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Short communication

Covid-19 convalescent plasma therapy: Analyzing the factors that led to its failure in India

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1. Introduction

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) resulted in a global pandemic in early 2020. Various investigational treatment options were introduced for the treatment of COVID-19 patients, COVID-19 convalescent plasma (CCP) therapy being one of them [1]. The CCP therapy has been used in various viral infectious diseases in the past, such as influenza and Ebola viral disease [2]. Several clinical trials have been conducted in different parts of the world to study the role of CCP therapy in the management of COVID-19 patients [3]. In India, CCP was introduced as part of a multicentre clinical trial (PLACID trial) involving 39 tertiary care hospitals in India in the month of April 2020 [4]. In October 2020, the PLACID trial results were published and it was concluded that the CCP did not decrease mortality in COVID-19 patients. Subsequently, in November 2020, the Indian Council of Medical Research (ICMR) updated the guidelines for CCP therapy in India, which mandated the use of convalescent plasma containing high titre IgG antibody against SARS-CoV-2 [5]. It was also mentioned in the guidelines that CCP therapy should be used only in the early stage of COVID-19 disease (within 3-7 days of symptom onset and no longer than 10 days). However, on 17th May 2021 CCP therapy was removed from the treatment protocols for COVID-19 in India [6]. Various factors can be attributed to the failure of CCP therapy in managing the COVID-19 patients in India.

2. The unscientific use of CCP in patients with severe COVID-19 symptoms

Based on the pathological findings, it has now been established that in patients of COVID-19, the cause of mortality is not directly due to the SARS-CoV-2 virus, rather it is due to the SARS-CoV-2 virus-induced cytokine storm and the systemic inflammatory response syndrome [7]. SARS-CoV-2 generates a specific primary immune response in the body, which then results in the production and release of various kinds of cytokines. These cytokines neutralize the SARS-CoV-2 virus, but also act on the normal tissues and organs, resulting in a cytokine storm [8]. A simplified diagram of the pathophysiology of SARS-CoV-2 virus-induced cytokine storm is shown (Fig. 1). Upon entry inside the human body, it takes a few days for the primary immune response to be produced against the virus [9]. Therefore, if CCP therapy is given during this period, the passive IgG anti-SARS-CoV-2 antibodies can neutralize the virus, prevent the patient's cytokine response, and help reduce patient mortality. In fact, one of the authors himself recovered from COVID-19 after early CCP therapy was done during his treatment due to the falling oxygen saturation. However, the CCP therapy was being prescribed practically by the clinicians in patients who had the severe COVID[HYPHEN]19 disease in association with a fully developed cytokine storm. CCP is not just unlikely to be effective in such patients, it can hardly decrease the patient mortality in such a scenario. In fact, in a tertiary care hospital in India, request for CCP fell overnight by around 50% after one of the blood centres introduced a mandatory requisition form for CCP that demanded information about the various clinical parameters of the patient from the prescribing clinician [10]. Undoubtedly, there has been an unscientific and irrational practice of CCP usage nationwide.

3. Use of CCP without testing for SARS-CoV-2 neutralizing antibody titre

ICMR had clearly mentioned in the guidelines that the convalescent plasma must contain high titre IgG neutralizing antibodies against SARS-CoV-2 [5]. In a large multicenter study in the USA involving 35,322 patients, it was demonstrated that the use of high titre CCP resulted in a significant decrease in 30-day patient mortality compared to low titre CCP [11]. However, many hospitals in India are resource-constrained and many blood centres have no facility to perform a quantitative antibody titre. Hence, at many places the neutralizing antibody titre against SARS-CoV-2 was not being performed, whereas at other places only qualitative rapid card-based methods were used to test for neutralizing antibodies against SARS-CoV-2. Transfusion of CCP lacking high titre neutralizing antibodies against SARS-CoV-2 will not be effective; rather it could end up being more harmful to the recipient.

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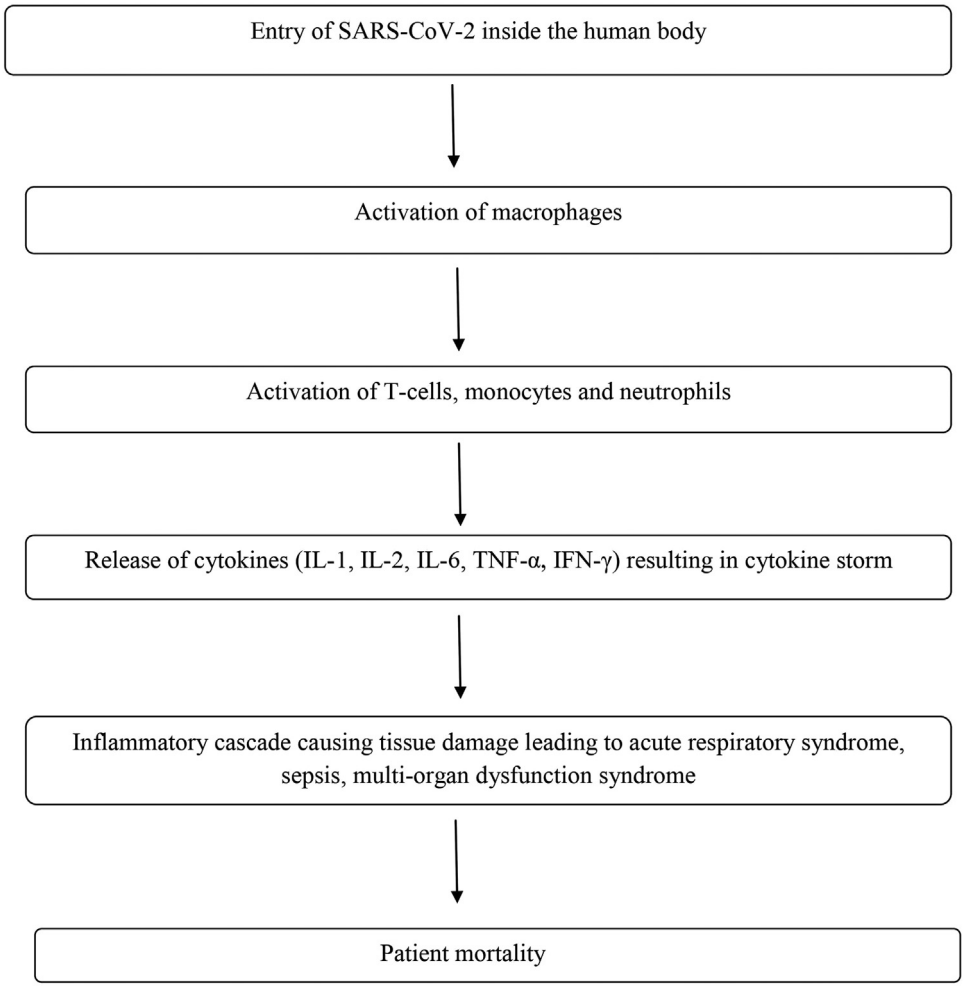

Fig. 1. Pathophysiology of SARS-CoV-2 induced cytokine storm.

4. Concern that indiscriminate use of CCP can generate mutant strains of SARS-CoV-2

In a case report published, it was demonstrated that the use of polyclonal CCP for the management of COVID-19 in an immunosuppressed patient resulted in the generation of viral mutant strain with immune escape potential [12]. In another study, SARS-CoV-2 was co-incubated with CCP containing high titre neutralizing antibodies in vitro. It was seen that the CCP was successfully able to neutralize the virus initially, but the SARS-CoV-2 underwent an evolution and a new variant was produced after 80 days, which then became resistant to neutralization by the CCP [13]. On the contrary, Raturi et al. from India have hypothesized that harvesting CCP from locally recovered individuals could specifically be beneficial for the regionally affected COVID-19 sufferers to help in combating not only the founder SARS-CoV-2 virus but also the geographically confined albeit emerging SARS-CoV-2 variants [14]. Nonetheless, it is still postulated that the indiscriminate use of low titre neutralizing antibodies against SARS-CoV-2 can result in incomplete neutralization of SARS-CoV-2 and could possibly help generate the mutant strains

5. Conclusion

CCP therapy remains a double-edged sword and therefore needs to be used judiciously in the early management of patients who are at an increased risk of developing severe COVID-19 infection. In fact, such patients can be identified at the time of diagnosis by using a novel scoring system which should be rapid, simple, objective and a reproducible assessment tool. Therefore, rather than discontinuing CCP therapy as a management option for COVID-19 patients in India, efforts should have been made to ensure its scientific and rational use. This would have been achieved by the establishment of a hospital transfusion committee (HTC) in every Indian hospital where CCP was being harvested. Moreover, HTC acts as a bridge for better coordination between the clinician and the transfusion medicine specialist and is also involved in the audit of the transfusion triggers and indications for transfusion. However, the scientific evidence of the fact that a low titre CCP can lead to the generation of the viral mutants with immune escape potential must be realized as a serious issue and warrant additional research.

Authors' contributions

Naveen Bansal contributed to the conceptual design, literature search, data compilation, manuscript preparation, editing and review, while Yashik Bansal contributed to the manuscript editing and review. Manish Raturi contributed to the manuscript preparation, editing, review as well as being the guarantor who takes the complete responsibility for the integrity of the work done as a whole, right from its inception to the published article.

Disclosure of interest

The authors declare that they have no competing interest.

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