing pandemic. Further, no objection was raised by the CDSCO for the conduct of clinical trial subject to few amendments in the trial protocol and various conditions specified in the Drugs and Clinical Trial Rules, 2019 [46].

The Union Health ministry released clinical management protocols for COVID-19 on June 27, 2020. They allowed the use of convalescent plasma (off-label) to treat COVID-19 patients in a moderate stage of the illness under "investigational therapies," as mentioned in the CDSCO notice, "Information on Convalescent Plasma in COVID-19." As per the CDSCO notice, convalescent plasma may be used in moderately infected patients and those that are not improving (the oxygen requirement is progressively increasing) despite the steroidal therapy. Further, the recipient should be kept under strict observation for several hours after transfusion to monitor any adverse events. The application of convalescent plasma should be prevented in patients with immunoglobulin allergy of immunoglobulin A deficiency [47].

CLINICAL TRIALS TO ASSESS THE EFFICACY AND SAFETY OF HUMAN ANTI-SARS-COV-2 PLASMA

The use of convalescent plasma has documented successful historical records, as many controlled trials have been conducted to assess its efficacy as an emergency application during epidemics. In the current situation, at least five clinical trials should be carried out to evaluate the effectiveness of human anti-SARS-CoV-2 plasma for the prevention and treatment of COVID-19.

The first trial involves the use of human anti-SARS-CoV-2 plasma as post-exposure prophylaxis: a randomized, blinded Phase II trial for comparing the safety, and efficacy of human anti-SARS-CoV-2 plasma against control (SARS-CoV-2 non-immune plasma) in adults (age more than 18 years) who have had close contact exposure to COVID-19, but are asymptomatic. Close contact exposure refers to be in the periphery of within approximately 2 m (6 ft) of a COVID-19 patient for a substantial duration without personal protective equipment. Close contact also refers to living with, visiting, caring for, or sharing a healthcare waiting area or room with a COVID-19 infected individual or direct contact with infectious secretions of a COVID-19 patient without PPE.

If the first trial is successful, safe, and effective, post-exposure prophylaxis will offer therapeutic intervention for vulnerable populations, namely immunocompromised patients, health care workers, nursing home residents, and individuals with respiratory, following exposure. This would confer direct clinical benefit for those at high risk and would impact more significant social benefits to the frontline workers in the pandemic.

The second trial will assess human anti-SARS-CoV-2 plasma for offering initial help to mildly infected patients. The target population can be symptomatic individuals with confirmed SARS-CoV-2. The clinical endpoints would be the prevention of hypoxemia in room air, suppression of symptoms, or progression to severe disease, reflecting a decline in complications not requiring hospitalization.

In the third trial, moderately ill patients will be investigated to assess the effect of human anti-SARS-CoV-2 plasma on them. The target population will be hospitalized COVID-19 patients showing clinical symptoms but not requiring ICU admission (specifically mechanical ventilation). Aversion to critical illness could avoid overburdening of essential resources of care.

A fourth trial could assess whether human anti-SARS-CoV-2 plasma can act as a rescue intervention in COVID-19 patients requiring mechanical ventilation. This target group is significant as it is a group, for which the data are most challenging to interpret due to the confounding variables, including other putative therapies for COVID-19.

Finally, a fifth trial evaluates the safety and pharmacokinetics of convalescent plasma in high-risk pediatric patients. Although comparatively rare, severe illness, and even deaths due to COVID-19 have been described in children [48], requiring the need to address the risk to children.

Complementing these four trials, studies are being designed to collect and mine data from emergency use of convalescent plasma or expanded access treatment.

REPORTED CLINICAL TRIALS

Institute of Liver and Biliary Sciences, India, has undertaken clinical trials to determine the effectiveness of convalescent plasma therapy in severely infected COVID-19 patients. A randomized controlled trial was planned to evaluate the efficacy of this therapy in COVID-19 patients. Five hundred milliliters of convalescent plasma were collected from the COVID-19 recovered patient after 14 days of clinical and radiological recovery with two consecutive COVID-19 negative tests by PCR. Further, the samples from the collected plasma for COVID-19 specific antibodies and their titer were tested. This plasma was frozen and sent to the treating center (Maulana Azad Medical College). 200–600 ml of convalescent plasma was transfused to patients fulfilling the eligibility criteria and was randomized

to the convalescent plasma group. This was accomplished in critically ill patients. The data were collected for the clinical benefit and monitored the adverse events related to the transfusion [17].

Globally, various clinical trials have been recruited or are yet to be recruited to evaluate the efficacy of convalescent plasma therapy in COVID-19 patients. A few of them are listed in Table 4.

Table 4: Details of clinical trials to assess the efficacy of convalescent plasma therapy in COVID-19 patients [49,50]

Study title	Intervention	Status	Location
Convalescent plasma trial in COVID-19 patients [51]	Other: Plasma therapy using convalescent plasma with the antibody against SARS-CoV-2 Other: Routine care for COVID-19 patients	Completed	Royal College of Surgeons, Ireland
Convalescent Plasma Therapy vs. SOC for the Treatment of COVID19 in Hospitalized Patients [52]	Other: Blood and derivatives. Drug: Standard of Care	Recruiting	Hospital Clínico Universitario Lozano Blesa Zaragoza, Aragón, Spain Hospital Universitario Severo Ochoa Leganés, Madrid, Spain Hospital Universitario Puerta de Hierro Majadahonda Majadahonda, Madrid, Spain
Efficacy of convalescent plasma therapy in severely sick COVID-19 patients [17]	Drug: Convalescent Plasma Transfusion Other: Supportive Care Drug: Random Donor Plasma	Completed	Maulana Azad medical College New Delhi, Delhi, India Institute of Liver and Biliary Sciences New Delhi, Delhi, India
Convalescent Plasma as Therapy for Covid-19 Severe SARS-CoV-2 Disease (CONCOVID Study) [53]	Biological: Convalescent plasma	Recruiting	Erasmus Medical Center Rotterdam, Zuid-Holland, Netherlands NoordWest Ziekenhuisgroep Alkmaar, Netherlands Onze Lieve Vrouwen Gasthuis Amsterdam, Netherlands
Efficacy of Convalescent Plasma Therapy in Patients With COVID-19 [54]	Biological: Convalescent Plasma Other: Standard of Care	Recruiting	Maulana Azad Medical College, New Delhi, India Institute of Liver & Biliary Sciences, New Delhi, India Rajiv Gandhi Super Specialty Hospital New Delhi, India
Convalescent Plasma Therapy in Patients With COVID-19 [55]	Biological: Convalescent plasma	Completed	Gatot Soebroto central army presidential hospital Jakarta Pusat, Indonesia
Convalescent Plasma Therapy on Critically-ill Novel Coronavirus (COVID-19) Patients [56]	Biological: Convalescent plasma Drug: Hydroxychloroquine with Azithromycin	Completed	Alkarkh Health directorate Baghdad, Iraq
Convalescent Plasma Therapy in Severe COVID-19 Infection [57]	Biological: Convalescent plasma	Recruiting	Bangabandhu Sheikh Mujib Medical University Dhaka, Bangladesh
Amotosalen-UV A pathogen-inactivated convalescent plasma in addition to best supportive care and antiviral therapy on clinical deterioration in adults presenting with moderate to severe COVID-19 [58]	Other: Convalescent plasma administration to SARS-CoV-2 infected patients	Completed	Blutspendezentrum SRK beider Basel, University Hospital Basel, Switzerland
Convalescent Plasma for Treatment of COVID-19: An Exploratory Dose Identifying Study [59]	Biological: SARS-CoV-2 convalescent plasma	Recruiting	Danderyd Hospital, Danderyd, Stockholm, Sweden Karolinska University Hospital, Stockholm, Sweden
Convalescent Plasma Treatment in COVID-19 [60]	Biological: convalescent plasma (CP) Other: Drugs and supportive care	Recruiting	Aga Khan University Hospital, Karachi, Sind, Pakistan
Evaluation of SARS-CoV-2 (COVID-19) Antibody-containing Plasma therapy [61]	Biological: High-Titer COVID-19 Convalescent Plasma (HT-CCP) Biological: Standard Plasma	Recruiting	Brigham and Women's Hospital, Boston, Massachusetts, United States
Plasma therapy of COVID-19 in critically ill patients [62]	Biological: Convalescent plasma (anti-SARS-CoV-2 plasma) Biological: Non-convalescent Plasma (control plasma)	Recruiting	Columbia University Irving Medical Center/NYP New York, New York, United States
Treatment of patients with COVID-19 with convalescent plasma [63]	Biological: convalescent plasma	Recruiting	General Hospital, University of Sao Paulo, Brazil
Convalescent plasma for the treatment of COVID-19 [64]	Drug: Convalescent plasma	Recruiting	Thomas Jefferson University Hospital, Philadelphia, Pennsylvania, United States
Assessment of the effect of convalescent plasma therapy in patients with Life-threatening COVID19 infection [65]	Biological: Convalescent plasma	Recruiting	Cairo University Hospital Cairo, Egypt

(Contd...)

Table 4: ***(Continued)***

Study title	Intervention	Status	Location
Convalescent Plasma for the Treatment of Patients With COVID-19 [66]	Biological: COVID-19 convalescent plasma	Available	Children's Hospital Colorado, Aurora, Colorado, United States UC Health Memorial Hospital North Colorado Springs, Colorado, United States
Convalescent Plasma as Treatment for Hospitalized Subjects With COVID-19 infection [67]	Biological: Convalescent plasma	Recruiting	Hackensack University Medical Center Hackensack, New Jersey, United States
Convalescent plasma for the treatment of patients with severe COVID-19 infection [68]	Procedure: Convalescent Plasma	Recruiting	"Evangelismos" General Hospital, Athens, Attiki, Greece "Agios Savvas" Oncology Hospital, Athens, Attiki, Greece "Alexandra" General Hospital, Athens, Attiki, Greece
Convalescent plasma as a possible treatment for COVID-19 [69]	Biological: Convalescent plasma Biological: Placebo	Recruiting	University of Illinois at Chicago, Chicago, Illinois, United States
Treatment With Investigational Convalescent Plasma and Measure Antibody Levels in Patients Hospitalized With COVID-19 [70]	Drug: Convalescent Plasma	Recruiting	University of New Mexico Health Sciences Center Albuquerque, New Mexico, United States
Expanded access to convalescent plasma for the treatment of patients with COVID-19 [71]	Biological: COVID-19 convalescent plasma	Available	Mayo Clinic Health System in Albert Lea, Albert Lea, Minnesota, United States
Experimental Expanded Access Treatment With Convalescent Plasma for the Treatment of Patients With COVID-19 [72]	Biological: Convalescent Plasma	Available	UMass Medical School Worcester, Massachusetts, United States
Safety in Convalescent Plasma Transfusion to COVID-19 [73]	Biological: Convalescent Plasma	Recruiting	Hospital San José, Monterrey, Nuevo Leon, Mexico
Convalescent plasma versus human immunoglobulin to treat COVID-19 pneumonia [74]	Drug: Plasma from COVID-19 convalescent patient Drug: Human immunoglobulin	Recruiting	Centenario Hospital Miguel Hidalgo, Aguascalientes, Mexico

CONCLUSION

The risks due to COVID-19 infection are vast. Convalescent plasma obtained from recovered COVID-19 patients has been proposed to be a potentially effective and safe therapy for treatment and post-exposure prophylaxis alike. Several evidence of benefit with prior use for viral infections offers strong precedent for such an approach. The availability of limited data from precisely controlled clinical trials of convalescent plasma necessitates evaluating its use objectively for a range of indications and patient populations. However, performing well-controlled clinical trials is critically important to confirm efficacy, so rational evidence-based decision-making can be made.

AUTHORS' CONTRIBUTIONS

Amit Porwal: Writing-original draft preparation. Kamla Pathak: Writing-reviewing, and Editing. Devender Pathak: Validation. Ramakant Yadav: Conceptualization and Review

CONFLICTS OF INTEREST

There are no conflicts of interest.

FUNDING

As this is a review article, no funding was provided for this study.

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