Perspectives

Has plasma therapy failed in Covid-19 or we have failed in using it properly in India?–Lessons learned through the pandemic

S. Sankha Datta [a,*], R. Chakrabarty [b]

[a] Department of Transfusion Medicine, Tata Medical Center, Newtown, Rajarhat, Kolkata Pin-700160, India
[b] Department of Transfusion Medicine, AMRI Hospital Dhakuria, Kolkata, India

A R T I C L E   I N F O

A B S T R A C T

India has literally been devastated by the second wave of the Covid-19. Convalescent plasma (CP) therapy which was approved initially for Covid-19 in India has been recently excluded from the Covid-19 management protocol. Herein we would like to explore the major challenges for CP therapy in India that we observed during the current pandemic.

© 2021 Société française de transfusion sanguine (SFTS). Published by Elsevier Masson SAS. All rights reserved.

1. Introduction

India has literally been devastated by the second wave of the Covid-19. As of July 15, more than 30 million cases of Covid-19 had been reported, together with more than 400000 deaths. In India, the permission for use of convalescent plasma (CP) in Covid-19 was given in April, 2020 and it was authorized as an 'off-label/emergency use authorization' therapy by the Drug Controller General, India. Subsequently it was also included in the 'Clinical guidance for management of adult Covid-19 patients' by the Government of India [1]. However, after publication of the ICMR-PLACID trial data [2] and the RECOVERY trial results [3] in May, 2021, CP therapy has been excluded as a treatment option for Covid-19 in India [4]. Herein we would like to explore the major challenges for CP therapy in India that we observed during the current pandemic.

1.1. Unavailability of adequate CP donor

The implementation of donor recruitment strategies to maintain a CP repository in a country like India is always challenging where the overall shortfall of the blood supply is highest in the world [5]. In addition to the fear of contracting the infection again by visiting the nearby blood centres as discussed by Al-Riyami et al. [6], the scenario was further worsened by the stringent lockdown measures, with inaccessibility to the public transports, which ultimately restricted donor visit to the blood centres. A well-organized targeted intervention strategy for CP donor recruitment would be ideal for Indian population [7] where in general the self-motivation for blood donation is less. Unfortunately, such strategies were unavailable in most of the blood centres which led to the crisis to get an adequate number of CP donors.

1.2. Inadequate plasma collection facilities

It is a known fact that the CP collection by apheresis is ideal because it optimizes efficiency and frequency of collections. But apheresis derived products are relatively expensive and require technical expertise. Again the apheresis facilities are still restricted to very few blood centres in India predominantly located in the big cities. Considering the large numbers of people living in the sub-urban and rural areas, few resources constrained Indian states took an alternative approach to collect CP derived from the whole blood [8] but that too had certain limitations like decrease in the availability of repeat CP donors due to the 90 days of deferral period between subsequent blood donations.

1.3. Limited testing facilities

There was enormous variability in testing platforms with lack of standardization between blood centres to determine an appropriate titer of SARS-CoV-2 antibodies. Formal neutralization assays (e.g., plaque reduction neutralization tests [PRNT]) were not available in most of the blood centres in India as it requires Bio-safety level 3 laboratories, and sophisticated expertise. Testing of SARS-CoV-2 IgG antibodies to spike protein, receptor-binding domain (S1-RBD) was widely used as a surrogate marker for neutralizing

* Corresponding author.
E-mail addresses: suvro.datta@gmail.com (S. Sankha Datta), dr_ritam@yahoo.co.in (R. Chakrabarty).

antibodies to distinguish between high and low titer CP [9]. Unfortunately, even for that there was lack of agreement as to what antibody titer should be acceptable as appropriate cut off to label a CP unit as high titer plasma. Finally, there were enormous logistical challenges in rural India given very limited laboratory capacity to conduct antibody testing for SARS-CoV-2.

1.4. Inappropriate selection of patients and wrong timing of CP administration

On several occasions CP was administered in critically ill hospitalized patients with prolonged illness, and end-organ damages despite consistent findings and evidence that support administration of CP early relative to symptom onset, preferably within three days of hospitalization [10]. As the primary hypothesis for the efficacy of CP is antibody-mediated SARS-CoV-2 viral neutralization and interference with viral replication, those inappropriate selections of patients and wrong timing of CP administrations together had become the major contributing factor to reduce the impact of CP in Covid-19 management.

1.5. Overemphasize on skewed evidence

The decision to exclude CP from the Covid-19 management protocol was primarily taken in India based on the ICMR-PLACID trial data [2]. Although the PLACID trial did fail to meet its primary endpoint, it showed significant improvement in clinical status and significantly more viral clearance on day 7 in CP recipients. The trial included a large heterogeneous population where 70% of patients who received CP were collected from donors who had a history of mild illness. A significant proportion (30%) of those CP donors either had no detectable neutralizing antibody or had low levels of SARS-CoV-2 neutralizing antibodies which were less than 1:80. Moreover, the median time of patient enrolment after onset of symptoms in plasma arm was day 8 and detectable neutralizing antibodies were found in 83% of patients before CP administration indicating that most of the participants may not have had early disease. Therefore, there was a lack of biological plausibility in the PLACID trial results. Recently the RECOVERY trial data [3] also showed no significant benefits of CP therapy in Covid-19 where CP was administered at a median of 9 days after onset of symptoms. But the trial data did show that odds ratios for CP recipients were consistently lower in subgroups with disease at an early stage.

2. Conclusion

Although multiple Indian studies [11–15] including propensity score-matched case-control studies and randomized controlled trials did show benefits of CP therapy in Covid-19 patients, plasma therapy was prematurely halted without even considering the cumulative evidence. In response to the Covid-19 pandemic, the Mayo Clinic initiated the Covid-19 'Convalescent Plasma Expanded-Access Program' in 2020 under the compassionate use scheme [16] and after the analysis of 3082 patients by Joyner et al. [17] it was concluded that among patients hospitalized with Covid-19 who were not receiving mechanical ventilation, transfusion of CP with higher anti–SARS-CoV-2 IgG antibody levels was associated with a lower risk of death than transfusion of plasma with lower antibody levels. In agreement to their data a recent study from the USA which reported a strong inverse correlation between CP use and mortality per admission also demonstrated population level evidence that CP does reduce mortality in Covid-19 [18]. Another concern that CP therapy might induce the emergence of new SARS-CoV-2 variants is devoid of any evidence. Thus, we suggest that the decision of suspending CP therapy altogether from the Covid-19 management protocol in India should be reconsidered in anticipation of future

waves of pandemic due to emergence of new variants. Finally, we conclude that the collection of high titer CP by using a centralized inventory system and its administration to Covid-19 patients early in their illnesses could significantly benefit India as a nation to manage the ongoing pandemic situation and it may also reduce the bed crisis in the hospitals by decreasing the length of ICU stay.

Disclosure of interest

The authors declare that they have no competing interest.

References

[1] Clinical guidance for management of adult COVID-19 patients. AIIMS/ICMR-COVID-19 National Task Force/Joint Monitoring Group, MoHFW, GoI. https://www.mohfw.gov.in/pdf/ClinicalManagementProtocolforCOVID19 dated27062020.pdf.[Accessed on 01.07.2020].

[2] Agarwal A, Mukherjee A, Kumar G, Chatterjee P, Bhatnagar T, Malhotra P, et al. Convalescent plasma in the management of moderate covid-19 in adults in India: open label phase II multicentre randomised controlled trial (PLACID Trial). BMJ 2020;371:m3939, http://dx.doi.org/10.1136/bmj.m3939 [Erratum in: BMJ 2020 Nov 3; 371:m4232].

[3] RECOVERY Collaborative Group. Convalescent plasma in patients admitted to hospital with COVID-19 (RECOVERY): a randomised controlled, open-label, platform trial. Lancet 2021;397:2049–59.

[4] Clinical guidance for management of adult COVID-19 patients. AIIMS/ICMR-COVID-19 National Task Force/Joint Monitoring Group, MoHFW, GoI. https://www.icmr.gov.in/pdf/covid/techdoc/COVID_Management_Algorithm_ 17052021.pdf.[Accessed on 17.05.2021].

[5] Roberts N, James S, Delaney M, Fitzmaurice C. The global need and availability of blood products: a modelling study. Lancet Haematol 2019;6:e606–15.

[6] Al-Riyami AZ, Abdella YE, Badawi MA, Panchatcharam SM, Ghaleb Y, Maghsudlu M, et al. The impact of COVID-19 pandemic on blood supplies and transfusion services in Eastern Mediterranean Region. Transfus Clin Biol 2021;28:16–24.

[7] Biswas D, Maiti C, Talukder B, Azharuddin M, Saha S, Pandey S, et al. A prospective study on COVID-19 convalescent plasma donor (CCP) recruitment strategies in a resource constrained blood centre. ISBT Sci Ser 2021, http://dx.doi.org/10.1111/voxs.12639 [Published online on 13.05.2021].

[8] Mandal A, Chakrabarty R, Datta SS. Whole blood derived covid convalescent plasma: a practical experience from India. Transfus Apher Sci 2021:103140, http://dx.doi.org/10.1016/j.transci.2021.103140.

[9] Tiwari AK, Negi G, Jaiswal RM, Aggarwal G, Yadav N, Kumar V, et al. Correlation of sample-to-cut-off ratio of anti-SARS-CoV-2 IgG antibody chemiluminescent assay with neutralization activity: a prospective multi-centric study in India. ISBT Sci Ser 2021, http://dx.doi.org/10.1111/voxs.12644 [Published online on 28.06.2021].

[10] Libster R, Pérez Marc G, Wappner D, Coviello S, Bianchi A, Braem V, et al. Early high-titer plasma therapy to prevent severe Covid-19 in older adults. N Engl J Med 2021;384:610–8.

[11] Mahapatra S, Rattan R, Mohanty CBK. Convalescent Plasma Therapy in the management of COVID-19 patients-The newer dimensions. Transfus Clin Biol 2021, http://dx.doi.org/10.1016/j.tracli.2021.04.009 [S1246-7820(21)00070-7].

[12] Ray Y, Paul SR, Bandopadhyay P, D'Rozario R, Sarif J, Lahiriet A, et al. Clinical and immunological benefits of convalescent plasma therapy in severe COVID-19: insights from a single center open label randomised control trial. medRxiv 2020, https://www.medrxiv.org/content/10.1101/2020.11.25.20237883v1 [Accessed on 25.01.2021].

[13] Bajpai M, Kumar S, Maheshwari A, Chhabra K, Kale P, Gupta A, et al. Efficacy of convalescent plasma therapy compared to fresh frozen plasma in severely ill COVID-19 patients: a pilot randomized controlled trial. medRxiv. https://www.medrxiv.org/content/10.1101/2020.10.25.20219337v1.[Accessed on 31.01.2021.].

[14] Budhiraja S, Dewan A, Aggarwal R, Singh O, Juneja D, Pathak S, et al. Effectiveness of convalescent plasma in Indian patients with COVID-19. Blood Cells Mol Dis 2021;88:102548, http://dx.doi.org/10.1016/j.bcmd.2021.102548.

[15] Bandopadhyay P, Rozario R, Lahiri A, Sarif J, Ray Y, Paul SR, et al. Nature and dimensions of the systemic hyper-inflammation and its attenuation by convalescent plasma in severe COVID-19. J Infect Dis 2021:jiab010, http://dx.doi.org/10.1093/infdis/jiab010.

[16] Joyner MJ, Bruno KA, Klassen SA, Kunze KL, Johnson PW, Lesser ER, et al. Safety update: COVID-19 convalescent plasma in 20,000 hospitalized patients. Mayo Clin Proc 2020:1888–97.

[17] Joyner MJ, Carter RE, Senefeld JW, Klassen SA, Mills JR, Johnson PW, et al. Convalescent plasma antibody levels and the risk of death from Covid-19. N Engl J Med 2021;384:1015–27.

[18] Casadevall A, Dragotakes Q, Johnson PW, Senefeld JW, Klassen SA, Wright RS, et al. Convalescent plasma use in the USA was inversely correlated with COVID-19 mortality. Elife 2021;10:e69866, http://dx.doi.org/10.7554/eLife.69866.