



Reviewing the Ethical Concerns of the Convalescent Plasma Therapy in COVID-19

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Abstract

Keywords

- ▶ asymptomatic carriers
- ▶ ethical concerns
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- ▶ blood safety
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- ▶ COVID-19
- ▶ regular screening

The understanding of coronavirus disease 2019 (COVID-19) is evolving periodically. There is also a marked increase in COVID-19 patients' demand for the provision of COVID-19 convalescent plasma (CCP) therapy. With the review of the literature, the stage of speculation is quickly moving towards conformity, with the interim guidelines given by the Food and Drug Administration (FDA) in the United States, United Kingdom's blood transfusion services, Saudi's FDA, and the Indian Council for Medical Research, in addition to the European health authorities. It is prudent to address the ethical concerns that merit consideration while harvesting and utilizing CCP as a therapeutic tool in local hospital setting.

Introduction

In the month of December 2019, a novel coronavirus (nCoV) was reported from Wuhan, China.¹ This nCoV is known to cause coronavirus disease 2019 (COVID-19), renamed as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). With deaths accounting in millions, this virus quickly spread across the globe. In fact, on January 31, 2020, the World Health Organization (WHO) declared this pandemic as a public health emergency of international concern (PHIEC).² It may be observed in a variety of cases, from the asymptomatic carrier condition to a fully developed active respiratory illness. The COVID-19 pandemic has also affected the blood community adversely. Raturi and Kusum have documented a reduction in the number of blood donors, collections, demands, and issuances during this

pandemic.³ Additionally, blood safety concerns merit a logical consideration, because they include blood donors who are without any symptoms and arrive at the blood centers as fairly healthy individuals. These symptomless, innocent blood donors (IBD), are entirely oblivious of their viral status and, therefore, the published self-assessment tools can be utilized prior to their whole blood donations (WBDs).⁴ These IBDs may, therefore, pose a significant health concern to not only the blood transfusion services (BTS) but also the entire blood community. While the WHO stated in 2003 that there were no transfusion-borne cases of SARS-CoV, the theoretical risk of the transfusion of this nCoV remains a viable possibility. The current recommendations are largely based on the recent directives from the American Association of Blood Banks (AABB), but a cautious approach is crucial now more than ever, including a rigorous donor scrutiny.⁵ The Food

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and Drug Administration (FDA) has also unanimously implemented the use of the COVID-19 convalescent plasma (CCP) by apheresis from recovered patients on a case-by-case basis, provided that they fulfill the qualifying criteria for such a donation.⁶ When it comes to the WBD, the AABB and the FDA evaluate these individuals according to the established eligibility requirements for their donation unless they have been diagnosed with flu-like diseases. In addition, regular screening of blood donors, in combination with “mini-physical,” helps deter any such symptomatic donors from giving blood.⁷ CCP, on the other hand, is harvested from recovered COVID-19 patients, which is helpful in eradicating the culprit pathogen not just from the plasma but from other tissues as well, particularly in the respiratory system. Although the use of good-quality plasma is reasonably safe, the existing global compliance with healthy donors’ plasma usage according to the established recommendations is explicitly moderate to low in some developing countries. However, innumerable flaws are seen while ordering this specific blood component. Raturi et al have shown that its prophylactic use is not only doubtful but also unjustified, with the exception of clinical use, such as in coagulopathy with bleeding, prior to any invasive treatment and reversal of the effect of anticoagulants.⁸ In addition, CCP therapy is historically well-known to have anticipated benefits in COVID-19 patients. The recommendations in this regard have recently been revised by the U.S. FDA, UK BTS, Saudi FDA, and the Indian Council for Medical Research (ICMR), in addition to the European health authorities.⁹ While the interim criteria for donor eligibility have already been found by the U.S. FDA, United Kingdom BTS, Saudi FDA, ICMR, and other regional health authorities in conjunction with the process details and eligibility criteria for the recipients, these recommendations do not enlighten us much about the legal and ethical concerns that must be addressed while harvesting and using CCP as a therapeutic tool.

Historical Aspects of CCP Therapy

Historically, long before vaccines became available for most highly infectious diseases, CCP was used in the cases of polio, measles, mumps, and influenza.¹⁰⁻¹³ A meta-analysis of 1,703 patients who suffered the influenza pandemic during the 1918 Spanish flu reported a diminished mortality rate of CCP recipients.¹⁴ Conversely, in a double-blinded, randomized, placebo-controlled trial for those diagnosed with influenza A, CCP was not found to be superior to placebo.¹⁵ Moreover, 84 Ebola virus patients receiving CCP therapy without the established levels of neutralizing antibodies appeared to have little survival benefit.¹⁶ During the preceding SARS coronavirus outbreaks between 2002 and 2004, CCP was also investigated. In a study undertaken by Cheng et al, with 80 patients, it was found that patients receiving CCP had better outcomes, that is, early hospital discharge, as compared to patients receiving CCP after day 14 of the infection (15.6 vs. 58.3%; $p < 0.001$).¹⁷ Due to the lack of adequate treatment for the outbreak of COVID-19, clinical trials of CCP therapy have recently been approved by the U.S. FDA,

with enhanced access under the category of single-patient emergency investigational new drug, and by the ICMR as an “off-label” therapy.¹⁸

Role of Blood Transfusion Services

Addressing the Ethical Concerns of Blood Donors

In all circumstances, the harvest of either WBD or CCP must be voluntary and nonremunerated as published in the ICMR guidelines; no coercion should be imposed on the donor, including indemnity, which is an obligation by the patient party to provide compensation (either in cash or kind) for either a WBD or a CCP donation. Besides that, the informed consent and confidentiality of the donor merit ethical consideration. Further, in compliance with the internationally established and local/regional guidelines, all processes, including apheresis, must be defined and performed appropriately. In principle, all CCP donors should qualify as regular healthy blood donors based on history (including recent recovery from COVID-19), physical examination, and rigorous testing for transfusion-transmitted infection (TTI) markers according to local guidelines. Collections and their justified use are worthy of critical evaluation through regular audits. Additionally, product wastage must be avoided by all possible means.¹⁹

Facilitating Eligibility, Recruitment, and Transportation for Donors

The U.S. FDA, United Kingdom BTS, Saudi FDA, ICMR, and other regional health authorities define the criteria for one’s eligibility to be a CCP donor as follows:

- Laboratory evidence of COVID-19 disease is confirmed by either a nasopharyngeal swab and/or a positive serological test for SARS-CoV-2 antibodies.
- Complete symptom resolution 28 days before apheresis at the earliest.

Before apheresis, it is important to bear in mind that only those female donors are eligible who are nulliparous; if multiparous, they must carry laboratory evidence of the absence of human leukocyte antigen (HLA) antibodies. This decreases the recipient’s risk of acquiring transfusion-related acute lung injury (TRALI) that may happen due to the presence of anti-HLA antibodies in their CCP. Therefore, both ICMR and FDA recommend testing for SARS-CoV-2 neutralizing antibody titers, if the option is available. A neutralizing antibody titer of at least 1:160 is likely to be more beneficial. Otherwise, for the estimation of antibody levels, a sample from the donated CCP should be retained later on.⁹ Saudi Arabian national collaborative study opted for an interesting strategy of utilizing a rapid antibody screening using a handy lateral flow cartridge method to mandate evidence of anti-SARS-CoV2 IgG antibodies in prospective CCP donors and saved aliquots of donated CCP for later testing when this facility would widely be available in the country.²⁰ Further, in other studies, CCP donors were selected based on a predefined minimum neutralizing antibodies titer only.^{21,22} Besides, to

assess their eligibility for blood donation, CCP donors may even be encouraged to travel to the nearest blood center. Conveyances could also be provided, if needed, to facilitate travel for the same intention.

Safety Assessments and Adverse Event Reporting

- Any unfavorable event that occurs in a patient receiving regular donor plasma or CCP therapy is an adverse event (AE).^{23,24} In general, it is possible to further identify these as:
 - AEs related to donors: These events are differentiated into local and systemic reactions. Based on their intensity, they can also be classified as mild, moderate, or severe. Hypotensive reactions, citrate reactions, hematomas, loss of consciousness, seizures, and allergic reactions may further be described in an etiology-based classification.
 - Equipment- and/or kit-related AEs: These events are secondary to disposable sets that are defective or erroneous. They can lead to hemolysis, formation of thrombosis, air embolism, leakage, infection due to improper equipment installations, and so on.
 - Recipient-based AEs: A transfusion-related AE in a recipient is a consequence that is momentarily related to the administration of blood or blood components. TRALI, transfusion-related circulatory overload, allergic/anaphylactic reactions, TTI transmission, and febrile non-hemolytic transfusion events make up the majority of semilethal and medically curable AEs generally associated with plasma transfusions.

Addressing the Ethical Concerns of Recipients

Before any blood or blood component transfusion, recipients are entitled to receive adequate and legible information on the associated risks of plasma transfusions, particularly the AEs. If any extra steps have been taken to mitigate the risk of TTI (for example, pathogen reduction treatment), it should be mentioned in the informed consent. Their informed consent forms must be kept safely, following local hospital transfusion policies.¹⁹ Signed documents must then be collected and kept in the medical records of the patients, and the doctors must ensure that they do so regularly. Besides that, all paper and computer data entered in the recipient's medical record must be kept confidential and accessible to authorized personnel only. These confidential records and data can be stored under the properly specified disposition policies at the local hospital facilities. Although the relevant country/regional guidelines do mention recommendations toward one's candidature for CCP therapy, they do not provide a decision-making benchmark as to who should be the first to start receiving CCP therapy. They leave it entirely up to the clinicians and hospitals to decide who would need it the most. This merits ethical consideration on the part of the treating physician and the hospitals

collaboratively. The best approach may be to have a multidisciplinary team make a decision. To resolve this ethical problem, hospitals may opt to use a predetermined randomization model, such that the decision does not fall within the scope of their individual preference. Another resolution could be the use of CCP therapy in recipients on a first-come-and-first-served basis. The hospitalization costs incurred and the facility for availing medical insurance claims also need to be critically analyzed.

Conclusion

In conclusion, the understanding of COVID-19 is evolving periodically. In fact, ethical concerns about priorities would ease as more people are tested, treated, and come forward to donate their CCP for their local as well as community needs. Given our limited experience with nCoV, we expect additional changes to the interim guidelines in an attempt to adapt further. In fact, we are still at a speculation stage and an attempt to comply with these interim guidelines along with an assessment of the latest available literature could, in principle, help to address all ethical concerns when harvesting and using CCP as a therapeutic tool for patients.

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None.

Informed Consent

As per the department policy, an informed consent is obtained from all donors prior to blood donation in accordance with our department protocol.

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the Institutional Ethics Committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The article does not contain any regulated human participant or animal research.

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Authors' Contribution List

Manish Raturi and Mansi Kala designed the concept. Manish Raturi and Kunal Das did the literature search. Manish Raturi compiled the data. Manish Raturi, Mansi Kala, Kunal Das, and Anuradha Kusum prepared and edited the manuscript. Manish Raturi, Mansi Kala, Kunal Das, and Anuradha Kusum reviewed the manuscript. Manish Raturi, as a guarantor, takes the responsibility of the integrity of the work, as a whole, right from its inception to being a published article.

Conflict of Interest

None declared.

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