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*Editorial*

# Convalescent plasma therapy in COVID-19: Does it merit a deeper probe?

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In recent times, there has been much discussion about the efficacy of convalescent plasma therapy (CPT) in India, primarily due to its relative ease of availability and its favorable effect on other allied conditions.[1-3] During the formative stages of the pandemic, before the use of drugs to fight COVID-19, CPT was considered a silver bullet to improve the symptoms of the disease. However, in the past month, a variety of studies conducted to assess the efficacy of CPT across the world have reported varied results and opinions. In India too, CPT has yielded varied outcomes.[4] While many individual hospitals have seen better results,[1] few trials have advised it only as an adjuvant therapy in end-stage COVID-19 cases,[4] and few others[5] have not reported any statistically significant improvement.

However, it is pertinent to note one grave concern that has surfaced only recently: Current clinical trials, largely driven by the urgency of treatment, are operating at the expense of rigorous scientific and ethical standards. This could pose an immediate risk of imperfect evaluation of CPT safety/compatibility, which then may lead to inconclusive results.

Recently, Indian Council of Medical Research declared the outcomes of the PLACID trial involving 39 hospitals across 14 states.[5] The finding suggested no benefit of CPT in reducing the mortality or arresting progression of the disease.[5]

According to a recent study published in Lancet,[6] the median time to negative PCR is 20 days. However, in the ICMR PLACID trial, less than 54% patients have negative PCR by day 7.[5] This means that patients have been infused plasma on a median of 14 days, which is conceptually late. Hence, it necessitates the clarification for the median day of infusion of CP since the onset of symptoms. As per the Mayo Clinic data,[7] infusion within 3 days of admission is useful, and this stipulation has not been practiced uniformly in India.

In the methods of the PLACID trial,[5] details of nAb titers and IgG in the infused CP need to be clarified. The optimum titers play a pivotal role for the success of CPT; in the ICMR study, they have only mentioned that the titers were detectable but the % of high, moderate and low titers has not been mentioned.

on the question of neutralizing antibody titers, IgG titers are typically associated with the severity of disease[8] and decline in the early convalescent phase[9] in less severe forms of the disease. In the PLACID trial,[5] most of the donors (94.2%) had mild disease. Moreover, the fact that antibody titers were not measured in CP before transfusion, due to lack of validated and reliable

commercial tests for qualitative or quantitative antibody measurement, could be another key confounding factor.

The heterogeneity of the PLACID trial[5] across its 39 study sites, especially in the severity of disease of enrolled participants, estimation of nAB (timing and method), and the "Standard of Care," could impinge on the reliability of the study data.

Variation in the antibody titers may result in heterogeneity in CP potency, and studies using conventional treatment as controls instead of placebo may complicate our evaluation of CPT efficacy. Although this has ethical implications, it may have a bearing on the statistical outcome.

Further, in the ICMR study,[5] 67.9% of CPT group are PCR negative by day 7 when compared to 54.6% of non-CPT. This perhaps can be considered as beneficial impact of CPT which helps in decreasing community transmission. This data can also be used to tighten the discharge criteria to enable faster discharges, thus improving the availability of beds for a worsening pandemic.

Notably, the dosage of CP administered is also variable. Some trials[10] are administering doses as high as 600 ml, in single infusions or divided doses, up to five transfusion sessions. The consensus about effective CP dose is yet to be elucidated.

If we carefully examine the existing global preliminary data, they indicate a positive outcome of CPT for management of critically ill patients diagnosed with COVID-19. Hence, the need of the hour is to conduct further randomized controlled trials with larger sample sizes and homogeneity of data. Moreover, standardized diagnostic tools are required to evaluate the real efficacy of CPT in greater detail. The initial data of Mayo Clinic provides robust evidence that transfusion of convalescent plasma is safe in hospitalized COVID-19 patients and credibly supports the notion that early administration within the clinical course is more likely to reduce mortality. CPT can hence be safely used as an effective adjuvant therapy against COVID-19 associated mortality.

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