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Convalescent Plasma Immunotherapy - A Possible Mitigation Strategy for SARS-CoV-2 Pandemic

Rajendran Manikandan, Mithilesh Singh, Vishal Chander, Gaurav Kumar Sharma, Suresh Bindu and Murali Dinesh

Abstract

Recently, a newly emerged severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) caused a pandemic coronavirus disease (COVID-19). More than 10 million confirmed cases and 503,867 associated deaths of SARS-CoV-2 have been reported worldwide to WHO in the end of July 2020. According to WHO guidelines, there is no effective therapy available for treating devastating SARS-CoV-2. Consequently, lack of evidence for appropriate treatment and vaccines has led to the re-emergence of convalescent plasma (CP) immunotherapy. Herein, we discuss the historical perspectives of CP against SARS-CoV, MERS-CoV, H1N1 pandemic and mainly the clinical outcomes of COVID-19 patients with respect to neutralizing antibodies (nAbs). A brief possible clinical protocol for CP transfusion with its adverse effects and limitation were also highlighted. It is concluded that, CP transfusion with high neutralizing antibody titer administered in early course of disease significantly improved clinical outcomes in COVID-19 patients by reducing morbidity and mortality. Thus, CP immunotherapy is considered as noteworthy candidate to be further re-evaluated as a most suitable therapeutic option against SARS-CoV-2 pandemic.

Keywords: SARS-CoV-2, COVID-19, Convalescent Plasma, Neutralizing antibodies, Pandemic

1. Introduction

In December 2019, a newly emerged respiratory diseases associated with pneumonia from Wuhan, China caused by a initially named 2019 novel coronavirus (2019-nCoV) [1] and recently referred as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) producing coronavirus disease (COVID-19). Thus 2019-nCoV, caused a pandemic across the globe, the World Health Organization (WHO) declared it as a 'Public Health Emergency of International Concern (PHEIC)' on January 30th, 2020. Considering its devastating threats worldwide, WHO declared SARS-CoV-2 as a pandemic spread on March, 2020 [2]. As per WHO guidelines, no effective therapy is available to treat devastating SARS-CoV-2, the treatment is mainly symptomatic and supportive. Thus, the current lack of evidence for effective treatment and vaccines, led to the re-emergence of classical and historical intervention called convalescent

plasma (CP) immunotherapy. Since the early 20th century, a passive CP immunization strategy has been used in prevention and control of infectious disease [3]. CP seems to be the first line of defense against the SARS-CoV-2, since it has been more successfully adapted in the treatment of SARS, MERS (Middle East Respiratory Syndrome) and H1N1 pandemic with significant efficacy and safety. In order to combat current devastating pandemic, this review mainly highlights on the clinical immunotherapy studies conducted in the fields of neutralizing antibodies (nAbs) predominately present in convalescent plasma (CP) for the treatment and management of COVID-19.

2. Virology of SARS-CoV-2

Coronaviruses (CoVs) belongs to the family *Coronaviridae* and the order *Nidovirales* possessing a single-stranded, positive-sense RNA genome ranging from 26 to 32 kb in length [4]. SARS-CoV and SARS-CoV-2 comes under the genus *Betacoronavirus* of the subfamily *Orthocoronavirinae* and is further belongs to subgenus *Sarbecovirus* [5].

Based on the phylogenetic tree analysis, nucleotides of SARS-CoV-2 shares 96% sequence identity with the SARS-like (SL) virus named BatCoV-RaTG13/Bat-SL-RaTG13 [6] and 88–88.2% identity [6–8] with bat-derived SARS-like coronaviruses named Bat-SL-CoV-ZC45 and Bat-SL-CoV-ZXC21, suggesting that bats are the most likely reservoir. Interestingly, the phylogenetic study showed that MERS-CoV and SARS-CoV were about 50% and 79% similar to SARS-CoV-2, respectively [6, 7]. The Spike (S) protein of SARS-CoV-2 was found to be approximately 75% homologous to the SARS-CoV spike [6].

The organization of the CoV genome contains a 5'-leader-UTR-replicase-S(Spike)- E (Envelope)- M(Membrane)- N(Nucleocapsid)-3' UTR-poly(A) tail with accessory genes interspersed in the structural genes on the 3' end of the genome [9]. In 5' terminal, 2/3rd of viral RNA primarily locates the first ORF (ORF1a/b) which translates 2 polyproteins namely, pp1a and pp1ab, and encodes 16 non-structural proteins (NSP), while the remaining ORFs encode accessory and structural proteins [10]. The structural proteins of SARS-CoV-2 contains spike (S), an envelope (E), membrane (M) and nucleocapsid (N) protein that are located at the one third 3' terminal of the genome [11]. The critical step for SARS-CoV-2 entry is binding of trimeric spike (S) glycoprotein to host cell angiotensin-converting enzyme 2 (ACE2) receptors similar to that of SARS-CoV entry [6]. Coronavirus nAbs targets primarily surface spike glycoprotein that mediate viral entry into host cells. The symptoms of COVID-19 most commonly are fever, cough, myalgia or fatigue, dyspnoea, pneumonia and lesser common were sputum production, headache and diarrhea. The complication of SARS-CoV-2 are mostly acute respiratory distress syndrome (ARDS), followed by shock, myocardial dysfunction and acute kidney injury [12, 13]. A detailed overview of COVID-19 disease progression was discussed, with particular reference to immunopathology and immunobiology [14].

SARS and MERS are caused by zoonotic coronaviruses that belong to the genus *Betacoronavirus* within *Coronaviridae*. SARS-CoV emerged in southern China in 2003 and caused 8098 cases worldwide, including 774 related deaths with an estimated 14–15% case-fatality rate [15]. In 2012, the first case of MERS occurred in Saudi Arabia. A sum of 2,494 cases and 858 related deaths with an overall case-fatality rate up to 34.4% [16]. More than 10 million confirmed cases of SARS-CoV-2 were reported globally by WHO, including 503,867 associated deaths as on the date of compilation 30th June-2020 (**Figures 1 and 2**). A total of 566,840 confirmed cases of SARS-CoV-2 were reported in India, including 16,893 associated deaths as on the date of compilation 30th June-2020 (<https://covid19.who.int/>) (**Figures 3 and 4**).

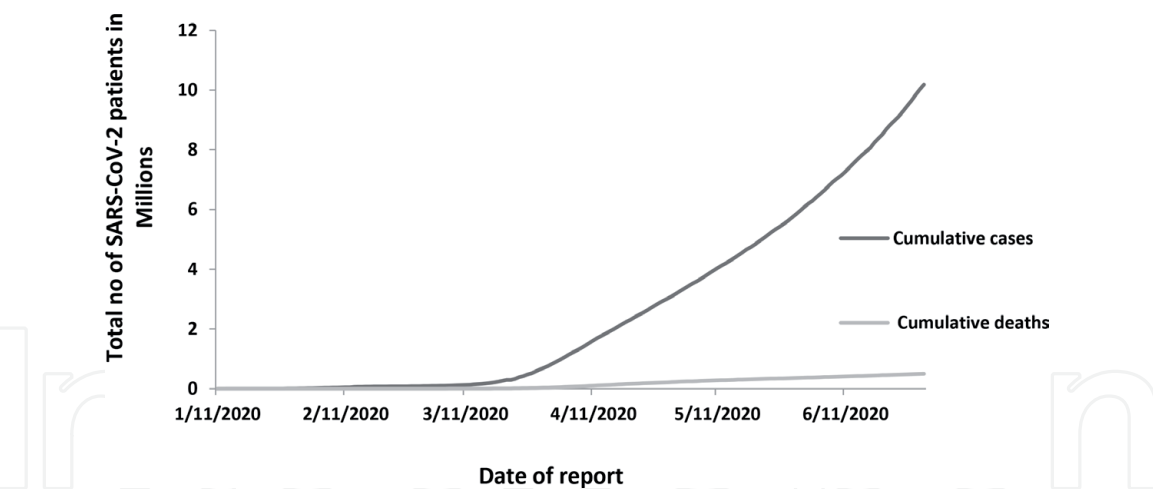


Figure 1.
Total number of cumulative SARS-CoV-2 cases and deaths across the globe during current pandemic. Source adapted from (<https://covid19.who.int/>). [accessed 2020-06-30].

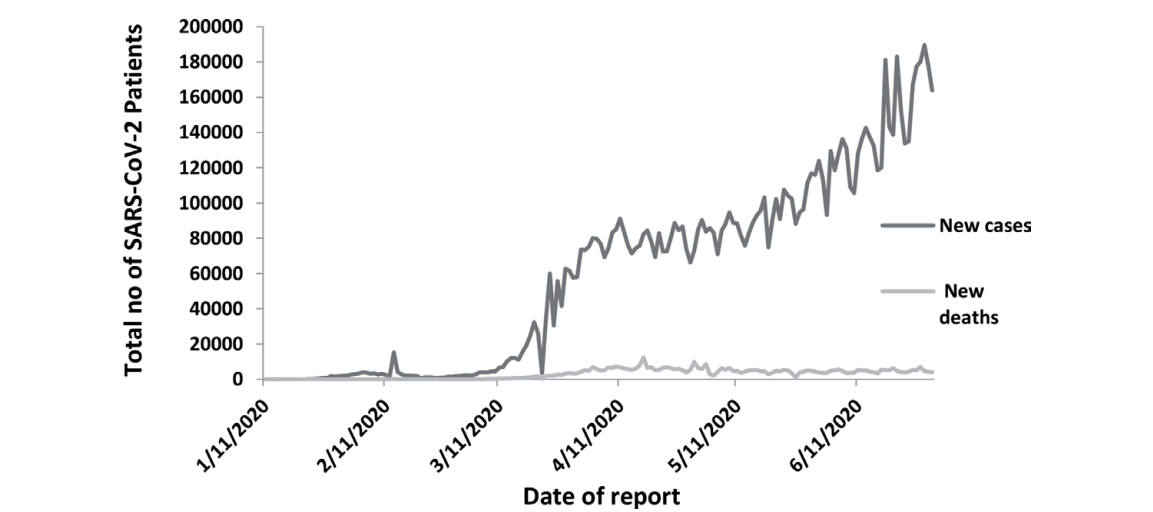


Figure 2.
Total number of daily new confirmed SARS-CoV-2 cases and deaths across the globe during current pandemic. Source adapted from (<https://covid19.who.int/>). [accessed 2020-06-30].

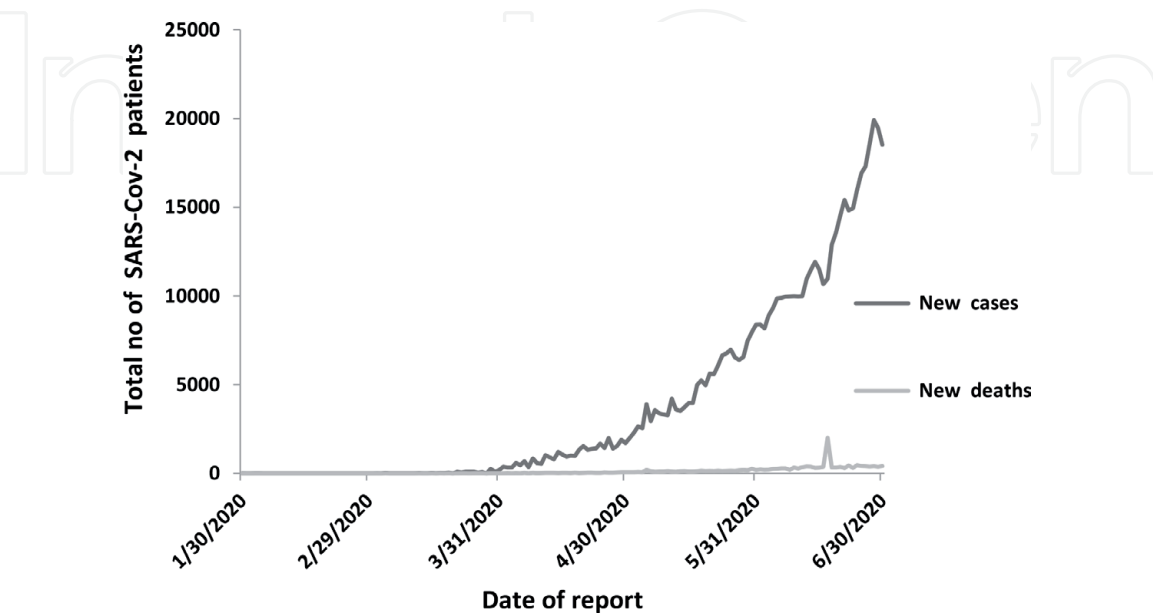


Figure 3.
Total number of daily new confirmed SARS-CoV-2 cases and deaths in India during current pandemic. Source adapted from (<https://covid19.who.int/>). [accessed 2020-06-30].

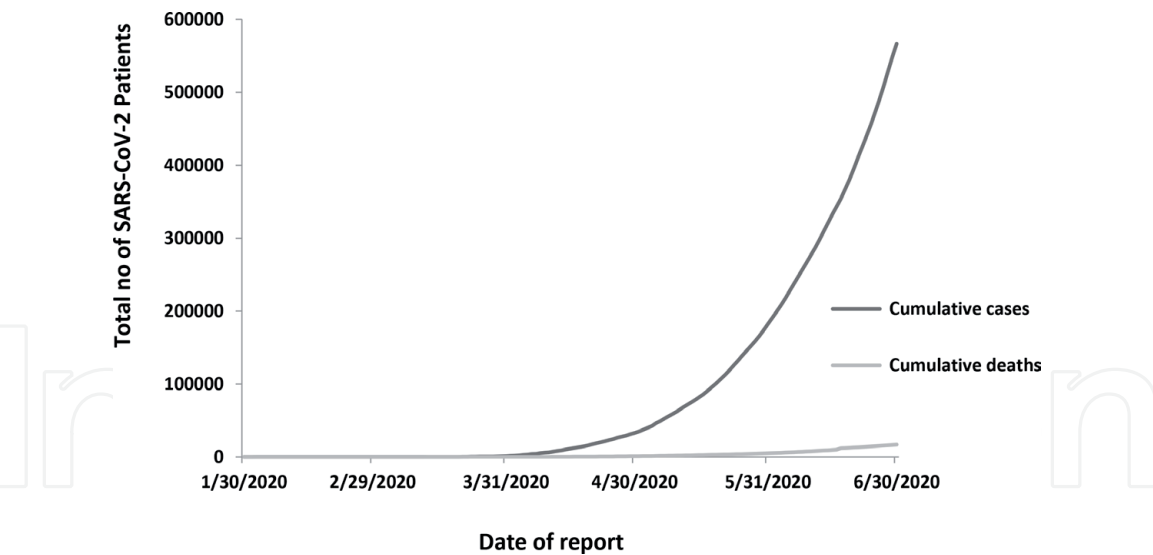


Figure 4. Total number of SARS-CoV-2 cumulative cases and deaths in India during current pandemic. Source adapted from (<https://covid19.who.int/>). [accessed 2020-06-30].

3. Historical perspectives of CP

Serum therapy was the only effective treatment option for infectious diseases prior to the discovery of antibiotics. In the year 1890, serum therapy was founded by Emil von Behring. The use of serum blood therapy has been proposed for treating diphtheria. At the same time Behring and Kitasato developed an effective therapeutic serum against tetanus.

Documented reports of the Spanish flu H1N1 pandemic (1918–1920) stated that transfusion of influenza-convalescent human blood products (whole blood, plasma, or serum) reduced morbidity and mortality. Hence, convalescent plasma could be an effective therapy during viral outbreaks and pandemics [17]. Treatment of severe H1N1 infection with convalescent plasma revealed that 1 dose of convalescent plasma with $>1:160$ neutralizing antibody was successful in reducing mortality and the viral load of the respiratory tract decreased by $>3\log_{10}$ copies/mL within 48 h of plasma therapy [18]. H5N1-infected BALB/c mice treated with H5N1-specific F(ab')₂ fragments derived from horses provided proof that passive immunotherapy is effective for immunologically competent and incompetent hosts [19].

A Lyophile serum was used effectively to prevent and/or treat many diseases such as measles, chickenpox, mumps, German measles, erysipelas, hemolytic streptococcal infections and scarlet fever [20]. Argentine hemorrhagic fever (AFH) caused by Junin virus is one of the few infectious viral disease in which CP administration is a specific treatment of choice that can neutralize viremia after immune plasma transfusion [21]. CP has been used with varied outcomes in combating Lassa fever and Ebola virus [22, 23]. For most viral diseases, the first week of infection peaks with viremia. The patient typically produces a primary immune response by day 10–14 followed by virus clearance.

In the SARS-CoV-1 outbreak, CP therapy was used and found to be more effective in patients who received transfusions within 14 days of the onset of symptoms [24]. The analysis further revealed that virus was cleared 1 day after CP transfusion, preceded by fever subsidence and pulmonary infiltrate resolution. CP transfusion may be considered as alternative treatment in cases where SARS-CoV patients experience severe deterioration and fail to respond to the available treatment such as ribavirin or methylprednisone [25].

Meta-analysis by Nottingham University-World Health Organization Collaborating Center showed that CP containing MERS-CoV-specific antibodies from recovered patients could be the most promising near-term therapy for infected individuals. In MERS-CoV patients, treatment with CP was restricted by a limited pool of donors with adequate antibody levels [26] and the usage of CP in three critically ill respiratory failure MERS-CoV patients in South Korea resulted in significant clinical improvements [27].

4. Convalescent plasma (CP)

The first and foremost important criteria for the convalescent plasma immunotherapy is that recovered SARS-CoV-2 donor should have high neutralizing antibody (nAb) titer and specific to the virus [28]. It is proposed that SARS-CoV-2 specific nAbs may reduce the viral load, severity of diseases and further also increase the nAb titer level of COVID-19 patients. CP may be a potentially effective strategy and first line of defense against the current wreaked havoc SARS-CoV-2 viral pandemic.

4.1 Clinical outcomes of CP

A Single dose of CP with a high concentration of nAbs rapidly reduced the viral load and eventually increased clinical outcomes of ten severe adult SARS-CoV-2 patient from china by successful use of the CP immunotherapy. Single dose of 200 mL of inactivated CP with high neutralization titer of >1:640 was transfused according to the WHO blood transfusion protocol. Interestingly this recent study showed significant increase in nAb titer level, disappearance of SARS-CoV-2 RNA at an undetectable level, reduction of pulmonary lesions and amelioration of laboratory parameters in all patients after CP transfusion. The clinical symptoms were improved within 3 days and the viraemia was also disappeared on 7 days of CP immunotherapy (**Figure 5**) [28].

The recent study from China over 175 patients recovered from SARS-CoV-2 clearly showed the production of SARS-CoV-2-specific neutralizing antibodies after 10–15 days of infection. Interestingly this study had several findings that convalescent plasma recovered from SARS-CoV-2 patients specifically inhibited SARS-CoV-2 alone, but not the SARS-CoV infection, the peak of neutralizing antibodies were detected in all patients after 10 days of infection and variations in nAb titers

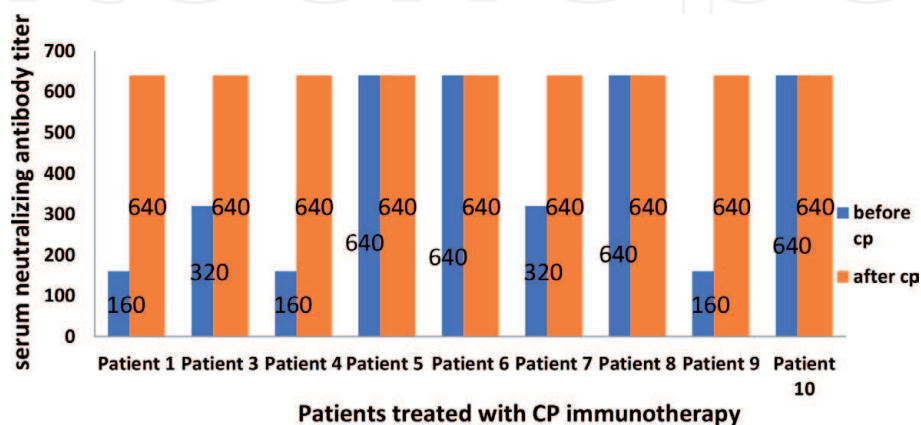


Figure 5. Comparison of serum neutralizing antibody titer before and after CP immunotherapy. [CP, Convalescent plasma]. Source adapted from Duan et al. [28].

were observed as 30% of infected patients corresponds to low nAb titer (< 500), 17% to medium-low titers (500–999), 39% to medium-high titers (1000–2500) and 14% to high nAb titers (>2500). Moreover, the elderly and middle-aged patients had substantially higher plasma nAb titers and spike-binding antibodies than young aged SARS-CoV-2 infected patients [29]. Further this study showed the noteworthy findings of CP immunotherapy can be specifically used for the prevention and treatment of SARS-CoV-2.

Five critical patients from china with SARS-CoV-2 and acute respiratory distress syndrome (ARDS) had eventually recovered after CP immunotherapy. Clinically significant improvement of four out of five were reported promptly. This recent study showed increase in nAb titer level (**Figure 6**) and titers of IgG and IgM in the sera got increased in a time-dependent manner after convalescent plasma transfusion. It was observed that the Ct value of all patients seems to be negative after 12 days of transfer of CP immunotherapy [30].

Ye et al. reported an increase in anti-SARS-CoV-2 nAb titers and further increase in IgG and IgM antibodies. CP transfusion resulted in the resolution of ground glass opacities and consolidation in patients lung. The clinically significant outcome of this study is that all the six SARS-CoV-2 infected patients were found negative in throat swab analysis by real-time PCR assay due to reduction in the viral load after CP immunotherapy [31].

SARS-CoV-2 infected patients over the age of sixty years received CP treatment had a significantly prolonged recovery time estimated by viral clearance (10 to 29 days) compared to younger patients, who recovered from the disease in less than a week after receiving CP immunotherapy [32].

The level of specific neutralizing antibody against SARS-CoV peaked at 4 months and gradually disappearing to an undetectable level of 25.8% (IgG) and 16.1% (nAbs) in serum after 3 years of recovery [33]. Similarly, MERS-CoV infected patients showed a low prevalence of 2.7% IgG seroreactivity and the antibodies titer dropped rapidly within 3 months of recovery [26].

Even though the level of specific nAb titers in sera were decreasing gradually, it is also possible to isolate potent neutralizing human monoclonal antibodies (mAbs) from memory B cell repertoire of convalescent patients against SARS-CoV [34] and SARS-CoV-2 [35]. The detailed possible FDA approved protocol for convalescent plasma immunotherapy transfusion was discussed in this recent studies for SARS-CoV-2 [36] and Ebola virus [37]. The possible protocol of CP immunotherapy transfusion for COVID-19 patients is depicted in **Figure 7**.

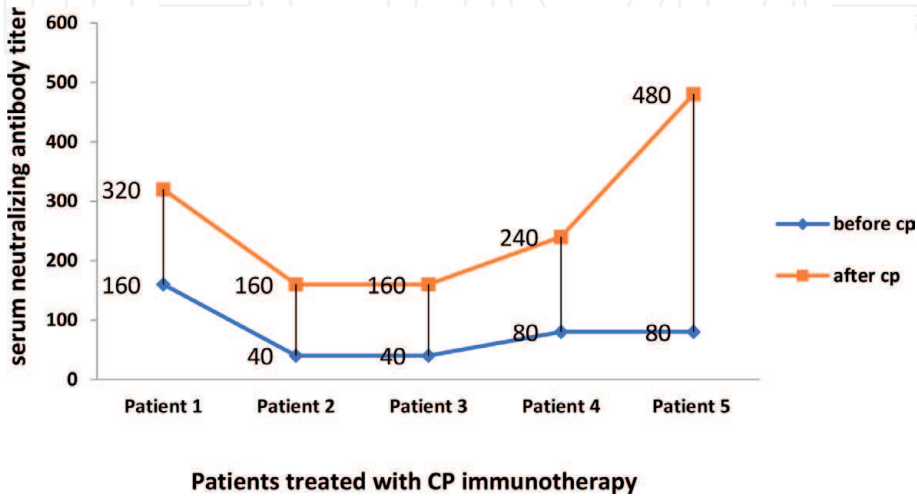


Figure 6. Comparison of serum neutralizing antibody titer before and after CP immunotherapy. [CP, Convalescent plasma]. Source adapted from Shen et al. [30].

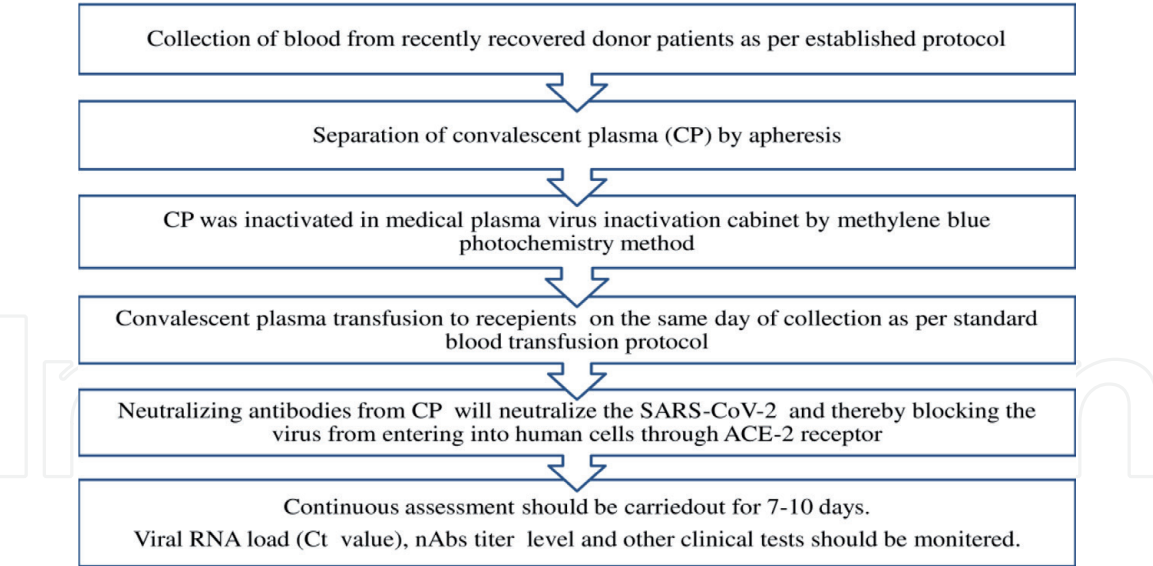


Figure 7.
Schematic representation of CP immunotherapy for SARS-CoV-2 patients highlighting the major steps.

4.2 Immunomodulatory effects

In a mouse model study, SARS-CoV pathogenesis is directly regulated by complement and its absence showed significantly reduced respiratory disease, decreased neutrophilia in their lungs, reduced systemic inflammation and viral load remains unchanged in a complement-deficient mice. Since SARS-CoV pathogenesis was mainly immune-driven, inhibiting the complement signaling pathway after SARS-CoV infection is also an effective immune therapeutic strategy [38]. By scavenging complement fragments of C3a and C5a, intravenous immunoglobulin prevents immune damage and restricts the development of immune complexes [39]. Similarly, passive antibody transfer may limit the cellular damage induced by the activation of complement cascade in an excessive inflammatory area.

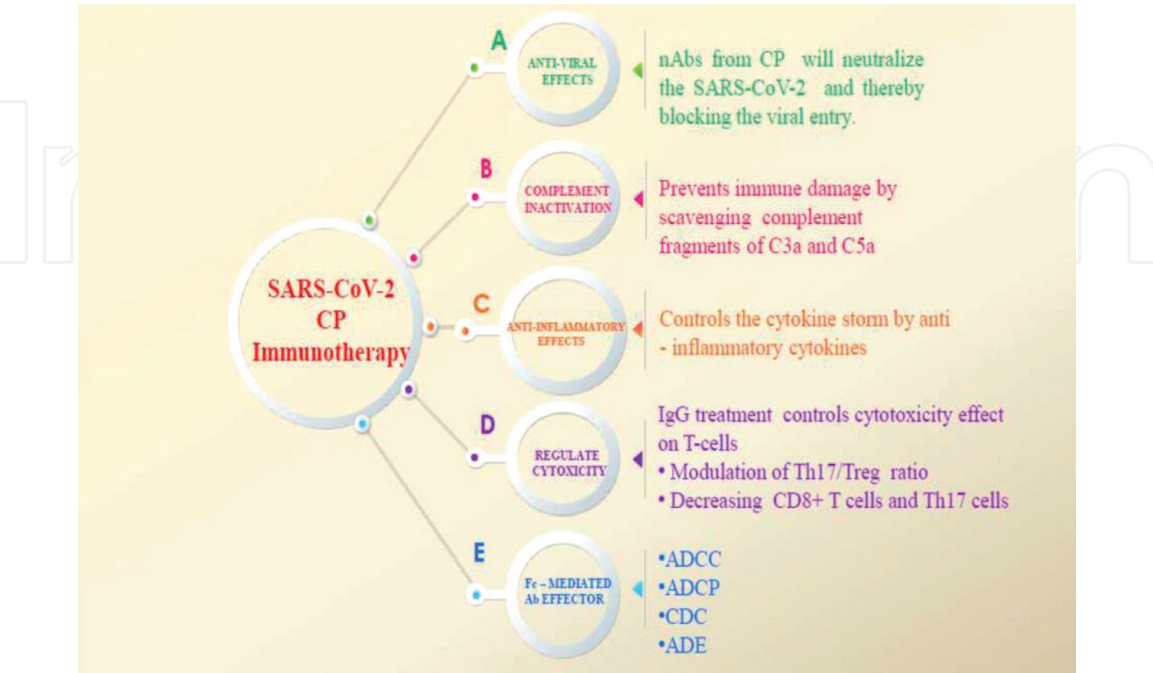


Figure 8.
A brief overview of possible mechanisms of action of CP immunotherapy. [nAb, neutralizing antibody titer; ADCC, antibody-dependent cellular cytotoxicity; ADCP, antibody-dependent cell mediated phagocytosis; CDC, complement-dependent cytotoxicity; ADE, antibody-dependent enhancement.

IgG therapy controls the cytotoxic effect of T-cells by modulating the balance of Th17/Treg and decreasing CD8⁺ T cells and Th17 cells [40]. The possible mechanisms of action of CP immunotherapy are summarized in **Figure 8**.

Feline coronaviruses, HIV and dengue viruses use an antibody-dependent enhancement (ADE) phenomenon to take advantage of pre-existing poorly nAbs to effectively infect host target cells in order to combat anti-viral humoral immune response [41].

In vitro assays with human promonocyte cell lines HL-CZ demonstrated that ADE was primarily mediated by highly diluted antibodies against spike proteins, significantly increasing the rate of apoptosis of SARS-CoV infected cells [42].

5. Adverse effects

Previous studies did not find any adverse effects associated with CP immunotherapy during historical influenza A (H1N1), SARS-CoV, or MERS-CoV epidemics [18, 26, 43]. In case of Ebola, it was associated with mild adverse effects such as fever, nausea, skin erythema, and no other significant adverse events were found [44]. A self-limited facial erythema occurred in 2 out of 10 SARS-CoV-2 infected patients with no major adverse events found during the transfusion study [28]. The therapy was well tolerated in most of the patients while some reported only mild adverse effects. Several studies of SARS-CoV-2 have shown that CP immunotherapy is safe and not associated with any significant adverse effects.

6. Limitations

The risk of Hepatitis B virus, Hepatitis C virus and HIV disease transmission through the donated plasma should be thoroughly investigated before CP transfusion. The nucleic acid test for this viruses is strictly mandatory to ensure the safety of SARS-CoV-2 infected CP recipients [45].

Vaccine development should consider ADE phenomenon in COVID-19 patients as ADE may promote intensity of infection and administration of CP in those coronaviruses endemic areas should be carried out with caution since ADE appears to be harmful to actively infected patients [46].

All the recovered patients received not only the CP transfusion but also other standard care like antiviral treatment. As a consequence, these antiviral agents may also lead to the subsequent recovery of patients, or may synergize with the therapeutic effect of CP, which cannot be ruled out.

Taken together, these studies suggested that convalescent plasma from recently recovered patients with high neutralizing antibody titers against SARS-CoV-2 would be more effective for CP immunotherapy. A warranted random clinical trial in larger groups is required for dose optimization and to overcome possible adverse side effects of CP immunotherapy.

Furthermore, the kinetics of nAbs titers against SARS-CoV-2 need to be critically evaluated because of neutralizing antibodies represented short term humoral immune response.

7. Conclusion

The clinical trials of Convalescent plasma therapy conducted/initiated against SARS-CoV-2 pandemic across the world are getting increased day-by-day due to the

significant outcomes of infected patients with a high positive recovery rate when compared to all other modes of treatment against SARS-CoV-2 pandemic crisis. In SARS-CoV-2, many reports have shown that administration of CP immunotherapy is safe with significant potential efficacy and it was not associated with any major adverse events. Even in the autoimmune conditions also CP is considered to be safe. Thus, CP immunotherapy is considered as classical and historically noteworthy candidate to be further re-evaluated as a most suitable therapeutic option against SARS-CoV-2 pandemic.

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Conflict of interest

“The authors declare no conflict of interest.”

Appendices and nomenclature

WHO	World Health Organization
PHEIC	Public Health Emergency of International Concern
CP	Convalescent Plasma
nAbs	Neutralizing Antibodies
ADCC	Antibody-dependent cellular cytotoxicity
ADCP	Antibody-dependent cell mediated phagocytosis
CDC	Complement-dependent cytotoxicity
ADE	Antibody-dependent enhancement

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Author details

Rajendran Manikandan¹, Mithilesh Singh^{1*}, Vishal Chander²,
Gaurav Kumar Sharma², Suresh Bindu¹ and Murali Dinesh³

1 Immunology Section, ICAR-Indian Veterinary Research Institute, Izatnagar, UP, India

2 CADRAD, ICAR-Indian Veterinary Research Institute, Izatnagar, UP, India

3 Division of Pathology, ICAR-Indian Veterinary Research Institute, Izatnagar, UP, India

*Address all correspondence to: drmithileshsingh@yahoo.com

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