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COVID-19 Pandemic and the Convalescent Plasma Therapy: Possible Benefits and Risks

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Abstract

Purpose of Review COVID-19 pandemic has been the major threat to the global public health for a year (last of 2019–till date); and unfortunately, there is still as no specific antiviral agent which can be effectively used against this disease curation. Present review focused on the application of the convalescent plasma (CP) therapy as a quick remediation of the disease severity.

Recent Findings While several drugs have been repurposed based on a number of completed clinical trials together with a huge ongoing effort to develop appropriate vaccine against the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), the therapeutic approach of the CP therapy appears to be one of the effective methods to rescue the severely affected COVID-19 patients. Such a therapy based on passive immunity evolved from the SARS-CoV-2-infected patients who have fully recovered from COVID-19; and hence these individuals are quite likely to possess high titers of the SARS-CoV-2-neutralizing immunoglobulins (antibodies). However, there are some risks such therapy, and its effectivity also appeared doubtful in some cases. Thus, the current review discussed the issues raised by the administration of such plasma into the SARS-CoV-2-infected individuals.

Summary Application of CP therapy has been conducted since long time; and for the mitigation of COVID-19 severity, such pharmaceutical strategy is also being employed in spite of several risks which actually can be monitored as well as optimized in order to combat the SARS-CoV-2 infection.

Keywords COVID-19 pandemic · SARS-CoV-2 · Convalescent plasma (CP) therapy

Introduction

Convalescent plasma (CP) therapy or the passive antibody therapy, which has been implemented for over a century, is known to involve the administration of antibodies against a specific pathogen or a group of pathogens to a susceptible individual in order to mitigate the infectious disease(s) [1, 2]. Indeed, such forms of passive immunity were the only means of treating infectious diseases prior to the development of the successful antimicrobial therapy [2, 3]. In case of failure of designing/obtaining appropriate drug(s) or vaccine(s), the infecting pathogen can be indirectly utilized which is obviously capable to instigate the immune response producing the neutralizing antibodies [4]. Passive transfusion of the convalescent blood products (CBPs), prepared by collecting usually the whole blood from a convalescent donor (the person who has recovered from the infection), has been known to be as a feasible therapeutic strategy for more than hundred years effectiveness especially in lowering the mortality rate of the COVID-19 patients in the current days [5–7]. The objective of CBP of the CP therapy is the complete elimination of viruses (typically within 10 to 14 days after infection) in the recipient patient [4, 6]. Besides, the transfusion of influenza-convalescent human blood products was found to reduce the mortality rate during the Spanish influenza whereby the treatments for H5N1 influenza were disappointing, but the convalescent human plasma consisting of the H5N1 was found to be an effective therapeutic strategy [2]. At present, passive antibody therapy depends mainly on pooled immunoglobulin (antibody) preparations usually of high titer, whereas the plasma therapy is employed in case of epidemic/pandemic emergency cases where there is insufficient time or resources to produce antibodies [1]. There

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are numerous examples of historical and modern approaches, in which convalescent plasma was successfully used as post-exposure prophylaxis (e.g., hepatitis, mumps, polio, measles, rabies) and/or treatment for a myriad of infectious diseases (principally, influenza, Argentine hemorrhagic fever, severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1) infection, the Middle East respiratory syndrome coronavirus (MERS-CoV) infection, and Ebola virus infection) [1, 3–11].

Indeed, the CP constitutes a significant quick remedy in the current COVID-19 pandemic situation which has already resulted in 3,698,621 deaths out of 171,782,908 confirmed cases, and already the possible mechanisms of action of CP and the positive consequence of the CP therapy in controlling COVID-19 pathogenesis have been well noticed besides the administration of vaccines (so far 1,546,316,352 vaccine doses have been administered) [12]. Indeed, prior to the large-scale commercial use especially of the Pfizer-BioNTech (BNT162b2) or Moderna (mRNA-1273) vaccines as well as of the repurposed antivirals and immunomodulatory agents, the CP therapy appeared to be the only strategy to immunize the SARS-CoV-2-infected serious patients (defined as the presence of dyspnea, hypoxemia, etc.) and the critical patients (with the presence of respiratory failure, septic shock, and/or multiple organ dysfunctions) within a short time [12–15]. According to several clinical studies, donors had been found to possess the anti-SARS-CoV-2 antibody titer greater than 1:1000, with the neutralizing antibody titer higher than 40 (in case of 400 mL CP administration), whereas in case of 200 mL CP administration, the neutralized antibody titer was 1:640 (together with the treatment of the antivirals and steroid) [4, 14]. It is worth noting that several trials (e.g., ClinicalTrials.gov registration no. NCT04359602, NCT04360278, NCT04344977, NCT04344015) have started to create registries in the USA to collect the plasma with titers of >1:64 from the convalescent donors without immediate reinfusion; and such plasma banking strategies can be used during the after-waves of the ongoing COVID-19 pandemic [4].

The immune plasma neutralizes the invading SARS-CoV-2 as well as also delivers the passive immunomodulatory features permitting the recipient individual to regulate the elevated cytokine levels induced by the viral infection [13]. Besides the use of several repurposed antiviral drugs including favipiravir, lopinavir and ritonavir, hydroxychloroquine, azithromycin, and remdesivir, the application of CP in SARS-CoV-1 was also found to be effective in terms of decreased mortality; and at present, such strategy is also being noticed to be very much effective in reducing the viral load with the concomitant improvement of clinical conditions in the COVID-19 patients [14, 16, 17]. While the patients who have recovered successfully from COVID-19 may play valuable role as the donors for CP therapy, the disposition of the convalescent serum prophylaxis for COVID-19 patients must comply with the availability of donors, standard settings of blood bank facilities to process the sera, serological and viral assay facilities, appropriate prophylaxis, and therapeutic protocols along with the regulatory compliance. CP transfusion has been found to be effective especially when transfused within the first 20 days of the SARS-CoV-2 infection [14]. Therefore, both the dosage and transfusion timing are important for assuring the necessary safety and usefulness of such treatment [14]. Current review outlined the pros and cons of such application of passive immunity through the CP therapy.

Evolution and Effectiveness of Convalescent Plasma (CP) Therapy

The concept of CP infusion evolved in 1880 whereby immunity was noticed against diphtheria which had been instigated from the existing antibody titer in blood from animals purposely immunized with non-lethal doses of toxins [13]. Besides, in the early 1950s, the purified and concentrated immunoglobulins both from the healthy individuals and the recovered patients from disease imparted an opportunity for the treatment of serious infectious diseases [13]. The severe H1N1 2009 infection could be treated with CP as the viral load was found to be decreased upon transfusion as well as the cytokine storm was under control, resulting in the decline in mortality [11]. It is worth noting that meta-analysis of 1918 influenza A (H1N1) pandemic as well as the treatment of severe influenza A by H5N1 subtype infection unraveled that the CP therapy could be a potential treatment strategy [18]. The methods for the detection of the neutralizing antibodies of severe acute respiratory syndrome (SARS) convalescent sera (i.e., anti-SARS antibodies) were well endorsed in 2003, including the enzyme-linked immunosorbent assay (ELISA), neutralization assay, and Western blot; and the evaluation of the efficacy of CP therapy with severe SARS patients revealed good outcome (decrease in the viral load within a day of transfusion with simultaneous increase in the anti-SARS-CoV immunoglobulins IgM and IgG) [11, 17–21].

Indeed, the protocol for application of the CP for SARS was established in 2015 [22]. Possible sources of CP therapy against SARS-CoV-2 are human convalescent sera from individuals who have recovered from COVID-19 (Figure 1). Another option is preparations generated in certain animal hosts, such as genetically engineered cows that produce human antibody [23]. The benefits of CP therapy in the COVID-19 mitigation has been observed through the direct neutralization of invading SARS-CoV-2, regulation of the cytokine dysbiosis (precisely the cytokine storm), complement activation, and immunomodulation thereby reducing the mortality rate [13]. In a study with the hospitalized severe patients, the plasma transfusion was noticed to (1) normalize body temperature of the maximum patients, (2) the sequential organ failure

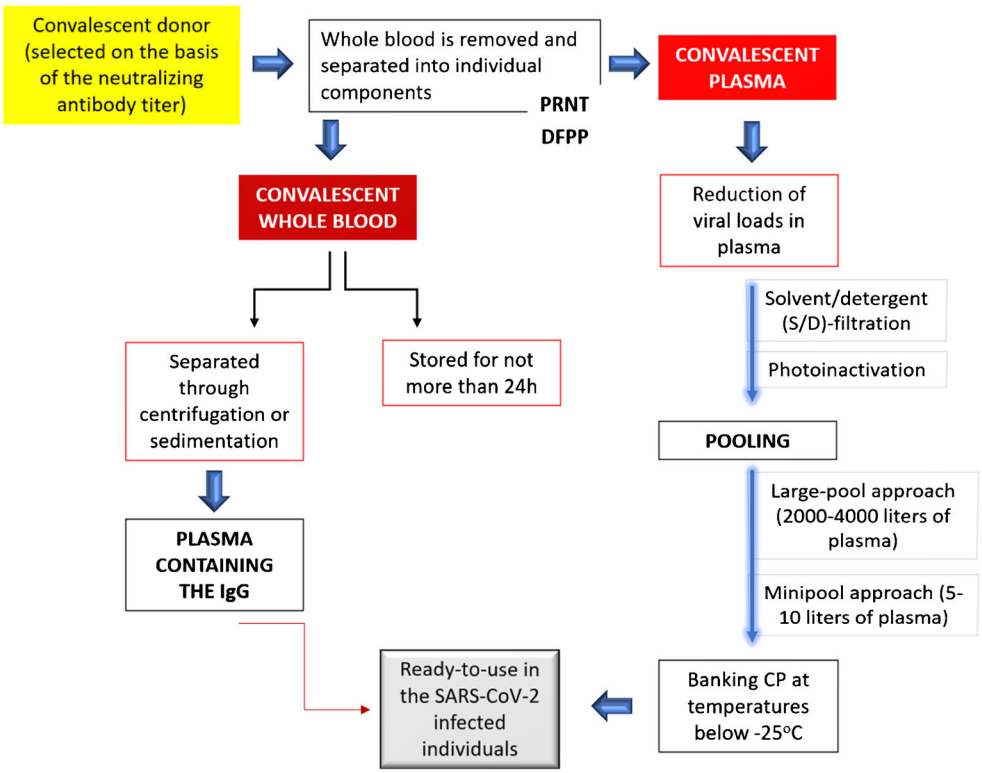

Figure 1 Preparation and pooling of the convalescent blood products (CBP). The CP manufacturing scheme presented here is adapted from Focosi et al. (2020) [4]. The convalescent donor is usually selected through the neutralizing antibody titer which is assessed through the plaque reduction neutralization test (PRNT) requiring a viable isolate, replication-competent cell lines, and skilled personnel. Alternatively, an enzyme-linked immunosorbent assay (ELISA) can also be used which targets the recombinant receptor binding domains (RBDs) of the viral anti-receptor, followed by the correlation measurements between ELISA ratios/indexes with the PRNT titers. CP can be harvested by apheresis (plasma fractionation) using the double filtration plasmapheresis (DFPP) with fractionation filter 2A20 (trial NCT04346589) or, alternatively, collecting immunoglobulins from the convalescent donors by immunoadsorption (trial NCT04264858). The pathogenic load is reduced or eliminated from the plasma by employing the (1) solvent/detergent (S/D)-filtration, providing the quick inactivation of >4 logs of most enveloped viruses, or (2) by applying photoinactivation (combinations of methylene blue and visible light, theraflex, amotosalen (S-59) and UV A, and riboflavin and UV B, or (3) by using caprylic acid and octanoic acid (which also can inactivate the enveloped viruses). The next step is the pooling of CP together with the intravenous immunoglobulin (IVIg) by means of fractionation. In case of large-pool approach, the pharmaceutical-grade facilities characteristically pool 100–2500 donors to manufacture S/D-inactivated plasma; and the IVIgs are similarly prepared from pools of 2000–4000 L of plasma. In contrast, in case of minipool fractionation scale (MPFS) process, 5–10 L of plasma can be obtained. Finally, the harvested CP can be aliquoted into 200–300 mL quantities which can be preserved below −25°C prior to use [4].

assessment (SOFA) score was found to be decreased, (3) the acute respiratory distress syndrome (ARDS) was found to be eliminated in 80% cases, (4) normalized levels of C-reactive protein (CRP), alanine aminotransferase, and aspartate aminotransferase, (5) the SARS-CoV-2 load declined; and surprisingly, (6) the patients were tested to be virus negative after 12 days of transfusion [13]. Besides, as stated elsewhere, in the immunological perspective, the lymphocyte counts in the peripheral blood may significantly decrease upon CP therapy; and also, the level of the cytokines in plasma including the interleukin (IL)-6, IL-10, tumor necrosis factor (TNF)-α, and the granulocyte macrophage colony stimulating factor (GMCSF) are likely to be reduced [1, 13, 16, 24]. Moreover, the CP therapy was found to shorten the duration in the intensive care unit (ICU), the rate of mechanical ventilation (MV) support, and vasopressor support for the serious COVID-19 patients [14]. Thus, the convalescent sera obtained from the recovered COVID-19 individuals who had established humoral immunity against SARS-CoV-2 consist of significant level of neutralizing antibodies against the virus which can further help eradicating the same virus from the systemic circulation as well as the pulmonary tissues in the other COVID-19 patients if CP treatment is employed.

Possible Risks Associated with CP Therapy

Although the CP therapy appears to be a potential strategy for the treatment of the severe COVID-19 patients, still some challenges rise with the side effects such as chills, fever, transfusion-related acute lung injury, and anaphylactic reactions [25]. In addition to antibodies, the convalescent whole blood (CWB) may impart the regulation of the hemorrhagic events as was noticed in case of the Ebola virus disease (EVD)

cases (Figure 1) [4, 7]. Moreover, CP infusion may have its latent threat like the aggravating hyperimmune attacks since CP therapy is completely based on the passive immunity with administering pathogen-specific immunoglobulins to the infected individuals [25, 26]. Indeed, the CP therapy can be more effective at the earlier stage of COVID-19, and hence, the peak timing of administering CP into the COVID-19 patients demands careful consideration [26]. However, with the advantage of one dose of 200 mL CP transfusion to significantly improve the clinical symptoms as well as to increase the oxyhemoglobin saturation with the concomitant neutralization of the viral load, facial red spots may be an adverse effect [27]. The other risks may include the transmission of the virus during plasma transfusion [27]. The most important risk may be the antibody-dependent entry (ADE) of the SARS-CoV-2 during CP therapy which in turn may suppress the innate antiviral state [15, 27, 28]. In addition, in case of emergency, donor screening and the conventional viral nucleic acid testing (NAT) especially for the human immunodeficiency virus (HIV), hepatitis C virus (HCV), and hepatitis B virus (HBV) are sometimes not be sufficient to guarantee the CP safety [4]. Moreover, although the convalescent plasma is habitually administered into the COVID-19 based on the experimental data with the aim of better clinical consequences, a clinical trial (PlasmAr ClinicalTrials.gov number, NCT04383535) showed no substantial differences between the COVID-19 patients treated with the convalescent plasma and those who received placebo [29]. Such a relatively neutral result may be explained by the logic that the patients who received the CP therapy; i.e., the plasma before day 14 of the onset of symptoms are usually more likely to recover with a lower mortality rate than those who receive such CP treatment after day 14 of the development of the COVID-19 symptom. Inclusive of other clinical trials, a 75% recovery rate was noticed through the CP therapy [29]. However, the role of CP also needs to be reevaluated now that highly efficacious COVID-19 vaccines are available and a cocktail of monoclonal antibodies is likely to be effective [14, 30, 31, 32].

Conclusion

Although there are unsatisfactory results as well as some risks exist upon convalescent plasma (CP) therapy, still its application especially on the frontline COVID-19 workers (healthcare providers) may help to avoid the SARS-CoV-2 infection quickly. Indeed, the transmission dynamics of SARS-CoV-2 is so fast, and during the current pandemic, countless patients are in need of ICU and the mechanical ventilation (MV) support. As is already known, there is no specific antiviral drug against SARS-CoV-2 nor any vaccine has been globally disseminated. Thus, strategies which can reduce the requirement of ICU and MV supports are of significance. In such circumstance, the CP therapy is undoubtedly operative for the mitigation of the disease.

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