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Convalescent Plasma Transfusion in COVID-19 Patients

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Abstract

Convalescent Plasma Transfusion (CPT) is a well-known therapy in different scenarios. Still, because of a lack of Randomized Controlled Studies (RCT), the various national and international health organizations have difficulties recommending CPT as a primary measure in COVID-19 patients with severe disease courses. CPT was used against the 1918 pandemic flu, measles, Middle East Respiratory Syndrome Coronavirus (MERS-CoV), 2003's Severe Acute Respiratory Syndrome (SARS), and Ebola virus disease. First results shows that CPT therapy in COVID-19 patient appears safe, clinically effective and reduces mortality. As long as the indications and conditions are fulfilled, CPT does not harm the patients; it is only right that it be supported until RCTs show the opposite. As it is cheap and straightforward, no equivalent specific therapy has emerged.

Keywords: Convalescent plasma transfusion; COVID-19; Severe acute respiratory syndrome

Introduction

The recent emergence of COVID-19 pandemic has reassessed the usefulness of historic Convalescent Plasma Transfusion (CPT) due to a lack of an adequate evidence-based treatment strategy. There are currently no therapeutic drugs available directly active against SARS-CoV-2. Several antivirals (Remdesivir, Favipiravir) and antimalarials (chloroquine, hydroxychloroquine) have emerged as potential therapies. Remdesivir and convalescent plasma are considerations in the treatment of critically ill COVID-19 patients with respiratory failure, but access to these therapies is limited at present [1]. After a positive clinical study, the United States exceptionally approved Remdesivir for use in COVID-19 patients. The drug initially developed for use against Ebola may shorten the recovery time. The study of 1,063 patients is the most extensive and most strict test of the drug and included a comparison group that received just usual care, so Remdesivir's effects could be rigorously evaluated. Those given the drug were able to leave the

hospital in 11 days on average versus 15 days for the comparison group [2]. The drug also might be reducing deaths, although that is not certain from the partial results revealed so far.

CPT is a well-known therapy in different scenarios. Still, because of a lack of Randomized Controlled Studies (RCT), the various national and international health organizations have difficulties recommending CPT as a primary measure in COVID-19 patients with severe disease courses. A recent Cochrane review says that there is still uncertainty whether convalescent plasma is beneficial for people admitted to hospital with COVID-19 [3]. The authors especially point out limited information regarding grade 3 and 4 Adverse Events (AE) and clinically relevant Severe AEs (SAE). There are 138 ongoing studies evaluating CPT and hyperimmune immunoglobulin, of which 73 are RCTs.

As CPT is an old concept, pharmaceutical companies do not consider research into it profitable, and scientific interest remains limited. Ironically, CPT is an affordable treatment with global, potentially limitless resources. We endeavour to share a short description of the history of CPT and its adverse effects. We will then review the experiences in viral diseases, including COVID-19, and finally share the basis of our recommendation for the use of CPT over supportive treatment alone.

What is known about CPT

CPT was first used in 1893 when serum from immunized animals was given to patients suffering from diphtheria. This work from Emil von Behring demonstrated that neutralizing antibodies, or antitoxins, could be transferred from one person or animal to another. Over the next century CPT was also used against the 1918 pandemic flu, measles, Middle East Respiratory Syndrome Coronavirus (MERS-CoV), 2003's Severe Acute Respiratory Syndrome (SARS) and Ebola virus disease.

Immune serum globulin, which contains a high concentration of antibodies to a specific pathogen, is prepared for administration to recipients. For this purpose, human monoclonal antibodies or homologous antibodies produced from cell cultures are the preferred sources for the administered antibodies. Extracts from the blood (convalescent serum) of previously infected people or animals, or heterologous antibodies to the specific pathogen can be alternative sources. Such passive immunization is, therefore, an emergency measure utilized in post-exposure prophylaxis. Examples include injuries with contamination of the wound (suspected infection with tetanus), bites due to or mucous membrane contact with wild animals (suspected rabies), or the contact of medical personnel with blood from patients who are carriers of the pathogen of hepatitis B (in particular after needlestick injury).The advantage of immune sera is the faster onset of protection. The antibodies do not have to be formed within one to two weeks but are available immediately after the injection of the immune serum. The disadvantage is that the protection only lasts for a few weeks, after which the administered antibodies are broken down by the recipient, and his organism is at risk again from a new infection with the same pathogen. The protection conferred by the immune serum globulin is short-lived as the immune system is not actively stimulated by the administration of immune serum globulin to develop its immune memory against the pathogens via memory cells.

If the immune serum comes from animals or humans, there is a further disadvantage that, apart from the desired antibodies, it may contain traces of foreign protein or donor polysaccharides. The recipient's immune system then initiates a cascade of immunological reactions against these components, which are perceived as foreign antigens. This means that the antibodies enriched in the vaccine serum are excreted faster and thus remain effective for less than desired. Repeated administration of foreign serum, especially from the same animal species, can also lead to an undesirable allergic reaction of the recipient in the form of a serum disease or an allergic shock. Therefore, if possible, such immune sera are replaced by monoclonal antibodies. For example, until around 1965, there were no human antibodies against tetanus so that one was dependent on animal ones. Here, the order horse, cattle, mutton had been established. A significant and widespread natural form of passive immunization against infectious diseases is mother-child immunization. Passive immunizations that sare not directed against infectious diseases include the injection of anti-D immune serum to pregnant women if the newborn is at risk of haemolyticus neonatorum and the infusion of antivenin after snake bites.

CPT in SARS, MERS, influenza, Ebola and COVID-19 patients

As long as monoclonal antibodies or specific immune sera are not available the complete plasma which includes the antibodies is the most suitable product. CPT has been used to improve the survival rate of patients with SARS whose condition continued to deteriorate despite treatment with pulsed methylprednisolone. Several studies showed a shorter hospital stay and lower mortality in patients treated with convalescent plasma than those who were not treated with convalescent plasma [4-6]. At Prince of Wales Hospital, Hong Kong, 80 SARS patients were treated with CPT between 20 March and 26 May 2003. Favourable outcome was defined as discharge by day 22 following the onset of SARS symptoms. Poor outcome was defined as death or hospitalization beyond 22 days. A higher day-22 discharge rate was observed among patients who were given convalescentplasma before day 14 of illness (58.3% vs 15.6%; $p<0.001$) and among those who were PCR positive and seronegative for coronavirus at the time of plasma infusion (66.7% vs 20%; $p=0.001$) [6].

A protocol for the use of CPT in the treatment of MERS was established in 2015 [7]. Subjects with anti-MERS-CoV IFA titer of $\geq$1:160 and no clinical or laboratory evidence of MERS-CoV

infection were accepted for plasma donation according to standard donation criteria. In the CPT phase, critically ill patients admitted to the intensive care unit with laboratory-confirmed MERS-CoV infection were enrolled and receive two units of CP. Mortality rates for patients treated with CPT were reported in 2 studies. Due to a considerable bias the results a not such persuading. One retrospective cohort study [8,9], reported no association between CPT and the mortality rate (70% vs 65%; p = 0.69). A single study [9,10], at critical patients reported no association between treatment with convalescent plasma and the mortality rate.

In terms of patients with pandemic 2009 influenza A H1N1 (H1N1pdm09) virus infection, a prospective cohort study by Hung and colleagues showed a significant reduction in the relative risk of mortality (odds ratio 0.20 [95% CI 0.06 – 0.69], p=0.01) for patients with CPT [11]. Additionally, in a subgroup analysis, viral load after CPT was significantly lower on days 3, 5, and 7 after intensive care unit admission. No adverse events were observed. A multicentre, prospective, double-blind, RCT showed that using CPT from patients who recovered from the influenza A virus infection to treat patients with severe influenza A H1N1 infection was associated with a lower viral load and reduced mortality within five days of symptom onset [12]. A meta-analysis showed that the mortality was reduced after receiving various doses of convalescent plasma in patients with severe acute respiratory infections, with no adverse events or complications after treatment [13]. Another meta-analysis identified eight studies involving 1703 patients with 1918 influenza pneumonia from 1918 to 1925 who received an infusion of influenza-convalescent human blood products, which showed a pooled absolute reduction of 21% (95% CI 15 – 27; p<0.001) in the overall crude case fatality rate at low risk of bias [14].

In 2014, the WHO recommended the use of Ebola CPT as an empirical treatment for Ebola-infected people in the outbreaks of the disease [15]. While there is no proven treatment available for Ebola Virus Disease (EVD), whole blood collected from patients in the convalescent phase of infection has been used as an empirical treatment with promising results in a small group of EVD cases [16]. During the current ongoing EVD outbreak, whole blood and plasma collected from EVD recovered patients have been prioritized for investigation, as one of the treatment modalities [17]. The concept that this treatment could be efficacious is biologically plausible, as convalescent plasma has been used successfully for the treatment of a variety of infectious agents [18].

CPT was also used in COVID-19 patients [19-26]. Some recent reports are listed in Table 1. Rajendran et al. from India did a review about CPT in COVID-19 patients based on five studies, including 27 patients: 15 males and 12 females aged 28 to 75 years [27]. All studies but one (South Korea) were conducted in China. Comorbidities were COPD (n = 2), cardiovascular and cerebrovascular diseases (n = 1), hypertension (n = 7), chronic renal failure (n = 1), Sjogren syndrome (n = 1) and pregnancy with a gestation period of 35 week (n = 1). All studies reported good outcome after CPT performance. Still, all were considered to have a risk of bias owing to a combination of non-randomized evaluations, confounding, predictor description and poor methodological conduct for participant selection, the dosage of CPT and duration of therapy. This heterogeneity did not permit us to perform a meta-analysis. The main findings from available data were: First, CPT may reduce mortality in critically ill patients. Second, an increase in neutralizing antibody titers and the disappearance of SARS-CoV-2 RNA was observed in almost all the patients after CPT therapy. Third, a beneficial effect on clinical symptoms after administration of convalescent plasma. The authors concluded, that based on the limited scientific data, CPT therapy in COVID-19 patient appears safe, clinically effective and reduces mortality [27].

Authors, Country	Design	Patients	Results
Gonzales et al., Argentina [33].	multicenter retrospective	272 consecutive patients, 100 with pneumonia and/or oxygen requirement (WARD; 87 ICU admission (ICU); 56 ICU admission with requirement of MV (ICU-MV), 29 ICU-MV plus septic shock (ICU-MV-SS.	A favorable evolution occurred in 81.4% of WARD patients; in 70.9% of ICU; in 39.6% of ICU-MV and in 27.6% of ICU-MV-SS patients.
Gemici et al., Turkey [34].	single center, retrospective	40 consecutive patients, 2020 Sep 28;7: 100 % were classified as having severe COVID-19 infection. Over a half of the patients harbored an oxygen saturation of less than 90 despite of a continuous 5lt/min support of O_2. 82.5 % of the patients had a need for MV and 45.5 % had a need for invasive MV.	9 out of 10 patients who have received CPT outside ICU have totally recovered from COVID-19 at a median of 9 days, half of the patients who needed ICU-MV were successfully free of MV support and managed to recover from COVID-19.

Hartmann et al., USA [35].	single center, retrospective	16 severe patients and 15 life-threatened patients	94% of transfused patients with severe disease avoided escalation to ICU care and mechanical ventilation. 67% of patients with life-threatening disease were able to be extubated.
Agarval et al., India [36].	an open label, parallel arm, phase II, multicentre, RCT	464 adult patients admitted to hospital with confirmed moderate covid-19	Progression to severe disease or all cause mortality at 28 days after enrolment occurred in 44 (19%) participants in the intervention arm and 41 (18%) in the control arm (risk difference 0.008 (95% confidence interval -0.062 to 0.078); risk ratio 1.04, 95% confidence interval 0.71 to 1.54)

Table 1: List of some recent studies on CPT in COVID-19. Given are the author, the country, the design, some patient's characteristics and main results. (MV = Mechanical Ventilation).

Khulood from India published a review of eight studies conducted on CPT in patients with COVID-19 wherein 25,028 patients above 18 years of age were involved. The vast majority of patients reported favorable outcomes when treated with CP with <1% serious adverse events [28].

The already mentioned Cochrane review [3], included 19 studies with 38,160 participants, of whom 36,081 received CPT. Based on these studies the overall certainty of evidence was low to very low, due to study limitations and results including both potential benefits and harms. The results from two RCTs, both stopped early, with 189 participants, of whom 95 received CPT suppose a decrease of all-cause mortality at hospital discharge (risk ratio (RR) 0.55, 95% Confidence Interval (CI) 0.22 to 1.34; 1 RCT, 86 participants; low-certainty evidence) and decreased mortality (time to event) (Hazard Ratio (HR) 0.64, 95% CI 0.33 to 1.25; 2 RCTs) but with low-certainty evidence. The controlled studies reported on AEs and SAEs only in participants receiving convalescent plasma. Some, but not all, studies included death as a SAE. There were 146 SAEs within four hours and 1136 SAEs within seven days post-transfusion. These were predominantly allergic or respiratory, thrombotic or thromboembolic and cardiac events. We are uncertain whether convalescent plasma therapy results in a clinically relevant increased risk of SAEs (low-certainty evidence).

Teofili from Italy published the study protocol of a randomized, open-label, parallel group, phase II/III study with a superiority framework to demonstrate that COVID-19 CPT prevents progression to severe pneumonia in elderly COVID-19 pneumonia patients with chronic comorbidities. Secondary objectives are to demonstrate that CCP decreases the viral load in nasopharyngeal swabs and increases the anti-SARS-CoV-2 antibody titre in recipients. Numbers to be randomized were estimated with 114 patients (57 per arm) in phase II and 82 patients (91 per arm) in phase III. Trial recruitment started on May 27, 2020. The anticipated date of recruitment completion is April 30, 2021 [29].

Discussion

COVID-19 is a pandemic that needs an immediate and robust therapeutic solution. Such an answer does not exist, and the shutdown- and stay-at-home policies in each country destroys complex economic structures.

There are significant efforts to establish effective therapy by antiviral treatment or vaccines. Developing these therapies, however, takes time. On the other hand, PCT is an established but historical therapy used worldwide in different diseases. Yet virtually everything that is known about the use of CPT against infectious diseases comes from studies in which every patient received the treatment [30]. CPT is used when one has no treatment option but is in need to help as many people as possible [26]. Of course, well-designed extensive multicenter clinical trial studies should be conducted urgently to establish the efficacy of CPT to COVID-19 patients, but time is running. Health politician and doctors have to decide how to treat COVId-19 patients with severe symptoms to prevent intensive care treatment or even death.

Recently, the US Food and Drug Administration in the United States has approved the use of plasma from recovered patients to treat seriously ill COVID-19-infected individuals [31]. The transfused plasma must be obtained from donors tested negative for COVID-19 when plasma collection is performed, before day 28 of clinical recovery, and must be collected from recovered patients without symptoms for at least 14 days. Epstein and Thierry from the FDA and Taipei Medical University prepared and endorsed by the Working Party on Global Blood Safety of the International Society of Blood Transfusion presents elements to take into consideration in the preparation and transfusion of COVID-19 convalescent plasma as a possible treatment approach of COVID-19 [32]. A similar paper was published for the use of CPT in EBOLA by the WHO in [24]. Because the safety and efficacy of convalescent COVID-19 plasma as a treatment for COVID-19 are unproven at this time, the clinical use of this product should be managed as an experimental therapy consistent with ethical and legal safeguards

(informed consent of donors and patients, institutional approval, special labelling as an investigational product, compliance with applicable regulatory requirements). Ideally, COVID-19 plasma should be used in the context of an organized research study designed to determine its safety and efficacy in comparison with the standard of care or other therapeutic interventions. Even if used empirically, it is vital to ensure the monitoring of patient outcomes, including clinical and laboratory indicators of safety and efficacy to maximize the knowledge that might be gained.

Worldwide, there are currently hundreds of thousands of patients who have recovered from COVID-19 who could be recruited and become COVID-19 convalescent plasma donors after a cautious clinical and laboratory evaluation. The SARS-CoV-2-specific IgG antibodies passively transferred by the transfused plasma might neutralize viral particles and activate the complement system, thus promoting viral elimination.

Conclusion

There are pros and cons to CPT, even though this method has been utilized for the last century in many countries. Based on current evidence, CPT is a specific therapy against COVID-19 and gives hope to critically ill patients, if not a promise for a cure. As long as the indications and conditions are fulfilled, the therapy does not harm the patients; it is only right that it be supported. As it is cheap and straightforward, no equivalent specific therapy has emerged. We support further research on CPT or comparable options.

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