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Cite this as: *BMJ* 2020;371:m4072

<http://dx.doi.org/10.1136/bmj.m4072>

Published: 23 October 2020

Convalescent plasma is ineffective for covid-19

Lessons from the Placid Trial

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Convalescent plasma generated great enthusiasm in the earliest days of the coronavirus disease 2019 (covid-19) pandemic because of a plausible mechanism of action,¹ its 100 year history of use in the treatment of other infectious diseases,² and rapid availability from voluntary donors.³

In the linked PLACID Trial, Agarwal and colleagues (doi:10.1136/bmj.m3939) evaluated convalescent plasma for the treatment of moderate covid-19 in patients admitted to hospital in India.⁴ Strengths of the study included a primary “hard” outcome meaningful to patients, “real world” patient enrollment with no exclusions for comorbidities, careful attention to donor selection and safety screening of donated plasma, post facto quantitative testing of antibody titers in all plasma samples, assessment of secondary patient outcomes, and evaluation of the efficacy of the subsample of plasma donations that contained detectable titers of antibodies to severe acute respiratory coronavirus 2 (SARS-CoV-2), the virus responsible for covid-19.

In prespecified, intention-to-treat analyses, the PLACID Trial investigators found no net benefit associated with convalescent plasma in patients admitted to hospital with moderate covid-19. The composite primary outcome (progression to severe disease or all cause mortality at 28 days) occurred in 19% (44/235) of patients in the intervention arm and 18% (41/229) of patients in the control arm (risk ratio 1.04, 95% confidence interval 0.71 to 1.54). Restricting the comparison to the subset of patients who received plasma with detectable antibody titers did not change the outcome.⁴

Small beneficial effects were found for resolution of shortness of breath and fatigue. However, these results should be interpreted with caution, because the trial was not blinded, so knowledge of treatment status could have influenced the reporting of subjective symptoms by patients who survived to day 7.

The primary hypothesized mechanism of benefit from convalescent plasma is through direct antiviral action of neutralizing antibodies on SARS-CoV-2 RNA.¹ In the PLACID Trial, a statistically significant 20% higher rate of conversion to a negative result for SARS-CoV-2 RNA occurred on day 7 among patients in the intervention arm.

In plain English, this means that convalescent plasma did exactly what the investigators hoped it would do, yet there was no net clinical benefit to patients. Why might this be the case?

The most common use of therapeutic plasma, which contains more than 1000 different proteins,¹ is for the management of acute bleeding and complex

coagulopathies.⁵ Despite the presence in plasma of anticoagulation factors such as antithrombin and protein C, the net effect of plasma is prothrombotic.⁵ Immunoglobulin therapy, which is derived from whole plasma, is subject to a US Food and Drug Administration warning about the risks of thrombosis, particularly in older patients, those with cardiovascular risk factors, and those with hypercoagulable conditions.⁵

It is now widely recognized that covid-19 is a life threatening thrombotic disorder.^{6–8} An excellent recent pathophysiology synthesis concluded that “SARS-CoV-2 not only produces an inflammatory and hypercoagulable state, but also a hypofibrinolytic state not seen with most other types of coagulopathy.”⁷ Most recently, plasma from convalescent covid-19 patients has been shown to directly cause endothelial cell damage *in vitro*.⁹

Following suggestions of benefit from observational studies, convalescent plasma was given to more than 100 000 patients admitted to hospital with covid-19 in the US between April and August—under the FDA’s expanded access treatment protocol.¹⁰ The authors of the safety update on the first 20 000 recipients said their results provided “robust evidence that transfusion of CP [convalescent plasma] is safe.”¹¹

However, close examination reveals that adjudication of the “relatedness” of serious adverse thrombotic and cardiac events was conducted by the treating physician, with no defined protocol and no independent review.¹¹ Most of the 677 cardiac events (88.2%) and 113 thrombotic events (66.3%) were judged not to be related to transfusion, and these events were therefore excluded from the reported adverse event rates.

Thrombotic events were not a prespecified outcome in the PLACID Trial and were not reported. Nonetheless, it is notable that progression to severe disease or death occurred in 20% (13/64) of patients who received convalescent plasma with no detected neutralizing antibodies compared with 18% (41/229) of controls.

The PLACID Trial was a rigorous randomized controlled study on a topic of enormous global importance, ethically designed and implemented given the contemporaneous state of scientific knowledge about SARS-CoV-2.⁴ With publication of the findings, the bar has been raised for all ongoing and future trials.

The following recommendations should be carefully considered by both safety monitoring and institutional review boards in light of the PLACID Trial findings: First, the potential harms of the non-immune components of convalescent plasma

should be rigorously investigated, especially prothrombotic risks, and considered when choosing trial outcomes and participant exclusion criteria. Second, only donor plasma with detectable titers of neutralizing antibodies should be given to trial participants, to ensure that the potential for benefit exists for all intervention arm patients. Third, double blind designs with sham procedure controls should be the gold standard for future trials. Low risk sham procedures can be ethically acceptable under prescribed conditions.¹²

Fourth, non-immune plasma should not be used as a control intervention, because of potential harms and availability of lower risk alternatives such as normal saline.

The desperation engendered by covid-19 demands that we strongly resist the urge to succumb to pandemic research exceptionalism.¹³ High quality clinical research must be an integral part of a coordinated international response.¹³ Specifically, scientific validity is a necessary component of ethical research.¹⁴ Low quality research not only wastes scarce resources, it is also inherently unethical.¹⁴

Finally, when multiple research teams require participants, triage committees are needed to direct recruitment away from low priority, duplicative, or underpowered trials with little potential for usable findings.^{13,15} Institutions must guarantee that patients with covid-19 are informed of all available trial options and assured autonomy in their decisions about participation.¹⁵

Competing interests: The BMJ has judged that there are no disqualifying financial ties to commercial companies. The authors declare the following other interests: EBP is the director of The COVKID Project, which conducts covid-19 surveillance for children and teenagers.

The BMJ policy on financial interests is here: <https://www.bmj.com/sites/default/files/attachments/resources/2016/03/16-current-bmj-education-coi-form.pdf>.

Provenance and peer review: Commissioned; not externally peer reviewed.

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