www.CCPP19.org May 16, 2021

Dr. K Vijay Raghavan, Principal Scientific Adviser,
Government of India;

Prof. Balram Bhargava, Secretary DHR;
Director General, Indian Council of Medical Research (ICMR);

Dr. Randeep Guleria, Professor and Director,
Department of Pulmonary Medicine and Sleep Disorders
All India Institute of Medical Sciences (AIIMS):

Re: Response to open letter expressing concerns about convalescent plasma for COVID-19

Dear Colleagues:

We write in response to the recent open letter from 18 Indian health professionals urging India to cease using COVID-19 convalescent plasma (CCP). The undersigned are the leadership group of the **US National Convalescent plasma project (ccpp19.org),** physicians who convened in March 2020 to evaluate the safety, effectiveness, and optimal use of CCP.

We would like to share our experiences from more than a year of work with CCP in the US in the hope that the lessons we have learned will help ease some of the suffering that your nation is enduring. We believe that when used properly, CCP can save lives and should still be considered a treatment option for certain Indian patients with COVID-19.

Convalescent plasma is beneficial in COVID-19 when three basic principles are followed:

First, blood bank screening procedures, including the detection of pathogens, are essential to make CCP as safe as possible. With such precautions, CCP is as safe as standard plasma.[1]

Second, it is advisable to test antibody levels in donors or in the plasma itself prior to infusion and to select only high titer plasma for use in patients. CCP must have enough anti-SARS CoV-2 antibodies to be effective. The US FDA now recommends use of 'high titer' plasma.[2] In studies of thousands of patients, we[3] and others[4] have shown that high titer CCP reduces mortality in patients with CCP compared to recipients of lower-titer plasma. These findings were the basis of the US FDA's Emergency Use Authorization for CCP.

Third, CCP should be given to patients early in the course of disease when viral neutralization is most likely to be effective. The history of CCP use for COVID-19 and other infectious diseases,[5] underscores that its efficacy depends on early use. It is unlikely to be useful later in COVID-19 when endogenous antibodies have already been produced and/or when the disease process is dominated by inflammation. It is in during this later phase of the disease that patients require intensive care unit admission, mechanical ventilation, and corticosteroid and anticoagulant therapy.

An important exception to these principles is in the management of immunocompromised patients who have impaired humoral immunity. In these patients, CCP may be effective at any stage of disease.

The open letter references three randomized trials in which mortality was not reduced by CCP – that of Agarwal et al,[6] the RECOVERY collaborative group,[7] and Simonovich et al.[8] These trials, like nearly all CCP trials, were conducted amid epidemic surges in hospitalized patients with advanced disease.

While the Agarwal et al trial did not meet its pre-specified primary endpoint, it did report significant improvement in clinical status and significantly more viral eradication on day 7 in CCP recipients. In this trial, plasma was collected from mildly ill individuals, 30% of whom had no detectable neutralizing antibody and a similar fraction had neutralizing antibody titers < 1:80. Moreover, 83% of participants had detectable neutralizing antibodies at the onset of treatment, indicating they may not have had early disease.

In RECOVERY, CCP was administered at a median of 9 days after symptom onset in a population with a mortality rate of 24%. Although the trial's pre-specified criteria for efficacy was not reached, odds ratios for CCP receipt were consistently lower in subgroups with earlier/milder illness: not receiving oxygen, not receiving steroids, treated within 7 days of symptom onset, and SARS-CoV-2 antibody seronegative.

It is helpful to contrast the Simonovich trial, which also enrolled severely ill patients, with another study from Buenos Aires, the Libster outpatient trial conducted in elderly COVID-19 patients soon after symptom onset.[9] In the latter trial, CCP reduced progression to severe illness by 48%, and by 73% in patients who received CCP with the highest titers.

Several other studies are of importance. In a recently published RCT conducted in NYC and Brazil - the only trial fully double-blinded by using pre-pandemic plasma in the control group - mortality was reduced by 50% in CCP recipients.[10] Another RCT in India, by Ray et al found lower mortality in CPP treated participants less than age 65, perhaps because the more rapid progression of disease in older patients indicates a need for earlier therapy.[11] Several matched treatment-control studies have shown lower mortality in patients treated with CCP early in disease.[12] Of great concern is the finding of an inverse relationship between CCP use and mortality in the US where more than 500,000 COVID-19 patients have received CCP. This study estimated that reduced use of CCP in the first quarter of 2021 was associated with some 30,000 excess deaths.[13]

Regarding variants, it is very unlikely that circulating SARS-CoV-2 variants emerged from patients treated with CCP. While CCP treatment may select for antibody-resistant variants in immunocompromised patients, such patients constitute an extremely small fraction of SARS-CoV-2-infected persons. Moreover, such patients are treated in hospital settings where transmission precautions are enforced and therefore cannot account for the widespread emergence of variants in the general population. The most likely cause of the emergence of variants is the massive viral replication occurring in the general population where the normal immune response exerts pressure selecting for adaptive mutations to enhance viral survival in the human host.[14] Concerns that CCP induces the emergence of variants is not supported by evidence.

We hope that our experience studying CCP treatment for COVID-19 is helpful to you. If India can safely collect high titer CCP and administer it to COVID-19 patients early in their illnesses, great benefit may accrue to the health of your nation. In addition to saving lives, CCP use may also reduce the need for intensive care beds. If you choose to continue CCP use in India, we hope you will collect data on patients who receive it to add to the growing body of evidence on appropriate CCP use. Your experience can inform the rest of the world about best practices for CCP usage.

Sincerely,

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