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Convalescent Plasma – A Review of this Potential Therapeutic Strategy for Combating Novel Coronavirus Disease 2019

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Abstract

Coronavirus disease 2019 (COVID-19) poses a significant threat to global health and World Health Organization (WHO) has declared this outbreak as a "public health emergency of international concern" on January 31, 2020. Globally, there is currently no effective post-infection prophylaxis for the treatment of COVID-19, although some drugs are being repurposed. Some vaccines have been developed and vaccination in different countries are undergoing at present, but duration of such vaccination in the long term protection is still unknown to us. Many therapeutic drugs, including chloroquine or hydroxychloroquine with or without azithromycin, remdesivir, favipiravir, nitazoxanide, ribavirin, baricitinib, penciclovir, ritonavir, and arbidol, have been tried as experimental medicine as they are thought to be reducing the viral load by different mechanisms but only a few has shown slight promising viral impact in the initial study. There are no antibodies for the prevention of COVID-19. Immune (i.e., "convalescent") plasma (CP) refers to plasma that is collected from individuals, following resolution of infection and development of antibodies. Antibody therapy can be used to treat patients who are already manifesting symptoms of varying severity. CP has shown limited and moderate success, previously for Severe Acute Respiratory Syndrome-1 and Middle East Respiratory Syndrome, and for COVID-19 in China, and could serve as a short-term solution to suppress mortality rates in India and worldwide. Based on the limited scientific data, convalescent plasma transfusion (CPT) therapy in COVID-19 patient appears safe, clinically effective, and reduces mortality. Well-designed large multicenter clinical trial studies should be conducted urgently to establish the efficacy of CPT to COVID-19 patients. At present, in India ICMR-CP trial (Placid Trial) on COVID-19 patients had been done. CP was not associated with a reduction in progression to severe COVID-19 or all-cause mortality. With this review, we have tried to highlight progress of CP on COVID-19 patients.

Keywords: Coronavirus disease 2019, Severe acute respiratory syndrome-coronaviruses, Convalescent plasma, World Health Organization, Passive immunization, Treatment

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Introduction

Coronaviruses (CoV) are usually known for mild-to-moderate respiratory and gastrointestinal diseases. However, in the last two decades, three novel CoV, Severe Acute Respiratory Syndrome (SARS)-CoV, Middle East Respiratory Syndrome (MERS)-CoV, and SARS-CoV2, have spread to humans from other species and invoked significant outbreaks. These cause high infectivity as well as moderate-to-high fatality in humans.[1,2] The latest human pathogenic coronavirus, SARS-CoV2, having a single-stranded positive-sense RNA genome, is a novel enveloped beta-coronavirus and belongs to the subfamily Orthocoronavirinae in the family of Coronaviridae in the order Nidovirales.[2] It is the cause of the disease coronavirus disease 2019 (COVID-19), which is causing a catastrophic pandemic with worldwide spread, high infectivity with numerous deaths, thus causing more or less universal lockdown across different countries for months to mitigate the infection. As of the time of this writing, more than 16 crores cases of COVID-19 have been reported worldwide besides contributing more than 33 lakh deaths.[3] The global health crisis is unprecedented in modern history, and more so as there are currently neither any proven options for prophylaxis for the exposed to SARS-CoV-2 nor therapy for those who have developed the disease COVID-19. There are currently no vaccine or specific effective evidence-based antiviral therapies for COVID-19.

Passive Antibody Therapy

Passive antibody therapy has been tracing back to the 1890s and was the only way of managing several contagious diseases before the advancement of antimicrobial treatment in the 1940s. Before the 1940s, passive antibody (serum) administration was helpful in the management of various contagious diseases. However, antibiotic chemotherapy was later observed to be more effective and less toxic than antibody therapy.[4] Recently, in India, besides other countries such as China and US, the management of COVID 19 has been started with trials of Convalescent Plasma (CP). At this juncture, it is crucial to review back the evidence surrounding its use.

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Passive immunity involves the transfer of preformed antibodies from an immune individual to a nonimmune individual to confer temporary immunity. Antibodies were continually used for more than a century for the prevention and treatment of different infectious diseases. In case of bacterial infections, antibodies developed in the host neutralize toxins from bacterial protein, helps in opsonization, and, thus promote bacteriolysis; in case viral infection, these antibodies block entry of virus into still noninfected host cells, augment natural killer cells, and antibody-directed cell-mediated cytotoxicity, and thus neutralize the virus.[5] These antibodies can be administered as human or animal plasma or serum, as pooled human immunoglobulin for intravenous or intramuscular use, as high-titer human immunoglobulin from immunized or convalescing donors, besides the newer ways of monoclonal antibodies.[5] Immune or CP refers to plasma that is collected from individuals, following resolution of infection and development of antibodies.

Passive antibody therapy, through transfusion of CP, may prevent clinical infection or blunt clinical severity in individuals with recent pathogen exposure.[6] A general principle of passive antibody therapy is that it is more effective when used for prophylaxis than for treatment of disease. When used for therapy, antibody is most effective when administered shortly after the onset of symptoms. The reason for temporal variation in efficacy is not well understood but could reflect that passive antibody works by neutralizing the initial inoculum, which is likely to be much smaller than that of established disease.[7] Another explanation is that antibody works by modifying the inflammatory response, which is also more easily achieved during the initial immune response, a stage that may be asymptomatic. Passive immunization, thus, is a technique to achieve immediate short-term immunization against infectious agents by administering pathogen-specific antibodies. Although antibiotics have largely supplanted the use of it in bacterial infections, it still remains an important tool in the treatment of many viral infections when vaccines or other specific treatments are not available in emergency situations like pandemic.

Transfusion of convalescent blood products (CBP) may be considered for treating patients affected by emerging infectious agents when no other specific treatment is yet available and if the infection generates effective protective antibodies. Transfusing CBP has demonstrated some efficacy in fighting various viral or bacterial infectious diseases, including influenza, measles, chickenpox, and, more recently, SARS and the HIN1 and H5N1 avian flu viruses.[8] CP therapy, classic adoptive immunotherapy, has been applied to the prevention and treatment of many infectious diseases for more than one century. Over the past two decades, CP therapy was successfully used in the treatment of SARS, MERS, and 2009 H1N1 pandemic with satisfactory efficacy and safety.

CBP

CBP, obtained by collecting whole blood or plasma from a patient who has survived a previous infection and developed humoral immunity against the pathogen responsible for the disease in question, are a possible source of specific antibodies of human origin. The transfusion of CBP is able to neutralize the pathogen and eventually leads to its eradication from the blood circulation. Different CBP have been used to achieve artificially acquired passive immunity:[1-4] (i) convalescent whole blood, CP or convalescent serum (CS); (ii) pooled human immunoglobulin (Ig) for intravenous or intramuscular administration; (iii) high-titer human Ig; and (iv) polyclonal or monoclonal antibodies. CP has been the subject of increasing attention, especially in the wake of large-scale epidemics. Apheresis plasma is currently the preferred therapeutic tool for several reasons: larger volumes collected per session, the possibility of more frequent donations, and the absence of impact on the donor's hemoglobin thanks to the reinfusion of his or her red blood cells.

The recruitment of donors living in areas in which an epidemic has broken out can offer the added value of providing specific, artificially acquired passive immunity against the local infectious agent while CBP supplied from other regions may be less effective due to (possible) strain variation of the pathogen in question.[9,10] Importantly, passive antibody administration offers the only short-term strategy to confer immediate immunity to susceptible individuals. This is particularly the case in the setting of a novel, emerging infectious disease such as SARS-CoV-2/COVID-19. CP has been used in two other coronavirus epidemics in the 21st century: SARS1 in 2003 and MERS in 2012 to the present. Trials from those outbreaks show that CP contains neutralizing antibodies.[6] While fractionated plasma products (e.g., hyperimmune globulin, monoclonal antibodies) and/or vaccination may offer durable therapeutic options, human anti-SARS-CoV-2 plasma is the only therapeutic strategy that is immediately available for use to prevent and treat COVID-19.[6]

For passive antibody therapy to be effective, a sufficient amount of antibody must be administered. When given to a susceptible person, this antibody will circulate in the blood, reach tissues, and provide protection against infection. Depending on the antibody amount and composition, the protection conferred by the transferred immunoglobulin can last from weeks to months.[7]

Suggested Uses of CP

Studies on Spanish influenza pandemic of 1918–1920 suggested that the use of CBP might be effective and for the 1st time, CP was identified as a potential therapy for a number of viral infections.[10] Throughout the years ahead, passive transfer of convalescent human sera deemed to be a possible therapy for the management of different diseases such as influenza, measles, Argentine hemorrhagic fever, chickenpox, infections by cytomegalovirus, parvovirus B19, MERS-CoV, H1N1 and H5N1 avian flu, arenaviruses (Lassa, Junin), filoviruses (Ebola, Marburg), and other severe acute respiratory infections (SARI) viruses. Furthermore, animal models of influenza pneumonia have shown the benefit of these convalescent sera (protection against H1 and H3 challenge), equine hyperimmune F(ab')2 globulin (protection against H5N1 challenge), and monoclonal antibodies (against H1, H3, and H5N1 challenge).[10] However, the positive findings have not been proven and reinstated by controlled clinical trials in most of the cases.

Experiments of CP in Ebola Virus Disease

Usage in Ebola virus disease showed no serious adverse reactions associated with the transfusion of CP, and the procedure was acceptable to both donors and patients. In this non-randomized, comparative study in the adjusted analysis, the risk of death was found to be slightly lower in the convalescent-plasma group than in the control group, but the difference was not significant. Possible reasons may be the unknown levels of neutralizing

antibodies in CP and transfusion timing.[11] In a prospective cohort study with patients of severe H1N1 2009 infection requiring intensive care, treatment with CP with a neutralizing antibody titer of ≥1:160, harvested by apheresis from patients recovering from H1N1 2009 infection, reduced respiratory tract viral load, serum cytokine response, and mortality.[12] In a study in SARS, patients with progressive disease after ribavirin and methylprednisolone treatment were given either CP or further pulsed methylprednisolone in a retrospective non-randomized manner. Patients in the plasma group had a shorter hospital stay (P = 0.001) and lower mortality (P = 0.049) than the comparator group.[13]

Recent Studies on CP

In one study from China, one dose of 200 mL of CP derived from recently recovered donors with the neutralizing antibody titers above 1:640 was transfused to severe patients confirmed by real-time viral RNA test besides maximal supportive care and antiviral agents. After CP transfusion, the level of neutralizing antibody increased rapidly up to 1:640 in five cases, while that of the other four cases maintained at a high level (1:640). The clinical symptoms were significantly improved along with an increase of oxyhemoglobin saturation within 3 days. Several parameters tended to improve as compared to pretransfusion, such as increased lymphocyte, decreased C-reactive protein, and varying degrees of absorption of lung lesions within 7 days in radiological examinations. The viral load was undetectable after transfusion in seven patients who had the previous viremia. No severe adverse effects were observed.[14] In another study from China, 5 patients who were critically ill with COVID-19 and were in mechanical ventilation were treated with CP. Viral load declined within days of treatment with CP, and the clinical conditions of these patients improved, as indicated by body temperature reduction, improved Pao_2/Fio_2, and chest imaging, though the patients were on antiviral drugs besides CP administration.[15]

A recent meta-analysis of observational studies using passive immunotherapy for the treatment of SARI of viral etiology suggests that CP therapy was associated with a reduction in mortality (odds ratio 0.25, 95% confidence interval [CI] 0.14–0.45).[16] The post hoc pooled meta-analysis across all viral etiologies also revealed that a statistically significant 75% reduction in the odds of mortality among those who were treated with CP or serum without any evidence of serious adverse events or complications. Evidence from studies of SARS-CoV infection and Spanish influenza A (H1N1) infection showed a survival benefit following CP treatment within 14 days and 4 days of symptom onset, respectively. Thus, early initiation of treatment would be more beneficial in reducing mortality in SARI of viral etiology.[16] In another study of Hong Kong, after giving CP in 80 patients, a higher day-22 discharge rate was observed among those who were given CP 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.[17] In another study on MERS, of the 443 tested samples, 12 (2.7%) had a reactive ELISA result, and 9 of the 12 had reactive indirect fluorescent antibody and microneutralization assay titers, concluding that clinical trials of CP for passive immunotherapy of MERS-CoV infection may be feasible, but such trials might be challenging because of the small pool of potential donors with sufficiently high antibody titers.[18] In one randomized, double-blind, phase 3 trial at 41 US medical centers to assess the efficacy of high-titer anti-influenza plasma (hemagglutination inhibition antibody titer ≥1:80) compared with low-titer plasma (≤1:10) showed that high-titer anti-influenza plasma conferred no significant benefit over non-immune plasma.[19] However, as the data on the efficacy as well as safety of CP are quite limited, and the target for sufficient levels of neutralizing antibody titers against SARS-CoV-2 is unknown, and also citing the uncertainty surrounding the optimal preparation of CP and its safety, Surviving Sepsis Campaign: Guidelines recommend that it should not be routinely used in treating patients with COVID-19 until more evidence is available.[20]

Risks of Passive of Administration Convalescent SERA

Risks of passive of administration convalescent sera fall into two categories, known and theoretical. Known risks are those associated with the transfer of blood substances, which include inadvertent infection with another infectious disease agent and reactions to serum constituents, including immunological reactions such as serum sickness. With modern blood banking techniques that screen for blood-borne pathogens and match the blood type of donors and recipients, the risks of inadvertently transferring known infectious agents or triggering transfusion reactions are low. However, convalescent sera used in a therapeutic mode would likely be administered to individuals with pulmonary disease, in whom plasma infusion carries some risk for transfusion-related acute lung injury.[7]

Studies already showed that with SARS, the specific IgG began to increase around week 3 after onset, and with influenza CP with a NAT level of ≥1:160 reduced mortality.[12,21] Thus, CP from donors who have recovered and who are at week 12 after onset with a NAT level of not <1:160 is expected to be more effective. Since there are various limitations of acquiring CP such as age, weight, state of health, informed consent, the amount of CP required, and the ratio of recovered patients to those who need plasma might cause a shortage of it. Thus, the source of CP may limit its wide application, especially in countries which are in the acceleration stage and late accumulation stage of COVID-19 development.[22]

PLACID Trial – An ICMR Initiative

ICMR has initiated a multicenter clinical trial, titled "A Phase II, Open-Label, Randomized Controlled Trial to Assess the Safety and Efficacy of CP to Limit COVID-19 Associated Complications in Moderate Disease" (PLACID Trial). ICMR launched a call inviting letters of interest from sites which had the facilities to undertake the study. Expression of interest was received from 113 institutions. As of May 10, 2020, ICMR has approved the following 28 institutions in the PLACID Trial.[23]

Recent Studies on CP on COVID-19 Subjects Worldwide

In Zeng QL study, 6 COVID-19 subjects with respiratory failure received CP at a median of 21.5 days after first detection of viral shedding, all tested negative for SARS-CoV-2 RNA by 3 days after infusion, and 5 died eventually. The study concluded, CP treatment can discontinue SARS-CoV-2 shedding but cannot reduce mortality in critically end-stage COVID-19 patients, and treatment should be initiated earlier.[24]

Ahn *et al.* study revealed cases suggest that CP from patients who have recovered from COVID-19 infection might be an additional option to treat patients without causing any severe adverse effects. Furthermore, when used with systemic corticosteroids, might expect the possibility of reducing excessive inflammatory response by corticosteroids as well as promoting the reduction of viral loads by CP simultaneously.[25]

Systematic review by Rajendran *et al.* included 5 studies reporting convalescent plasma transfusion (CPT) to COVID-19 patients. The main findings from their systematic review are as follows: (1) CP may reduce mortality in critically ill patients, (2) increase in neutralizing antibody titers and disappearance of SARS-CoV-2 RNA was observed in almost all the patients after CPT therapy, and (3) beneficial effect on clinical symptoms after administration of CP.[26]

Besides this, there is always uncertainty of adequate antibody titer for protection as well as problem of large-scale clinical trials with this in this dire hour. Therefore, at the end, different questions and confusions remained like the appropriate dose and duration of CP to reach the clinical benefit, adequate therapeutic titer of IgG, and neutralization antibodies to select the COVID-19 CP donor, CP from donors having a different virus genome infection whether having protective effect for all patients with COVID-19 and the ideal moment to transfuse the CP, etc.[27] There may also be antibody-dependent enhancement (ADE) following transfusion of human antiSARS-CoV-2 plasma. ADE is a process where antibodies developed during a prior infection exacerbate clinical severity as a result of infection with a different viral serotype. This risk of ADE in COVID-19 is largely theoretical and may be due to the antibodies potentiating infection upon exposure to other strains of coronavirus.[6]

Indian Scenario

In India, like other countries, the cases of coronavirus infections are continually rising amidst massive 2nd wave of the pandemic now causing havoc, with more than 2 crores infected and over 2.58 lakhs deaths at the time of writing.[28] Different clinical studies have also been started to find out whether CP therapy can be effective in Indian scenario also. This can be a cost-effective and feasible option. With the increased number of infections still on, the number of patients from whom the harvested CP can be obtained can also be increased and thus more available for therapy. Therefore, CP is a good option to try for the management of COVID 19 and thus, well-controlled larger trials across different countries are needed so that the benefits and potential risks can be delineated more transparently.

New Updates

Clinical Efficacy of CP for Treatment of COVID-19 Infections

A systematic review noted that there was no standardization in terms of the time of administration of plasma therapy. Existing research suggests that SARS viral viremia peaks during the 1st week of infection and patients usually start to develop primary immune response by the end of the 2nd week of their infection. Therefore, the administration of plasma early during the early stage of the disease might lead to more favorable clinical outcomes.[29]

Abolghasemi H study revealed that CP substantially reduced all-cause mortality in treatment group compared with the control group (14.8% vs. 24.3%). However, this was not statistically different. CPT significantly reduced patients' hospitalization period from 12.88 days to 9.54 days. CPT also significantly reduced the needs to mechanical ventilation in the treatment group compared to the control group (7% vs. 20.3%).[30]

The non-randomized clinical trial presented here demonstrates the clinical efficacy of CP in COVID-19 infected patients and indicates that CP treatment should be considered as a safe and effective therapy for COVID-19 patients. CP therapy substantially improved patients' survival, significantly reduced the hospitalization period and needs for intubation in COVID-19 patients in comparison with the control group.[30]

The RECOVERY and REMAP-CAP trials are both evaluating CP in patients with COVID-19 being treated at 190 hospitals in the UK. Results are expected by the end of 2020, although completion ultimately depends on rates of admission for covid-19 in participating hospitals. What is certain is that high-quality evidence from randomized controlled trials is needed to drive the development of large-scale plasma collection internationally, to inform reliable guidelines for clinical use, and to provide the maximum benefit to patients.[31]

Among patients with severe or life-threatening COVID-19, CP therapy added to standard treatment, compared with standard treatment alone, did not result in a statistically significant improvement in time to clinical improvement within 28 days. Interpretation is limited by early termination of the trial, which may have been underpowered to detect a clinically important difference.[32]

CP therapy could soon be discontinued as a treatment for COVID-19 patients, the Centre has said Tuesday. The therapy continues to be used widely across the country. This, after plasma therapy failed to benefit COVID-19 patients in the largest randomized trial conducted in India, carried out by the ICMR in August. The study found that plasma did not particularly help lower mortality or severity of COVID-19 in patients treated with it.[33] Open-label phase II multicenter randomized controlled trial (PLACID Trial) had revealed 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% CI −0.062–0.078]; risk ratio 1.04, 95% CI 0.71–1.54).[34]

The use of CP from patients who have recovered from SARS-CoV-2 is another example of passive immunity. Antibodies from recovered patients are transfused to a new host with the goal of mediating protection through suspected viral neutralization. However, all viruses are different and thus behave differently. Therefore, we cannot assume or expect that CP will work for SARS-CoV-2 just because it worked for other viruses.[35]

CP therapy for COVID-19 presents with its own unique social and ethical challenges. Although unproven in efficacy, there is a demand for CP therapy, especially in critically ill hospitalized patients. Avoidance of monetary or other coercion is necessary to avoid the exploitation of CP donors. Plasma donation appeals should be only of pro-social altruistic nature and should be completely voluntary. It is necessary to ensure that available plasma is rationed in an unbiased and evidence-based manner. Documentation of outcomes should be mandatory.[36]

CP was not associated with a reduction in progression to severe COVID-19 or all-cause mortality. This trial has high

generalizability and approximates CP use in real-life settings with limited laboratory capacity. A priori measurement of neutralizing antibody titers in donors and participants might further clarify the role of CP in the management of COVID-19.[34]

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