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Opinion

On the Safety of the COVID-19 Convalescent Plasma Treatment: Thrombotic and Thromboembolic Concerns

Fatma Elrashdy [1], Elrashdy M. Redwan [2] and Vladimir N. Uversky [3,*]

[1] Department of Endemic Medicine and Hepatogastroenterology, Kasr Alainy, Cairo University, Cairo 12111, Egypt; Fatmaelrashdy@kasralainy.edu.eg
[2] Biological Science Department, Faculty of Science, King Abdulaziz University, Jeddah 21589, Saudi Arabia; lradwan@kau.edu.sa
[3] Department of Molecular Medicine, University of South Florida, Tampa, FL 33612, USA
* Correspondence: vuversky@usf.edu; Tel.: +1-813-974-5816

Abstract: Recently, it was reported that near-sourced COVID-19 convalescent plasma (CP) is more efficient than distantly sourced CP. What was left behind in this analysis is the investigation of the possible causes of mortality associated with the CP transfusion itself. Knowing this information is important for determining whether not receiving CP of near source is the main cause of high rate of death in the group of patients who received distantly sourced CP. We argue that the thrombotic and thromboembolic events may act as risk factors for adverse complications and death associated with CP transfusion. Therefore, they have to be considered and carefully accounted for in population studies as they can affect the CP safety profiles and change the interpretation of the cause of death in the studied groups.

Keywords: COVID-19; SARS-CoV-2; convalescent plasma; thromboembolic event; thrombotic events

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Recently, Kunze et al. [1] reported that near-sourced COVID-19 convalescent plasma (CP) is more efficient than distantly sourced CP. This conclusion was based on the observation of lower mortality rates within 30 days of transfusion when the CP donor and treated patient were in close geographic proximity (≤150 miles), in comparison with treatment using distantly sourced CP (>150 miles) [1]. To explain the observed phenomenon that CP has a higher efficacy when the donor and treated patient are in close geographic proximity, it was hypothesized that the near-sourced CP plasma is likely to reflect the antigenic composition of local viral strains [1]. What was left behind in this analysis is the investigation of the possible causes of mortality associated with the CP transfusion itself. Knowing this information is important for determining whether not receiving CP of near source is the main cause of the high rate of death in the group of patients who received distantly sourced CP. It is known that multiple side effects can be associated with CP transfusion. Although some of these effects are mild (fever, chills, or mild allergic reaction), there is also a risk of more adverse reactions, such as CP transfusion-related lung injury with serious breathing difficulty, circulatory overload, cardiac rhythm irregularities, anaphylactic reaction, as well as thromboembolic or thrombotic events.

A recent study recruited 20,000 hospitalized patients with COVID-19 who received CP to assess the safety of this treatment [2]. The occurrence of thrombotic and thromboembolic events (n = 113; <1%) and cardiac events (n = 677, ~3%) was reported [2]. Although the incidence rate of these events is relatively low, they represent severe complications and require serious attention [2]. Thrombotic and thromboembolic events could be attributed to the procoagulant components of CP, especially in patients who are more prone to hypercoagulability (such as some COVID-19 patients). Sajmi et al. [3] found that CP therapy does not confer clinical benefits in moderate-to-severe SARS-CoV-2 infected patients with chronic kidney disease on hemodialysis. This study followed 68 moderate-to-severe COVID-19 patients, who were on maintenance hemodialysis or developed acute worsening of chronic

kidney disease that required initiation of hemodialysis [3]. Thirty-seven (54.4%) of these patients received CP, and it was found that although two out of 18 patients with arteriovenous (AV) fistula in the CP group (11.1%) had fistula thrombosis, none of the patients in the control group had any thrombotic events [3]. However, there was no difference in the mortality or duration of the hospitalization between CP and control groups [3]. As it follows from several studies (e.g., see [4–6]), the CP-based therapy has several issues of concern and requires careful comparative analysis of benefits versus safety and detrimental factors. However, it seems that there is a consensus that if CP is used on or within seven days post-infection in mild to moderate infection cases, it may induce viral burden reduction before the induction of own anti-viral neutralizing antibodies in those patients. On the other hand, other live studies as well as NIH analysis indicated that CP therapy, intravenous immune globulin (IVIG) treatment, and other antibody- or cellular-based interventions may not confer any meaningful benefit [4,7]. Important CP limitations were thoroughly investigated in many studies and more recently discussed in two systematic analyses [4,7]. The hipper-immune CP would have beneficial effects on recovery in the mild to moderate cases of COVID-19 infection through multiple mechanisms, including antigenic binding sites and F_c of these antibodies via direct neutralizing capacity (directly on the viral molecule), and/or through up/down regulation of multiple immunomodulatory pathways [8], or even in synergistic action with many other medications [9].

A possible explanation for the thrombotic and thromboembolic events is that CP may contain anti-platelet factor-4 antibodies (anti-PF4) that bind to platelets, causing their activation, aggregation, and consumption with subsequent thrombosis and thrombocytopenia [10,11]. It was broadly reported that the SARS-CoV-2 infection induces high titers of anti-PF4 even without pre-exposure to heparin (see for example [12,13]). Furthermore, COVID-19 patients often show strong circulating reactivity in PF4/heparin antigen tests even without the presence of the platelet-activating antibodies [12]. Of note, the anti-PF4 autoantibodies recognize PF4 and activate platelets through their Fc receptors, leading to thrombi formation and production of platelet microparticles (PMPs). These are much smaller than platelets and show the ability to reach sites not easily accessible to platelets and harbor many phosphatidylserine and membrane proteins that bind to coagulation factors facilitating formation of thrombi [14,15].

It was pointed out that SARS-CoV-2 infection may trigger autoimmunity, and some COVID-19 patients were shown to develop multiple types of autoantibodies and autoimmune diseases [16–18]. In fact, the patients were shown to develop over 15 separate types of autoantibodies and more than 10 distinct autoimmune diseases [16]. Importantly, in addition to target somatic biomarkers, some of these SARS-CoV-2-induced autoantibodies encountered in the COVID-19 blood circulation were shown to be capable of neutralizing various interferons (INFs), such as IFN-α subtypes, IFN-β, IFN-ε, and IFN-ω [16–19]. In severe SARS-CoV-2 infection, impaired local intrinsic immunity was observed due to the abundances of autoantibodies for human IFNs of type I (13 partially homologous IFN-α subtypes, IFN-β, IFN-ε, IFN-τ, IFN-κ, IFN-ω, IFN-δ, and IFN-ζ), II (INF-γ) and III (IFN-λs 1, 2, 3, and 4) [20]. Furthermore, in addition to these anti-INF autoantibodies, many other detrimental co-factors, such as anti-ADAMTS13 or anti-MDA5 autoantibodies, as well as pro-coagulant extracellular vesicles, were found circulating within the transfuse CP [5]. Importantly, several different kinds of autoantibodies could activate a thrombotic cascade [21]. Recovered SARS-CoV-2 CP donors may have some or all of the above types of thrombosis inducers within their autoantibodies array, which would contribute to the complications and/or death of COVID-19 patients. The pro-coagulation potential may not be restricted to the quantity of coagulation factors, because even small quantities of these factors present in the CP can enhance the coagulation cascade in CP recipients [22].

Departure from the aforementioned autoimmunity-related implications raises an important question on the existence of specific agent(s), which are considered as a part of the anti-SARS-CoV-2 immunity, might have implications in thrombosis, and could be transferred with the CP. Zhu et al. [23] recently found several interesting and potentially

dangerous agents from this category. This study revealed that SARS-CoV-2 infection drives and activates a subset of the receptor-binding domain (RBD)-specific B cells to produce heparin-induced thrombocytopenia (HIT)-like platelet activating antibodies, which have activation properties and structural features similar to those of the pathogenic HIT antibodies, independent of heparin exposure [23]. These novel antibodies are capable of PF4-dependent platelet activation and may therefore contribute to the thrombotic complications seen in SARS-CoV-2 infection as they do in HIT [23]. Among the seven platelet-activating RBD-specific clones identified in their study, three were from a patient who did not receive heparin [23]. Since lymphocytes producing antibodies represent long living plasma/memory cells, this study clearly contains a very alarming message.

Taking all these observations together, it is clear that the thrombotic and thromboembolic events act as risk factors for adverse complications and death associated with CP transfusion. Therefore, they have to be considered and carefully accounted for in population studies as they can affect the CP safety profiles and change the interpretation of the cause of death in the studied groups.

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