

Convalescent Plasma Therapy for COVID-19: Current Status and Future Directions

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Abstract

The ongoing pandemic of coronavirus disease 2019 (COVID-19) has triggered a global health crisis probably due to a lack of a reliable cure till date. Several clinical trials are ongoing, but initial results have not been overly promising. Convalescent plasma (CP), which refers to plasma collected from individuals recovered from an illness and developed antibodies against the pathogen, is also being proposed as a therapeutic option for COVID-19 treatment in severe cases to achieve short-term immunity against the virus. Use of CP is not new, and it has been used in various outbreaks over the past century, ranging from the Spanish influenza outbreak in 1918 to the recent Middle East respiratory syndrome (MERS). However, data available on its use in COVID-19 patients is limited. Use of CP so far is restricted to a “rescue therapy” and needs further trials to assess its possible use in other situations (prevention, postexposure prophylaxis) and patient populations (considering age and comorbid illnesses). In this review, we will try to summarize the current status of use of CP for COVID-19 and ongoing trials in India and elsewhere and will discuss the possible avenues for its use in future.

Keywords

- ▶ convalescent plasma
- ▶ coronavirus
- ▶ COVID-19
- ▶ immunotherapy
- ▶ SARS-CoV-2

Introduction

Novel coronavirus disease 2019 (COVID-19) has become a pandemic now. The spectrum of clinical presentation of COVID-19 ranges from usual respiratory symptoms to more serious life-threatening events such as acute respiratory distress syndrome (ARDS), shock, cardiac injury, thromboembolic phenomenon, and even death.^{1,2} The uncertain pathophysiology and varied clinical course are the major hurdles in its management. Various pharmacological options (antiviral, anti-inflammatory agents, alone or in combination, monoclonal antibodies) have been tried so far with variable results without any definitive evidence on the efficacy of any of these agents. Other supportive treatments currently employed are oxygen supplementation, vasopressors, and mechanical ventilation, and extracorporeal membrane oxygenation ([ECMO] for severe cases).

Passive immunotherapy with convalescent plasma (CP) from recovered COVID-19 cases is now being explored as a treatment option for those cases classified as critical (respiratory failure, septic shock, multiorgan dysfunction).³ Passive immunotherapy involves administration of antigen-specific antibodies in an individual to achieve short-term immunity against the said pathogen to eradicate it from the bloodstream. CP has been used in the treatment of patients during previous outbreaks of coronaviruses (Middle-East respiratory syndrome [MERS] and severe acute respiratory syndrome [SARS]), H1N1 and H5N1 influenza A pandemics, as well as in hemorrhagic fevers caused by Ebola and Junín virus.^{4–9} Many ongoing studies are trying to explore the role of CP in COVID-19 cases, but its efficacy in COVID-19 management is still unclear. This review aims to provide the readers with an overview of available evidence for the use of CP in severe acute respiratory illness (SARI) of viral etiology and information about the trials on CP use in COVID-19 patients.

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Rationale for Convalescent Plasma

Convalescent blood or blood products are collected from an individual recently cured of a disease and developed humoral immunity against the pathogen, hence serve as the human source for specific antibodies. The presence of high titers of neutralizing antibodies in patients who recovered from the viral infection and the absence of such antibodies to the novel virus in the general population forms the basis of this treatment. The proposed mode of action is the rapid reduction in viremia (<48 hours following transfusion) followed by suppression of the proinflammatory state. This helps in rapid patient recovery from various complications such as ARDS. Use of CP in COVID-19 reduces the chances of emergence of antiviral drug resistance, and the polyclonal nature of these antibodies minimizes the risk of escape mutant (which can occur with monoclonal antibody treatment) and faster reduction of viremia as compared with antiviral medications.

Selection of Donors

During the previous SARS outbreak, the criteria adopted for CP donor selection included afebrile status for at least 7 days, chest radiographic improvement by at least 25%, no requirement of oxygen supplementation, and a minimum of 14 days following symptom onset.⁵ Similar criteria may be chosen for the present pandemic of COVID-19 because both outbreaks are caused by coronavirus, which primarily affects the respiratory system, progressing eventually to involve multiple system dysfunction. The most recent evidence available for CP in COVID-19 is a randomized trial comparing plasma therapy with standard treatment alone in 103 patients wherein laboratory-confirmed (reverse transcriptase-polymerase chain reaction [RT-PCR]) cases of COVID-19, fully recovered and discharged from hospital for more than 2 weeks with at least two negative follow-up RT-PCR, were considered for plasma donation.³ Similar criteria have been proposed by other authors as well.¹⁰ In a recent pilot study on COVID-19 patients, the donors chosen were the patients who were 3 weeks post-symptom onset and 4 days postdischarge.¹¹ The patient and donor eligibility criteria for CP therapy taken out from the U.S. Food and Drug Administration (FDA) guidelines are summarized in ► **Table 1**. This FDA guideline has recommendations for health care providers and investigators on the administration and study of investigational CP collected from individuals who have recovered from COVID-19. It also guides on the topics of pathways of use of CP, patient eligibility, collection of plasma, labeling, and record-keeping.¹² However, these FDA guidelines provide only information on the use of plasma and do not elaborate on indications for use, dosage, contraindications, or cautions. Nevertheless, it is imperative for the donors to be seropositive for coronavirus and screened negative for hepatitis B and C, HIV, and syphilis. It is prudent to follow previous World Health Organization (WHO) recommendations for the selection of blood donors considering important factors such as age, anemia, obesity, and other comorbidities.¹³ Informed consent of the donor for CP donation is mandatory.

Plasma Collection

Collection of plasma by apheresis technique and its use as a therapeutic pool is preferred as it allows for larger volumes of collection, more frequent donations (2 weekly intervals), and the possibility of reinfusion of red blood cells to donors, which eliminates any risk of lowering donor hemoglobin levels.¹⁴ The allowable plasma volume collection by apheresis is 625 mL for donors, with a bodyweight of 50 to 80 kg, and it can be performed at 2 weekly intervals.¹⁵ Although a recent FDA statement has termed guidelines for volume collection *obsolete*, it is preferable to restrict to this limit in the current scenario.¹⁶ This short time interval between two donations (2 weeks), when compared with the interval of 3 months for whole blood donations, is advantageous, although large-scale availability of apheresis machines and trained operators pose major obstacles.¹⁷ Similar to fresh frozen plasma, COVID-19 CP should be frozen within 8 hours after collection, stored in aliquots of 200 mL each, and stored at a temperature of -18°C or lower.

Estimation of Antibody Titers

Transfusion of CP containing high neutralizing antibody titer (NAT) helps to achieve an earlier and effective

Table 1 Summary of the patient and donor criteria for CP therapy¹²

Patient eligibility criteria
<ul style="list-style-type: none"> • Laboratory-confirmed COVID-19. • Severe or immediately life-threatening disease. Severe disease is defined as one or more of the following: dyspnea, tachypnea ($\geq 30/\text{min}$), $\text{SpO}_2 \leq 93\%$, $\text{PaO}_2/\text{FiO}_2 < 300$, and lung infiltrates $> 50\%$ within 24 to 48 h. The presence of respiratory failure, septic shock, and multiorgan dysfunction or failure is defined as life-threatening. • Informed consent provided by the patient or healthcare proxy.
Donor eligibility criteria
<ul style="list-style-type: none"> • Evidence of COVID-19 documented by a laboratory test either diagnostic (nasopharyngeal swab) at the time of illness or positive serology (SARS-CoV-2 antibodies) after recovery if prior diagnostic testing was not performed at the time COVID-19 was suspected. • Either complete resolution of symptoms at least 28 days prior to donation or complete resolution of symptoms at least 14 days prior to donation along with negative results for COVID-19 either from one or more nasopharyngeal swab specimens or by a molecular diagnostic test from blood. • Male donors, or female donors who have not been pregnant, or female donors who have been tested since their most recent pregnancy and results interpreted as negative for HLA antibodies. • SARS-CoV-2 NAT testing: when testing is available, neutralizing antibody titers of at least 1:160 is recommended. A titer of 1:80 may be considered acceptable if an alternative matched unit is not available. A sample maybe stored for estimation at a later date if measures for antibody titer estimation are not available at the time of collection/transfusion.

Abbreviations: COVID-19, coronavirus disease 2019; CP, convalescent plasma; HLA, human leukocyte antigen; NAT, neutralizing antibody titer; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

seroconversion. The titer of antibody is important as apparent from the fact that during the MERS outbreak, the use of CP did not help in clinical recovery, and one of the possible reasons suggested was the lack of proper estimation of NAT. It was hypothesized that the plasma transfused to the patients could have had low antibody titers since it was collected from cases who recovered from a mild illness and hence did not develop high antibody levels.^{4,18,19} The other problem with low serum antibody titers is an antibody-dependent enhancement (ADE) of the virus, which will be discussed later.²⁰ Li et al in their study on COVID-19 patients estimated the antibody titer against a spike protein on the receptor-binding domain (S-RBD) and showed that titers of at least 1:640 were required for transfusion.³ Evidence from the use of CP during previous viral outbreaks indicates toward the clinical efficacy of CP with an antibody titer of 1:160 in SARS and H1N1 influenza A.^{5,6} In their recommendations for investigational plasma treatment for COVID-19, the FDA suggests a NAT of 1:160, if the estimation is available.¹²

Volume of Convalescent Plasma Transfusion

Cheng et al in their study on CP in SARS patients used a mean plasma transfusion volume of 279 mL (range: 160–640 mL; 4–5 mL/kg) with a NAT of 1:160 in 80 adult patients (median age: 45 years). They found that the outcome was more dependent on the time of administration than the volume infused.⁵ Recent studies on COVID-19 patients in China reported the transfusion of one dose of 200 mL of inactivated CP with neutralization activity of >1:640 within 4 hours of collection.^{3,11} Shen et al reported the effects of plasma transfusion in five critically ill patients suffering from COVID-19, where 400 mL of plasma was transfused.²¹ A study on CP for Ebola patients used a strategy of total transfusion of 400 to 500 mL in two aliquots in an hour.^{22,23} Based on the current evidence, the use of standard aliquots of 200 mL of CP (4–5 mL/kg) in adults seems to be a rational choice.

Repeat Dose: When and How Much to Give?

Ko et al reported their experience of CP transfusion in the management of the MERS outbreak in 2015. Out of the 13 patients with respiratory failure, 3 patients received CP and 1 patient received a repeat transfusion 1 week after the initial dose as no seroconversion was observed after the initial dose.⁴ Arabi et al in their study planned to transfuse 2 units of plasma (250–350 mL/unit) in MERS CoV patients after assessing the feasibility of procuring CP from donors, but their study did not progress to this phase as they did not find donors with adequate antibody titers.¹⁸ One case report during the SARS outbreak mentions the use of 500 mL of CP, (250 mL transfused 12 hours apart). Despite clinical recovery with the initial dose, the second dose was also transfused as they planned to deliver 5 g of immunoglobulin (10 g/L of plasma).²⁴

Ideal Time of Administration of Convalescent Plasma

Most viral illnesses have maximum viremia at around the end of the first week of infection followed by activation of host immune responses and viral clearance after 2 weeks. In COVID-19, after an incubation period of 2 to 12 days (mean: 5–6 days), patients develop clinical symptoms that progress to severe illness around day 8 (5–10 days of symptom onset).²⁵ It is therefore ideal to administer CP early in the course of illness. In the study by Li et al, the median duration between symptom onset and randomization to the CP group was 27 days (interquartile range: 22–39). This finding is in stark contrast to all the available literature that favors the early administration of CP (less than 14 days).^{5,26} It is suggested that the lack of a significant outcome difference in this study (time to clinical improvement, discharge or mortality) compared with standard treatment is due to the delayed administration of plasmatherapy.^{3,27}

Monitoring for Response to Therapy

Assessment of response to CP treatment is based on various parameters like a clinical improvement (normalization of body temperature and oxygen saturation, and relief of dyspnea), changes in radiological parameters (resolution of lung lesions on chest CT), and estimation of viral load. A favorable response is usually evident within 2 to 3 days of plasma transfusion. Mair-Jenkins et al in their meta-analysis on the effectiveness of CP on SARI mentioned only one retrospective study that reported nonsignificant reductions in the duration of mechanical ventilation and ECMO following CP.^{28,29} The other published studies, they reported, did not show adequate data on critical care support and plasma therapy. Lymphocytopenia is a common finding in COVID-19 and is supposedly related to the consumption and inhibition of the host's immune function by the virus. An increase in lymphocyte count was observed after CP and was associated with clinical recovery.^{11,30} Although a reduction in viral load is evident as early as 24 hours of transfusion, its estimation is overshadowed by the more favored clinical, laboratory, and radiological recovery.

Adverse Events Following CP Transfusion

Febrile reactions and mild allergy in the form of urticaria can occur in 1% of those receiving plasma transfusions and are managed with supportive care, antihistamines, and small doses of corticosteroids if required. Risk of severe allergy and anaphylaxis is seen in <1 in 1,00,000 of cases. Rare complications include citrate toxicity (citrate induced hypocalcemia), transfusion-related acute lung injury (TRALI), and transfusion-associated circulatory overload.³¹ Although rare, significant attention needs to be paid toward TRALI as it may exacerbate the pulmonary injury caused by coronavirus.⁴ The other common adverse events are transient elevation of body temperature, jaundice, and phlebitis. Nonmatched ABO blood administration can lead to serious complications including anaphylaxis.³² The risk of transfusion-related transmission of

blood pathogen is very minimal with the current screening techniques employed. A rare complication that can occur is an ADE of the virus, which was initially observed in the dengue vaccine recipient. It was observed that the risk of severe secondary dengue in the form of dengue hemorrhagic fever (DHF) or dengue shock syndrome (DSS) was high in those with a low antibody titer from either previous illness or vaccination. Though not demonstrated in previous viral outbreaks such as SARS, MERS, and Ebola, a theoretical risk remains with a lower antibody titer in the donor plasma, which may enhance viral penetration in the host cells and hence their replication.²⁰

Limitations of Convalescent Plasma

None of the published studies on viral outbreaks, except one recent trial on COVID-19, has compared CP with other forms of treatment. Most of all studies mention CP as a last resort and given along with standard care including antiviral agents and corticosteroids in some cases, and hence the therapeutic efficacy of CP alone could not be asserted. Even the recent randomized trial was limited by its sample size due to early termination as the disease spread was contained. Limitations of treatment exist at various levels, ranging from donor selection, collection of plasma, estimation of antibody titers, transfusion into the recipient, to its effects on the patient. The selected donor must be free from the virus at the time of selection or else it exposes the health care worker to the disease during screening and collection. Convalescent plasma collection may result in a reduction in the collection of whole blood and blood products, resulting in a shortage/crisis. Given the reports of reinfection following clinical recovery and negative molecular reports, it becomes mandatory to include retesting for the virus in a potential donor even if he/she has tested negative already.

In an unexpected outbreak with a large requirement of plasma, it may not be feasible to estimate NAT as it requires biosafety level 3 laboratory and may have to rely on ELISA (enzyme-linked immunosorbent assay) for estimation immunoglobulin (Ig) M/IgG.³³ Accordingly, if plasma with inadequate NAT is transfused, seroconversion in recipient may not occur or produce an immediate response leading to worsening.⁴ There is no certainty regarding the optimal dose and dosage of plasma transfusion in COVID-19. Furthermore, there are no data or trials to support transfusions in pediatric patients.

Available Literature and Current Trials

► **Table 2** provides a summary of studies on CP therapy in SARI of viral etiology. A Cochrane review on CP in COVID-19 that was recently published assessed eight studies (seven case series and one prospective single-arm intervention

study) with a total of 32 participants. They identified “very low-certainty” evidence on the clinical effectiveness (weaning off respiratory support and mortality outcomes) and safety of CP, with all included studies having low reporting quality and high risk of bias; the results of 47 ongoing studies (22 randomized controlled trials) are awaited.³⁴ In the Indian context, a “Phase-II, Open-label, Randomised Controlled Trial to Assess the Safety and Efficacy of Convalescent Plasma to Limit COVID-19 Associated Complications in Moderate Disease” (PLACID Trial) is currently undergoing under the Indian Council for Medical Research. This study is planned as a multicenter clinical trial with an estimated sample size of 452 and 46 participating institutions in India. This study involves administration of 2 doses of 200 mL each of CP to laboratory-confirmed cases of COVID-19 with moderate disease (as defined by respiratory rate > 24/minute; PaO₂:FiO₂ of 200–300) and assesses the avoidance of progression to severe ARDS or mortality at 28 days. Seven other trials are ongoing at various centers in the country and are in the recruitment phase, with results awaited. Most of them are designed as randomized trials to compare the efficacy of CP transfusion with the usual standard of care.^{35,36} “National COVID-19 Convalescent Plasma Project” is currently undergoing in the United States to assess the efficacy of CP.³⁷

Future Directions

The current literature on CP focuses mainly on its use in critically ill patients. Considering the frequent and unexpected outbreaks of viral illness in this century thus far, it is important to consider plasma as an option not only for treatment in severe cases but also for prophylaxis. Postexposure prophylaxis in the vulnerable population (health care workers, immunocompromised, individuals with comorbidities, etc.) would certainly offer clinical as well as social benefits. Trials are required to test the efficacy of plasma in patients presenting with mild/moderate illness to prevent their worsening to a stage requiring mechanical ventilation. Also, there is no evidence for its use in the pediatric population as they also form a part of the vulnerable population.

Conclusion

At present, CP offers scope as a rescue therapy in the current pandemic COVID-19, even though it is inadequately supported with large randomized trials. Hopefully, more evidence will be available in the near future to support or refute the safety and efficacy of CP not just as a rescue therapy but also as a prophylactic measure in COVID-19 management.

Table 2 Summary of evidence for convalescent plasma therapy in SARI of viral etiology^{3,6,11,21,22,26,28,32,38,39}

Disease	Study details			Donor details ^a		Recipient details ^b		Summary of findings ^c
	Type	Sample size	Author	NAT	Day of sample collection	Dose and dosage	Time of administration	
SARS-CoV-2	Open-label randomized trial	103	Li et al ³	1:640 (s-RBD-specific IgG)	More than 2 weeks after recovery	Single dose: 200 mL	27 days after symptom onset (IQR: 22–39)	52 (CP group) vs. 51 (control) Primary outcome: clinical improvement in 28 days Secondary outcome: 28-days mortality No statistical difference in outcomes between the study groups No significant outcome difference among subgroups (severe and life-threatening) who received CP Limitation: small sample size, early termination of study
SARS CO-V2	Case series	4	Zhang et al ³⁸	Not provided	Not provided	300 mL (average); two patients received multiple doses (3-8)	Earliest: day 12 Last dose: day 30	Negative RT-PCR and off-ventilator 3–4 days after the last dose ECMO in two patients prior to transfusion; weaned off later Postpartum female: longer course of recovery
SARS CO-V2	Case series	5	Shen et al ²¹	>40	10 days after recovery	Single dose: 400 mL	10–22 days of admission	Critically ill patients on mechanical ventilation ↑ PaO ₂ /FIO ₂ , normal temperature, and resolution of chest lesions on imaging after CP
SARS CO-V2	Cohort	10	Duan et al ¹¹	>1:640	3 wk postsymptom onset and 4 days after discharge	Single dose: 200 mL	Median: 16.5 days (IQR: 11–19.9)	Better outcome if transfused <14 days of admission Correction of lymphocytopenia, correction of LFT Limitation: non-randomized
Ebola	Nonrandomized comparative	84 cases vs. 418 controls	van Griensven et al ²²	Not done	Details not available	200–250 mL; two doses; children: 10 mL/kg	2 days after diagnosis	Controls received only standard care before enrolling cases Plasma collection from recovered cases with mild illness No significant survival benefit (mortality 31 vs. 38%) due to low seroconversion Minor reactions to transfusions, such as fever, skin rash, requiring interruption or reduction of dosing
SARI	Meta-analysis	1,327 patients from 32 studies	Mair-Jenkins et al ²⁸					Survival benefit if given early in disease ↓ mortality in SARI (CP vs. placebo/no therapy) (Odds ratio: 0.25 [95% CI: 0.14–0.45])
SARS	Retrospective nonrandomized case/control	19 (plasma) vs. 21 (steroid)	Soo et al ²⁶	160–2,560	Not mentioned	Single dose: 200–400 mL	Not mentioned	600–900 mL plasma collected from donors Good response: discharge at day 22 74% (plasma) vs. 19% (steroid) Poor clinical response if given after day 16

(Continued)

Table 2 (Continued)

Disease	Study details		Donor details ^a		Recipient details ^b		Summary of findings ^c	
	Type	Sample size	Author	NAT	Day of sample collection	Dose and dosage		Time of administration
SARS	Case series	3	Yeh et al ³⁹	Not mentioned	Negative RT-PCR, standard screening	Single dose: 500 mL	Immediately in one patient and on days 10 and 11 in the other two patients	500 mL of plasma collected and transfused Viremia cleared in 24 hours
SARS	Retrospective	80	Cheng et al ⁵	Not done	>14 days of symptom onset and at least 7 days of recovery	Mean: 279 mL (range: 160–640 mL)	14 days of admission (range: 7–30 d)	600–900 mL plasma collected and stored in aliquots of 200–225 mL each Survival benefit if given within 14 days of onset Time of therapy and RT-PCR positivity at the time of infusion significantly affect outcome
MERS	Case series	3	Ko et al ⁴	PRNT ^d of 1:40 and 1:80	Two negative RT-PCRs, no clinical symptoms, third week of illness	Not mentioned	Between 8 and 14 days of illness	Seroconversion achieved in only one patient where PRNT was 1:80 All three patients survived Second dose was required in one patient
H1N1	Prospective cohort study	93	Hung et al ⁶	>1:160		Single dose: 500 mL	<7 days of symptom onset and requiring intensive care	21 patients transfused CP reduced mortality (odds ratio: 0.2) Suppression of cytokine storm 5 days after transfusion
Spanish influenza	Systematic review and meta-analysis	1,703 patients/eight studies	Luke et al ³²	Not mentioned	3–60 days after recovery (average: >10 d)	One to two doses: 100–250 mL	Specific range not mentioned	Early transfusion enhances recovery Fever, chills, jaundice, phlebitis reported No blinding No randomization

Abbreviations: CP, convalescent plasma; ECMO, extracorporeal membrane oxygenation; IgG, immunoglobulin G; IQR, interquartile range; LFT, liver function test; MERS, Middle East respiratory syndrome; NAT, neutralizing antibody titer; PRNT, plaque reduction neutralization test; S-RBD, spike protein receptor-binding domain; RT-PCR, reverse transcriptase-polymerase chain reaction; SARI, severe acute respiratory illness; SARS, severe acute respiratory syndrome; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

^aAll donors were fully recovered cases with negative RT-PCR for the virus, ABO compatibility, and pathogen screening mandatory in accordance with the World Health Organization guidelines. ^bMost recipients were critically ill and CP was used as rescue therapy. ^cAll recipients received standard care apart from CP: antivirals, corticosteroids, or both. No serious adverse effects were reported. ^dELISA (enzyme-linked immunosorbent assay) for IgG.

Conflict of Interest

None declared.

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