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Convalescent Plasma: An Evidence-Based Old Therapy to Treat Novel Coronavirus Patients

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Abstract

Novel Coronavirus (nCoV-2019) is a highly infectious viral outbreak that has so far infected more than 110 million people worldwide. Fast viral transmission and high infection rates have severely affected the entire population, especially the old aged and comorbid individuals leaving significantly less time to find some effective treatment strategy. In these challenging times, convalescent plasma (CP) therapy came as a ray of hope to save humankind. It is a form of passive immunization that has been used to treat various infectious diseases since 1890, including the 1918 Spanish flu, 2002/03 SARS-CoV, 2009 H1N1, 2012 MERS-CoV, and 2014 Ebola outbreak. The transfusion includes administration of CP containing a high value of neutralizing antibodies against the virus in hospitalized patients. This chapter summarizes the potential outcome of CP therapy in the treatment of nCoV-2019 patients.

Keywords: nCoV-2019, CP therapy, viral infection, neutralizing antibody

1. Introduction

Convalescent plasma (CP) is defined as a blood plasma that is withdrawn from an individual who had encountered some infectious disease and had recovered with a required amount of antibodies against the disease [1]. It is a way of passive immunization [2]. The concept has been widely used in medical sciences, especially in the case of infectious disease outbreaks. It is an old therapy used since late 1800 [3]. In Germany (1890), researchers treated diphtheria patients with sera from immunized animals. Afterward, the patients were treated with the sera from the recovered ones [4, 5]. The wide use of CP therapy was established during the Spanish influenza outbreak between 1918 to 1920 [6]. Humanity faces a great survival challenge when a new infectious disease emerges and becomes a pandemic. We do not have much to do in such cases, and we mostly rely on our scientific or medical fraternity. Therefore, during such a pandemic/epidemic, there is an urgent need to have a quick, available therapeutic option [3]. A study estimates that on an average basis, there have been 5.3 newly emerged viruses between 1940 to 2004, which includes 60–70% of viruses having an animal origin and have potential to infect humans [7]. In such circumstances where there are very few options available for

the treatment, and when a patient condition is worsening, CP therapy has always been an excellent choice for clinicians. Humans can get exposed to these viruses by different means of exposure, and generally, these are considered “unavoidable or by chance.” In viruses, the major therapeutic challenges arise because of the high degree of genetic changes, which may be due to mutation or genomic instability [8].

In December 2019, a new virus emerged in the Huanan Seafood market and resulted in a dreadful outbreak in China, and the virus rapidly spread to more than 200 countries globally [9]. Further sequence-based analysis of respiratory tract samples identified a novel strain, which was distinct from the other known coronavirus strains, subsequently named Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), and the disease caused by SARS-CoV-2 infection was designated as novel coronavirus-2019 (nCoV-2019) by the World Health Organization (WHO) [10]. The emergence of novel coronavirus came up as a big challenge for the concerned authorities of the various country [11]. Clinicians had no clue regarding its treatment approaches that made the situation even worse [12]. Soon, on March 11, 2020, WHO declared it a pandemic. In its initial days, the unavailability of any potential drug/therapy resulted in an exponential increase in infections.

For more than a century, this therapy has been widely explored against various outbreaks. During the 2002/3 SARS-CoV outbreak, 2012 Middle East Respiratory Syndrome (MERS-CoV) outbreak, and H1N1 pandemic (2009), CP therapy was successfully explored [13–16]. Similarly, for the 2013/14 Ebola virus infection treatment, CP therapy was recommended as an empirical treatment approach [17]. Based on previous experiences and similarities in terms of virological and clinical characteristics among the SARS-CoV, MERS-CoV, and nCoV-2019 [18], CP therapy was explored for its efficacy in the battle against newly emerged (nCoV-2019) pandemic. In February 2020, for the first time, a group of researchers from China reported and published the usefulness of CP in nCoV-2019 severe patients in Journals like JAMA [17] and PNAS [16]. CP therapy can be used as a prophylaxis for various infectious diseases, primarily when an outbreak occurs.

Many studies showed a significant correlation between CP therapy and improved clinical symptoms. In a preliminary study involving 5 critically ill nCoV-2019 patients, 400 mL CP administration (high neutralizing antibody (NAb) titer >40) resulted in improved clinical characteristics [17]. A similar study with 10 critically ill patients who received 200 mL of CP (one dose; NAb>1:640) significantly improved clinical symptoms within 3 days and viremia resolution within 7 days [16]. Altuntas et al. carried out a CP-based study on 888 patients, reported that CP administration reduced the ICU stay ($p = 0.001$) and MV support ($p = 0.02$) [19]. However, there is some uncertainty with large-scale CP transfusion. A PLACID trial published on 464 patients found that CP therapy did not reduce the progression to severe illness or 28-day mortality (19% treatment Vs. 18% control group) [20]. A clinical trial on 228 patients reported no significant benefits in symptoms and overall mortality between the intervention (10.93%) and the placebo group (11.43%) [21]. Similarly, a review article that studied 20 articles reflected that the efficacy of CP therapy in nCoV-2019 patients is uncertain [22]. Therefore, the US FDA recommended the use of CP as an investigational product [23]. Here, in this chapter, we have explored CP therapy potentials on nCoV-2019 based on available literature.

2. Methods

Relevant review search was done using keywords “nCoV-2019 or COVID-19, Convalescent Plasma or Plasma therapy”. The search engine included electronic databases like PubMed, Google Scholar, and ClinicalTrials.gov.

3. History of convalescent plasma

This therapy is not new for nCoV-2019, as physicians used this therapy more than a century ago [24]. Convalescent plasma has been used historically for a long time to develop passive immunity in patients suffering from various bacterial and viral diseases such as measles [25], mumps [26], and poliomyelitis [27] by transferring plasma carrying NAb from previously recovered patients. Although antibiotics have replaced CP usage in bacterial diseases, it remains a useful tool for novel viral infections for which the vaccine is not available.

A literature study reported that serotherapy was used during the Spanish flu (influenza A) pandemic in 1918–1920 for the first time, but this therapy was also used before the Spanish flu pandemic [3]. Serotherapy was tried as a therapeutic treatment in a poliomyelitis outbreak in New York in 1916 [28]. In 1916 (Tunis), some researchers again performed this therapy for the measles [6]. Hess AF in 1915 applied serotherapy to treat mumps and successfully prevented the testicular complications in the affected patients [29]. However, the credit goes to the Italian Francesco Cenci, who for the first time used convalescent serum as a therapeutic means to save the children that were exposed to measles [30]. Cenci performed this experiment by withdrawing 600 mL blood from a patient who recovered from measles after 21 days. After that, he administered this therapy to four children aged 4–8 years [30]. The results were overwhelming as the children did not contract measles following the treatment. Since the mortality rate in measles was high, ranging from 6–7%, this prophylactic therapy lasted for a long time [31]. There was again a measles outbreak in December 1906 in Italy where this therapy was administrated in forty sick children, and all the patients recovered successfully. One children had severe symptoms, but after therapy, the child showed milder symptoms. Luigi Concetti performed a similar therapy in 1900 on two children affected with diphtheria in Rome, Italy [6, 32]. After that, CP therapy was used for treating many diseases like MERS, Ebola, SARS etc. (**Table 1**) [33].

During H1N1 influenza epidemics in 2009, CP therapy was given to the patients who were in critical conditions and were presented to the hospitals with severe respiratory problems. The patients showed reduced viral load in the respiratory system and there was also decreased cytokine response and mortality rate [14]. CP therapy was also used in the Ebola epidemic in 2013 in West Africa regions [34]. SARS-CoV in 2002/2003 and MERS-CoV in 2012, the two outbreaks with

Disease (epidemic/pandemic)	Country	Year
Diphtheria	Italy	1900
Measles	Italy	1906
Mumps (epidemic)	USA	1915
Poliomyelitis	USA	1916
Measles (epidemic)	Tunis	1916
Influenza A (pandemic)	Spain	1918
SARS1 (epidemic)	China	2002/3
MERS (endemic)	Middle East	2012
Ebola (pandemic)	West Africa	2013
COVID-19 (pandemic)	China	2019

Table 1.
Use of CP therapy during various diseases outbreak.

high mortality occurred in early 21st century [35]. In South Korea, MERS became endemic, and there was an urgent need for CP therapy as the mortality rate was very high, and there was no effective treatment available [35]. Eighty patients of SARS-CoV in Hong Kong were given early administration of convalescent plasma, and they demonstrated an increased prognosis and got early discharge from the hospital [15]. A study in Taiwan showed that the administration of CP in 3 patients reduced the viral load [36].

4. Significance of convalescent plasma therapy during SARS-CoV and MERS-CoV outbreaks

Earlier, CP therapy was used to treat similar coronavirus outbreaks, i.e., SARS and the MERS in the last two decades (**Table 2**).

4.1 SARS-CoV outbreak

The first outbreak of the twentieth century that surfaced from China in 2002 led to severe respiratory illness and pneumonia-like symptoms in patients. A case study published in 2003 reports that CP administration as an adjunctive treatment along-with ribavirin and prednisolone in a 57-year-old SARS patient on Day 14 reduces the viral load and fever within a few days. Further, a better resolution of a basal lung infiltrate was seen in chest X-ray post- convalescent plasma treatment [40]. A group of Hong-Kong-based researchers, Soo et al. (2004) and Cheng et al. (2005), first reported using convalescent plasma as an emergency therapy to contain this outbreak. They found that patients treated with steroids and CP had low mortality and got early discharge from the hospitals compared to patients treated with steroids alone [15, 37, 41].

Further, they have found that patients with early administration of convalescent plasma (before 14 days of symptoms onset) have shorter hospital stay and have less mortality ($p = 0.08$) than those who received convalescent plasma after 14 days [15]. A similar study by Yeh et al. reports about the beneficial effect of CP administration in SARS infected Health-workers who were severely ill and showed no response to available antiviral treatments. The CP administration in them resulted in a reduced viral load and fever within a day, followed by resolution of pulmonary infiltrates and a time-dependent increase in anti-SARS-CoV IgM and IgG antibodies [36]. In conclusion, early administration of convalescent plasma led to better patient outcomes in terms of fast recovery, short hospital stays, reduction in viral load, and improvement in clinical symptoms.

4.2 MERS-CoV outbreak

This outbreak took place due to another strain of respiratory illness causing coronaviruses, referred to as MERS, pointing to its origin from central-east Asia (Arabian countries). From the prior experience of using CP during SARS-CoV outbreak, passive immunotherapy by administering NAb in patients serves as a vital tool in battle with this disease. Chan et al. in 2012, found that convalescent sera of previously recovered SARS patients have cross-reactive NAb that can work effectively against novel coronavirus strains [42]. Corti et al. in 2015, based on anecdotal evidence, studied the prevalence of MERS specific antibodies in dromedary camels from the middle east (Oman) and European countries (Netherlands and Chile). They found that all Omani camels in their study group had MERS-CoV-specific NAb in their serum compared to European animals,

Sr. No.	Title of the study	Year	Indication	Outcomes	References
1.	Retrospective comparison of convalescent plasma with continuing high-dose methylprednisolone treatment in SARS patients	2004	SARS	Low mortality was observed in patients treated with convalescent plasma with no adverse effects	[37]
2.	Use of convalescent plasma therapy in SARS patients in Hong Kong	2005	SARS	Low mortality rate and a better outcome was observed in patients treated with convalescent plasma	[15]
3.	Experience of using convalescent plasma for severe acute respiratory syndrome among healthcare workers in a Taiwan hospital	2005	SARS	Fast recovery with reduced viral load was observed in patients treated with convalescent plasma	[36]
4.	Middle East respiratory syndrome coronavirus neutralising serum antibodies in dromedary camels: a comparative serological study	2013	MERS	MERS-CoV specific neutralizing antibodies were found in serum Omani camels	[38]
5.	Efficacy of antibody-based therapies against Middle East respiratory syndrome coronavirus (MERS-CoV) in common marmosets	2017	MERS	Reduction in viral load and severity in marmosets treated with convalescent plasma	[39]

Table 2.
List of studies describing the significance of CP therapy during SARS-CoV and MERS-CoV outbreaks.

highlighting the importance of passive immunotherapy upon successfully detecting the transmission source. These antibodies of CP have the potential to neutralize the MERS-CoV if administered in the patients [38]. The effectiveness of CP was also reported by van Dorelman et al. in 2017, in common marmosets infected with MERS-CoV. They found that marmosets treated with hyperimmune plasma and m336 (monoclonal antibodies) showed a reduction in viral load and overall severity [39]. However, the use of MERS-CoV antibodies is very challenging, as some studies report that they are produced at a low level and are short-lived in mild infections [43, 44].

5. Mechanism of action of convalescent plasma

Convalescent plasma to be donated contains specific antibodies for particular infectious diseases or pathogens. These antibodies possess neutralization activity. This activity is achieved in different ways: either by impeding the binding of viral

particles with the endosomes, by hindering the viral protein proteolytic cleavage, by blocking the release of viral progeny, or by inhibiting the viral surface glycoproteins from invading the human cells [45]. A report published by Lu *et al.* suggests that when a neutralizing antibody (NAb-3BNC117) was passively administered on mice model, it helped block NAb helped block the new infection, enhanced clearance of the infected cells, and accelerated the HIV-1 infected cell clearance [46].

The other mode of action includes antibody-dependent-cellular-phagocytosis (ADCP), complement system activation, and antibody-dependent cellular-mediated cytotoxicity (ADCC). CP antibodies induce clearance of virus-infected cells by ADCP. A cross-talk is established among the CP antibodies, which helps in eliciting the Fc-dependent effector functions. The activated complement system helps eliminate the virus by two means. First, by direct means i.e., through complement dependent cytotoxicity. Second, indirect means, i.e., by phagocytosis, help clear the associated complement targets. In the case of nCoV-2019, the recovered patients may develop serum antibody response (IgG) against various virus epitopes [1]. This IgG competes with the angiotensin-converting enzyme-2 receptor (ACE-2) to bind with the virus receptor-binding domain (RBD) and may neutralize the nCoV-2019 infection. Therefore, in this case, the binding domain acts as both, i.e., the epitope for antibody and a binding site for the receptor enzyme [2]. Literature suggests that when CP therapy is administered at an early stage of nCoV-2019 infection, the therapeutic effect may be more effective [47]. In most viral infections, the peak of viremia starts appearing in the early first week of the illness. However, between days 10–14 or early in some cases, the host primary immune response starts exerting its potential effect [47].

6. Use of CP therapy on nCoV-2019 patients

In the absence of any specific treatment of nCoV-2019 and vaccines with proven long-term results, CP administration comes to the rescue for an effective treatment for critically ill nCoV-2019 patients (**Tables 3 and 4**). This is a kind of passive immunization method where CP from a recovered nCoV-2019 individual is obtained and uses them on diseased individuals to resolve the symptoms and reduce disease course by suppressing the viremia [18]. The use of passive immunotherapy is a widely used approach to combat various infectious diseases, which consisted of various formulations such as whole blood, pooled human sera containing immunoglobulin and convalescent plasma. Plasma collected through apheresis with subsequent CP transfusion is the most commonly used passive immunotherapy approach to battle against pandemics happened earlier [24]. Theoretically, a person who got infected from an infectious disease, upon recovery, blood is screened for NAb specific to the causative pathogen suffered earlier. The convalescent plasma containing a high-titer NAb is used as a therapy to maximize the capacity to neutralize an infecting pathogen (**Figure 1**) [56].

Studies from the current nCoV-2019 pandemic suggested that it elicits a robust immune response resulting in cytokine storm which generates high levels of IgM and IgG mostly that persists for months even after the symptom disappears. Thus, a large window period and maximum chances of successful extraction of high titer anti-SARS-CoV-2 immunoglobulins act as a boon to utilize it as passive immunotherapy [57, 58]. Further studies have elaborated on NAb response. More severe disease may lead to higher antibody response levels [58], and antibody level decreases considerably within the first 90 days after symptom start among individuals suffered from the mild disease [59].

SN	Trial No.	Title	Type	Country	Phase	Status	Sample size	Primary/Secondary outcome measures		Trial result (based on publications posted on clinicaltrials.gov)
								Primary	Secondary	
1	NCT04343261	Convalescent Plasma in the Treatment of COVID 19	Interventional	United States	Phase 2	Completed	48	Mortality, viral load, serum antibody titer.	—	Early administration of CP with sufficient antibody titer is safer and helpful in recovery and survival of COVID-19 patients.
2	NCT04747158	COVID-19 Convalescent Plasma Therapy (TPCC)	Interventional (Clinical Trial)	Paraguay	Phase 2/3	Completed	350	Evaluation of the efficacy of CP therapy. To decrease mortality in the patients hospitalized with COVID-19 and who exhibit risk factor for clinical deterioration.	Disease severity, difference in the level of inflammatory marker viz. ferritin, D dimer, leukocytes. To check adverse effects and frequency of the patients' admission in ICU.	Updated safety data from 20000 COVID-19 patients suggests that early administration of CP is safer and helpful in reducing mortality.

SN	Trial No.	Title	Type	Country	Phase	Status	Sample size	Primary/Secondary outcome measures		Trial result (based on publications posted on clinicaltrials.gov)
								Primary	Secondary	
3	NCT04407208	Convalescent Plasma Therapy in Patients With COVID-19	Interventional	Indonesia	Phase 1	Completed	10	Assessment of C-Reactive Protein (CRP), D-dimer, Plaque reduction neutralization test (PNRT), International Normalized Ratio (INR), Oxygenation Index, X-ray of chest.	Duration of hospitalization, severe adverse events.	—
4	NCT04476888	Convalescent Plasma Treatment in COVID-19 (COLLATE)	Interventional (Clinical Trial), Non-Randomized	Pakistan	NA	Completed	110	Assessment of the stay period in hospital/ ICU/SCU, mortality, adverse effects after CP transfusion.	Clinical status of COVID-19 patient, level of serum ferritin, procalcitonin, C-reactive protein, D-Dimer, Complete blood count. X-ray observation of chest.	—
5	NCT04616976	COVID-19 With Convalescent Plasma	Observational	China	NA	Completed	78	Mortality of severe COVID-19 patients.	Viral shedding	—

SN	Trial No.	Title	Type	Country	Phase	Status	Sample size	Primary/Secondary outcome measures		Trial result (based on publications posted on clinicaltrials.gov)
								Primary	Secondary	
6	NCT04332835	Convalescent Plasma for Patients With COVID-19: A Randomized, Single Blinded, Parallel, Controlled Clinical Study (CP-COVID-19)	Single Blinded, Randomized, Controlled Clinical Study	Colombia	Phase 2 Phase 3	Completed	92	Alteration in the level of viral load, IgM and IgG COVID-19 antibody titer.	Proportion of the admission and duration of the stay in hospital/ ICU. Requirement and period of mechanical ventilation. Clinical status and mortality.	—
7	NCT04405310	Convalescent Plasma of Covid-19 to Treat SARS-COV-2 a Randomized Doble Blind 2 Center Trial (CPC-SARS)	Randomized Doble Blind 2 Center Trial	Mexico	Phase 2	Completed	42	Mortality	Duration of the stay in ICU, duration of mechanical ventilation and supplemental oxygen. Viral load, level of inflammatory markers viz. ferritine, D Dimer, IL-6, PCR, IL-8, IL-10. SOFA scaling.	NA Expected: Recovery of the patients with normal body temperature, reduced viral load, no progression to ARDS, and liberation of the patient from mechanical ventilation.

SN	Trial No.	Title	Type	Country	Phase	Status	Sample size	Primary/Secondary outcome measures		Trial result (based on publications posted on clinicaltrials.gov)
								Primary	Secondary	
8	NCT04458363	Convalescent Plasma in Pediatric COVID-19	Interventional, Feasibility Study	United States	Early Phase 1	Completed	3	Safety of CP in pediatric COVID-19 patients.	Mortality. Duration of the stay in hospital/ ICU. Requirement of respiratory support and duration of ventilation. Assessment of kidney dysfunction or/ and multisystem-organ failure. IL-6 level, circulating T cells diversity, ARS-CoV-2 Antibody Titer, and SARS-CoV-2 Neutralizing antibody titer.	—

SN	Trial No.	Title	Type	Country	Phase	Status	Sample size	Primary/Secondary outcome measures		Trial result (based on publications posted on clinicaltrials.gov)
								Primary	Secondary	
9	NCT04346446	Efficacy of Convalescent Plasma Therapy in Severely Sick COVID-19 Patients	Pilot Randomized Controlled Trial	India	Phase 2	Completed	29	Number of the patients without mechanical ventilation.	Mortality. Assessment of improvement in PaO2/FiO2 ratio and SOFA score. Need of Vasopressor. Duration of the stay in hospital/ ICU. Time length of free of dialysis.	CP administration shortened the recovery, and improved respiratory parameters
10	NCT04381858	Convalescent Plasma vs. Human Immunoglobulin to Treat COVID-19 Pneumonia	Randomized Controlled Trial	Mexico	Phase 3	Completed	196	Period of hospitalization. PaO2/FiO2, severe ARDS evolution. Mortality and duration of invasive mechanical ventilation.	Time frame of RT-qPCR SARS-CoV-2 negative test.	—
11	NCT04542941	Assessment of Safety and Efficacy of CCP (COVIDIT)	Randomised Controlled Trial	Uganda	NA	Completed	136	Time frame of RT-PCR SARS-CoV-2 negative test.	Time frame of primary symptoms resolution. Assessment of clinical improvement of the patients and adverse events.	—

SN	Trial No.	Title	Type	Country	Phase	Status	Sample size	Primary/Secondary outcome measures		Trial result (based on publications posted on clinicaltrials.gov)
								Primary	Secondary	
12	NCT04389944	Amotosalen-Ultraviolet 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	Interventional	Switzerland	NA	Completed	15	Post CP treatment serious adverse events, Virologic clearance in nasopharyngeal swab and plasma of treated patients, Transfer to ICU in-hospital death	SARS-CoV-2 antibody titer to see the humoral immune response, Time of hospital discharge.	—

SN	Trial No.	Title	Type	Country	Phase	Status	Sample size	Primary/Secondary outcome measures		Trial result (based on publications posted on clinicaltrials.gov)
								Primary	Secondary	
13	NCT04547660	Convalescent Plasma for Severe COVID-19 Patients (PLACOVID)	Interventional, Randomized, Open-label	Brazil	Phase 3	Completed	160	Clinical improvement.	Mortality, hospital stay, PaO2/FiO2 ratio, duration of Mechanical ventilation, Lactate Dehydrogenase, Troponin I, C Reactive Protein, D-Dimers, Fibrinogen, Prothrombin Time, Activated Partial Thromboplastin Time, TNF-Alfa, Sequential Organ Failure, Safety, and Adverse Events, National Early Warning Score 2.	—
14	NCT04332380	Convalescent Plasma for Patients With COVID-19: A Pilot Study (CP-COVID-19)	Interventional, Pilot Study	Colombia	Phase 2	Completed	10	Change in Viral Load, IgM and IgG COVID-19 antibodies titers.	Duration of ICU and hospital stay, mechanical ventilation, Clinical status and mortality.	—

SN	Trial No.	Title	Type	Country	Phase	Status	Sample size	Primary/Secondary outcome measures		Trial result (based on publications posted on clinicaltrials.gov)
								Primary	Secondary	
15	NCT04356534	Convalescent Plasma Trial in COVID -19 Patients	Interventional, Randomized	Bahrain	NA	Completed	40	Assessment of requirement for invasive ventilation after CP transfusion	viral clearance, X-ray, C reactive protein, white cell count, lactate dehydrogenase, Procalcitonin measurement, D Dimer, Ferritin measurement, Troponin T, Brain naturetic peptide measurement, and mortality.	—
16	NCT04340050	COVID-19 Convalescent Plasma	Interventional	United States	Early Phase 1	Completed	10	Feasibility of administration of anti-SARS-CoV-2 CP. Respiratory support required by the patients 28 days after CP administration.	Cardiac arrest, Duration of ICU and hospital stay, mortality, duration without ventilator, survival	—
17	NCT04338360	Expanded Access to Convalescent Plasma for the Treatment of Patients With COVID-19	Expanded Access	United States	NA	Approved for marketing	5000 (expanded)	—	—	Administration of CP is safe in critically ill COVID-19 patients. No excessive mortality observed.

SN	Trial No.	Title	Type	Country	Phase	Status	Sample size	Primary/Secondary outcome measures		Trial result (based on publications posted on clinicaltrials.gov)
								Primary	Secondary	
18	NCT04321421	Hyperimmune Plasma for Critical Patients With COVID-19 (COV19-PLASMA)	Interventional (proof-of-concept)	Italy	NA	Completed	49	Death	Extubation timing, ICU stay period, CPAP weaning, viral load, and immune response.	—
19	NCT04441424	Convalescent Plasma Therapy on Critically-ill Novel Coronavirus (COVID-19) Patients	Interventional, Randomized	Iraq	NA	Completed	49	Mortality	Duration of the stay in hospitals.	CP therapy is effective if administered at early stage
20	NCT04569188	Convalescent Plasma in COVID-19 Elderly Patients (RESCUE)	Interventional	Italy	Phase 2	Completed	21	Death	Viral load	—
21	NCT04383535	Convalescent Plasma and Placebo for the Treatment of COVID-19 Severe Pneumonia (PLASM-AR)	Interventional, Randomized	Argentina	NA	Completed	333	Clinical Status	Clinical status, discharge from ICU and hospital, complete functional recovery, adverse events, negative PCR results, D-dimer, ferritin, neutralizing antibodies concentration in plasma, death.	The difference in clinical status and mortality between the two groups (CP treated vs. placebo) was not significant.

SN	Trial No.	Title	Type	Country	Phase	Status	Sample size	Primary/Secondary outcome measures		Trial result (based on publications posted on clinicaltrials.gov)
								Primary	Secondary	
22	NCT04392414	Hyperimmune Convalescent Plasma in Moderate and Severe COVID-19 Disease	Interventional, Randomized	Russian Federation	Phase 2	Completed	60	Normal body temperature post CP transfusion	Requirement of mechanical ventilation, oxygen therapy, days in ICU/ hospital, SARS-CoV-2 antibodies titer, plasma level of cytokines, requirement of cytokine storm inhibitor, CRP level, mortality rate.	—
23	NCT04375098	Efficacy and Safety of Early COVID-19 Convalescent Plasma in Patients Admitted for COVID-19 Infection	Interventional, Randomized	Chile	Phase 2	Completed	58	Hospitalization, Mechanical ventilation, death	1 year follow-up of: Median duration of fever, mechanical ventilation, ICU stay, viral clearance and admission length. Hospital mortality and 30 day mortality. Readmission rate.	—

SN	Trial No.	Title	Type	Country	Phase	Status	Sample size	Primary/Secondary outcome measures		Trial result (based on publications posted on clinicaltrials.gov)
								Primary	Secondary	
24	NCT04479163	Prevention of Severe Covid-19 in Infected Elderly by Early Administration of Convalescent Plasma With High-titers of Antibody Against SARS-CoV2	Interventional, Randomized	Argentina	NA	Completed	165	respiratory rate > 30 and/or an O2 sat < 93%	Severe respiratory disease, respiratory failure, death, requirement and duration of oxygen support.	Early infusion of high titer CP in mildly ill COVID-19 older adults resulted in slower progression of the disease with no adverse events.
25	NCT04492501	Investigational Treatments for COVID-19 in Tertiary Care Hospital of Pakistan	Interventional, Non-Randomized	Pakistan	NA	Completed	600	Survival	Period of hospitalization, time length to normalize symptoms, viral clearance, complications.	—
26	NCT04521309	SARS-CoV-2 Antibodies Based IVIG Therapy for COVID-19 Patients	Interventional, Randomized	Pakistan	Phase 1 Phase 2	Completed	50	Mortality, need of supplemental oxygen, days to shift from ICU to ward, hospital discharge, adverse events, CRP level, difference in neutrophil lymphocyte ratio.	Change in Ferritin levels, LDH, Sodium, Potassium, Chloride, Bicarbonate, chest X-ray findings fever, Anti-SARS-CoV-2 antibody titer	—

SN	Trial No.	Title	Type	Country	Phase	Status	Sample size	Primary/Secondary outcome measures		Trial result (based on publications posted on clinicaltrials.gov)
								Primary	Secondary	
27	NCT04442958	Effectiveness of Convalescent Immune Plasma Therapy	Interventional, Randomized	Turkey	NA	Completed	60	Level of ferritin, C Reactive Protein, D-Dimers, Fibrinogen, procalcitonin, Lymphocyte count	Arterial oxygenation, Partial Oxygen Saturation	—

Table 3.
List of completed CP based Clinical trials registered on ClinicalTrial.gov nCoV-2019 patients.

S. No.	Type of Study (group)	Country	Sample size	Volume of CP administered	Overall Mortality rates	Adverse events reported	Reported outcome
1	Multicentred/open-labelled/uncontrolled trial- Gazitúa et al., 2020 [48]	Chile (NCT04384588)	192	200-mL (twice)	1). 7 day- 5.7% (95% CI: 10.0%) 2). 30 day- 16.1% (95% CI: 22.1%-%)	11 (2.9%)	CP administration was found to be safe.
2	Retrospective study (expanded access)/Joyner et al., 2021 [49]	USA (NCT04338360)	3082	—	30 day- 26.9% (95% CI: 25.4–28.5%)	—	CP administration in hospitalized nCoV-2019 patients was found to be potentially beneficial
3	Case series/Xia et al., 2020 [50]	China	138	200–1200- mL (based on body weight and clinical condition)	2.2%	-No severe transfusion issues	CP transfusion can improve the clinical symptoms and mortality rate in nCoV-2019 severe patients
4	Multiceter trial/Abolghasemi et al., 2020 [51]	Iran (IRCT20200325046860N1)	189 (115 CP)	500 cc - one unit (another unit, if needed)	14.8%	-1 (0.87%) (transient mild fever and chill)	Early administration of CP may be more effective
5.	Multicenter/open-labeled/expanded access/Joyner et al., 2020 [52]	USA	20,000	—	7 day- 12.96% (95% CI: 12.5–13.44%)	<1% serious adverse events	CP therapy is safe with no or little complications
6.	Retrospective/matched-control study/Shenoy et al., 2021 [53]	USA	526 (263 CP)	200–500 mL (one/ two units)	1). 7 day- 9.1% 2). 14 day-14.8% 3). 28 day- 25.5%	—	CP administration may provide immediate mortality benefits (at 7-day and 14-day, but not at 28-day)

S. No.	Type of Study (group)	Country	Sample size	Volume of CP administered	Overall Mortality rates	Adverse events reported	Reported outcome
7	multicenter randomized, double-blind, placebo-controlled clinical trial/ Simonovich VA et al., 2020 [54]	Argentina (NCT04383535)	333 (228 CP)	500 mL (IQ range, 415–600)	30 day-10.96%	11 (4.8% in CP group)	CP therapy in COVID-19 patients with severe pneumonia did not reduce mortality.
8	Prospective study/ Tworek et al., 2020 [55]	Poland	204 (102 CP)	200 mL (once or more depending upon the condition)	13.7%	—	CP therapy was found to be safe and effective in high risk nCoV-2019 patients
9	multicentre randomised (PLACID)/ Agarwal et al., 2020 [20]	India (CTRI/2020/04/024775)	464 (235 CP)	200 mL	19%	Non-life-threatening adverse events in some cases	CP therapy was not relayed to the reduction in all-cause mortality

Table 4.
Status of mortality rate after CP administration in hospitalized nCoV-19 patients (studies with sample size >100).

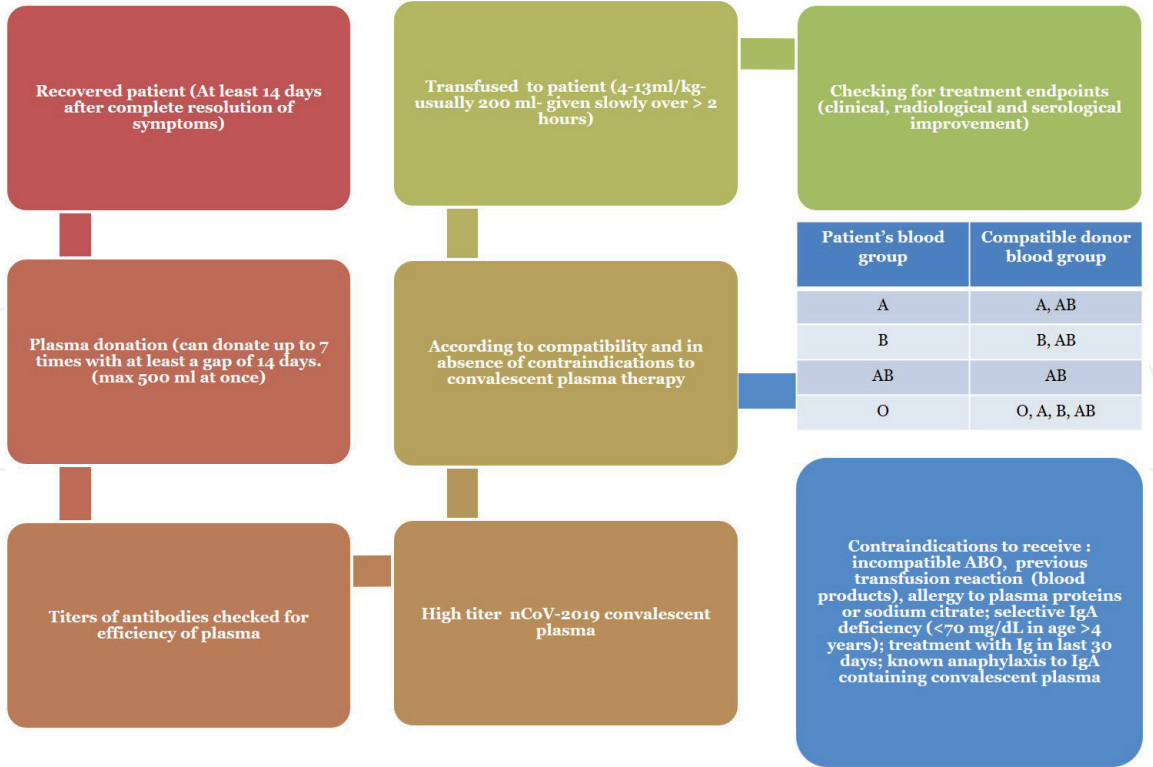


Figure 1.
Diagrammatic representation of the use of CP in nCoV-2019 patients.

6.1 Source/donor requirement

In order to overcome various challenges for enrolment of successful plasma donors during the outbreak different strategies such as social distancing, travel restrictions, and imposed lockdowns have been implemented. To recruit possible plasma contributors, this includes donor self-identification, social awareness utilizing social/formal/e-media outlets and clinician referral of individuals got previous exposure to the infection [60]. NAb titres can be examined in possible donor or CP units through ELISA/chemiluminescence assay or pseudovirus neutralization assays which are known as indirect methods or directly under biosafety level 3 conditions by using live SARS-CoV-2 neutralization assays. USFDA has permitted the use of CP therapy under the clause of EUA for hospitalised nCoV-2019 infected patients [61]. CP units were categorized as lower or higher antibody titre based on qualitative chemiluminescent immunoassay for detection of neutralizing IgG against SARS-CoV2 spike protein [60]. The collected plasma is treated for pathogen inactivation to avoid the risk of transfusion transmitted infections. A donor can donate CP weekly for several months till the antibody titers are high. There are several factors that restrict the donation, including the individuals who already received the CP for their nCoV-2019 treatment (minimum of 90 days) are not allowed to donate blood products.

6.2 Who can donate CP

- Person who has confirmed validated diagnostic record of SARS-CoV-2 infection.
- Physical examination, including the absence of fever and respiratory symptoms. Minimum of 14-day post-recovery with no symptoms.
- A person who meets the standard routine blood donation criteria. The donor and recipient should be ensured for ABO compatibility

- CP must be free of HIV, HCV, HBV syphilis, human T-cell lymphotropic virus 1 and 2, and *Trypanosoma cruzi* and any other transfusion/locally transmitted infections.
- CP from either male donors or from female donors with no pregnancy history is preferentially used to avoid any risk of TRALI (Transfusion Related Acute Lung Injury) [62].
- For retrospective testing and scientific investigations, donors blood products (serum, plasma, whole blood) should be saved at -80°C .

6.3 Plasma donation

Convalescent plasma donors may be identified during national disease-specific cohorts, during hospitalization of the patient, by the practitioners treating outpatients, and through various specific online/social helpline-networks.

6.3.1 FDA guidelines

The FDA recommends three approaches for the administration of CP. First is directed for the treatment of patients of nCoV-2019 through EUA. Second, patients with severe nCoV-2019 illness who are unable to participate in RCT through expanded access protocol. The third one involves clinical trials where clinicians are advised to enroll patients in the trials to examine the effectiveness of CP therapy in nCoV-2019 [63].

6.4 Dosage

Various dosage regimens were utilized in various hospital setups for the management of SARS-CoV2 infected patients. Universally 200 ml of convalescent plasma in 1 or 2 doses with an infusion rate of 100 to 200 ml/h are administered with an interval of 12 hr. apart. The dosage regimen is decided according to body weight and antibody titer [64]. Standard hospital procedures and recommendations should be followed for thawing and transfusion of plasma through a peripheral or central venous catheter.

6.5 Follow up

CP therapy is still an experimental model. For future scientific investigations and correlations, the blood products of the recipient should be stored (prior and after transfusion). As per published trials, the response post CP therapy is mainly assessed i.e., PaO₂/FiO₂ ratio clinically or through Ct scan or X-ray (radiological) of the infected organ. However, elicitation of nCoV-2019 antibody titer or increased ALC in recipients, as well as a decline in SARS-CoV2 viral load either in terms of absolute quantification or increase of cycle threshold (Ct) value, could be considered as surrogate endpoints [65].

7. Risk associated with the use of CP therapy

Major adverse events associated with CP transfusion are not much evident so far. However, risk assessment before/after the transfusion is important. Several studies/clinical trials have shown that the use of CP therapy in severely ill nCoV-2019

patients is safe and early administration with adequate anti-SARS-CoV-2-NAb titer is helpful in faster recovery and survival of nCoV-2019 patients [18, 66]. CP therapy is contraindicated in certain individuals such as those who are allergic to plasma protein or sodium citrate, patients with selective IgA deficiency (70 mg/dl in patients four years old or older), or the ones who received treatment with immunoglobulins in the last 30 days as it could lead to the development of serum sickness [67].

However, large U.S. national registry, through its interim report, showed that among over 100,000 hospitalized adults that had nCoV-2019 infection, low incidences of transfusion reactions were documented in the first 5,000, and 20,000 patients transfused with nCoV-2019 CP therapy, which is suggestive of the fact that transfusion of convalescent plasma is safe and poses no additional risk of complications among hospitalized patients with nCoV-2019 [52, 68]. An RCT compared the safety of convalescent plasma transfusion with fresh frozen plasma transfusion documented a comparatively less rates between the controls (7%) and CP (4%) group of patients and highlighted the safety profile of CP transfusion [69].

8. Conclusions

In the absence of any effective antiviral drug and vaccine (long term effect is not yet established) to prevent the infection, several approaches have been explored to reduce the duration of the disease course. One therapeutic approach that is being utilized globally is convalescent plasma therapy against nCoV-2019. Once the person recovers from nCoV-2019, the blood contains antibodies against the causative virus. In emergency situations, these antibodies can be given to other affected people to provide immediate immunity against the virus, reducing the severity and helping in faster recovery. FDA has not yet approved the use of CP as a treatment of nCoV-2019. It is administered under the EUA or an IND. However, further large-scale, world-wide controlled clinical trials are needed to prove the efficacy of the CP therapy for the current pandemic.

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Conflict of interest

The authors declare no conflict of interest.

Acronyms and abbreviations

nCoV-2019	Novel Coronavirus
CP	Convalescent Plasma
SARS	Severe Acute Respiratory Syndrome Coronavirus
WHO	World Health Organization

MERS	Middle East Respiratory Syndrome
NAb	Neutralizing Antibody
ADCP	Antibody-Dependent-Cellular-Phagocytosis
ADCC	Antibody-Dependent-Cellular-Mediated Cytotoxicity
ACE-2	Angiotensin-Converting Enzyme-2 Receptor
RBD	Receptor-Binding Domain

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