



Review Article

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Convalescent plasma (CP) is one major key factor to cure COVID-19 as a life-saving medicine: A comprehensive overview

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Abstract

This review highlights all aspects of using convalescent plasma (CP) to treat COVID-19 patients. MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials was scanned for any published clinical information, and Cochrane Database of Abstracts of Reviews of Effects, as well as foreign literature with English translations. Extra information and data have been collected from Google Scholar. This manuscript is presented as a novel and international helpful guide for hematologists as there is currently no standard therapy or effective safe vaccine to cure or prevent COVID-19. Also, all the medicines used for the treatment of COVID-19 are merely trials and only a few of them are approved for emergency use (such as dexamethasone and remdesivir). Therefore, one of the best ways to treat COVID-19 severe cases is by supplying them with the CP collected from recovered COVID-19 patients under certain conditions. This review article covers all the topics with regard to CP therapy.

Keywords Convalescent plasma (CP), COVID-19, Transfusion, Life-saving method, Passive immunity.

Introduction

There is an increasing talk about treating new cases of COVID-19 with CP, a treatment method that withdraws antibodies from the blood of people who had recovered from infection and transferred to COVID-19 severe patients to build up immunity (viral neutralization) against the disease which may completely eliminate the virus (Duan et al., 2020b; Tiberghien et al., 2020; Zeng et al., 2020; Zhang et al., 2020). Many countries around the world officially announced the start of experiments on this type of treatment, while highlighting many important facts that should be found in order to be familiarized with this type of treatment (Rajendran et al., 2020; Rojas et al., 2020; Rubin, 2020; Syal, 2020; Zhang et al., 2020; Zhou et al., 2020). However, the efficiency of this method (treatment with CP) did not exceed 80% (the percentage of survivals) in curing COVID-19 patients, thus, it is not the best method, but it worked well (Zhai et al., 2020). Food and Drug Administration (FDA), an international

American institutions approved CP as the first therapy for COVID-19, as an effective life-saving medicine to treat COVID-19 severe and critically ill patients (Tanne, 2020). Later, Emergency Use Authorization (EUA) for CP use was issued (US-FDA, 2020a). Finally, FDA issued an official document in September 2020 and gave its instructions about CP, hence recommendations for investigational COVID-19 CP were released (US-FDA, 2020b, 2020c). Up to date, COVID-19 has killed 3,847,778 and infected 177,777,052 (data recorded on the 17th of June 2021) and the numbers are increasing (Worldmeter, 2021). The drugs used to treat COVID-19 disease are not guaranteed perfect cures even for those approved by FDA. For example, chloroquine and hydroxychloroquine (FDA approved then withdrawn) were thought to cause deaths (NPHEC, 2020). Therefore, FDA unapproved its use for COVID-19 in July 2020, and it was banned (US-FDA, 2020d). Recently, WHO announced on 15 October 2020 that remdesivir, hydroxychloroquine, lopinavir/

ritonavir, and interferon were limited or not effective against COVID-19, and therefore these medicines would not be used (WHO, 2020). From the authors' point of view, CP therapy is the top priority medicine used as a life-saving successful method for the treatment of COVID-19.

Methodology

MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials was scanned for any published clinical information, and Cochrane Database of Abstracts of Reviews of Effects, as well as foreign literature with English translations. Extra information and data have been collected from Google Scholar.

Historical background of using CP

Convalescent plasma (CP) was first used in history approximately more than 100 years ago to treat viral diseases such as influenza (Lesne et al., 1919). Later, CP was used to cure an outbreak of Lassa fever which was endemic in Liberia (Frame et al., 1984; Jahrling et al., 1985). During the 1940s, CP therapy was used successfully to cure Mumps and viral hepatitis cases (Beeson et al., 1944; Hawley et al., 1944; McFarlan and Chesney, 1944; Rambar, 1946). In the 1970s, CP was used to treat Ebola and Marburg viruses outbreaks and infections (Brainard et al., 2016; Cross et al., 2018; Natesan et al., 2016; WHO, 1977). In 2007, CP method was in China the life-saving method to cure patients of severe H5N1 Influenza infection (Zhou et al., 2007). In 2009, CP therapy was successfully used to cure pandemic influenza type A patients in Africa (Hung et al., 2011). However, it seems that CP therapy is not always the golden solution for the treatment of epidemics such as Ebola where the method is thought to be not effective after assessment by WHO in Guinea (Van Griensven et al., 2016). In the last decade, CP was used to neutralize viral particles of Middle East Respiratory Syndrome Coronavirus (MERS-CoV) and Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) as both of them belong to Corona Viridae (the same family for SARS-CoV-2 virus, the causative agent of COVID-19 disease) (Mair-Jenkins et al., 2015). The method of using CP therapy to cure COVID-19 severe cases was approved by FDA in late March 2020 and is considered the only available facility to rescue affected COVID-19 severe cases from death (Tanne, 2020). FDA urged recovered COVID-19 patients to donate blood (Tanne, 2020). After approval of the method, it was publicized globally as a life-saving method (Ahn et al., 2020; Bloch et al., 2020; Casadevall and Pirofski, 2020; Chen et al., 2020; Cunningham et al., 2020; Duan et al., 2020a; Keith et al., 2020; Roback and Guarner, 2020; Shen et al., 2020; Ye et al., 2020).

Definition of blood plasma

Blood plasma is one of the main blood components along with red and white cells and platelets, which is a transparent liquid material, that transports water, salts and key nutrients to all parts of the body. Blood CP is rich in antibodies after getting a recent infection (Roback and Guarner, 2020).

Blood plasma components

The plasma is a liquid that contains substances with high or low molecular weights that are about 8-10% of its volume, as they consist of water 90%-92% of its volume, plasma proteins 7%, which include albumin (60%), globulin (35%), and fibrinogen (4%), and other proteins (1%), such as enzymes and hormones. Plasma contains also inorganic ions such as bicarbonate, chlorine, phosphates, calcium, sodium, magnesium, potassium. Finally, plasma contains other organic materials such as carbohydrates, especially glucose, fats, amino acids, lactic acid, and cholesterol as well as dissolved gases (Dowty et al., 1975; Gowda and McNichols, 2002; Hamilton and Archibald, 1944; Linder, 2016).

The procedure of collection of CP from recovered COVID-19

CP is collected by a special device called the Plasmapheresis machine. After the blood is withdrawn from the donor, the device isolates the plasma and some of the blood platelets from the remaining blood cells so that the plasma goes into a special bag and the cells return to the body of the donor by adding the nourishing saline (Burnouf and Seghatchian, 2014; Cheng et al., 2005; Duan et al., 2020a; Milkins et al., 2013; Salin et al., 1957; Van Griensven et al., 2016; WHO, 2014; Ye et al., 2020).

What are the matched recipient blood groups?

Certainly, plasma must be given to the appropriate blood group in terms of the ABO system as described below (Hoffbrand et al., 2016; Milkins et al., 2013; WHO, 2014; Ye et al., 2020) see table 1

- Patient whom blood type A receives from O or B donor
- Patient whom blood type B receives from O or A donor
- Patient with AB blood type receives from AB blood donor only
- Patient who has blood type O gives to all groups, but only receives from O (Hoffbrand et al., 2016; Milkins et al., 2013; WHO, 2014; Ye et al., 2020).

Table 1. Matched blood group for CP transfusion (Hoffbrand et al., 2016; Milkins et al., 2013; Ye et al., 2020).

Patient group	Compatible plasma donor
A	A, AB
B	B, AB
AB	AB
O	O, AB, A, B

The use of CP in treatment

CP is collected from people with a strong immune system who fought and eradicated COVID-19 when infected and eliminated it. They have antibodies circulating in the blood, which is the main factor that helps in the process of recovery from the disease. If a person donates only CP, their blood is withdrawn through a tube, and the CP is separated by spinning and the rest is returned to the donor's body. The plasma is then tested and purified to ensure that it does not contain any blood-borne viruses or bacteria and is safe to use. Then injecting COVID-19 patients with it intravenously (Bloch et al., 2020; Duan et al., 2020a; Shen et al., 2020; WHO, 2014). It takes about a month to build antibodies in the CP, from the date of infection with the virus. Those “antibodies” present in the plasma of convalescing patients are believed to neutralize the virus in patients with exacerbated cases of COVID-19, and to describe antibodies, these are protein molecules manufactured by the immune system (secreted by plasma cells that derived from B cells upon stimulation) that can target and neutralize the virus (Duan et al., 2020a; Tanne, 2020; Van Griensven et al., 2016; Zhang et al., 2020).

Conditions that must be met by CP donors

These include the following (Hoffbrand et al., 2016)

1. The presence of evidence of a positive smear of the COVID-19 emerging virus.
2. Negative smears were withdrawn (evidence of recovery of the patient).
3. No less than 14 days have passed since the donor recovered from the last negative smear with no other symptoms of the virus.
4. Age should be from 18 up to 60 years.
5. Weight should be more than 50 kg.
6. Patient should be free from chronic heart or chest diseases and has not performed major operations before.
7. Donation conditions do not apply to patients with certain diseases (such as hepatitis, immunodeficiency, syphilis, oncology patients, and diabetic patients who use insulin injections to treat Diabetes), while donation terms apply to those with chronic diseases of diabetes and regular pressure due to taking special drug doses (Ahn et al., 2020; Duan et al., 2020a; Hoffbrand et al., 2016; Roback and Guarner, 2020; Yeh et al., 2005; Zhang et al., 2020).

CP Safety Analysis

Carrying out safety analyses before CP injection includes (Hoffbrand et al., 2016)

1. Analyses of blood type, antibody of the species, virus-immunofluorescence analysis for detection of hepatitis C-B diseases, HIV, and syphilis.
2. Detection of DNA viruses by applying Nucleic Acid Technology (NAT), or so-called PCR. This method is

the most accurate tool analysis to ensure blood safety and security.

3. CP efficiency analyzes and measurements of the proportion of antibody to the "COVID-19" virus are also carried out, and the efficacy of those antibodies against the virus is checked (Chen et al., 2020; Duan et al., 2020a; Zhang et al., 2020).

Amount of blood donated by the recovered donor

After the donor has performed the necessary tests, from 500 to 600 ml of CP is taken (1-1.5 liters blood) and there has been no harm to the donor or the patient (Burnouf and Radosevich, 2003; Cheng et al., 2005; Van Griensven et al., 2016; Wong et al., 2003; Wong et al., 2010; Yeh et al., 2005; Ye et al., 2020).

Duration of the plasma separation procedure and quantity

The donation process takes roughly about 45 minutes, during which the blood is filtered into a special plasma extracting device, and this process is technically called “plasma separation” while the name of the apparatus is “Plasmapheresis machine”. The amount of plasma donated from each recovered patient is sufficient to treat 2-3 people with COVID-19 (Dowty et al., 1975; Linder, 2016; NPHEC, 2020; WHO, 2020).

What is the route of CP administration? How much CP volume should be given? What is the protocol for CP transfusion?

After blood is withdrawn from the donor, CP should be stored at a freezing temperature of -20°C. When needed, CP thawed and injected into the recipient (COVID-19 critical case) as 200 ml intravenously (the first dose). The patient should be monitored carefully, especially (breathing, pulse, and pressure as well as allergies) and overall total body condition. If symptoms clear which includes improvement of (heat, cough, general fatigue, and other respiratory symptoms), there are no further doses are given. If not improved, the second dose of 200 ml (IV) should be given. The total dose should not exceed 600 ml in general to the patients depending on the patient's response (Hoffbrand et al., 2016).

When is the best time to prescribe CP to COVID-19 patients?

Based on data obtained from previous studies, it seems that CP is highly recommended to be given in the first week of infection (viremia stage) to patients with SARS (Cheng et al., 2005). In addition, treatment with CP therapy could decrease serum cytokine production, decreased mortality rates, and lowered down viral load of H5N1 influenza virus in the respiratory system of patients in the first week of infection (Hung et al., 2011). However, SARS patients develop deadly immune responses represented by cytokine storms during the second week of infection (Cheng et al., 2005; Peiris et al.,

2003). In general, it sounds that the best time to give CP therapy to SARS patients during early stages of infection (Cheng et al., 2005; Hung et al., 2011; Soo et al., 2004). Therefore, and based on previous data, it is recommended to give CP therapy in the early stages for COVID-19 patients.

Does CP work like a vaccine? What are the adverse effects?

Basically yes, it works like a vaccine but unlike the vaccine, any protection will only be temporary. This is called passive immunity. There is no problem or risk for the patient and the method is relatively safe (Marano et al., 2016; Roback and Guarner, 2020; Zhao and He, 2020). The main adverse effects of CP therapy to the recipients (COVID-19 patients) is not published yet but based on previously published data, the adverse effects of CP therapy for Spanish influenza patients included chills, hyperthermia, anaphylaxis, acute respiratory injury, circulatory disorders, and blood hemolysis, thrombosis, renal toxicity, and meningitis as well as death (irresponsive cases) (Luke et al., 2006; MacLennan and Barbara, 2006). There were some more noted side effects of using CP therapy which is characterized by further co-infection with HIV, hepatitis B and C viruses, as well as syphilis due to contamination during the transfusion or as a result from an ill donor (WHO, 2014). Finally, concerning safety issues of using the CP therapy method and to avoid complications, it has been strongly recommended to study the safety margins of using CP therapy in the case of COVID-19 patients (Chen et al., 2020; Zhang et al., 2020). The method (the use of CP therapy) was thought to be “safe” for COVID-19 patients as described in mid-March 2020 in a study done on 10 COVID-19 positive patients diagnosed by real-time PCR, which claimed no harmful or risky issues with regards to the use of CP therapy method (Duan et al., 2020a).

Complications

There have been no complications seen, reported, or noticed with regards to CP transfusion. The method seems relatively safe.

Is there any recurrent infection after recovery with CP therapy? To what extent reinfection with SARS-CoV-2 can happen?

There is no data available about those who recovered after receiving CP therapy. Research is urgently required in this regard. However, a recent review study revealed that there is no reinfection neither recurrent infection to those who have been naturally infected with COVID-19 and recovered with or without receiving CP therapy (Ota, 2020).

Limitations of using CP therapy

One of the biggest challenges to the use of CP therapy is that the titer of antibodies (especially IgG) which is not high enough to provide sufficient protection. This has been confirmed in a study published in Nature Medicine Journal (Xu et al., 2020) where 17,368 asymptomatic or subclinical

COVID-19 positive person examined for IgM and IgG in Wuhan (China). The individuals showed very low levels of antibodies titers ranged between 3.2% to 3.8%. Furthermore, another study published also in Nature Medicine Journal (Long et al., 2020) referred to the presence of 37 asymptomatic COVID-19 inpatients (tested positive by RT-PCR) in Wanzhou (China) showed the capability of these patients to shed the virus for 19 days (average) after being admitted to the hospital. This is challenging to the protocol of blood donation to obtain CP.

Further readings (for the specialists)

Investigational COVID-19 Convalescent Plasma Guidance for Industry <https://www.fda.gov/media/136798/download>. Guideline on the clinical use of apheresis procedures for the treatment of patients and collection of cellular therapy products https://www.researchgate.net/publication/277412950_Guideline_on_the_clinical_use_of_apheresis_procedures_for_the_treatment_of_patients_and_collection_of_cellular_therapy_products Guideline on the clinical use of apheresis procedures

Conflict of Interest

The author hereby declares no conflict of interest.

Consent for publication

The author declares that the work has consent for publication.

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