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REVIEW PAPER

Anecdotal use of convalescent plasma: an option in severe COVID-19 patients

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ABSTRACT

Originating from Wuhan, China the Coronavirus Disease (COVID-19) has now achieved proportions of a massive pandemic. The threat posed by the disease has mutilated health systems across the world. Time and again, researchers have strived to discover a definite cure but with no success so far. The time required to propound a vaccine might take a year or more. The healthcare delivery system has employed antivirals, supportive care, and isolation strategies over the months. In this dire scenario, convalescent plasma therapy (CPT) could be a harbinger of hope, given its success in the previous influenza-like illnesses. Though this disease has salient features quite different from classical influenza, yet the symptoms are roughly similar. Plasma therapy experiments conducted throughout different countries yielded variable results, yet not negative. Patient factors, the severity of the disease, and the strain of the virus could have a drastic effect in the course of therapy. India, too, has conducted some successful passive antibody transfusions, but the wide-scale result is not precise. The potential merits can be obscure presently. We have to consider the willingness of the donors at the same time. CPT has emerged to be feasible and might prove to be efficacious in the long run.

Keywords: *Plasma transfusion; passive immunity; passive antibody transfer; SARSCoV-2; pandemic.*

INTRODUCTION

Over the last few months, a lot has changed across the globe. Pneumonia of unknown cause detected in Wuhan, China was first reported to the WHO country office in China on 31st December 2019,[1] which spread rapidly, with cases now affecting 213 countries and territories around the world and 2 international conveyances.[2]

Strangely, the impact of the disease is different in different countries. These differences are attributed to differences in cultural norms, mitigation efforts, and health infrastructure.[3]

Researchers from China's Centre for Disease Control and Prevention (CDCP) describe the clinical findings on more than 72,000 COVID-19 cases reported in mainland China, which reveal a case-fatality rate of 2.3% and suggest most cases are mild, but the disease hits the elderly the hardest.[4]

A total of 81% of cases in the JAMA study were classified as mild, meaning they did not result in pneumonia or resulted in only mild pneumonia, 14% of cases were severe (with difficulty in breathing) and 5% were critical (in respiratory failure, septic shock, and/or multiple organ dysfunction or failure).[4]

The mortality rate of COVID-19 is varied country to country but in India, it is 2.82% among the lowest in the world compared to a global mortality rate of 6.13% on June 4, 2020.[5]

Therapeutic options including antimalarials, antivirals, and vaccines are under study. Meanwhile, the current pandemic has called attention over old therapeutic tools to treat infectious diseases.[6]

Recently much has been talked about the CP in the line of

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treatment of COVID-19 patients around the world recently. Therefore, the authors aim through this short review paper, to explore the feasibility of CP transfusion to rescue severe COVID-19 patients in the current situation.

CONVALESCENT PLASMA (CP) AND ITS RELATED ISSUES

CP refers to the plasma separated from the blood of patients who have recovered from a particular disease. It consists of immunoglobulin IgG or IgM that has the potential to act against the antigens in new active patients. The transfusion of this plasma to an active patient helps in neutralizing the pathogenic microorganism, thus, enabling the patient to mount an immune response against the said pathogen. However, the implementation of a convalescent plasma transfusion program might need comprehensive planning. As we consider its use in the battle against this new strain of coronavirus, it is prudent to review the knowledge from past experiences. There is a lack of evidence for the treatment of COVID-19 and vaccines. Therefore, Classical and historical interventions have re-emerged as options for the control of the disease.[7]

Several pieces of research are still on the run. The world is dealing with a new virus, but no vaccine has developed that could provide a cure. The characteristics of the virus are also not determined. There are wide speculations about the course it would follow.

CP constitutes the first option in the current situation since it has been successfully used in other coronaviruses outbreaks.[6] Therefore, it may be considered as an alternative to the treatment of COVID-19 until an efficient vaccine or drug is universally approved.

Timeline of COVID-19

Before substantial investigations into management could be underway, WHO had to declare the outbreak of pneumonia-like illness of unknown cause detected in Wuhan on 31st December 2019, as a Public Health Emergency of International Concern on the 30th of January 2020. Currently tagged as a global pandemic, it has encompassed all boundaries

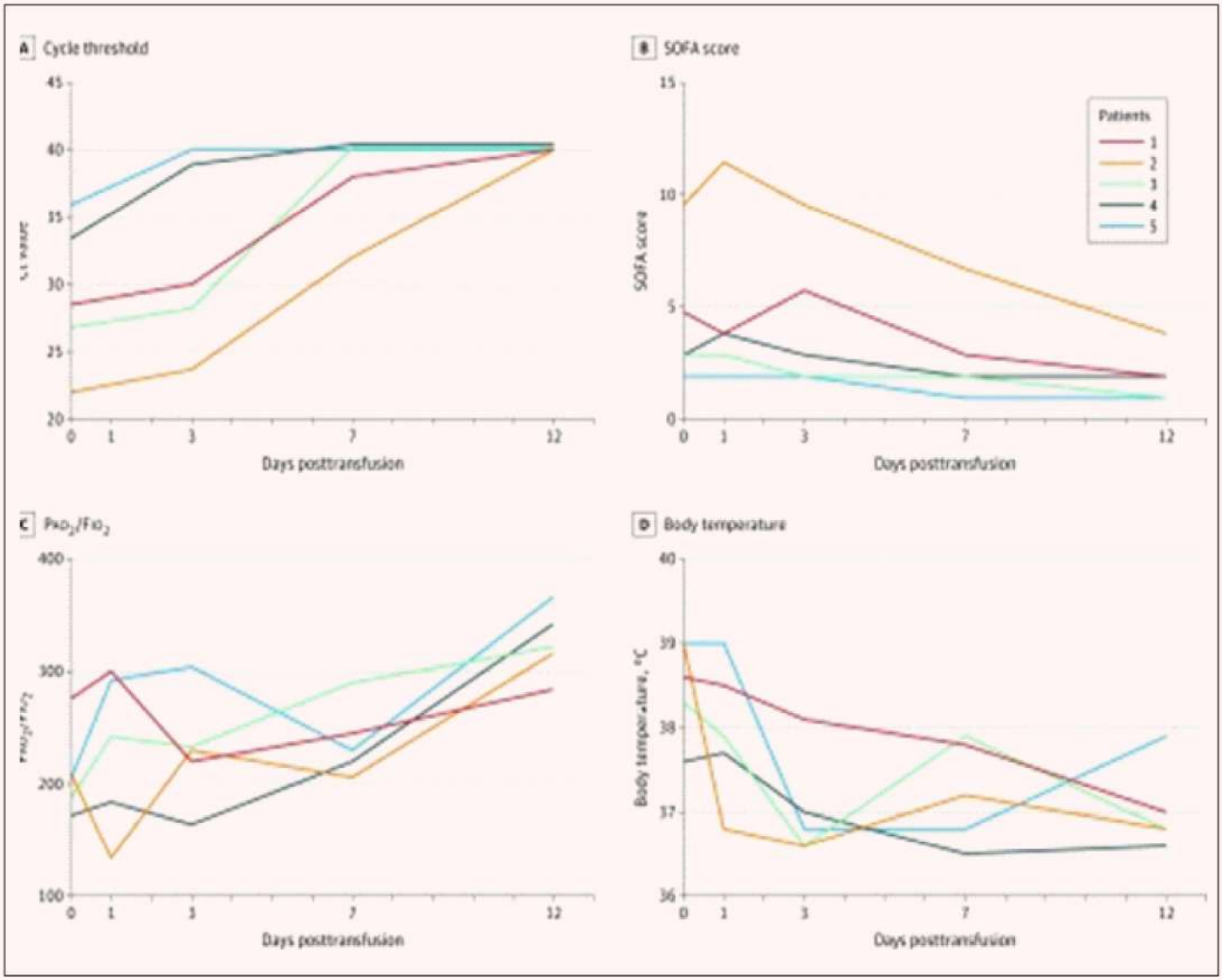

Figure 1 Post-transfusion changes[10]

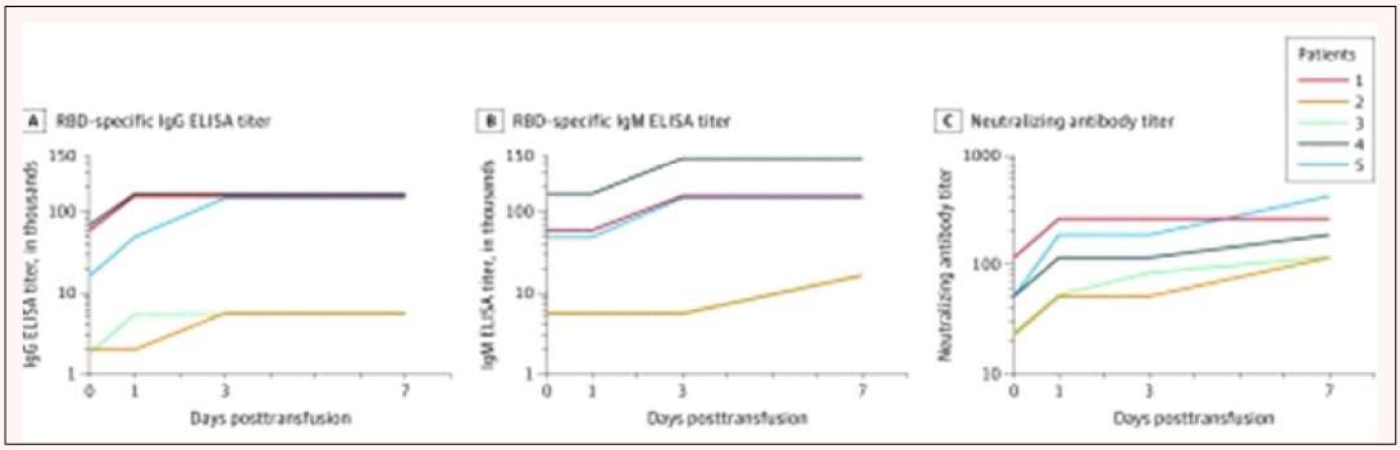

Figure 2 Changes in antibody titers[10]

with 10 million reported cases and 500 thousand deaths.[8]

Health facilities worldwide are facing the worst possible nightmare with huge patient inflow and still no well-determined cure. The virus was identified as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a member of the family of coronaviruses, which were known to cause previous epidemics like SARS-Cov-1 and MERS-CoV. This new disease was named COVID-19 (coronavirus disease 2019) on 11th February 2020.[8]

Trials across the world

Medical research institutes have taken up clinical trials to test many drugs and therapies. Researchers are taking into consideration the proposal of using CPT. Passive immunization for the prevention and treatment of human infectious diseases has been traced back to the 20th century. CP has been a therapeutic modality employed for over a hundred years for various infectious pathogens. The recent Ebola virus outbreak, which had a mortality rate of 8% (as against 2% of COVID-19), had shown the benefits of using CP or convalescent whole blood.[9]

The infectious disease department at Third People's Hospital in Shenzhen, China, took up a study from January 20, 2020, to March 25, 2020. Five COVID-19 positive patients were administered to CP. These patients were in the age range of 36-65 years (2 women). They were receiving mechanical ventilation at the time of treatment, and all had received antiviral drugs along with methylprednisolone. Following plasma transfusion, body temperature normalized within three days in 4 of 5 patients, the **Sequential Organ Failure Assessment** (SOFA) score decreased, and Pao2/Fio2 increased within 12 days (range, 172-276 before and 284-366 after).[10]

SOFA score helps us track a patient's status during their Intensive Care Unit stay to determine to what extent the person's organs are functioning or whether the organs are deteriorating into failure. Furthermore, even viral loads decreased and became negative within 12 days after the transfusion, and SARS-CoV-2-specific ELISA and neutralizing antibody titers increased following the transfusion (range, 40-60 before and 80-320 on day 7). Four patients with Acute respiratory distress syndrome (ARDS) recovered at 12 days after transfusion, and three patients no longer required mechanical ventilation within two weeks. Of the five patients, three got discharged from the hospital (length of stay: 53, 51, and 55 days), and two are in stable condition at 37 days after transfusion[10] (**Figure 1** and **Figure 2**).

Trials in India

Following these studies published across the world, India as well took up CPT trials. India's Central Drugs Standard Control Organisation (CDSCO) permitted the Indian Council of Medical Research (ICMR) to conduct a clinical trial of CP for the treatment of COVID-19.[11] ICMR also submitted a list of institutes that have shown an interest in the proposed trial. This trial was conducted as an open-label, randomized, controlled Phase II to evaluate the safety and efficacy of convalescent plasma in patients with moderate COVID-19 infection.[12]

On April 26th, Max Hospital, Delhi announced that an active case showed "progressive improvement" with CPT. In another very recent advancement, at Blood Bank Sassoon Gov Hospital at Pune, the first CPT has been performed successfully, as announced on 22nd May. The patient was given plasma for two continuous days on 10th and 11th May.[13] These achievements play a monumental role in defining the behaviour of this virus. However, this calls for tremendous foresight and sustainability goals when it comes to using CPT on a large scale for a developing country like India grappling with more than 530 thousand cases recorded presently.

Standard procedures lay down that the convalescent donors must undergo a stipulated pre-donation assessment to ensure compliance with current regulations regarding plasma donation. Currently, convalescent donors between 18 and 65 years are considered subjects. They should be without infectious symptomatology and test a negative for COVID-19 after 14 days of recovery. These tests must be repeated 48 hours later and at the moment of donation. Apheresis is the recommended procedure to obtain plasma. This procedure allows selective collection of plasma, based on continuous

centrifugation of blood from a donor. The efficiency of this technique is around 400–800 ml from a single apheresis donation. This amount of plasma could be stored in units of 200 or 250 ml, and frozen within 24 hours of collection, for use in further transfusions. There is not a standard transfusion dose of CP. In different studies for coronaviruses, the administration of CP ranges between 200 and 500 ml in single or double scheme dosages.[14]

ln addition, donor eligibility criteria for whole blood and plasmapheresis donation will be followed in accordance to the Drugs & Cosmetics Act 1940 and rules 1945 therein (as amended till March 2020).[15]

Currently, the recommendation is to administrate 3 ml/kg per dose in two days. This strategy facilitates the distribution of plasma units (250 ml per unit) and provides a standard option of delivery in public health strategies. Interestingly, it is supposed that plasma from healthy donors provides immunomodulatory effects *via* the infusion of anti-inflammatory cytokines and antibodies that blockade complement, inflammatory cytokines, and autoantibodies.[16]

These factors may influence the immunomodulatory effect of CP in patients with COVID-19. This is because, during apheresis, in addition to neutralizing antibodies, other proteins such as anti-inflammatory cytokines, clotting factors, natural antibodies, defensins, pentraxins, and other undefined proteins are obtained from donors. In this sense, transfusion of CP to infected patients may provide further benefits such as immunomodulation *via* amelioration of severe inflammatory response.[17]

Pro and cons

The pros would include possible clinical efficacy, immediate availability from a large donor pool, relative ease of procuring plasma through current approved methods, and potential cost advantages over some of the more experimental antivirals.[18] Additionally, CP may also offer prophylactic benefits, which could keep our healthcare workers on the frontlines healthy as well as prevent self-quarantine after exposure, which risks decreasing an already overstretched workforce.[19] Clinically, some investigators have attempted to assess the prophylactic potential of convalescent plasma.[20]

The cons also include basic administrative and logistical barriers of identifying, consenting, collecting, and testing donors. Finding donors with the robust humoral response could be a hurdle as well, as not all recovered patients have detectable antibodies in the convalescent stage.[21,22] Besides, the antibodies being highly specific, may not be effective against mutant forms of the viruses. Individual variations have to be covered simultaneously.[8]

Additionally, the current lack of widely available and validated SARS-CoV-2 antibody assays, particularly assays detecting neutralizing antibodies, may hamper identification of ideal donors. Concentrating for neutralizing activity may also mitigate potential viral antibody-dependent enhancement (ADE), a process in which plasma antibodies exacerbate disease by enhancing viral cell entry and viral replication by various mechanisms, some of which have been described in MERS infectious model.[23,24] Theoretically, ADE could exacerbate COVID-19 infection in patients who receive CP from donors who were not tested for SARS-CoV-2 specific neutralizing antibodies. Moreover, the administration of passive antibodies can suppress the recipient's humoral immune system from generating pathogen-specific antibodies thereby leaving an individual susceptible to reinfection.[25]

Pathogen reduction could improve the safety profile of CP. One study found that psoralen treatment did not substantially reduce the titers of anti-EBOV specific antibodies or their neutralizing effect.[26] These findings are promising as they indicate that CP can be safely modified to reduce infectious risk without disrupting possible efficacy. Finally, there are non-infectious hazards of transfusion[27] which include transfusion reactions such as transfusion-related acute lung injury, transfusion-associated dyspnea, transfusion circulatory overload, and serve allergic reactions with associated bronchospasm, all of which could worsen respiratory disease in COVID-19 patients, especially those who are already on supplemental oxygen and/or intubated. Therefore, much more work is needed on CP before drawing definitive conclusions.

Ethical consideration

The WHO Guidelines on drawing blood: best practices in phlebotomy may provide a useful source of information.[28] Informed consent should be obtained for the donation of convalescent whole blood or plasma. The informed consent for transfusion of CP is to be obtained from the patient or the family members as well.[15]

CONCLUSION

The questions which might emerge here is, how well the general population would receive this treatment modality and what recovery rates it might anchor at large. Questions that still might remain unanswered include, whether we will find an established cure or do we have to resort to other strategies. It may take an enormous length of time to formulate a vaccine. Thus, in these times of crisis, plasma therapy can open new doors to recovery, survival strategies and emerge as a beacon of hope. What is required is extensive research and an indomitable spirit. "Medicine is a science of uncertainty and an art of probability" – as William Osler has said.

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