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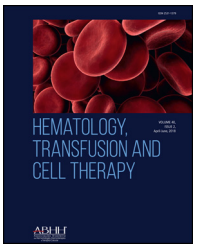


Scientific Comment

# COVID-19 convalescent plasma transfusion

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The pandemic caused by the novel coronavirus, called SARS-CoV-2, affected more than one million people around the world. The COVID-19, the acronym derived from the coronavirus disease 2019, was first reported in December 2019 in the province of Hubei (China) and disseminated to other parts of that country and has now become a global threat, in Brazil as well.

The clinical spectrum of COVID-19 varies from asymptomatic in a high percentage of infected people to severe acute respiratory syndrome (SARS), the main cause of death. No specific treatment has been found to be completely effective against the virus and no vaccine is available yet to prevent the infection. Therefore, all therapeutic options for the potentially lethal COVID-19 infection must be discussed ethically and scientifically. Historically, convalescent plasma (CP), a passive immunotherapy, has been used as a possible therapeutic option when no proven specific vaccine or drug is available for emerging infections.[1,2]

The administration of convalescent plasma or immunoglobulins has been shown to shorten the hospital stay and reduce the mortality rate in patients with SARS who did not respond to methylprednisolone in uncontrolled non-randomized clinical trials.[3,4] Cheng et al. investigated 1775 SARS patients and found that 80 patients transfused with SARS convalescent plasma had a lower mortality rate, compared to non-transfused patients (12.5% *vs.* 17%).[4]

Hung and colleagues conducted a prospective cohort study offering treatment with H1N1 convalescent plasma (antibody titer >1:160) to infected patients in intensive care. They found that the relative risk of mortality by an H1N1 infection was significantly reduced in patients transfused with convalescent plasma, compared to a control group of patients who declined the plasma treatment (20.0% *vs.* 54.8%; $p = 0.01$). In addition, the viral load and the level of interleukin 6, interleukin 10 and tumor necrosis factor $\alpha$ decreased significantly in a subgroup of infected patients.[5] The same group of investigators conducted a multicenter, prospective, double-blind, randomized, controlled clinical trial using H1N1 convalescent plasma fractionated to hyperimmune IV immunoglobulin (H-IVIG), in comparison to normal IV manufactured immunoglobulin, to treat severely infected H1N1 patients on standard antiviral treatment requiring intensive care and ventilatory support. Their results showed that the infusion of H-IVIG was associated with a lower viral load and reduced mortality within 5 days of the symptom onset.[6]

In 2014, the WHO recommended the use of Ebola convalescent plasma transfusion as an empirical treatment for Ebola-infected people in the outbreaks of the disease.[7]

A systematic review and exploratory meta-analysis of 32 studies assessed the overall evidence of the clinical benefit of the administration of convalescent plasma, serum or hyperimmune immunoglobulin in the treatment of severe acute respiratory infections. The authors found that the mortality rate was significantly reduced following infusions, with no serious adverse effects.[8] Another meta-analysis that evaluated 8 studies, including 1703 patients with Spanish influenza pneumonia, found an absolute 21% reduction in the case-fatality among patients transfused with blood products derived from influenza convalescent individuals.[9]

Over the past weeks, some investigators have reported the potential use of COVID-19 convalescent plasma transfusion as

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an adjunct alternative therapy for severe COVID-19 hospitalized patients.[2,10,11]

Shen and colleagues have described the use of plasma therapy in 5 (3 males) infected patients based on their critical condition, including severe pneumonia, adult respiratory distress syndrome (ARDS), mechanical ventilation support and rapid disease progression with a high viral load.[10] All of the patients were not over 65 (35–65) years of age and had already been treated with several antiviral drugs, plus methylprednisolone, when they received COVID-19 convalescent plasma transfusion, between 10 and 22 days after hospital admission. The ABO compatible plasma units were collected by apheresis from 5 (18–60 years) asymptomatic patients who had recovered from the COVID-19 infection. The transfused convalescent plasma contained a SARS-CoV-2-specific IgG antibody with a binding titer greater than 1:1000, evaluated by an enzyme-linked immunosorbent assay (ELISA) and a neutralization titer greater than 40. All donors tested negative for SARS-CoV-2, other respiratory viruses, syphilis, HIV and hepatitis B and C virus at the time of the plasma donation. The 400 mL of convalescent plasma was administered on the same day of the apheresis collection. All of the patients were evaluated before and after the COVID-19 convalescent plasma transfusion for changes in body temperature, sequential organ failure assessment (SOFA), ARDS, ventilatory and extracorporeal membrane oxygenation (ECMO), viral load, serum antibody titer and blood biochemical values. The authors observed that after plasma transfusion, 4 of 5 patients had their body temperature normalized within 3 days; the PAO2/FIO2 increased within 12 days; 4 patients had ARDS resolved within 12 days; the viral loads were also negative at 12 days, and; both the IgG and neutralizing antibody titers increased on day 7. Most importantly, 3 of 5 patients were discharged from the hospital after 51, 53 and 55 days of stay and the other 2 patients were in stable clinical status at 37 days after the convalescent plasma transfusion. The authors concluded that their data showed a potential benefit of COVID-19 convalescent plasma transfusion in critically ill patients. However, the small number of patients and the absence of a control group preclude a definitive statement about the potential effectiveness of this therapy, but provide some evidence for further evaluation in randomized clinical trials.[10]

## Conclusions

Analogous to the SARS, the COVID-19 infection progresses with an intense inflammatory response that eventually causes serious lung damage, increasing the mortality risk. In the absence of a definitive curative management, many treatment algorithms have been explored in the treatment of the COVID-19. Among possible interventions, the use of plasma collected from recovered patients shows an initial promise, however published results of rigorous clinical trials are needed before we may draw definitive effectiveness conclusions on this passive antibody therapy.

The administration of the COVID-19 convalescent plasma must, however, fulfill some requirements related to availability of COVID-19 recovered donors: well-designed study protocols to guarantee the efficacy analysis of such an intervention; governmental and institutional compliance, and; laboratory support to perform serological and molecular assays, including the measurement of viral neutralization and immune response.[11] In addition, the connection between hospitals, blood centers and the plasma industry must follow flawless strategies, as plasma units may be frozen before distribution or be manufactured as concentrated COVID-19 immunoglobulin.

Recently, the US Food and Drug Administration in United States has approved the use of plasma from recovered patients to treat seriously ill COVID-19-infected individuals. The transfused plasma must be obtained from donors tested negative for COVID-19 when plasma collection is performed, before day 28 of clinical recovery, and must be collected from recovered patients without symptoms for at least 14 days.[12]

Worldwide, there are currently hundreds of thousands of patients who have recovered from COVID-19 who could be recruited and become COVID-19 convalescent plasma donors after a cautious clinical and laboratorial evaluation. The SARS-CoV-2-specific IgG antibodies passively transferred by the transfused plasma might neutralize viral particles and activate the complement system, thus promoting viral elimination. However, it is also important to recognize that plasma transfusions may be associated with transfusion reactions such as allergic reactions, transfusion-related acute lung injury (TRALI) and circulatory overload.

## Final remarks and questions to be addressed

1. Promptness is essential since the strategy of administering the COVID-19 convalescent plasma has not yet been evaluated by randomized clinical trials. Data are only from a small number of case series with no control groups.
2. Would patients improve after transfusion of the COVID-19 convalescent plasma despite receiving other antiviral and anti-inflammatory therapies?
3. Would the use of the COVID-19 convalescent plasma transfusion reduce the infection-associated fatality rate and abbreviate the hospital stay?
4. What would be the necessary dose of convalescent plasma to reach the clinical benefit? For how many days?
5. What would be the adequate therapeutic titer of IgG and neutralization antibodies indicated to select the COVID-19 convalescent plasma donor?
6. Is the plasma from donors with confirmed laboratory diagnosis of the COVID-19 and no clinical symptoms more protectible than those with clinical symptoms?
7. Does the convalescent plasma from donors having a different virus genome infection have the protective effect for all patients with COVID-19?
8. Besides neutralizing antibodies, what other factors could possibly be involved in inducing a clinical response?
9. What is the best moment to transfuse the convalescent plasma? Should it be earlier (<10 days of symptoms) or is late (>10 days of beginning symptoms) transfusion of CP still effective?



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## Conflicts of interest

The authors declare no conflicts of interest.

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