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REVIEW

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Convalescent plasma and COVID-19: Time for a second—second look?

Michael J. Joyner[1] | Rickey E. Carter[2] | DeLisa Fairweather[3] | R. Scott Wright[4]

[1]Department of Anesthesiology & Perioperative Medicine, Mayo Clinic, Rochester, Minnesota, USA

[2]Department of Quantitative Health Sciences, Division of Clinical Trials & Biostatistics, Mayo Clinic, Jacksonville, Florida, USA

[3]Department of Cardiovascular Diseases, Mayo Clinic, Jacksonville, Florida, USA

[4]Department of Cardiovascular Diseases, Mayo Clinic, Rochester, Minnesota, USA

Correspondence
Michael J. Joyner, Department of Anesthesiology & Perioperative Medicine, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA.
Email: joyner.michael@mayo.edu

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Abstract

In this short narrative, we highlight some of our experiences leading the US Convalescent Plasma Program at the beginning of the pandemic in the spring and summer of 2020. This includes a brief summary of how the program emerged and high-level lessons we learned. We also share our impressions about why convalescent plasma was used at scale in the United States, early in the pandemic and share ideas that might inform the use of convalescent plasma in future outbreaks of novel infectious diseases.

KEYWORDS
convalescent plasma, pandemic preparedness, real-world evidence

Convalescent plasma (CP) has been used worldwide to treat COVID-19 since the start of the pandemic. In the United States alone, more than 500 000 hospitalised COVID-19 patients have received CP since March 2020.[1] CP use in the United States started as compassionate use treatments for individual patients who were severely ill in the intensive care unit (ICU). The plasma was obtained by blood centres across the United States, who used approaches based on their experience with recruitment techniques and consistent with Food and Drug Administration (FDA) guidelines to capture CP donors. Officials at the US FDA quickly realised a single patient approach to treatment would lead to hundreds of individual emergency use IND applications (e-IND) with little organisation, safety oversight or coordination. Leadership at the US FDA contacted Mayo Clinic scientists to organise a national expanded access program (EAP), which became the US Convalescent Plasma Program (USCPP). The USCPP utilised an expanded access regulatory mechanism coupled with a research design that enabled the systematic collection of safety and high order outcome data on all patients enrolled into the expanded access program. The US Convalescent Plasma study was an analysis of data extracted from the USCPP organised as a real-world evidence (RWE) approach.[2] The goals were to evaluate safety directly and efficacy through several potential mechanisms including outcomes by neutralising antibody titre, timing of administration and electronic health record studies (to add a control group of patients not treated with convalescent plasma). These study elements were designed in close collaboration with the US FDA. The use of a randomised clinical trial mechanism was not endorsed by the FDA at the start of the USCPP in April 2020, so a RCT was not an authorised design option despite the criticisms post facto by many for not choosing a RCT Design.[3] The USCPP was facilitated by initial funding from Mayo Clinic and later by full funding from the US Biomedical Advanced Research and Development Authority (BARDA). There were substantial non-financial contributions from the public and private sector, numerous individuals, and media programs to promote donor awareness campaigns. We also acknowledge substantial contributions by specific community partners and the US Blood Banking network. For those interested, a more detailed narrative history is available here.[4]

The FDA expanded access mechanism was ideal for CP and the COVID-19 pandemic because it allowed the use of an experimental therapy in a life-threatening situation where limited treatment options existed.[5] This regulatory mechanism also provided access to CP for hospitalised patients with COVID-19 who were being treated at non-academic, non-research facilities with minimal regulatory barriers to initiating the protocol across the country. The original vision for the

USCPP was a modest sized demonstration project, expecting at most 5000 patients with a focus on providing broad access and understanding if CP was safe. Safety was defined primarily by the incidence of transfusion-related adverse effects within 4 h of transfusion. To monitor safety, a real-time data analytic workstream was established to generate weekly Data and Safety Monitoring Board reports. These safety reports were reviewed by a physician panel that included experts from critical care, transfusion medicine and clinical trials. Historical incidence of transfusion-related adverse effects were used to frame comparisons regarding the incidence observed in the treatment of COVID-19.

From a regulatory perspective, the study design allowed the evaluation to be conducted with a bioethical regulatory framework, with safety, ethical and regulatory oversight. All participants were enrolled using a standard informed consent process approved by the central IRB without substantial local modifications. All physicians administering CP had to be registered as local physician investigators with a valid medical licence, and all hospital and acute care sites where CP was administered had to utilise the study's central IRB. Sites with their own IRBs deferred to the central IRB. The acquisition of CP and its delivery were not part of the research process. The national standards of care and existing medical system processes for blood products were followed with close collaboration by national and local leaders in the blood banking community, again designed to maximise the safe and expedited collection and distribution of CP.

Utilisation of CP tracked the disease incidence across much of the country.[6] It is presumed that the high utilisation was largely due to a lack of other COVID-19 evidence-based life-saving therapies and broad, non-restrictive inclusion criteria coupled with the published safety data on CP. Enrolment ultimately included over 105 000 consented participants with over 94 000 receiving CP prior to September 2020. Additionally, hundreds of thousands more patients were treated with CP when the USCPP transitioned to an Emergency Use Authorization (EUA) in late August of 2020.[7] The sudden and rapid growth of CP use in the United States significantly beyond initial expectations occurred for multiple reasons including (1) lack of any established therapies which reduced mortality in patients who were perceived to be at high risk for disease progression and/or death, (2) the history of CP as an effective therapy in patients with acute respiratory illnesses associated with pandemics,[8] (3) anecdotal reports by physicians, families and the media of efficacy, (4) an intense desire by the health care community and the public writ large to offer all potentially efficacious treatments with minimal safety concerns, (5) the rapid spread of the infection which outstripped other available therapies, and (6) coverage of the cost of collection and production of CP at blood centres allowed the product to be provided to hospitals at no cost.

The FDA charge to evaluate efficacy with the USCPP included assimilation of data from large, non-public datasets and analyses using neutralising antibody titres (nAb) from donated plasma, when such diagnostic tests were available on stored residual aliquots from the donated CP. It was expected that we would explore efficacy in late 2020 or into 2021 (Marks P, US FDA personal communication). In the meantime, as 2020 progressed, matched control studies, some early small RCTs, and case reports in patients who could not generate endogenous antibodies to COVID-19 infection began to appear and generally showed at least some signals of efficacy.[9,10] The massive scale of the USCPP also increased pressure for us to see what efficacy signals might be embedded in our growing registry even though it lacked a "traditional" control arm. There was also significant interest from policy makers about any potential efficacy given the substantial public funding supporting the program. In this context, after in this context collaboration with officials at the US FDA, we hypothesized that 'early' treatment of patients with 'higher nAb plasma' would be associated with reduced rates of mortality. All the CP utilised in the USCPP was distributed to sites and patients without any prior knowledge of the nAb titre value. Thus, the distribution of CP without a prior knowledge led to random distribution of 'high titer nAb' plasma, 'low titer nAb' plasma and 'intermediate titer nAb'. Since neither the distributor of plasma nor the treating clinicians had knowledge about nAb titre levels within the CCP being administered. All of us were blinded as to the treatment allocated since the nAb titres had not been defined prior to administration of CCP. Because antibody testing of CP units was not available early in the pandemic, none of the treatment decisions were based on nAb titre knowledge. Thus, we were able to compare mortality across these titres comparing low titre to high titre nAb where we found a positive benefit from the high-titre nAb CP as hypothesized.[11]

By mid-summer 2020, early signals of efficacy were emerging from these efforts. Prior to elaborating further on those, it is helpful to understand some terminology. The US Convalescent Plasma study was conducted on the "expanded access" regulatory pathway. This pathway allows for compassionate use of investigational products outside of standard clinical trials. Like other clinical studies, expanded access protocols require standard research principles (e.g. consent, presumed favourable risk to benefit ratio, collection of and monitoring for safety and adverse events). An emergency use authorization (EUA) is a higher level of regulatory approval, which can be granted during a public health emergency.[12] In an emerging pandemic such as the COVID-19 pandemic, very few treatments can be fully tested and approved using the regular regulatory pathways for drugs and devices. To avoid catastrophic loss of life while the evidence is accumulated, the EUA pathway allows for products where it is 'reasonable to believe the product may be effective' and that have 'known and potential benefits [that likely] outweigh the known and potential risks' to be approved. FDA's issuance of the EUA for CP in August 2020 was based on, in part, the data that was rapidly gathered by the US Convalescent Plasma study.[13]

We suggest that those who identified limitations in our study design and analysis recognise the randomised aspect of the analysis of high-titre nAb CP, as well as the constraints we faced early in the pandemic of gathering a limited dataset from extraordinarily busy health care providers caring for critically ill patients during a global crisis. We were not afforded the customary approach to a RCT, with time for site training, investigator meetings, GCP training/certification and availability of trained monitors who could travel for site training and site monitoring. Many of our site PIs were working in conditions of

extreme duress—at a time when the vast majority of the world's population was sheltering in place. These front-line providers were facing an uncertain future with a virus that was incompletely understood with regard to risk, spread and mitigation. We captured the essential safety, demographic and vital status data to answer the primary goal—an assessment of safety with the finding that CP was safe to use. Efficacy was pre-planned but was a secondary goal with our study. As we look back on how and when these and other signals of efficacy for CP emerged and reflect about what we have learned for any potential 'next time' or simply to improve large scale trials, it is also important to address the shortcomings and criticisms related to how the CP story evolved in the United States.

The first lesson is that CP will almost always be the first antibody therapy available to treat an outbreak of a novel infectious disease. In this context, optimal use of CP should follow the historical principles of successful antibody therapy that have emerged during the late 19th century and prior to World War II.[14] Namely that (1) early treatment with plasma (2) that has sufficient antibodies specific for the pathogen is essential. Since the initiation of the USCPP, several important RCTs have been conducted for CP as a treatment for COVID-19 with a number of 'negative' studies that showed no harm but no benefit and a number of studies that found reduced mortality.[15,16,17,18] A careful analysis of all studies reveals that even so-called 'negative' trials show signals of efficacy when data are analysed using high titre plasma that is used early in the course of disease.[19,20,21] Some of these studies evaluated CP in a RCT in patients that we saw no signal of efficacy and contrary to all historical evidence. One must rhetorically ask why ethical boards approved such experimental plans despite the likely result of futility? An extension of this lesson is that one must be mindful of the source of CP that is used in the treatment. Matching CP with the circulating regional variant, something many initial clinical trials were not able to do, was later shown to be important.[22]

The second lesson is that assay systems are necessary to understand the properties of CP and other elements of the immune response generated against a novel infectious agent. In this context, if assay systems were developed against a suite of "model" viruses it should be possible to have adaptable tools that could be quickly modified by experts in assay development. These tools could then be used at scale to quantify the immune response to the novel agent, and antibody titres in CP from recovered patients. Basic research on the CP itself may reveal individuals that develop the optimal protective immune response (antibody and other factors) versus those that are more susceptible to disease progression, so that targeted immune strategies can be developed to prevent severe disease and death. If a nationwide expanded access program for CP is used in a future pandemic it may relatively quickly reveal differences in susceptibility across populations that could be used to inform strategies that reduce infection. Thus, platform technology needs to be developed for diagnostic testing and assay systems as well as vaccines in anticipation of CP use the *next time*.

The third lesson or lessons all relate to questions about what it takes to conduct randomised controlled trials in a pandemic. Beyond obvious regulatory issues like streamlined and coordinated approaches to IRB oversight, informed consent and data management—at least 11 other important questions need to be considered:

1. What is the use case under study—prophylactic, or early versus late disease?
2. What simple endpoints might give definitive answers in a chaotic situation with maximally stressed hospitals and staff?
3. What would be the right comparator?
4. In a rapidly changing treatment landscape, is it reasonable to hold all treatments identical except for the randomization of comparator versus plasma?
5. How do you characterise the plasma and know what dose to give?
6. How should (or even should) CP be prepositioned ahead of time—especially when regional variation in plasma may impact local efficacy?
7. As the disease erupts, waxes and wanes regionally, how do you anticipate where the sites will be ahead of time? What site selection criteria are essential for initial screening since ultimate participation will depend on disease incidence?
8. How do you train the study staff, especially when travel is suspended?
9. How do you monitor trial, after conduct especially when travel is suspended?
10. How do you overcome ethical and perceptual issues about randomization with a deadly illness, especially in scenarios where the preliminary data are returning some signals of efficacy?
11. In a huge country with diffuse approaches to medical care, what do you tell patients, loved ones and dedicated physicians seeking promising therapies in non-research settings?

All the considerations and caveats above relate to larger questions concerning 'did the US jump the gun on plasma use early in the COVID-19 pandemic before doing trials' instead of deploying CP in a more systematic way? In this context, the early establishment of CP safety by the EAP (later confirmed by large RCTs) demonstrated that CP did no harm.[23,24] Next, when the mosaic of data from all sources is considered, signals of efficacy consistent with the principles of antibody therapy noted earlier are clearly present for CP and COVID-19.9,10 So-called 'Real World Data' indicates that tens of thousands or even more than 100 000 lives were saved.[1] Additionally, there is strong observational evidence for CP efficacy in patients with conditions that limit their ability to generate endogenous antibodies.[25,26] Evidence for this use case may never have occurred or occurred later in the pandemic if only classical trials of CP for COVID-19 had been conducted. We also note that non-academic treating physicians seemed to have figured out the early use case for CP because treatment of mechanically ventilated patients dropped dramatically in the first several months of the USCCP prior to studies establishing the likely futility in late disease.[27] Finally, nothing prevented large academic centres and

networks from *not* participating in the USCCP and EUA for CP, and nothing prevented them from conducting traditional trials—in fact several did—there were certainly enough patients to sustain both. In fact, as 2021 progressed numerous RCTs, as highlighted by the Johns Hopkins' early outpatient treatment trial, demonstrated efficacy with early administration or high titre CP.[28] Finally, during the second and third years of the pandemic the issue of "escape" by newer variants has rendered many monoclonal antibody therapies ineffective. In this context, CP from donors that have been both vaccinated and recovered from infection generates a very high titre and may be especially useful as replacement therapy in the immune suppressed.[29,30] However, the cost of production and reimbursement issues remain a concern in the United States.

So, when there is a *next time* will it be possible to provide broad based access to a promising therapy like CP and at the same time study it in a controlled fashion? The short answer is yes, but the longer answer is not without some planning and intentionality of design. If we had waited the months required to set up a "proper" series of trials, tens of thousands of additional deaths or more would have occurred. If CP treatment had been focussed on early use from the outset and the CP administered had been better characterised, perhaps even more lives could have been saved. The good news is that we showed that it is possible to launch a successful nationwide program to make CP available during a crisis and from the lessons we have learned improvements can be made.

AUTHOR CONTRIBUTIONS

MJJ drafted the manuscript with subsequent detailed input and feedback from the co-authors.

CONFLICT OF INTEREST

The authors have no financial conflicts.

DATA AVAILABILITY STATEMENT

This is a brief review/commentary no original data included.

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