

Review Article

Convalescent plasma transfusion a promising therapy for coronavirus diseases 2019 (COVID-19): current updates

Henu Kumar Verma ^{1,*}, Batoul Farran² and Lakkakula V.K.S. Bhaskar³

¹Stem Cell Lab Institute of Endocrinology and Oncology, Naples, 80131, Italy, ²Department of Hematology and Medical Oncology, Winship Cancer Institute, Emory University, Atlanta, GA 30322, USA, and ³Department of Zoology, Guru Ghasidas Vishwavidyalaya, Bilaspur, 495009, India

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ABSTRACT

While there is no proven treatment available for coronavirus disease 2019 (COVID-19), convalescent plasma (CP) may provide therapeutic relief as the number of cases escalate steeply world-wide. At the time of writing this review, vaccines, monoclonal antibodies or drugs are still lacking for the recent large COVID-19 outbreak, which restores the interest in CP as an empirical life-saving treatment. However, formal proof of efficacy is needed. The purpose of this review is to summarize all historical clinical trials on COVID-19 infected patients treated with CP to provide precise evidence for the efficacy and effectiveness of CP therapy in severe COVID-19 patients. Although there are many clinical trials in progress, high-quality clinical evidence is still lacking to analyze the existing problems. Meanwhile, based on the previous successful outcomes, we recommend healthcare systems to use CP therapy cautiously in critically ill COVID-19 patients.

Statement of Significance: COVID-19 requires urgent development of effective treatment modality. This review first summarize all historical clinical trials of COVID-19 patients treated with convalescent plasma (CP) to provide precise evidence with a specific focus on potential applications and use of CP may be the first possible option to consider during this pandemic.

KEYWORDS: corona virus; COVID-19; pathogen inactivation; convalescent plasma; serology; Clinical trials

INTRODUCTION

World populations are currently facing an unprecedented health crisis caused by the spread of an infectious virus, the coronavirus-induced pneumonia, known as the Novel Coronaviruses disease (COVID-19), which has seriously affected human health worldwide [1]. Patients infected with this virus suffer from potential damage to vital organs especially the lungs, heart, liver and kidney [2, 3]. Furthermore, this infection poses a considerable risk to patients due to the high frequency of pneumonia, fever and dry cough [4].

many vaccines are often not affordable in developing countries, and their production is hard to scale up in short times, which further contributes to the severity of the pandemic.

A few treatment trials have been conducted since the emergence of COVID-19, in an effort to contain and restrain its effects, with limited success so far. For instance, a recent trial (ChiCTR2000029308) investigating lopinavir/ritonavir showed no significant benefit for SARS-CoV-2 infection [11]. Earlier, it was proven that transfusion of convalescent blood products (CBP), especially

*To whom correspondence should be addressed. Henu Kumar Verma, Institute of Experimental Endocrinology and Oncology CNR, Naples, Italy. Tel: +91 9770476810/+39 3922185508; Email: henu.verma@yahoo.com

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convalescent plasma transfusion (CPT), might be useful against a variety of pandemic outbreaks, including influenza, Ebola virus, SARS, MERS by reducing the hospital stays and improving patient survival [12].

The latest pilot study on CP therapy shows a potential emergent therapeutic effect and low risk in COVID-19 patients [13]. As we know, since COVID-19 is a novel infectious disease, scientists and doctors still lack the in-depth understanding of its mechanisms of transmission, infection and action that would permit the development of effective vaccines or therapies. To date, not a single clinical intervention trial of CP in COVID-19 has been completed, highlighting the necessity for conducting thorough research and meta-analyses to uncover novel treatments that will allow disease control and prevention. In order to palliate the lack of updated clinical trial reviews assessing the existing challenge and its potential clinical solutions, we have endeavored to summarize all clinical trials of COVID-19 patients treated with CP in an effort to provide updated evidence for the effectiveness and efficacy of this strategy in treating COVID-19.

METHODS

Search strategy and selection criteria

All registered clinical trials studies that were published from 1 January 2020 to 14 April 2020 were identified from Chinese Clinical Trial Registry (chiCTR), European union clinical trials database (EUCTD), Clinicatrial.gov, Pubmed, National Library of Medicine (NLM), using the keywords CP and novel coronavirus 2019, CP and COVID-19, comorbidities, clinical manifestation, immunotherapy, vaccine and SARS CoV-2. Eligible studies were extracted by electronic searching of databases and an additional search was performed using the International Clinical Trials Registry Platform (WHO ICTRP) to identify ongoing trials. The last analysis was executed on 14 April 2020.

Literature inclusion and exclusion criteria

Two investigators selected the eligible studies independently. Inclusion criteria were: (1) case-control with COVID-19 patients, (2) clinical trials with a CP protocol, (3) published full-text with maximum detail on COVID-19 therapy, (4) any type of study design (interventional and observational), (5) studies involving the treatment of COVID-19 with CP and (6) studies written in English were preferred. Exclusion criteria were: (1) studies with duplicate data; (2) studies with no specific control group and (3) unclear theoretical research, and unregistered clinical trials.

Study quality assessment

The quality evaluation of all registered clinical studies and data extraction of each literature was critically appraised and discrepancy between investigators was resolved by dialogue. All studies were tabulated and summarized narratively and grouped by the treatment strategy. We categorized the table depending on trial numbers.

Furthermore, we classified results as: type of study, title of study, sponsor, recruitment status, intervention, age, phase, date enrollment, study type, country and the number of patients included in that study.

RESULTS

Trial search outcomes

Searches were performed until 14 April 2020, using EUCTD, ChiCTR and NIH (Clinical Trails.gov), and 25 registered clinical trials of COVID-19 were retrieved with active and recruiting status. Subsequent screening of headings and abstracts allowed us to exclude withdrawn clinical trials. Overall, 22 studies used CP alone, one study used CP with combinations (Hydroxychloroquine, Azithromycin), one trial used umbilical cord blood plasma and one investigation used IgG Antibody Testing Kit for clinical trials. Summaries of detailed studies were presented in [Table 1](#). Most of the registered trials have cleared ethical statements. Some of the studies are still in the recruiting stage, 10 trials have started to the recruitment of patients. Finally, remaining trials showed an active status and it will start recruiting patients upcoming days.

Significance of convalescent plasma therapy for infectious diseases

During the pre-antibiotic era, infectious diseases had high morbidity and mortality. Plasma antibody was developed against a variety of infectious diseases because there were no alternative therapeutic options. Plasma antibody uses a potential therapeutic strategy initially obtained from immune survivors of an infectious disease that was formally introduced in 1910 for poliomyelitis in animal model [14]. Subsequently, plasma therapy was tested in human patients with acute poliomyelitis treated with CP from polio survivors and showed promising results [15]. CP was later introduced as a primary drug against several infectious diseases including influenza pneumonia, chicken pox, measles and mums [16, 17] Transfusion of CP has been shown to reduce viral load, serum cytokine response and mortality in severe H1N1 influenza patients [18]. Recently, Mair-Jenkins *et al.* have conducted a systematic review and meta-analysis to assess the effectiveness of CP, serum or hyperimmune immunoglobulin for the treatment of SARS coronavirus infection, severe influenza (H1N1, H5N1) and Ebola virus disease (EVD). Their results revealed that CP therapy significantly reduced mortality without causing any severe adverse effects [19, 20].

Convalescent plasma therapy for COVID-19

The US Food and Drug Administration (FDA) have recently approved the use of plasma therapy from recovered COVID-19 patients to treat critically ill patients. As per FDA recommendations, the plasma must be collected from a donor who showed no symptoms for the last 14 days and had negative recent COVID-19 results [21, 22]. The first pilot CP treatment study was conducted in three participating hospitals for 10 severe COVID-19

Table 1. Updated all historical ongoing clinical trials of COVID-19 infected patients treated with CP patients listed in World Health Organization International Clinical Trial Registry Platform (ICTRP) database

Trial ID	Scientific title	Sponsor	Recruitment status	Interventions	Inclusion age	Phase	Date enrollment	Study type	Enrollment	Countries
ChiCTR2000029850	Efficacy and safety of convalescent plasma treatment for severe patients with novel coronavirus pneumonia (COVID-19): a prospective cohort study	Zhejiang University School of Medicine	Recruiting	Convalescent plasma	18 Years and older	N/A	15-02-2020	Interventional	20	China
ChiCTR2000030179	Experimental study of novel coronavirus pneumonia rehabilitation plasma therapy severe novel coronavirus pneumonia (COVID-19)	Hospital of Nanchang University	Recruiting	Convalescent plasma	18 Years and older	N/A	24-02-2020	Interventional	100	China
ChiCTR2000030046	A single-arm trial to evaluate the efficacy and safety of anti-2019-nCoV inactivated convalescent plasma in the treatment of novel coronavirus pneumonia patient (COVID-19)	Hospital of Jiangxia District, Wuhan (Union JiangnanHospital)	Recruiting	Convalescent plasma	18 Years and older	N/A	07-02-2020	Interventional	10	China
ChiCTR2000030010	A randomized, double-blind, parallel-controlled, trial to evaluate the efficacy and safety of anti-SARS-CoV-2 virus inactivated plasma in the treatment of severe novel coronavirus pneumonia patients (COVID-19)	Wuhan Jinyintan Hospital (Wuhan Infectious Diseases Hospital)	Not Recruiting	Convalescent plasma	18 Years and older	N/A	19-02-2020	Interventional	100	China
ChiCTR2000030039	Clinical study for infusing convalescent plasma to treat patients with new coronavirus pneumonia (COVID-19)	Affiliated Hospital of Xuzhou Medical University	Recruiting	Convalescent plasma	18 Years and older	N/A	31-05-2020	Interventional	90	China
ChiCTR2000030627	Study on the application of convalescent plasma therapy in severe COVID-19	The First Affiliated Hospital of Zhengzhou University	Recruiting	Convalescent plasma	18 Years and older	N/A	01-02-2020	Interventional	30	China

(Continued)

Table 1. Continued

Trial ID	Scientific title	Sponsor	Recruitment status	Interventions	Inclusion age	Phase	Date enrollment	Study type	Enrollment	Countries
ChiCTR 2000029757	Convalescent plasma for the treatment of severe and critical novel coronavirus pneumonia (COVID-19): a prospective randomized controlled trial	China-Japan friendship hospital	Recruiting	Convalescent plasma	18 Years and older	N/A	14-02-2020	Interventional	200	China
NCT 04292340	The Efficacy and Safety of Anti-SARS-CoV-2 Inactivated Convalescent Plasma in the Treatment of Novel Coronavirus Pneumonia Patient (COVID-19): An Observational Study	Shanghai Public Health Clinical Center	Recruiting	Convalescent plasma	18 Years and older	Phase 2 Phase 3	01-02-2020	Observational	15	China
ChiCTR 2000030312	A single-center, open-label and single-arm trial to evaluate the efficacy and safety of anti-SARS-CoV-2 inactivated convalescent plasma in the treatment of novel coronavirus pneumonia (COVID-19) patient	First people's hospital of Jiangxi district, Wuhan	Not Recruiting	Convalescent plasma	18 Years and older	N/A	29-02-2020	Interventional	24	China
ChiCTR 2000030702	Convalescent plasma for the treatment of common COVID-19: a prospective randomized controlled trial	China-Japan friendship hospital	Recruiting	Convalescent plasma	18 Years and older	N/A	15-02-2020	Interventional	50	China
ChiCTR 2000030381	A randomized, open-label, controlled and single-center trial to evaluate the efficacy and safety of anti-SARS-CoV-2 inactivated convalescent plasma in the treatment of novel coronavirus pneumonia (COVID-19) patient	First people's hospital of Jiangxi district, Wuhan	Not Recruiting	Convalescent plasma	18 Years and older	N/A	29-02-2020	Interventional	40	China

(Continued)

Table 1. Continued

Trial ID	Scientific title	Sponsor	Recruitment status	Interventions	Inclusion age	Phase	Date enrollment	Study type	Enrollment	Countries
ChiCTR 2000029818	Clinical Study for Umbilical Cord Blood Plasma in the Treatment of Acute Novel Coronavirus Pneumonia (COVID-19)	Guangzhou reborn health management consultation co., LTD	Not Recruiting	Umbilical Cord Blood Plasma	18 Years and older	N/A	20-02-2020	Interventional	60	China
ChiCTR 2000030929	A randomized, double-blind, parallel-controlled trial to evaluate the efficacy and safety of anti-SARS-CoV-2 virus inactivated plasma in the treatment of severe novel coronavirus pneumonia (COVID-19)	Renmin Hospital of Wuhan University	Not Recruiting	Convalescent plasma	18 Years and older	N/A	17-03-2020	Interventional	60	China
NCT 04323800	Convalescent Plasma to Stem Coronavirus: A Randomized, Blinded Phase 2 Study Comparing the Efficacy and Safety Human Coronavirus Immune Plasma (HCIP) vs. Control (SARS-CoV-2 Non-immune Plasma) Among Adults Exposed to COVID-19	Johns Hopkins University	Not recruiting	Convalescent plasma	18 Years and older	Phase 2	01-04-2020	Interventional	N/A	United States
NCT 04321421	Plasma From Donors Recovered From New Coronavirus 2019 As Therapy For Critical Patients With COVID-19	Foundation IRCCS San Matteo Hospital	Not recruiting	Convalescent plasma	18 Years and older	N/A	17-03-2020	Interventional	N/A	Italy
NCT 04325672	Convalescent Plasma to Limit Coronavirus Associated Complications: An Open-Label, Phase 2A Study of High-Titer Anti-SARS-CoV-2 Plasma in Hospitalized Patients With COVID-19	Mayo Clinic	Not recruiting	Convalescent plasma	18 Years and older	Phase 2	01-04-2020	Interventional	NA	United States

(Continued)

Table 1. Continued

Trial ID	Scientific title	Sponsor	Recruitment status	Interventions	Inclusion age	Phase	Date enrollment	Study type	Enrollment	Countries
NCT 04342182	Convalescent Plasma Therapy From Recovered Patients to Treat Severe SARS-CoV-2 Disease (CONCOVID Study)	Erasmus Medical Center Maasstad Hospital	Recruiting	Convalescent plasma	18 Years and older	Phase 2 Phase 3	01-04-2020	Randomized	426	Netherlands
NCT 04334876	Rapid SARS-CoV-2 IgG Antibody Testing in High Risk Healthcare Workers	Indiana University	Not yet recruiting	Diagnostic Test: SARS-CoV-2 IgG Antibody Testing Kit	18 Years and older	N/A	01-04-2020	Observational	340	United States
NCT 04338360	Expanded Access to Convalescent Plasma for the Treatment of Patients With COVID-19	Mayo Clinic	Available	Convalescent plasma	18 Years and older	N/A	N/A	N/A	N/A	United States
NCT 04333355	Safety in Convalescent Plasma Transfusion to COVID-19	Hospital San Jose Tec de Monterrey Tecnologico de Monterrey	Not yet recruiting	Convalescent Plasma	18 Years and older	Phase 1	15-04-2020	Interventional	20	Mexico
NCT 04332835	Convalescent Plasma for Patients With COVID-19: A Randomized, Open Label, Parallel, Controlled Clinical Study (CP-COVID-19)	Universidad del Rosario	Not yet recruiting	Plasma, Hydroxy-chloroquine, Azithromycin	18 Years and older	Phase 2 Phase 3	01-04-2020	Interventional	80	Universidad del Rosario
NCT 04325672	Convalescent Plasma to Limit Coronavirus Associated Complications: An Open label, Phase 2A Study of High-Titer Anti-SARS-CoV-2 plasma in hospitalized patients with COVID-19	Johns Hopkins via a national IND	Not yet recruiting (stop)	Convalescent plasma	18 Years and older	2A Open Label	27-03-2020	Interventional	5	United States

(Continued)

Table 1. Continued

Trial ID	Scientific title	Sponsor	Recruitment status	Interventions	Inclusion age	Phase	Date enrollment	Study type	Enrollment	Countries
NCT 04323800	Convalescent Plasma to Stem Coronavirus: A Randomized Controlled Double Blinded Phase 2 Study Comparing the Efficacy and Safety of Human Coronavirus Immune Plasma (HCIP) vs. control (SARS-CoV-2 non-immune plasma) among Adults Exposed to COVID-19	Johns Hopkins University	NA	Convalescent plasma	18 Years and older	Phase 2	01-04-2020	Interventional	150	United States
NCT 04332380	Convalescent Plasmap for Patients With COVID-19: A Pilot Study (CP-COVID-19)	Universidad del Rosario	Not yet recruiting	Convalescent plasma	18 Years and older	Phase 2	01-04-2020	Interventional	10	Spain
NCT 04327349	Investigating Effect of Convalescent Plasma on COVID-19 Patients Outcome: A Clinical Trial	Mazandaran University of Medical Sciences	Enrolling by invitation	Convalescent Plasma	Age 30 to 70 years	N/A	28-03-2020	Interventional	30	Iran
NCT04373460	Convalescent Plasma to Limit SARS-CoV-2 Associated Complications (CSSC-004)	Johns Hopkins University	Not yet recruiting	Convalescent Plasma	18 Years and older	Phase 2	19-05-2020	Interventional	1344	United States
NCT04353206	Convalescent Plasma in ICU Patients With COVID-19-induced Respiratory Failure	Noah Merin	Recruiting	Convalescent plasma	18 Years and older	Early Phase II	14-05-2020	Interventional	60	United States

NA: not available

patients using a single dose of 200 ml CP and revealed that patients significantly increased or maintained the neutralizing antibodies at a high level while clinical symptoms rapidly improved within 3 days [13]. After COVID-19 was declared a global pandemic, many scientists suggested that CP could be used as a potential therapeutic strategy to alleviate the infection's symptoms [23–25]. A China-based study demonstrated that the inflammatory cytokine IL-6 levels were significantly elevated in critically ill COVID-19 patients, indicating that the viral load was strongly associated with a cytokine storm and can be used to predict poor COVID-19 prognosis [26]. Another case report study in five patients reported that maximal supportive care and administration of antiviral agents with CP transfusion (neutralizing antibody titers 1:640) could potentially improve clinical outcomes without severe adverse effects [27]. Furthermore, Zhang *et al.* showed that after 11 days of CP infusion, patients did not require mechanical ventilation and were moved to the general ward with better outcomes [28]. Additionally, six more confirmed COVID-19 patients showed better improvement after treatment with CP in Wuhan, China [29].

Based on these preliminary results, USA-based John Hopkins University is currently leading a randomized trial (Phase 2) on 150 older participants undergoing CP treatment with a titer of neutralizing antibody > 1:64 for post-exposure prevention [30]. A Mayo Clinic-sponsored phase 2 trial investigating CP treatment with a titer > 1:64 is also currently recruiting [31]. Another study analyzing results from 173 patients traced the dynamics of antibody responses during disease progression. Periodic antibody detection revealed that the appearance of antibodies was <40% among patients in the first week of COVID-19 infection, then rapidly increased to 100% Ab, 79.8% IgG and 94.3% IgM, respectively, since 2nd week after infection onset, highlighting the importance of routine testing in the context of COVID-19 infections [32]. Furthermore, it was noticed that the average IgG antibody level was higher in female patients than in male patients, particularly in severe cases, which could account for the differences in COVID-19 outcomes between genders [33]. Previous studies on the duration of the serological response profile in patients infected with earlier strains of the SARS coronavirus revealed that IgM was still detectable after 7 months of postinfection. Hence, a suitable donor could donate 200 × 3 times single dose of plasma during a period of 6 months [34]. Based on these findings, many pharma companies such as Israeli company Kamada are collecting plasma in different facilities from people who have recovered from this viral disease [35]. As the various results summarized in this section indicate, CP administration seems to reduce viral load and is a safe treatment strategy with minimal side effects. A CP collections workflow and protocol are presented in Fig. 1.

DISCUSSION

In this paper, we have summarized the current registered clinical trials on CP initiated following the onset of the COVID-19 pandemic outbreak. Despite the potential utility of CP treatments, there have been few concerted efforts

to use them as initial therapies against pandemic. The main contraindications to CP therapy are an allergic reaction to plasma protein. As in many other trials examining clinical-pathological symptoms observed during viral or bacterial infections, thrombosis, multiple organ failure, as well as pregnant or lactation schedules are also contraindications.

The advantages and disadvantages of human plasma therapies are often related to conventional antiviral drugs. However, Abs are specific in their modes of action in diverse therapeutic classes. Anti-COVID-19 plasma differs from regular human plasma only by the presence of antibodies against the coronavirus. Donor selection criteria are the same as outlined by FDA guidelines. Therefore, the risks to transfusion receivers are likely to be same as those of standard plasma therapy.

One of the major challenges and concerns with plasma therapies is ensuring the prevention of transfusion-transmitted infections (TTI). Recent pathogen inactivation (PI) technologies, combined with nucleic acid testing (NAT) of an individual donor may represent a good option to reduce the risk of additional TTIs. At present, due to globalization, regulatory systems may require further tests to ensure additional transfusion safety. For instance, one UK based study suggests that blood donors are not screened for HEV infections although this infection is widespread in English populations. In fact, it was reported that after CP transfusion, 10 recipients developed prolonged or persistent hepatitis E virus infection [36]. Although this does not preclude COVID-19 with CP from being therapeutically utilized in the UK, these risks should be considered in clinical trials at the individual patient level.

There are also some non-infectious risks linked with CPT, such as allergic transfusion reactions and transfusion associated circulatory overload (TACO). Another major concern is transfusion-related acute lung injury (TRALI), an immune-mediated transfusion reaction that can cause severe complications or even death. Previous reports have shown that female donors with a history of pregnancy have higher risk of TRALI [37, 38]. TRALI is particularly challenging in patients presenting with severe COVID-19 symptoms given the potential priming of the pulmonary endothelium. Male donors are the first choice to further decrease the risk of transfusing human leukocyte antigen (HLA) antibody from parous women. Recent COVID-19 data show that female patients display higher IgG levels [39]. In certain cases, the presence of specific antibodies may account for antibody-dependent enhancement (ADE) before this phenomenon is noticed for dengue virus [40]. This virus-specific antibody enhancement could theoretically increase COVID-19 virus entry in monocytes or macrophages cells and increase its severity. In this context, ADE infection could pose major concerns during vaccination. However, the identification and characterization of viral epitopes are important before CPT for COVID-19 [41].

A recent study of six COVID-19 patients with respiratory failure that received CPT after 21.5 days of first viral detection indicated that they all tested negative for COVID-19 by 3 days after infusion, and five died in due course. These findings suggest that CP treatment may reduce COVID-19 RNA shedding but cannot decrease mortality rates in

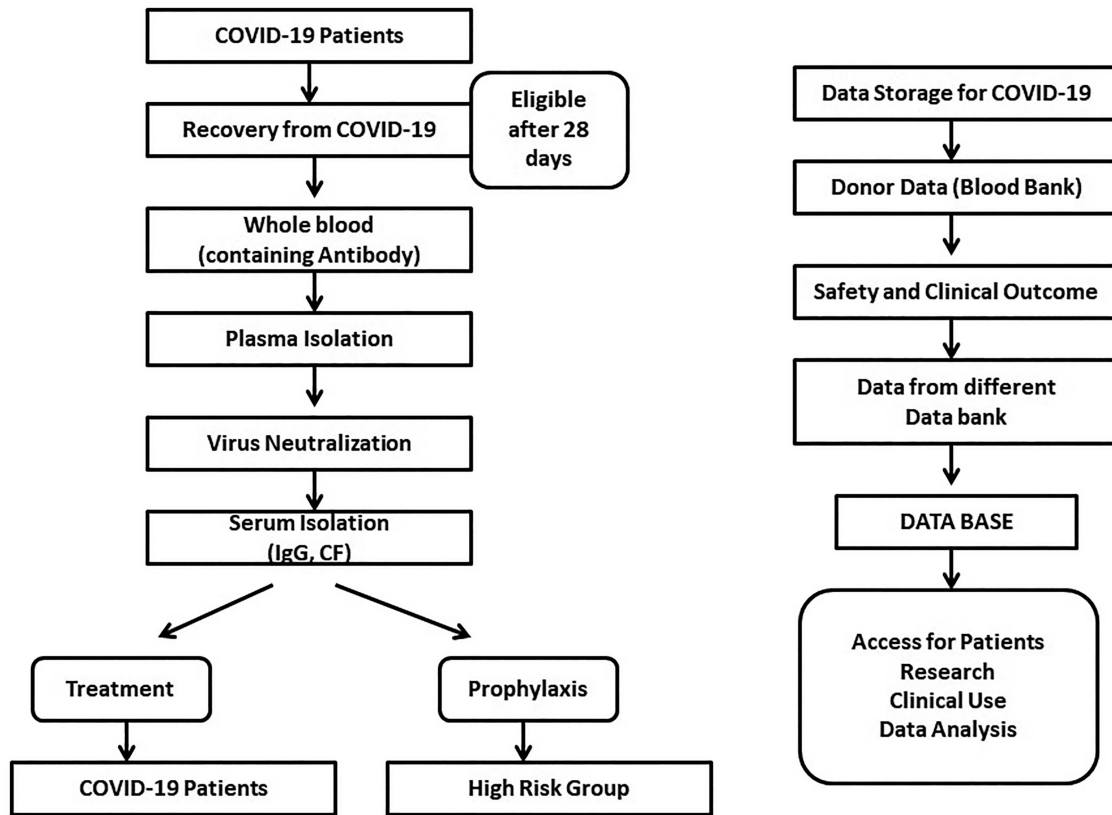


Figure 1. Flow for possible CP therapy and data storage of COVID-19 patients samples.

critical patients [42]. Deploying CP therapies against the COVID-19 patients provides an unprecedented opportunity to perform clinical research and gather evidence of the effectiveness of this treatment against viral infection. At present, both academic researchers and industry groups have started to investigate the effectiveness and clinical usefulness of CP therapies for COVID-19. If clinical trials results clearly establish the effectiveness and potential benefit of CP, the USA and other countries that have exponential growth of coronavirus deaths, may consider a national campaign to provide plasma treatment. Although a logistical challenge may be one an evidence-based approach to protect particularly high-risk populations.

LIMITATIONS

Based on the current study and available clinical trial results, we unable to make a definitive conclusion on CPT as a treatment option for COVID-19. Due to some limitations, first, insufficient clinical trial evidence. Most of these trials are still ongoing and their result has not been published yet. Second, it is unclear if patients would have improved with CP or other medication because at present, it is not clear that the administration timing of CP after admission. Third, whether CP treatment strategy would reduce mortality rates of COVID-19 patients is still unknown.

CONCLUSIONS

Plasma therapy from recovered COVID-19 patients is anticipated to be safe and potentially useful for treatment, based on the available data. In the current situation, COVID-19 requires urgent development of effective treatment modalities. The use of CP may be the first potential option to consider during this pandemic while antiviral drugs are being tested. Developing successful therapies will require the engagement and coordination of several different entities, such as blood banking specialists, virologists, hematologists and other health care workers, to ensure the proper interpretation of disease severity. It also requires ethical statements and controlled hygiene to ensure optimal safety to both donors and recipients. In the context of the public health emergency posed by COVID-19, the FDA has issued a special guidance (24 March 2020) on exploring the use of CP treatment against COVID-19. The released guidelines introduce measures for assessing the safety and efficacy of CP in clinical trials to monitor the success rates of the therapy and evaluate its safety and suitability in the clinical setting. As most countries are beginning to recover from the outbreak and ease lockdown measures, we recommend that, while the medical community still awaits the results of current randomized controlled trials of CP, hospitals can nonetheless consider the emergency use of CP to treat critically ill COVID-19 patients under the current challenging circumstances posed by the pandemic.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

CONSENT FOR PUBLICATION

All the authors have read the manuscript and have approved this submission.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

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CONTRIBUTION OF THE AUTHORS

All authors contributed equally.

CONFLICT OF INTEREST STATEMENT

None declared.

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