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REVIEW

Effectiveness of COVID-19 Convalescent Plasma (CCP) During the Pandemic Era: A Literature Review

Usha Rani Kandula, Techane Sisay Tuji, Dinkinesh Begna Gudeta, Kassech Leta Bulbula, Anwar Abdulwahed Mohammad, Ketema Diriba Wari, Ahmad Abbas

Department of Nursing, College of Health Sciences, Arsi University, Asella, Ethiopia

Correspondence: Usha Rani Kandula, Department of Nursing, College of Health Sciences, Arsi University, Oromia Region, P.O. Box-396, Asella, Ethiopia, Tel +251-939052408, Email usharani2020@arsiun.edu.et

Abstract: Worldwide pandemic with coronavirus disease-2019 (COVID-19) was caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). As November 2, 2022, World Health Organization (WHO) received 628,035,553 reported incidents on COVID-19, with 6,572,800 mortalities and, with a total 12,850,970,971 vaccine doses have been delivered as of October 31, 2022. The infection can cause mild or self-limiting symptoms of pulmonary and severe infections or death may be caused by SARS-CoV-2 infection. Simultaneously, antivirals, corticosteroids, immunological treatments, antibiotics, and anticoagulants have been proposed as potential medicines to cure COVID-19 affected patients. Among these initial treatments, COVID-19 convalescent plasma (CCP), which was retrieved from COVID-19 recovered patients to be used as passive immune therapy, in which antibodies from cured patients were given to infected patients to prevent illness. Such treatment has yielded the best results in earlier with preventative or early stages of illness. Convalescent plasma (CP) is the first treatment available when infectious disease initially appears, although few randomized controlled trials (RCTs) were conducted to evaluate its effectiveness. The historical record suggests with potential benefit for other respiratory infections, as coronaviruses like Severe Acute Respiratory Syndrome-CoV-I (SARS-CoV-I) and Middle Eastern Respiratory Syndrome (MERS), though the analysis of such research is constrained by some non-randomized experiments (NREs). Rigorous studies on CP are made more demanding by the following with the immediacy of the epidemics, CP use may restrict the ability to utilize it for clinical testing, non-homogenous nature of product, highly decentralized manufacturing process; constraints with capacity to measure biologic function, ultimate availability of substitute therapies, as antivirals, purified immune globulins, or monoclonal antibodies. Though, it is still not clear how effectively CCP works among hospitalized COVID-19 patients. The current review tries to focus on its efficiency and usage in clinical scenarios and identifying existing benefits of implementation during pandemic or how it may assist with future pandemic preventions.

Keywords: convalescent plasma, COVID-19 convalescent plasma, effectiveness, CCP, COVID-19, coronavirus disease-2019, SARA-CoV-2, severe acute respiratory distress syndrome-coronavirus-2, pandemic era, literature review

Introduction

In recent years, coronavirus infections have been the source of epidemics, and the concern was raised about SARS (Severe Acute Respiratory Syndrome) and MERS in 2002 and 2012, respectively. The SARS-CoV-2, a current recruit among coronavirus family with the most recent outbreak and designated with COVID-19.[1] The worldwide epidemic has been reported due to COVID-19[2] and, the WHO proclaimed worldwide pandemic immediately after its development and subsequent spread among human population during 2019. Around 4.4 million people have perished from virus affects, and infected with a minimum of 215 million.[3] At that movement, WHO stated on March 11, 2020, the spread of COVID-19 may pose significant and ongoing problems to the entire globe.[2]

Patients with COVID-19 are usually undiagnosed or exhibit mild respiratory concerns,[4] moreover, some patients appear with a variety of symptoms, ranging from mild or flu-symptomatology (81% of cases) to acute (14% of cases) and

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with severe (5%) clinical manifestations.[5] In addition to affecting people's daily lives, the SARS-CoV-2 infection also led to organ damage. An evidence reported that the SARS-CoV-2 either directly or indirectly promotes inflammasomes and, by inducing pyroptosis, an inflammatory form of cell demise, and aggravating tissue injury with endothelial malfunction, vasodilation and, the inflammatory cytokines may promote tissue damage and, the patient may exhibit with several clinical manifestations,[2,6] and multiple-organ failure may occur as a severe side effect of this inflammatory reaction.[2]

The Acute respiratory distress syndrome (ARDS), abnormal coagulation, multiple organ failure syndrome, or septic shock are some examples of infection processes other than direct viral infection that can cause severe effects in SARS-CoV-2. In some circumstances, adapted immunity is suppressed, which forces the innate immune system to respond more vigorously, and produced more inflammatory compounds than it should, may delay the clearance of viruses, and increase the number of immune cells that are activated at inflammation sites.[7] During pandemic demands, there is a need to move swiftly to offer therapeutic options in this circumstance. Considering advancements in vaccination and pharmaceutical research, notably medications using nanotechnology and naturally occurring bioactive constituents,[8] and with particular coronavirus's genetic diversity and rapid evolution, there is presently no special, effective treatment to prevent or treat the disease.[9,10]

People who are critically ill are more at risk of dying from an overactive immune system than from a viral infection alone. Significant increases in cytokines and other inflammatory biomarkers, such as interleukins, interferon, tumor necrosis factors, colony-stimulating factors, growth factors, ferritin, C-reactive proteins, and D-dimers, are present among majority of patients in the intensive care unit (ICU) with severe COVID-19.[11,12] Infiltration of further immune cells, such as lymphocytes, macrophages, and dendritic cells, may ensue from this excessive and prolonged cytokine response, which may exponentially increase the inflammation.[11,13] The patients with COVID-19 may experience illness exacerbation and mortality mostly because of this immune system imbalance, which causes a cytokine storm.[14] To prevent the illness worsening and lower mortality among COVID-19 patients, treatment may include rapid control of the cytokine storm syndrome (CSS) in addition to supportive therapies.[11,15]

For the movement, the sole option for new coronavirus pneumonia is general supportive care only,[4] with this reasons, from the hospital patients died at a rate ranging from 11% to 15%. Moreover, the amount of knowledge accessible in literary texts and official sources is steadily growing, despite the reality that COVID-19 is extremely contagious and has a high death rate.[2] Since late 2019, COVID-19 has become a concern for public health all around the world, and there has been a significant amount of debate and research towards finding a solution. Although, few strategies have proven to be effective, while others have failed.[16,17] In addition to that, almost two years into the COVID-19 epidemic, we still have a limited pharmacological arsenal to prevent or cure the disease's devastating effects among affected population.[18,19]

In progress towards the introduction of novel variations emphasizes the need for surveillance systems with update vaccination programs and treatment methods.[20] These variances are particularly worrisome because many regions of the world do not vaccinate their inhabitants due to a lack of infrastructure for mass manufacture and distribution, affordability and, with appropriate provisions.[21] There are still many active infections with SARS-CoV-2 infectivity, transmission, and fatality are altering even though the percentage of people globally who are protected against COVID-19 is expanding as a consequence of the availability of various vaccinations.[14] In this scenario, immunotherapies, cytokine inhibitors, monoclonal antibodies, and anti-inflammatory medications are instances of potentially effective therapy alternatives for COVID-19 prevention,[22,23] and by removing inflammatory cytokines and infective markers, therapeutic plasma exchange may be a useful treatment for CSS.[24,25]

Convalescent Plasma Therapy (CPT)

CPT is a passive immunization technique that has been employed for more than a couple of centuries as a reliable and efficient therapy for a wide range of infectious diseases, including COVID-19,[26] and it has been routinely employed in the treatment of hospitalized COVID-19 patients.[27,28] CCP was a common form of passive immunization during the initial stages of pandemic, with the risk of antibody-dependent acceleration of viral illness even if the preventative vaccine and monoclonal antibody treatment had been quickly developed and used[3] (Figure 1).

The United States Food and Drug Administration (FDA) currently suggests antivirals like remdesivir and anti-inflammatory medications like corticosteroids for hospitalized patients with who require supplementary oxygen (O_2), as

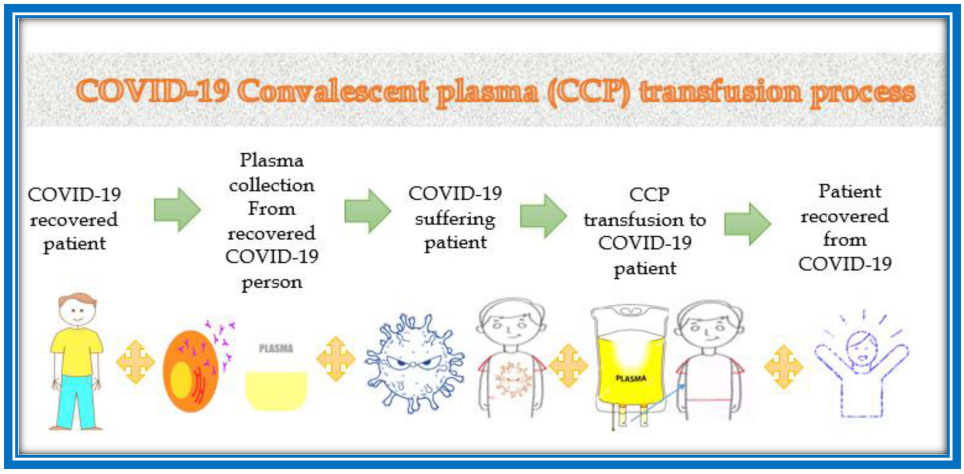

Figure 1 COVID-19 Convalescent plasma (CCP) transfusion process.

well as monoclonal antibodies targeted against SAS-CoV-2 spike protein for outpatients at high risk of disease development.[29] As everyone is aware, passive immunization has played an essential role in the treatment of infectious illnesses.[30] Soon as the commencement of COVID-19 epidemic, treatment options were predictably limited, forcing the reintroduction of a venerable method with passive immunization by transfusion of CP.[31]

Plasma transfusion from recuperating donors to acutely infected patients was one of the few treatment options available at the outset of the pandemic. In areas with limited resources, passive immunization employing CCP from formerly infected donors is still an effective therapeutic option. Despite a few positive results from CCP transfusion in patients with acute SARS-CoV-2 infection, the efficacy of this therapy still seems to be poorly or not thoroughly grasped.[32] As before COVID-19 pandemic, clinical trials with CP were rare and produced contradictory results with range of research designs, patient demographics, infecting pathogens, timing of infusion delivery about the duration of the illness, dosage, and the controls used in previous research.[33,34]

Moreover, High-titer CCP early delivery was shown to be safe and effective, with a lower risk of hospitalization and mortality compared with control groups.[35,36] These combined findings have influenced clinical guidelines that advocate for the early transfusion of CCP.[37] The option of CCP is also available to hospitalized patients who are unable to take other available antiviral medicines due to safety concerns or contraindications, such as pregnant women, and patients with severe chronic kidney disease, or severe chronic cirrhosis of the liver.[38]

During the 1918 Spanish flu pandemic,[39,40] and subsequent severe viral diseases, including SARS, H_1N_1 influenza, MERS, and the Ebola virus, we later adopted CP infusion method as passive immunization.[41–43] The pre-clinical animal models suggested that passive immunization therapeutics would be useful during the COVID-19 pandemic,[44–46] and non-human primate studies discovered that passive transfer of immunoglobulins could confer therapeutic efficacy after viral exposure and fight infection in a dose-dependent manner.[47,48] Additionally, case studies conducted early during pandemic demonstrated on positive outcomes for patients receiving CP from donors recovered through CCP transfusions.[49–51]

As anti-SARS-CoV-2 neutralizing antibodies (NAbs) are present in CCP and may be utilized as COVID-19 passive immunization in patients with high risk of severe illness and, also the plasma from recuperating patients may have additional immune-modulatory abilities when administered to COVID-19 patients.[52] Additionally, the use of CCP from previously infected individuals to passively transfer anti-SARS-CoV-2 antibodies and potentially treat or prevent COVID-19 is currently being investigated. Furthermore, CCP is acquired from individuals who have fully recovered from illness and preferably includes high titer of viral NAbs.[53]

Reduced Plasma Cryoprecipitate (Cryosupernatant)

As recent research findings suggest on using fresh frozen cryoprecipitate-depleted plasma or plasma with reduced cryoprecipitate instead of apheresis plasma from recovered COVID-19 patients as a source of anti-SARS-CoV-2 antibodies.[54] Since Judith Pool's original proposal in 1964,[55] the vast majority of blood manufacturers have been able to produce cryoprecipitate supernatant from fast frozen plasma. The SARS-CoV-2 antibody-containing plasma is rapidly cooled to a temperature of −70 °C or lower.

Treatment with CCP Among Other Viral Diseases

According to research that has been published, the CCP can be used to treat a variety of viral diseases, including influenza, Ebola virus, Spanish influenza, SARS, and MERS. The majority of patients observed positive effects from CCP transfusion without any challenges.[56,57]

Ebola virus,[56,57] the WHO has suggested the transfusion of CP or whole blood from patients who recovered from the Ebola virus as an empirical treatment for the Ebola outbreaks.[58]

The Spanish flu,[57] as the studies that examined convalescent blood products to treat Spanish influenza-related pneumonia in hospitals as early as the 1918–1925 pandemic presented an assessment versus a control or comparison group. A meta-analysis performed in 2006, almost a century later, revealed a significant decrease in the total crude mortality rate, from 37% among controls to 16% among patients receiving CP.[59]

H_1N_1,[57] a comparative study involving 99 patients, CP treatment was able to significantly lower respiratory tract viral load, serum cytokine response (interleukin-6, interleukin-19, and tumor necrosis factor-alpha), and mortality in context of pandemic influenza A (H_1N_1) 2009 virus infection. The probabilities of dying were reduced by 80%, making the decrease in mortality in that research study quite impressive.[42]

SARS,[57] Following a comprehensive review and meta-analysis of 32 studies on severe influenza and the SARS coronavirus emphasized the consistent evidence for a decrease in mortality, particularly in cases of early administration of CP and hyperimmune immunoglobulin following symptom onset. The study results indicated a reduction in mortality odds of 75%,[60] supporting the significant reduction in mortality odds as per the investigation findings.[60]

MERS,[57] the management of MERS with CP therapy planned protocol for people with illness was established during 2015. In accordance with protocol, individuals who had an anti-MERS coronavirus indirect fluorescent antibody titer of 1:160 or higher would be evaluated to identify, if they were eligible to donate plasma in accordance with standard donation guidelines and, provided that they had no signs of active MERS infection in the form of clinical or laboratory findings.[61]

The CP had also been used to treat measles,[62] poliomyelitis,[63] and mumps,[64] during the first half of 20th century (Figure 2).

History of CP

Dr Emil von Behring introduced passive immunization as a revolutionary treatment modality at the turn of 20th century, and when he established that the plasma from horses afflicted with diphtheria or tetanus could be applied to heal humans also. He was awarded with Nobel Prize for Medicine or Physiology in the year of 1901. This discovery opened the door for the treatment of infectious diseases with plasma from recovering patients, and CP has been used throughout history to treat a variety of infections, including poliomyelitis, Spanish influenza, Korean hemorrhagic fever, and more notably, Ebola virus and influenza virus (H_1N_I).[65]

The Arbeitskreis Blut, a working party as blood of the "German federal ministry of health", released a statement (S16) on the production and administration of CP in severe disease epidemics on October 20, 2015. During early 20th-century, occurrences of diphtheria as well as subsequent cases of SARS, H1N1, and Ebola were said to respond positively to this therapeutic intervention.[66] As the first therapeutic efficacy using plasma with anti-SARS-CoV-2 antibodies from convalescent donors was reported by Chinese doctors at the same time.[49,50,67] In addition to this, more than 15 years ago, the first CP infusions were undertaken to treat coronavirus infections. Further to this, the first published studies during the 2004 and 2005 Asian SARS outbreaks showed that patients who received plasma had shorter hospital stays and fewer deaths than those who received standard care.[41,68]

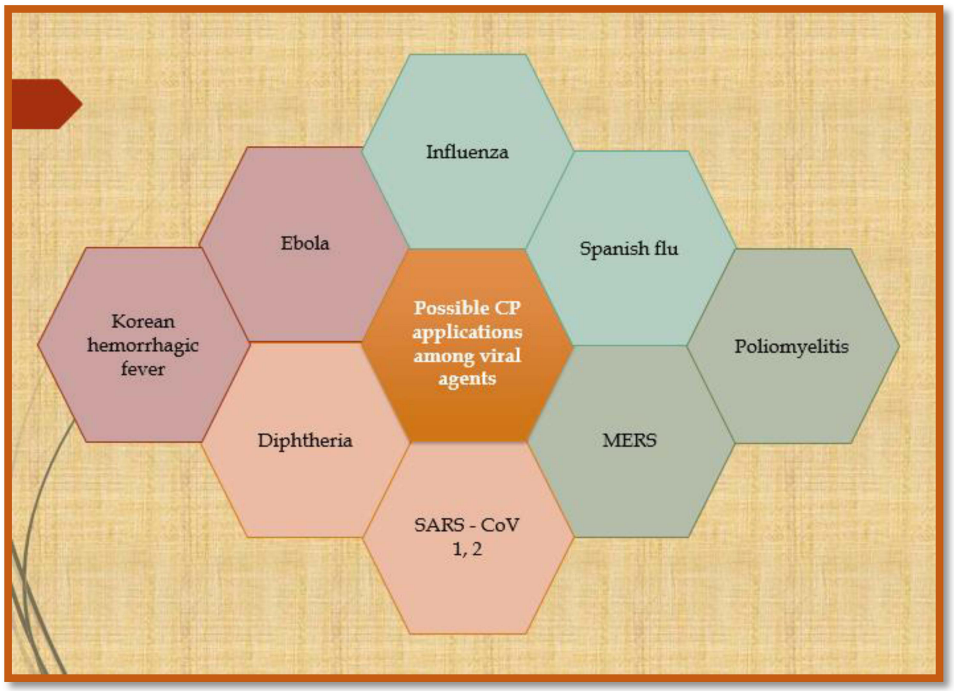

Figure 2 Possible convalescent plasma (CP) applications among viral agents.

According to the study, the first collection of CPT cases in SARS-CoV-2 patients was revealed by researchers in Asia at the beginning of 2020. As per the, first such trial, clinical and biological markers in five critically ill patients were reported to be improved by plasma infusion. There was also report on rapid neutralization of viral load process.[50] Further to this, the research paper below had 19 patients who had similar outcomes.[69] However, the European Commission developed guidelines for acquiring, analyzing, processing, preserving, disseminating, and regulating the use of CP in light of these preliminary results and the dearth of a viable etiological therapy for COVID-19, and the early applications of CP arose as an alternate therapy with a favorable safety profile in the absence of competent treatment.[70]

CP Collection (CPC)

As per the following guidelines provided by the regulatory organizations of the nation in which it is delivered, CCP must be processed and utilized as an investigational patient's blood. According to US, the FDA in charge of enforcing rule that only registered and authorized blood collection facilities may obtain blood products as strictly. The regulatory body is also in charge of establishing the criteria for donors to be eligible, which have been modified as per new information has emerged over the course of pandemic. As to direct newly recovered donors to blood facilities early in the epidemic, several strategies were employed, such as testing databases with automated referrals, conventional and social media, etc.[71]

Apheresis Technology (AT)

As per the requirement of higher output of plasma volumes per donation (approximately three to four units for a large donor) in comparison to whole blood collection, apheresis technology is broadly applied for collection, at least in high-income nations in order to treat complex diseases.[72] A medical treatment known as apheresis involves the temporary removal of blood components using centrifugal force, structural and size variations between blood components, and surface forces in microchannels as the basis of separation.[73]

CP Donor Criteria

Plasma apheresis was performed on convalescent patients who were at least 14 days post-symptom resolution and eligible for plasma donation,[74] as well as remaining protocols as per the regular blood donation and transfusion procedures.

CP Testing

Testing for blood-borne diseases, ABO type, and human leukocyte antigens (HLA) (in the context of parous women) is necessary in addition to anti-SARS-CoV-2 antibody testing. Throughout the pandemic, antibody levels for CCP qualification have been regularly revised. Additionally, inconvenient for high-throughput screening, formal neutralization assays are also challenging as for standardization. Instead, several tests have been proven to be effective, with a certain antibody level being shown to correspond to neutralization.[72]

CP Storage

Plasma treatment may be advantageous among patients with COVID-19 who have low humoral immunity or receiving B-cell depletion therapy for autoimmune diseases, multiple sclerosis, rheumatoid arthritis, or hematologic malignancies.[75,76] Indeed, the beneficial effects of passive immunization on the clinical trajectory have been demonstrated, for instance, in a patient with a humoral immunodeficiency.[77]

Institutional blood banks frequently keep CCP inventories. Each ABO-compatible type should ideally have an adequate supply to meet clinical demands, because only 4% of the population donates blood, and as demand for several blood type demands, particularly Group AB (universal donor), have proven challenging to collect as required quantity. These donations are usually intended to support the urgent use of plasma for the control of bleeding disorders. As Group "A" plasma may be substituted during routine trauma resuscitation if approved by the institutional policy since Group "AB" plasma as in limited supply conditions.[78]

The CCP is still under investigation, which may restrict its use in comparison to plasma, which is frequently used to alleviate coagulopathy and hemorrhage conditions. As an organizational policy concerning non-group plasma should be formulated when transfusions are administered, and the patients should be informed on the benefits and dangers, and also the documentation for transfusion permission should include with any necessary disclosures as per the institutional policies.[38]

Accordingly, clinical demand of CCP was higher than supply at the start of the epidemic. Because of the collection's rapid growth, most sizing-up blood facilities established a standing inventory, along with for responding to demand increases, having a CCP inventory on hand is crucial (eg, due to emerging variants). Later, as per the need decreased, and collecting came to an end as a result of vaccination process, and decrease in COVID-19 incidence, and evidence of the futility of treating advanced sickness. Due to this, earlier CCP inventories were inadequately suited to more recent variants like delta and omicron.[78]

This highlights the necessity of keeping a small supply of CCP on hand as well as the ability to find new donors, especially those who have recovered from an infection with a virus that is the same as the one that infected the intended recipient. It is logistically challenging, even though temporal and geographic matching are preferred. Despite poor matching, qualified CCPs (as described by the FDA) are still thought to be helpful.[71]

CP Transfusion Area

To protect patients, workers, and visitors in healthcare facilities from infection, providing clinical treatment to potentially infectious patients during a pandemic necessitates a special infrastructure. Numerous outpatient transfusion and infusion centers provide immunosuppressive or chemotherapeutic treatment to sensitive populations, and sharing space with individuals who are actively infected with SARS-CoV-2 poses a serious risk to these populations.[38]

It was a common infection control tactic to separate treatment facilities from ordinary care facilities. The logistical complexity of this system affects medical supplies and patients equally. Repurposing existing infrastructure for transfusion, such as negative pressure chambers used for the treatment of patients with airborne infections (such as TB), is one possibility for developing a new outpatient CCP transfusion center.[38]

CP Usage

Passive immunization with CP treatment became more common in patients with SARS-CoV-2 infection during COVID-19. To properly determine the use of this treatment in which patient groups at what dose and at what appropriate time interval, no controlled trial has been carried out. Studies have revealed that CP therapy is well tolerated, early treatment decisions can reduce mortality and ICU stay length, and it is not just a last-resort rescue strategy[79] (Table 1).

Table Evidences from Literature Report on the Efficacy of Convalescent Plasma Administration Among COVID-19 Patients

Reference and Author with Country	Title and Research Type	Research Design	Study Period	Setting	Population /Sample Size	Study Instruments	Intervention	Findings	Conclusion
Nada Amri et al[136]	• Plasma selection in COVID-19 CPT: Blood endothelial-cell extracellular vesicles.		24 April-12 July 2020		• 45 plasma donors who recovered from COVID-19 infection				• Regarding obtaining COVID-19 CP, it is crucial to take into consideration the age of the donor, the period since the donor's initial clinical symptom first emerged, and the intensity of those manifestations.
Meenu Bajpai et al From India[137]	Effectiveness and safety evaluation of CP versus FFP in patients with severe COVID-19	Open-labelled, Phase II; pilot RCT.		• Liver and biliary sciences, in coordination with the Internal medicine department, Lok Nayak hospital at Maulana Azad Medical College.	• 29 COVID-19 patients.		• In patients with severe COVID-19 infection, one group (n = 14) obtained CP in addition to regular medical services, whereas group 2 (n = 15) obtained random donor FFP as a comparison in addition to usual medical services.	• At day 7, 78.5% of CP patients and 93.3% of control patients had not attained SS (p = 0.258). • The respiratory rate, oxygen levels, and SOFA score all significantly improved in the CP group. • Both groups did not experience any negative side effects after undergoing plasma transfusion.	• In patients with COVID-19, CP treatment is secure and might be helpful.
Naveen Bansal et al[138]	• An innovative system of grading to identify which COVID-19 CPT individuals need to receive special attention: a conclusion from a hypothesis					• Based on this grading methodology, 2 groups of patients are created. • Group at low risk (LRG; score <5) • Group at high risk (HRG; score ≥5)	• Score 0–4: No intervention (Basic standard care and hospital management) • Score of ≥5: Early CP therapy, preferably before 72 hours	• To destroy the SARS-CoV-2 virus and prevent the CS from emerging, HRG should begin CP therapy within 72 hours following a definitive diagnosis of COVID-19.	• In a specific group of patients where it is most likely to be effective, CPT must be used with prudence.
Giovanni Belcari et al[99]	• Clinical and viral reaction to CP in a patient with COVID-19 pneumonitis and CLL (CR)				• Male patient, age 62	• Patient treated on • Rituximab plus bendamustine • LMWH, • Azithromycin and ciprofloxacin • Low-flow O_2 support	• CP in a COVID-19 Pneumonia patient with CLL	• The patient had a full clinical, radiological, and virological response following 6 infusions of 600 mL of HTCP from recovering and triple-vaccinated donors.	• This outstanding case adds weight to the expanding body of evidence demonstrating that, when HT dosages are given, CP is successful in curing ICPs.

(*Continued*)

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Table (Continued).

Reference and Author with Country	Title and Research Type	Research Design	Study Period	Setting	Population /Sample Size	Study Instruments	Intervention	Findings	Conclusion
Artur Belov et al[104]	• Clinical utility is moderate based on the earlier infusion of COVID-19 CP with a high AbsT concentration as determined by a live viral neutralized assay (ORA)				• 23,118 total patients • Received 1 unit of CP were separated into 2 groups those who received HTCP (>250 50%, ID 50; n = 13,636) and those receiving LTCP (≤250 ID 50; n = 9482).			• HTCP transfusions led to absolute improvements in average 7 and 28-day DR of 1.1% and 1.7%, respectively, when compared to non-intubated patients who administered LTCP.	• CP has only been demonstrated to have a moderate clinical benefit, but should viral variations emerge in the future that cannot be neutralized by currently available therapies, CP may play a role.
Mickael Beraud et al[27]	• CP for the Tx of COVID-19: Lessons learned and particular considerations for patients with IDs (Review)		March 1, 2020, and May 1, 2021.		• 37 articles; 261 identified publications report reliable controlled studies.	• From the 261 retrieved articles, 37 papers detailing robust controlled investigations in the whole population of patients with COVID-19 and 9 papers on ICPs with COVID-19 were selected.		• Only CP units with high NAbT should be infused in patients with low NAbT to better prepare for future epidemics/pandemics and to assess the possible benefits of CPT.	• Even while NAbT-containing CP infusions remain a safe, widely available, and potentially helpful therapeutic option for forthcoming pandemics and epidemics, CCP infusions did not improve COs for COVID-19 patients.
Rungsun Bhurayanontachai et al[133]	• The outcome of non-ABO-identical CPT in ARDS related to COVID-19: A CR. (CR)				• 45-year-old man		• Favipiravir, lopinavir, ritonavir, hydroxychloroquine, azithromycin and IV methylprednisolone, dexamethasone, remdesivir • 400 mL of CPT.	• After plasma transfusion was finished, neither hemolytic nor non-hemolytic transfusion responses were found.	• The ARDS patient, who was resistant to the current medical standard of care, reacted dramatically to an ABO-incompatible CP infusion without experiencing any TRs.
Soykan Bicim et al[26]	• CP for the preventive Tx of COVID-19 in a patient with RF and HL (CR)				• 22-year-old female patient	• 6 cycles of Adriamycin, Bleomycin, Vinblastine, and Dacarbazine Tx with the diagnosis of HL 2 years ago • Rituximab, Cisplatin, Cytarabine, Dexamethasone (Chemotherapy) • HD and RRT for 6 times.	• CCPT • RRT • Favipiravir, remdesivir, lopinavir-ritonavir, oseltamivir	• CP can be utilized as an additive therapeutic agent in patients where there is no standard Tx available and the DR is high owing to the underlying condition.	• In this regard, immune CPT is a promising therapeutic procedure.

Yeliz Bilir et al[79]	• A comparison of the effectiveness of early versus late coronavirus treatment in patients requiring ICU (ORA)	*RS* evaluation	• CP therapy between April and June 2020	Kartal Dr. Lütfi Kırdar City Hospital	• ICU admissions of 20 patients	• CP Administration.	• CPT results at early (G1) and late (G2) periods were compared.	• Along with the delay of CP administration day, the length of stay in the ICU grew.	
Natalie Bruiners et al[139]	• Beneficial CPT in a patient with COVID-19 revealed disease-resolution pathways by its biological correlates (CR)					Hydroxychloroquine, methotrexate, rituximab infusion, azithromycin	• 4-litter supplemental O_2 • Day 40: 400 mL of COVID-19 CCP from an unidentifiable donor • The patient was given 600 mL of her relative's CP on day 54.	• On day 54, the patient's O_2 saturation increased to the point where supplemental O_2 was no longer needed.	• Prognostic hints in severe COVID-19 cases may come from tracking specific innate immune cell subsets in peripheral blood.
P. Cacilhas et al. From Southern Brazil[86]	• Patients with COVID-19 receiving CPT: an NRCCS with concurrent control (ORA)	NRCCS	October 2020 and March 2021		• 12 patients were assigned to the EG, and the CG had 24 patients who were matched for CCI.			• Patients who had CP had lower inpatient mortality rates than those who did not (RR- 0.48; 95%, CI- 0.29 to 0.79).	• There were no variations in the rates of ICU admission across the groups (RR = 0.80; 95% CI: 0.47 to 1.35).
Natasha M. Clark et al[3]	• IgG and IgA Abs against SARS-CoV-2 do not promote viral infection in COVID-19 CP (ORA)				• 90 CCP donors			• These results support the notion that the IgG and IgA isotypes found in CCP do not influence the ADA of infection.	• The results thus indicate both the curative use of currently available Abs-based therapies, including the continuing use of CCP transfusion procedures, and the use of diverse vaccine portals in a prophylactic way.
Rongjuan Dai et al[2]	• The SR and MA of CPT's safety and efficacy in COVID-19 subjects (Review)			• Databases from the Cochrane Central Register of Controlling Trials, PubMed, Embase, Web of Science, and China National Knowledge Infrastructure.	• 13 RCTs with a total of 13,232 participants			• According to the study's findings, there was a reduced MR in the CP group and an SS difference between the DR of the 2 groups compared to the CG (RR: 0.70, 95% CI: 0.55, 0.89, Z = 2.92, P < 0.004 0.01).	• CPT can improve breath, ICs IL-6, and ferritin in COVID-19 patients while reducing mortality with no significant increase in side effects.

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Table (Continued).

Reference and Author with Country	Title and Research Type	Research Design	Study Period	Setting	Population /Sample Size	Study Instruments	Intervention	Findings	Conclusion
Giustina De Silvestro et al From Italy[140]	SARS-CoV-2 patient outcomes following CPT: a year's worth of data from the Veneto area registry in Italy (ORA)				• 209 out of 1517 patients who received CCP at the 30-day follow-up had died (14%).		• A maximum of 3 therapeutic CCP fractions with a NAbsT of less than ≥1:160 were administered to patients over 3 to 5 days.	• Overall, mortality among patients receiving CCP was significantly ($p < 0.001$) lower (14% vs 25%), particularly in the older patient group (23% vs 40%).	• The results demonstrate that, in the absence of specific adverse effects, early CCP Tx in patients with severe COVID-19 may contribute to a satisfactory result, with reduced mortality.
Giuseppe Gullo et al[141]	• CR and literature review on the usage of CP in women who are pregnant and have ARDS related to COVID-19 (CR)				• 34-year-old multipara woman with 27 weeks and 4th day of gestation.		• CP administration	After a total of 43 days, the patient was discharged in good general health, apyretic, and without any respiratory symptoms or signs.	• According to the research, the patient's health has temporarily and only partially improved. Unquestionably, a multidisciplinary team of obstetricians, anesthetists, and neonatologists should take the time of delivery into consideration.
Li Duan et al[142]	• Studying the effects of CP on Abs alterations and NAC in COVID-19 patients.				• 299 COVID-19 patients, 200 cases in the non-plasma transfusion group.			• IgM and IgG Abs were considerably (1–3 times greater) in the PIG compared to the non-PIG.	• CPT considerably raises the Abs content in serious and critical in patients.
Emma Diletta Stea et al[143]	• CPT in a SARS-CoV-2-infected HUS patient (Case Presentation)		October 2020	Polyclinic of Bari	• Female Caucasian, 52 years old		• HIP • CPAP • Enoxaparin, Dexamethasone, Azithromycin, Ceftriaxone, Daptomycin	• Blood gas measurement after the second plasma administration showed an improvement in the PO_2/FiO_2 ratio.	• Using the HIP as a sort of rescue therapy may be beneficial for patients with a history of HUS and mild to severe SARS-CoV-2 infection.
Seyit Ahmet Erol et al[144]	• An assessment of the outcomes of CPT given to pregnant women who were found to be COVID-19 positive in a pandemic center: A PC study (ORA)	-PC Study	28 August 2020 and 12 October 2020	Ankara City Hospital's OBG Dept	• 36 pregnant moms −12 mild and 24 moderate-severe.	• Comparison in respect of clinical characteristics, laboratory parameters, obstetric complications, and neonatal outcomes	• High neutralizing titers of 200 mL of CP (>1/80).	• The moderate-severe COVID-19 group's O_2 saturation levels were considerably lower both before and after the administration of CP ($p < 0.05$)	• Some research results suggest that in COVID-19 pregnant women with mild to moderate CP, early CP therapy may be associated with improvements in laboratory and ventilatory indicators.

Ignacio Esteban et al[145]	RCTs using CCP: Post-trial follow-up (ORA)	RCTs			• Older adults (142 patients)		• Participants were randomly assigned to receive either 250 mL of CP (with an IgG titer > 1:1000 towards SARS-CoV-2 SP) or 250 mL of placebo (0.9% NS) within 72 hours of the onset of symptoms.	• The chance of ARI-free survival (Log rank testing, p-value=0.63) and the percentage of ARIs (CP=11/72 and Placebo=9/70, p-value=0.678) among groups were both equal.	• Long-term COs or the risk of ARIs is not increased by COVID-19 CP, making it a safe intervention.
Noemi F. Freise et al[146]	• Analysis of the HR SARS-CoV-2 LEOSS cohort of patients receiving CPT using matched pairs (ORA)	• *RS* analysis			• 55 COVID-19 patients who are in hospitals		• 220 patients who received or did not get CP from the LEOSS-infected patients underwent an MPA (1:4).	• The overall intra-hospital DR was 41.8% (23/55), while the ISARIC-4C- Score predicted an MR of 26% (Range 0.3–59.1%).	• The largest mortality was found after CP Tx during the critical phase. • The data, however, lend support to the idea that early CP administration can reduce mortality.
Alieh Fazeli et al From Iran[147]	• Tx with early HTCP in individuals with moderate to severe COVID-19 (ORA)	• PC Study	Affected individuals who acquired CCP between November 21, 2020, and March 20, 2021	Iranian BTO	• 3097 people who have COVID-19 in mild to severe form			• The study's findings showed that early CCP therapy was more effective for COVID-19 individuals who had moderate disease and were being treated with high Abs titers.	• A strategy for selecting potential CCP donors who have strong anti-SARS-CoV-2 IgG antibody levels is provided by the current study.
Diego Fernandez-Lazaro et al[148]	• SR of CPT and therapeutic drug combinations for COVID-19 epidemics in the 20th century (SR)		Articles published up to January 2022	• Web of Science, SciELO, Cochrane library plus, Scopus, and Medline (PubMed)	−6 RTCs			• According to the results, CPT with a quantity between 200 and 500 mL and a single transfusion administered in 1 to 2 h lowered viral load, symptoms, the duration of infection, and death in hospitalized COVID-19 patients without having any significant adverse side effects compared to the CG.	• CP did affect COs and might be a therapy option, but more research is required
Veronica Fernandez-Sanchez et al[149]	• A randomized, double-blind, two-center trial employing CP to treat Covid-19 (ORA)	• A randomized controlled double-blind clinical study.	May 20 to December 10, 2020		• 39 participants exhibited COVID-19 phases that were moderate (II) or severe (III).		• Patients allocated to CP received 2 units of 300 mL IV with a NAbsT of ≥1:32, or 256 UP/mL, the first unit on day 1 and the second unit on day 3.	• The 21-day post-transfusion mortality was significantly reduced in the CP group compared to the CG (HR: 0.17 [95.0% CI 0.07–0.45, p < 0.001]).	• Compared to CG in the CP group, CP lowers mortality, proving its effectiveness and safety.

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Table (Continued).

Reference and Author with Country	Title and Research Type	Research Design	Study Period	Setting	Population /Sample Size	Study Instruments	Intervention	Findings	Conclusion
Daniele Focosi etal[95]	• Potential use of CP in immunocompromised and susceptible people to prevent and treat SARS-CoV-2 (Perspective)								• CP is a safe and efficient Tx for elderly ICPs when given while NAbsT is high.
Eszter Fodor et al[150]	• Early infusion of CP improves the CO in chronic SARS-CoV-2 infection (ORA)	• A prospective, open-label interventional study							• The research revealed that CCP transfusion is a safe and beneficial adjuvant therapy for hospitalized COVID-19 patients, with improved outcomes expected if utilized as early as possible.
Massimo Franchini et al From Italy[151]	• Single-center experience with CP for COVID-19 patients in hospitals (ORA)	• *RS* cohort study	April 2020 and April 2021				• 657 CCP units were administered to 405 consecutive COVID-19 patients.	• The 28-day crude MR was 12.6% (51/405)	• Early HTCCP administration was the first of its type in the western world with COVID-19 patients, and it was a safe and effective treatment for hospitalized patients.
Massimo Franchini et al[152]	• The seronegative hospitalized patient population's variant of concern-matched COVID-19 CP utilization (ORA)		October 2021 and March 2022	• Single Italian hospital	• 17,200 regular blood donors		• A high NAbsT CCP unit (titered against by the specific VOC impacting the recipient) was administered to 21 hospitalized patients with severe COVID-19 utilizing CCP from 32 vaccinated and recuperating normal blood donors.	• Patients median age was 66 years (IQR 50–74 years) - A 28-day MR of 14.3% (3/21) was documented, with age, advanced disease stage, and late CCP infusion connected with a worse prognosis.	• This practical experience also lends credence to the administration of CCP to seronegative COVID-19 hospitalized patients during the Delta and Omicron waves.
Arvind Gharbharan et al[153]	• Effects of Tx of coronavirus disease 2019 with CP in B-CD patients (Brief report)				–25 B-CD patients		• CP with high NAbT.	• Implying the potential therapeutic efficacy of this therapy in this specific demographic, 21 (84%) of the patients recovered.	• Abs-based therapy may be advantageous for B-CD patients.

Oren Gordon et al[154]	Pharmacokinetics of HT anti-SARS-CoV-2 human CP in HR children (ORA)	Prospectively enrollment	May 2020 and April 2021	Johns Hopkins Children's Center	• 14 HR children		• Registered prospectively for HT COVID-19 CP (>1:320 anti-spike IgG; Euroimmun)	• HT COVID-19 CP was administered to 14 HR children (median age, 7.5 years), 9 of whom received it within 5 days (range, 2–7 days) after the beginning of symptoms and 5 of whom received it within 4 days (range, 3–5 days) of SARS-CoV-2 exposure.	• Regardless of weight or age, CP transfused to HR children seems to be safe and has the observed Abs kinetics.
R. Jain et al From India[154]	• Analysis of SARS-CoV-2 seroprevalence among potential CP donors and their deferral patterns: Results from a tertiary care institution in western India (ORA)	Prospective study	August 2020 to December 2020	-The department of blood banks at the tertiary care referral center, Goa medical college in western India.	• 400 prospective CP donors			• IgG SARS-CoV-2 Abs seroprevalence was 87% in prospective CP donors.	• 13% of patients who recovered from SARS-CoV-2 infection did not produce IgG Abs.
Satoshi Kutsuna et al From Japan[155]	• The effectiveness of CPT for COVID-19 patients and viral kinetics investigation (Brief Report)	• Clinical study with the open-label.		The Japanese Red Cross Central Blood Institute			• 11 people with COVID-19 mild to severe illnesses received CP.	• In just 28 days, clinical improvement was observed in 10 patients (91%).	• In the 11 patients who got plasma therapy, there were no side effects associated with the Tx.
Johan Kurnianda et al From Indonesia[156]	• CP Tx for people with moderate to severe COVID-19: -A non-randomized comparative study with historical control in an Indonesian referral hospital (ORA)	• A non-randomized comparative study	June – September 2020	Indonesia's Yogyakarta Dr. Sardjito Hospital	• 15 from mild to severe sufferers of COVID-19.		• Plasma having an anti-SARS-CoV-2 specific IgG titer of more than 1:320.	• 10 survivors were left after 5 receivers died unexpectedly (a survival rate of 66.7%). • Recipients had a reduced MR compared to the controls (33.3% vs 46.7%; OR 0.75; CI 95% 0.17–3.33).	• CO for CP showed improvements, and recipients had a significant decrease in IMs.
Judith Leon et al[157]	• COVID-19 CP from healthy and vaccinated donors have distinct SARS-CoV-2 Abs (ORA)				• 25 recipients of CCP.		• 25 recipients of CCP had their plasma samples taken before and after the transfusion, and the levels of COVID-19 Abs were assessed.	• Patients who received 2 units had a higher chance of seroconversion than those who only received 1 unit.	• It is recommended to use CCP from donors who received the vaccine and have very strong Abs levels.
Ferenc Magyari et al From Hungary[158]	• Remdesivir combined with CPT given early is efficacious in treating COVID-19 pneumonia in B- CD patients with HMs (ORA)	An observational, single-center study	December 2020 and July 2021	Covid-19 epidemiology care center, University of Debrecen, Hungary	• 20 hematological patients with B-CD.		• Every patient got a minimum of a full course of remdesivir and a minimum of 1 unit of CP.	• Remdesivir and CP were given simultaneously, and the patients' time for O2 weaning after diagnosis, hospital stay, and PCR positivity all decreased significantly in comparison to those who obtained the drugs independently ($p = 0.017$, $p = 0.007$, and $p = 0.012$, correspondingly).	• The clinical remission from COVID-19 and the viral elimination of SARS-CoV-2 are improved by early AVs Tx in conjunction with PI.

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Table (Continued).

Reference and Author with Country	Title and Research Type	Research Design	Study Period	Setting	Population /Sample Size	Study Instruments	Intervention	Findings	Conclusion
Maddalena Marconato et al From Switzerland[159]	• SARS-CoV-2 clearance is aided by CP Abs in both those with and without endogenous Abs responses (ORA)	Phase I clinical trial with non-randomization, open-label.	April and December 2020	• One trial site, University Hospital Zurich in Zurich, Switzerland			• From the same ABO-compatible plasma donor, a total of 600 mL were given over 3 days as 200 mL plasma units.	• Both a parametric survival model (AHR, 3.0; 95% CI, 1.1–8.1; P = 0.026) and Kaplan–Meier analysis (P = 0.034) demonstrated a significant relationship between Tx with highly neutralizing plasma and faster virus clearance.	• The lack of adverse events due to transfusions and the low MR (3.3%) in this trial demonstrated the efficacy of CPT.
Marcial Delgado-Fernández et al From Spanish[121]	• An analysis of the literature and 3 consecutive cases of COVID-19 Tx with CP in patients with HIDs (Review)		March to mid-June 2021		• 3 patients		• Administration of CP in doses from 200 to 800 mL.	• Following transfusion, abs levels were either low or negative, indicating that they may have been used to neutralize SARS-CoV-2.	• COVID-19 and HIPs should be treated with CCP.
Antonio Mastroianni et al From Italy[160]	• Obstacles with CP infusion therapy during pregnancy case report (CR)		November 9th, 2020	Annunziata" Hospital in Cosenza	• Pregnant Somalian of 31 years	Dexamethasone, ceftriaxone, and enoxaparin • IV fluids, Supplemental O_2 • NEWS	• The first CP unit was transfused on the first day, and the 2nd unit was infused on the second day, in addition to getting standard care.	• CPT may be useful in pregnancy if used extremely early.	• Despite the need for the findings of more comprehensive randomized studies, the administration of CPT may be regarded as a significant Tx option that does not harm pregnant people.
Flordeluna Mesina et al[161]	• MC research on individuals with COVID-19 who were hospitalized examined the use of CPT together with the best available Tx.	A quasi-experimental (prospective analytical), and MC study			• 65 COVID-19 disease patients who got CP.		• Over 1–2 hours, patients were administered 250 to 500 mL of plasma while being monitored for TRs.	• The length of stay between individuals who received CP and those who did not was found to differ by SS (p = 0.00).	• Its use is safe for all patients, irrespective of the severity and clinical profile.
Katarina Nystrom et al[162]	• An analysis of a severe COVID-19 and HIs patient using targeted T-cell responses to manage CPT (CR)				A male with X-linked agammaglobulinemia.		• Ig replacement therapy, spirometry, O_2, paracetamol, cefotaxime, doxycycline, and LMWH • On 2 consecutive days, the patient received 300 mL of AB0-matched CCP without experiencing any transfusion-related side effects.	• - Clinical management for COVID-19 patients with HIs may benefit from the evaluation of SARS-CoV-2T-cell responses.	

Alexandru Noris Novacescu et al[163]	• CP transfusions followed by TPE in seriously ill COVID-19 patients: A single center non-RCT (ORA)	• Single-center non-RCT	August 8, 2020, and January 9, 2021	Emergency Clinical County Hospital at Dr. Teodor Andrei Municipal Hospital's ICU.	• 38 Caucasian patients		• TPE was initiated during the first 24 hours after ICU admission, and then CP was administered right away.	• In the TPE with CP group, 30-day survival was 47.37%, compared to 26.32% in the CG (P = 0.002)	• According to the study, severe and critically ill patients may benefit from an early initiation to TPE accompanied by CP infusion among COVID- 19 individuals.
Alexandru Noris Novacescu[164]	CR: Combining TPE with CP transfusion led to the patient's successful recovery from critical illness after COVID-19 (CR)		January 2021 in the emergency room.	Dr. Teodor Andrei' Municipal Hospital	–52-year-old male		• The patient had a 500 mL ABO compatible (A-II Rh-positive) CP infusion while being watched closely.	• The condition of the patient recovered over the following days, and mechanical breathing was discontinued after the super infection was managed.	• Early initiation of TPE followed by the infusion of CP may minimize the likelihood of the disease's progression and, ultimately, the probability of negative consequences in patients with severe and critical COVID-19.
Efry Sofyan Noor et al[165]	• Impact of CP administration on elevating blood IgG and IgM levels to avoid Covid-19-related fatalities in the ICU (ORA)	Quasi experimental design		Panglima Sebaya Hospital, Paser Regency, East Kalimantan	• 50 patients		• Administration of CP to COVID-19 patients in ICU.	• The results showed that the IgG level was 269, 18 ±217,341 before Tx and 1648, 1 ±490.140 following Tx (p-value = 0.000). Before treatment, the IgM level was 78, 06 ±53.757, and after treatment, it was 274, 16± 160.908 (p-value = 0.000).	• According to the study's findings, CP boosted IgG and IgM levels in the ICU, preventing COVID-19-related deaths.
Alessandra Oliva et al[166]	• CP for hematological patients with significant B-CD lymphocytes and SARS-CoV-2 pneumonia after anti-CD20 therapy (ORA)	*RS* observational study	October 2020 to May 2021		• Six COVID-19 patients with non-HL and a lack of B-cells were studied.		• CP was administered in the context of pneumonia with respiratory failure despite normal Tx and comprised 3 infusions on alternate days - Remdesivir, corticosteroids, and LMWH.	• CP was provided 51 days (range 9–120) following SARS-CoV-2 diagnosis, and all patients improved quickly, except one patient.	• The results of the trial revealed a quick clinical improvement and a probable survival advantage in COVID-19 patients with HMs and B-CD who had recurrent pneumonia managed with CP transfusion as a result of anti-CD20 therapy.
E.A. Ostrovskaya[166]	• CPT efficiency and safety in COVID-19 patients: An SR		June 7, 2021, to December 20, 2021	PubMed, MedRxiv, Cochrane Library	–29 full-text articles		• *RS* and prospective studies related to CP therapy	• The criteria for effectiveness and timing for transfusion of the CP were considered.	• In seronegative patients with COVID-19 during an early stage of the illness or the existence of the IDs state, CP administration is safe and appropriate.

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Table (Continued).

Reference and Author with Country	Title and Research Type	Research Design	Study Period	Setting	Population /Sample Size	Study Instruments	Intervention	Findings	Conclusion
Mila B. Ortigoza et al[167]	• COVID-19 CP effectiveness and safety in hospitalized patients: an RCT (ORA)	CCP trial that was randomized, double-blind, and placebo-controlled design	April 17, 2020, to March 15, 2021	21 hospitals in 7 locations in New York, Connecticut, Florida, Houston, Texas, Maryland, and Wisconsin.	• 941 participants	PRISMA checklist	• Out of a total of 941 patients, 473 obtained a placebo, and 468 administered CCP. • Following 24 hours of the randomization, 1 unit of CCP, or approximately 250 mL, was delivered at a rate of no more than 500 mL/h.	• In early analyses, CCP appeared to benefit those who were recruited when the majority of patients got HTCCP and were not receiving remdesivir and corticosteroids on randomization.	• Participants in CP may have recovered earlier in the pandemic when remdesivir and corticosteroids were not prescribed.
Chun Pan et al[168]	• CPT's efficacy in the management of COVID-19 infection among critically ill patients (ORA)	A case-matched *RS* cohort study	1 January 2020 and 29 February 2020	• 19 hospitals in the Hubei province's Wuhan and Huangshi have been designated for COVID-19.	• 26 patients in the group receiving CPT and 78 in the CG.		• Patients who underwent CPT were matched to a maximum of 3 COVID-19 patients who did not receive CPT based on age, gender, DM, HTN, HF, duration between the start of symptoms and hospital admission, RSP, LC, troponin, SOFA, glucocorticoids, and AV medicines.	• However, the CP group had a higher SARS-CoV-2 negative conversion rate for 60 days following admission (26.9 vs 65.4%, p = 0.002) than the CG. CPT did not affect the 60-day mortality rate (HR = 1.44, 95% CI 0.82–2.51, p = 0.20).	• Patients with severe and potentially fatal COVID-19 infection may benefit from CPT, which may raise SARS-CoV-2 negative conversion rates but not their 60-day MR.
Hyung Park et al From New York[105]	• CP may be beneficial for hospitalized COVID-19 patients; development and validation of a TBI (ORA)	• The COMPILE trial's data was used in the prognostic study.	April 2020 to March 2021		• A total of 2287 patients		• On days 14 and 28 following randomization, the 11-point WHO ordinal COVID-19 clinical status scale and its two derivatives (ie, WHO scores of 7–10 indicating MV to death and WHO scores of 10 indicating death) were administered. • From day 14, the WHO 11-point ordinal scale served as the primary metric for creating the TBI.	• For the day 14 ordinal WHO score, the posterior median CCP efficacy OR was 0.94 (95% CrI, 0.74–1.19).	• -The CCP TBI is a simple instrument that may be used to guide Tx suggestions by assessing the relative advantage of CCP Tx for a certain patient who is hospitalized with COVID-19. • The TBI precision medicine approach might be highly beneficial in the scenario of a pandemic.
A. Pratama et al[169]	• CPT efficiency and effectiveness in COVID-19 patients. • (Thematic poster session)		August-2022	Wahidin Sudirohusodo Hospital	• 6 COVID-19 patients		• Six COVID-19 patients received 200 mL of double-routine CPT.	• In comparison to patients receiving standard treatment, CPT did not affect clinical improvement or death. • Clinical terms, chest X-rays, and RT-PCR conversion were improved in COVID-19 patients with severe instances.	• The research found that patients with COVID-19 responded well to CPT.
Jinlv Qin[170]	• A SR and MA found that plasma exchange reduced mortality in COVID-19 patients (SR & MA)		August of 2020	Embase, Cochrane Library, and PubMed	• 343 patients altogether; 170 were designated as CG, and 173 as TPE groups.	• PRISMA	• TPE therapy for COVID-19 in controlled clinical studies was compared with a standard of care.	• TPE had a significant influence on mortality (RR 0.41, 95% CI 0.24 to 0.69; P = 0.0008).	• TPE significantly reduced mortality in hospitalized patients with mild to serious COVID-19.

Zahra Soleimani et al[171]	• Midterm pregnancy ARDS caused by COVID-19: Effective therapy with plasma transfusion and corticosteroids (Short report)		02 April 2020		• 30-year-old woman		• Enoxaparin, Lopinavir/ritonavir, Azithromycin, Methylprednisolone, Hydrocortisone • -CPT	• Patients without concurrent bacterial infection may have a better CO with early delivery of HIP during the peak of the viremia and prudent corticosteroid therapy to dampen the CS.	• Pregnant women with ARDS caused by SARS-CoV-2 infection but no concomitant bacterial disease may benefit from cautious corticosteroid therapy in conjunction with CPT to minimize viremia and CS.
Cristina Sanz etal[172]	• Early CPT with HT SARS-CoV-2 NAbs is effective in hospitalized COVID-19 patients (ORA)	Observational, propensity score MCCS design.	August 2020 to February 2021		• 261 of the 1604 patients that were examined received CCP, most of them (82%) within 24 hours of admission.		• Each patient received 2 sequential 250 mL units of ABO-compatible CCP from the same donor.	• Following PS matching, CCP transfusion was associated with a significant reduction in 30-day mortality (OR: 0.94, 95% CI: 0.91–0.98; p = 0.001) that lasted for 60 days following COVID-19 diagnosis (OR: 0.95, 95% CI: 0.92–0.99; p = 0.01).	The CCP may still be beneficial for some COVID-19 patients, and they urge additional research before CCP is taken out of the COVID-19 Tx arsenal.
Sapha Shibeeb et al[173]	• CPT efficiency in COVID-19 patients' HMs (Review)			Scopus, Web of Science, PubMed, Science Direct, etc	• 258 COVID-19 patients who were receiving CP therapy for HMs.			• CPT may be associated with improved clinical outcomes, such as (i) a higher survival rate, (ii) increased SARS-CoV-2 clearance and the existence of detectable anti-SARS-CoV-2 Abs following CP transfusion, (iii) expedited hospital discharge, and (iv) improved health after a month of CP therapy.	• Due to its safety and good effects on COs, CPT appears to be a useful supportive therapeutic strategy for COVID-19-infected individuals with HMs.
D.J. Sullivan et al[93]	• Early OP CPT for COVID-19 (ORA)	Double-blind, RCT	June 3, 2020, through October 1, 2021		Randomization involved 1225 people in all, and transfusions were given to 1181 of them.		• A total of 592 patients received 333 units of Covid-19 CP from distinct donors.	• The main outcome was experienced by 17 of the 592 individuals (2.9%) who received CP and 37 of the 589 participants (6.3%) who got control plasma (ARR, 3.4% points; 95% CI, 1.0 to 5.8; P=0.005), resulting in an RRR of 54%.	• CP administration within 9 days of the onset of symptoms in individuals with Covid-19, most of whom were unvaccinated, reduced the likelihood of illness development resulting in hospitalization.

Abbreviations: ORA, Original Research Article; CR, Case Report; COVID-19, Coronavirus disease-19; CCP, COVID-19 convalescent plasma; CCPT, COVID-19 convalescent plasma therapy; CPT, Convalescent Plasma Therapy; CP, Convalescent plasma; FFP, Fresh frozen plasma; RCT, Randomized Controlled Trial; Dept, Department; NRCCS, Non-Randomized Case-Control Study; n, Sample Size; SS, Statistical Significance; O2 Saturation, Oxygen saturation; SOFA score, Sequential organ failure assessment score; HRG, High risk group; LRG, Low risk group; CS, Cytokine Storm; CLL, Chronic lymphocytic leukemia; LMWH, Low molecular weight heparin; HT, High Titer; HTCP, High-titer convalescent plasma; LT, Low titer convalescent plasma; LTCP, Low Titer Convalescent Plasma; ID, Inhibitory Dilution; NAbT, Neutralizing Antibody Titers; IV, Intra Venous; ARDS, Acute Respiratory Distress Syndrome; RF, Renal Failure; HL, Hodgkin Lymphoma; HD, Hemodialysis; RRT, Renal replacement therapy; ICU, Intensive care unit; G, Group; RR, Relative risk; CI, Confidence Interval; IgG, Immunoglobulin G; IgA, Immunoglobulin A; SR, Systematic Review; MA, Meta Analysis; MC, Multi Center; RS, Retrospective; CG, Control Group; Abs, Antibodies; PlG, Plasma Infusion Group; HUS, Hemolytic Uremic Syndrome; PC, Prospective Cohort; OBG, Obstetrics and Gynecology; HIP, Hyper Immune Plasma; CPAP, Continuous Positive Airway Pressure; PO2, Partial pressure oxygen; FiO2, Fraction inspired oxygen; NS, Normal Saline; ARI, Acute Respiratory Infection; HR, High Risk; LEOSS, Lean European Open Survey SARS-CoV-2; DR, Death Rate; PRISMA, Preferred reporting items for systematic reviews and meta-analyses; ISARIC-4C, International severe acute respiratory infection consortium clinical characterization protocol; SciELO, Scientific Electronic Library Online; MR, Mortality Rate; BTO, Blood Transfusion Organization; VOC, variants of concern; IQR, interquartile range; COs, Clinical Outcomes; PCR, Polymerase chain reaction; HIPs, Humoral Immunodeficiency Patients; NEWS, National Early Warning Score; HIDs, Humoral Immunodeficiency's; Rh, Rhesus factor; TPE, Therapeutic plasma exchange; HMs, Hematological malignancies; DM, Diabetes mellitus; HTN, Hypertension; LC, Lymphocyte Count; CCI, Charlson Comorbidity Index; WHO, World Health Organization; MV, Mechanical Ventilation; CrI, Credible Interval; TBI, Treatment Benefit Index; RT-PCR, Reverse transcription polymerase chain reaction; NAbs, Neutralizing antibodies; MCCS, Matched Case Control Study; RRR, Relative Risk Reduction; PS, Propensity score; ARR, Absolute risk reduction; ICs, Inflammatory cytokines; IDs, immunodeficiency's; TRs, Transfusion reactions; Tx, Treatment; EG, Experimental Group; ADA, Antibody-dependent acceleration; NAC, Nucleic Acid Clearance; SARS-CoV-2, Severe acute respiratory syndrome-corona virus-2; COVID-19, Coronavirus 19; RA, Randomly Assigned; SP, Spike Protein; MPA, Matched Pairs Analysis; B-CD, B-cell depletion; IMs, Inflammatory Markers; AVs, Antivirals; HF, Heart Failure; OP, Out Patient, DAWn, plasma- Donated Antibodies Working against COVID-19.

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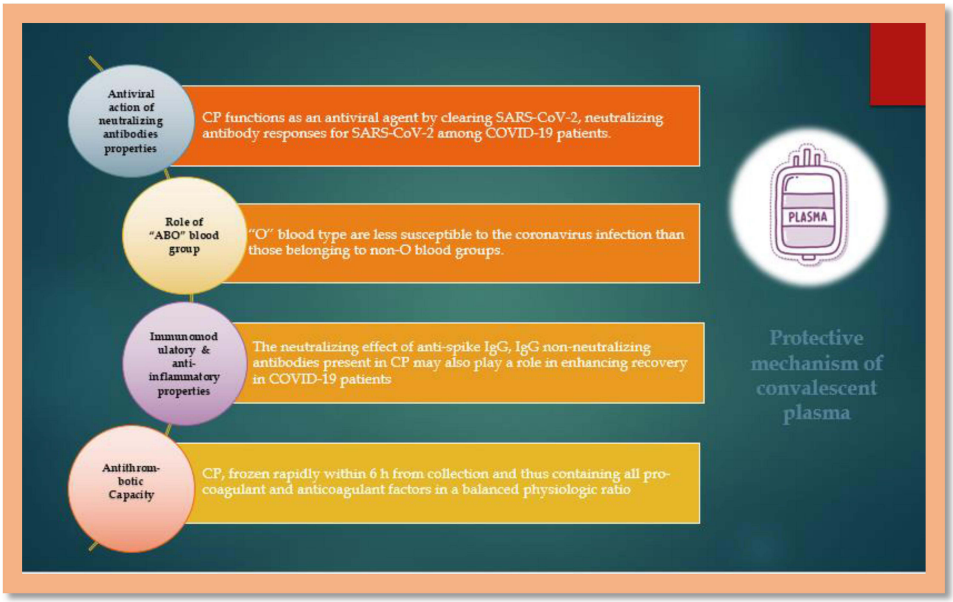

Figure 3 Protective mechanism of Convalescent plasma (CP).

Protective Mechanism of CP

Neutralizing Antibodies Had Antiviral Activity

Significantly, patients with severe disease who received COVID-19 had stronger neutralizing antibody responses against SARS-CoV-2,[80,81] and SARS-CoV-2 is eliminated by CP, which acts as an antiviral agent.[50]

The Function of the ABO Blood Group

The observation that people with the blood type "O" are less likely to get a coronavirus infection than those with blood groups other than "O" was later noticed in SARS-CoV-2 infected subjects.[82,83]

Anti-Inflammatory and Immune-Modulating Qualities

Anti-spike IgG and IgG non-neutralizing antibodies present in CP may also contribute to improving recovery in COVID-19 patients through their neutralizing effects.[53]

Anti-Thrombotic Capability

CP, which is quickly frozen within six hours of collection and contains all pro- and anticoagulant elements in a physiologically balanced ratio[84] (Figure 3).

Discussion

The treatment to halt the course of early COVID-19 is still elusive, and CCP was first studied as a therapy among COVID-19 in patients.[85] As CP treatment improved mortality in COVID-19 hospitalized patients,[86] in contrast, the findings of another study on CP administered to hospitalized patients were ineffective, perhaps the antibodies needed to be administered earlier in the course of illness.[87] These results differed from earlier research among hospitalized COVID-19 individuals with CP transfusions, and no randomized studies have shown a benefit for plasma in reducing mortality so far.[88,89] Furthermore, the benefits were indicated by Libster et al on earlier plasma provision with high antibody titers. Hence, the investigators further examined the antibody titer of plasma provision, and the early infusion of high titer CP among COVID-19 infections can stop disease progression.[87]

At this point during pandemic, it looks like the compromised host with COVID-19 who is unable to mount their own antibody responses to the vaccine or past infection may benefit the most from passive antibody treatment. In that case,

particularly in the absence of additional antiviral medications or progression despite normal therapy, high-titer CCP from a recently recovered donor is a viable option.[90] The findings for monoclonal antibodies are highest when activity for the infective variation is maintained, and some but not all trials have indicated benefit for CCP. However, the precise niche for CCP and other antibody therapies remains unknown today, and in large part because of most available evidence was generated in the absence of current standard prevention and care strategies, such as vaccines and antiviral agents such as nirmatrelvir-ritonavir.[91]

The PLACID investigation (a multicenter clinical study) from India demonstrated that, while the CCP was effective in neutralizing the SARS-CoV-2 virus, it did not lower patient mortality.[89] This conclusion might be explained by the fact that the most frequent cause of illness among COVID-19 individuals were SARS-CoV-2 virus-induced cytokine storm instead of the SARS-CoV-2 virus directly. The most likely cause of CCP therapy's ineffectiveness on patient mortality is CCP infusion in people who have already developed significant COVID-19 symptoms. Moreover, non-neutralizing antibodies in CP can promote viral entry into macrophages. The virus multiplies rapidly in macrophages, creating a pro-inflammatory microenvironment that perpetuates the cytokine storm.[92]

Some RCT results have consistently demonstrated clear benefits only among outpatients managed within 5 days of the initial symptoms.[87,93,94] Based on an optimistic case study, and an extensive case series,[95,96] the FDA reauthorized CCP transfusion for immune-compromised patients on January 2022. A rising amount of data endorses the benefits of hybrid plasma, ie, CCP acquired from convalescent donors who have been vaccinated at least twice,[97] as well as the significance of dose in CCP management.[98] As per the findings demonstrated, among patients received 6 units of plasma from donors who were both sick and triple-vaccinated, and as a response, their anti-spike antibody values were exceedingly high.[99]

However, the initial data from the Mayo-sponsored extended access program revealed a positive safety profile among study samples; and adverse reaction rates were similar to those of non-immune plasma transfusions,[36] and several observational studies, or NRSs, revealed beneficial results when compared to matched controls.[100–103] As per the given limitations of available data as on August 2020 and the extent of outbreak and CCP usage under the expanded access protocol was escalated, and initial statistics on the potential efficacy of CCP were necessary to support the regulatory decision-making process.[104]

Recently, a mechanism on forecasting the potential benefit of CCP based on patient attributes was also revealed, and which may assist in identifying individuals who will benefit most from the CCP infusion,[105] and as per the findings on 7 recently published RCTs, on treatment of CCP appears to be associated with improved outcomes, among 20 COVID-19 patients.[106] As per the data on CP use for MERS,[107,108] was limited, and studies in a small number of SARS patients suggested that CP may improve clinical outcomes when administered early in the illness or in those with severe disease.[41,109,110] However, CCP treatment was initiated early in pandemic as a short-term strategy of providing immediate passive immunization to susceptible people and managing the disease until an effective and targeted drug could be discovered.[111]

Primarily, CCP was employed in a variety of nations since it was the only readily accessible therapy capable of avoiding SARS-CoV-2 cellular infection, inhibiting viral replication, and curing COVID-19.[111,112] Fairly, CCP could be obtained swiftly as the number of patients recovering from the illness rose in high-income countries by exploiting established blood collection and transfusion infrastructures.[111] Due to extended issues with donor recruitment, blood collection, inability to purchase CCP, and the characterization of CCP units, CCP was utilized less often in poor and middle-income countries during the early phases of the epidemic.[113]

The only difference between CCP and ordinary plasma infusions was that CCP contained anti-SARS-CoV-2 antibodies,[37] and CCP was generally given to seriously or critically ill patients who were regularly in the ICU or under mechanical ventilation during the early phases of the epidemic.[114–116] As few trials found that CCP may be beneficial when administered to patients at an earlier stage of illness,[117,118] but these findings were not substantiated by more recent RCTs.[119,120]

The CCP NAbs may assist in restricting disease progression and activation of the inflammatory cascade leading to a cytokine storm in the early stages of the disease by blocking the viral entrance and intracellular replication.[87,112] According to 2 controlled studies in this cohort,[119,120] CCP treatment was shown to be related to considerably increased survival rates, while an uncontrolled case series revealed that CCP infusions resulted in clinical benefits.[121,122] In

Accordance with a preliminary study, immune-compromised patients with COVID-19 in an early stage of sickness and no detectable anti-SARS-CoV-2 antibodies are potential candidates for CCP treatment, and patients with a high post-transfusion antibody titer have the highest chance of success.[123]

Further to a recent evaluation, CCP with high titer NAbs is a safe and effective treatment for immune-compromised patients.[95] The reported benefits of CCP in these patients may be explained by their lower risk of hyper-inflammation and cytokine storm as well as their higher risk of persistent SARS-CoV-2 infections, which may be treated with CCP infusions.[96,123]

Despite the low level of evidence for CP's efficacy against other coronaviruses, the data indicated that CCP might be a potentially helpful treatment for COVID-19 patients,[27] and CCP was associated with raised antibody levels but not with better outcomes in 59 patients compared to 15 controls.[124] Another trial found that CCP infusions were well tolerated by the population. There were no reports related to transfusion reactions.[27] A recently published RCT recommended that CCP with high titer NAbs levels in addition to high IgG levels be used if more studies evaluated its use in persons with low humoral immunity.[125] So far, few data from adequately powered, randomized, controlled studies on CP therapy are available. In addition to that, several recent RCTs have revealed that CP treatment does not affect outcomes in patients with severe COVID-19.[88,89]

However, the current evidence, which is reinforced by the publication of Donated antibodies working against COVID-19 plasma and the clinical research of Sekine et al,[126] does not warrant the use of CP in the standard COVID-19 treatment. More additional evidenced data is expected to emerge soon to help decide if CP transfusion, administered within 72 hours of the onset of symptoms, and may benefit some subgroups of individuals with very specific clinical and biological aspects. Mainly, these findings emphasize the need for restricting the compassionate use of treatment, conducting well-designed RCTs, and restricting treatments to those that are evidence-based.

As of July 8, 2022, the COVID-19 pandemic had caused 554 million illnesses and 6.35 million deaths worldwide. While the majority of immune-competent patients who have been triple vaccinated do not acquire severe illness following SARS-CoV-2 infection, immune compromised patients, particularly those with B-cell depletion, do not react to vaccinations and are thus at higher risk of sequelae.[127]

CP is a potentially useful therapy; nevertheless, the data on its effectiveness to date has not been well studied and consistent. There are currently no protocols in place for collecting and administering it during pandemics, and collecting enough CP with high titer NAb to treat a substantial number of patients and quickly and efficiently performing RCTs with low bias risks during a pandemic are major obstacles. Currently, researchers have a better grasp on how to prepare for next epidemic or pandemic, more than 1.5 years after the COVID-19 pandemic began. According to the findings, the CP is only beneficial if the antibody levels in the infused units are high and the etiology of the sickness is unknown enough to determine the optimal therapeutic strategies.[27]

Additionally, it is necessary to develop a reliable procedure for selecting potential donors who have been cured of the ailment. As a result, consistent viral nucleic acid diagnostics and antibody assays should be established as quickly as possible for screening necessities, and only men or nulliparous women with no history of transfusions should be regarded as donors in the absence of testing, as they should be anti-HLA negative.[113]

The establishment of a CP donor registry might be beneficial in identifying possible donors for future donations. A frozen and ready-to-use CP plasma bank might also be built by collecting plasma from all potential donors once or twice, especially in the early stages of a pandemic. It is critical to determine if the virus may be transmitted by transfusion, and pathogen inactivation techniques should be investigated until this is proven, particularly if prophylactic CP infusion after a potential exposure is contemplated. Furthermore, in epidemics or pandemics, finding CP patients with low antibody levels is crucial for implementing a successful CP strategy.[27]

Adoption and application of CP treatment in later stages of pandemics may vary by nation. Because of practical problems, the early stages of CP therapy may be more difficult and necessitate unique solutions in underdeveloped countries. Researchers believe that CP, in addition to standard therapy, might be utilized to treat severe cases of COVID-19 pneumonia or individuals with decreased antibodies response to SAR-CoV-2 in the first week of symptoms or during the viremia phase.[113]

At this point in the pandemic, it looks like the immune-compromised patients with COVID-19 hosts who are unable to mount their own antibody response to the vaccine or prior infection will gain the most from passive antibody treatment. In that scenario, particularly in the absence of additional antiviral therapies or progression despite normal therapy, high-titer CCP from a recently recovered donor is a feasible strategy. In that context, findings for monoclonal antibodies are highest when activity for the infecting variation is maintained, and some but not all trials have indicated benefit for CCP.

Given the limited therapy choices and historical precedence, the FDA approved CCP for use beginning in April 2020. Concurrently, several RCTs with diverse trial designs and research populations, such as preventive, early outpatient usage, and hospitalized patients with severe disease, were approved under investigational new drug applications. Simultaneously, many RCTs with varied trial designs and research groups, such as prophylaxis, early opioid usage, and hospitalized patients with severe illness, proceeded forward under investigational new drug applications. Several observational studies, or NRSs, revealed beneficial results when compared to matched controls.

The case findings are as follows: the strengths of the analysis on early administration of CCP with high titer antibody content by live viral neutralization assay are associated with modest clinical efficacy, providing greater precision concerning CCP biologic activity and the power to detect modest treatment effects in the overall heterogeneous hospitalized population, reflecting real-world use of CCP in the early pandemic.[104]

The findings of studies in the hospitalized population, where effects may be seen only in subgroups, must be interpreted in light of the timing of CCP transfusion relative to the onset of the illness, the host immunological condition, and the neutralizing activity of the CCP transfused. The inquiry into how to most effectively use CCP and which patients may benefit the most from it is ongoing; RCTs, as well as an analysis of subgroups within RCTs, will remain crucial in identifying the potential role of CCP in COVID-19 treatment. The CCP may have an influence on COVID-19 treatment in vulnerable patients in the future if variations arise that are not reduced by existing known treatments, despite having just a little clinical effect in the current trial.

A meta-analysis discovered that CCP treatment, like CP infusions, had a clinically acceptable safety profile in COVID-19 patients. While the bulk of the 7 newly published RCTs confirms CCP's reassuring safety profile, the death rate was significantly lower or tended to be lower in all COVID-19 patients who took CCP compared to control patients. Individuals who got CCP had a longer hospital stay in several trials. Other studies found that CCP improved disease progression, hypoxic condition mitigation, WHO intensity score, respiratory specifications, rate and time to clinical benefit, need for mechanical ventilation, extubation rate, time for recovery from major illness, rate of mechanical ventilation and vasopressor assistance, rate of transition to mechanical ventilation, and clinical status in the overall study participants or specific subgroups of participants.

The most prevalent CCP transfusion-related issues in certain countries include allergic transfusion reactions, transfusion-related acute lung damage, and transfusion-associated circulatory overload, all of which are curable. Another potential risk of CCP infusions was antibody-dependent acceleration of infection, which is a process in which non-NAbs, commonly created after a previous infection with a different viral serotype, increase viral cellular entry, exacerbating symptoms.[128,129] This possible danger has not been observed with CCP infusions. Even though CP transfusions may be a beneficial treatment option in critically ill patients with other ailments, no positive impact of CCP was discerned in patients with COVID-19 at a delayed disease stage who were at high risk of death due to hyper-inflammation or health complications rather than the SARS-CoV-2 infection itself.[87,112]

For any future use of CP in the context of an emerging infectious disease outbreak, well-defined patient scoring systems based on characteristics other than time from symptom start or hospital admission or ICU are essential. In addition to symptom persistence (though disease progression varies from patient to patient), standardized criteria should be based on viral pathophysiology, illness intensity (eg, even without mechanical ventilation), and number of days post-hospital admission (correlated to symptom severity).

Later in the disease course, antibody testing may be useful in identifying patients who have not yet generated sufficient antibody levels and may benefit from CP. Furthermore, in people with early infection, binding antibody signals may not accurately indicate N-Abs levels and should not be used as the sole justification for commencing CP infusions.-[125,130] Another option for characterizing sickness stages is to routinely use the WHO clinical progression scale.[131]

CCP may enhance clinical outcomes in some subpopulations of COVID-19 patients, but its use in the general population does not appear to be beneficial. Researchers recognized immune compromised patients (eg, organ transplant recipients or patients with primary or secondary immunodeficiencies, B-cell depletion, or malignancies) as a prospective target population that may benefit more from CCP treatment based on existing research, clinical experience, and the pathophysiology of COVID-19.[96,123,132]

Potentially CCP-related reactions included anemia, urticarial, nausea, shortness of breath, irregular heartbeats, and tachycardia, as well as local injection site reactions (pain, chills, rash, redness, and itchy skin), intravenous cannula obstruction, transfusion-related acute pulmonary injury, transfusion-associated cardiovascular burdening, respiratory, allergic, febrile non-hemolytic, and hypotensive reactions, etc.

The study demonstrated how a critical acute respiratory distress syndrome patient who was refractory to current standard medical treatment responded dramatically to ABO-incompatible CP transfusion without any transfusion reactions. They further argued that CP transfusion in severe COVID-19 pneumonia is clinically helpful, especially in the less compatible ABO-blood group. However, this is simply an anecdotal report; a larger evaluation of CP transfusion in critically ill COVID-19 pneumonia patients is necessary before this can be suggested as standard treatment.[133]

Studies believe that the clinical improvement in the patient's condition was caused by other medications administered in conjunction with CP. In patients who do not have a conventional treatment and have a high death rate due to the underlying condition, CP can be used as an additional therapeutic agent. Finally, when administered to asymptomatic and immune-compromised patients with good infection control practices as soon as they are diagnosed, this therapy may be more beneficial.[26]

Complications and Limitations of CP Applications

Adverse Reactions

There have been reports of adverse reactions ranging from mild fever to allergic reactions to life-threatening bronchospasm, circulatory overload in patients with cardiorespiratory diseases, and renal impairment especially, among the elderly population.[111,134]

Immunological Reactions

The plasma administration may result in serious allergic responses. As allergic reaction to components of donor plasma or serum can cause serum sickness and anaphylaxis, and also bronchospasm may be linked to these reactions.[135]

Risk of Transfusion-Associated Infections

Administration of CP carries possibility of transferring possible pathogens, including SARS-CoV-2 itself as well as other pathogenic agents such as hepatitis B and C viruses, human immunodeficiency virus, and Treponema pallidum. This risk may present even though it is pretty uncommon, and thus necessary to screen for existence of these pathogens in order to reduce the risk of infections related to transfusions.[135]

Risk of Reinfection

Administration of CP, or passive antibodies, may decrease the formation of specific antibodies against SARS-CoV-2 by inhibiting or impairing the recipient's humoral immune response (pathogen-specific antibodies). This could increase a person's susceptibility to SARS-CoV-2 reinfection.[135]

Antibody-Dependent Enhancement

There is a remote possibility of antibody-dependent enhancement of the disease process. It is a process in which antibodies present in the donor's plasma may exacerbate disease by enhancing the entry of viruses into host cells and the multiplication of viruses.[135]

Other Adverse Reactions

There is a tiny possibility that an antibody-dependent enhancement of illness process may occur. As by facilitating virus entry into host cells and virus replication, antibodies found in donor plasma may aggravate illness.[135]

One of the patients who underwent CP therapy reportedly developed an ephemeral facial red spot,[49] and there have also been reports on phlebitis and widespread jaundice in certain patients.

Other limiting factors may be a lack of neutralizing antibodies in patient plasma, large infusion volumes, and the time of infusion administration, waning of plasma antibodies, bridging the gap between COVID-19 positive and recovered cases, basic administrative and logistical barriers, and also donor eligibility criteria.

Conclusion

The stability and high potential efficiency of CPT as a COVID-19 therapeutic approach CP treatment can reduce mortality in COVID-19 while enhancing respiration, inflammatory cytokines, interleukin-6, and ferritin with no rise in adverse effects. For immune compromised patients who do not react to vaccinations, the COVID-19 burden remains unchanged. Additionally, CCP therapy is being utilized as an experimental treatment as early as January 2020, and with the developing understanding of COVID-19, CCP treatment has emerged as an essential experimental therapeutic being employed in the management of the disease. Moreover, CP treatment is risk-free and may help COVID-19 patients.

Furthermore, the multiple trials have demonstrated that CCP infusions are ineffective in treating COVID-19 patients, the issue of whether plasma from vaccinated individuals could be useful remains unanswered. Along this, it was recently demonstrated that, while immunization reduced in vitro neutralization capacity against specific variations, vaccinated people preserved neutralization capability against the majority of developing variants. As a result, gathering CCP from people who have been vaccinated and recovered from the first illness is important.

The storage of plasma acquired after vaccination may have a role in the creation of a more aggressive variant or during the present vaccination gap in some countries, assisting in better preparedness for the next wave of diseases. However, CP infusions do not appear to be effective in critically ill patients for some viral infections when the life-threatening symptoms are not the direct result of viral cellular damage, such as COVID-19, but may enhance clinical outcomes in specific subpopulations.

In addition to this, the COVID-19 needs more investigation to determine whether CCP infusions may be beneficial in the early stages of immune-compromised disease. Focusing to, the CP treatment may stop infections in future pandemics or epidemics and should not be confined to seriously ill individuals but should be delivered at the early stages of the disease to all patients or certain subpopulations of vulnerable persons. Interestingly, in an ideal world, a standardized protocol for RCTs studying CP safety and efficacy would be devised, made available, and ready for use internationally.

Data Sharing Statement

The study used data available within the manuscript.

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Arsi University, College of Health Sciences, Ethiopia

Author Contributions

All authors made a significant contribution to the work reported, whether that was in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas; they took part in drafting, revising, or critically reviewing the article; they gave final approval of the version to be published; they agreed on the journal to which the article had been submitted; and they agreed to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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