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Short Communication

Apheresis methods in COVID-19 era: What about Long COVID?

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Abstract

COVID-19 disease is a contagious disease whose severity of symptomatology is probably due to uncontrollable systemic hyperinflammation called cytokine storm syndrome (CSS). The worst clinical manifestation is respiratory distress syndrome (ARDS) which is correlated with multiorgan failure and high mortality. Currently there is no effective therapy especially for critically ill patients. Several studies have focused on whether apheresis methods could attenuate the inflammatory response and improve the clinical course; however, the results are controversial. Furthermore, as the pandemic is evolving to less virulent variants with reduced mortality rate, there exists an increasing number of Long COVID patients. Extracorporeal apheresis methods could be a therapeutic option. Randomized clinical trials are required to accurately assess the effects of apheresis methods especially in Long COVID patients.

Keywords: Apheresis, COVID-19, Hyperinflammation, Long COVID

Short Communication

COVID-19 disease caused by the novel coronavirus SARS-CoV-2, emerged in Wuhan, China, and has spread worldwide. According to the World Health Organization (WHO), to date more than 750 million people have been infected with SARS-CoV2 and almost 7 million patients have died. The disease has a wide spectrum of symptoms from mild to life threatening conditions. Strong evidence has shown that the severity of the disease is due to high levels of circulating inflammatory mediators including cytokines and chemokines, leading to a condition of dysregulated innate immune response and uncontrollable systemic hyperinflammation called cytokine storm syndrome (CSS) [1]. Several studies have shown elevated cytokine levels, particularly in COVID-19 patients requiring ICU treatment [2]. Especially for IL-6, it has been demonstrated the need for mechanical ventilation, a potential thrombotic state with a poor outcome [3]. The syndrome is also characterized by hypercoagulable state with microvascular thrombosis and clot formation features and endothelial dysfunction [1]. The worst clinical manifestation of the syndrome is respiratory distress syndrome (ARDS) which is correlated with multiorgan failure and a high mortality [4].

The eradication of the virus for the time being is practically impossible, however, the wide use of COVID-19 vaccines from December 2020, has reduced the incidence, hospitalization, and mortality from the disease [5]. Currently there is no effective treatment strategy, particularly for patients with a critical illness. According to the National Institutes of Health (NIH) guidelines for COVID-19, antiviral medications such as Ritonvir boosted with nirmatrelvir, and Remdesivir are recommended as treatment for non -hospitalized patients, with the latter pharmaceutical being the only antiviral drug approved by the Food and Drug Administration (FDA). Regarding monoclonal antibodies, casirivimab plus imdevimab or bamlanivimab plus etesevimab ae recommended for outpatients with mild to moderate disease; however, they are not currently authorized for use in the United States because the dominant Omicron subvariants are not expected to be susceptible to these medicines. For hospitalized adults with progressive severe or critical COVID-19 disease with systemic inflammation, combined therapy with Remdesivir, dexamethasone, and immunomodulatory therapy such as tocilizumab or baricitinib is recommended.

In this context, several trials have focused on whether extracorporeal blood purification treatments could attenuate the inflammatory response and improve the clinical course and the outcome of critically ill COVID-19 patients. Different methods of extracorporeal treatment as Therapeutic Plasma Exchange (TPE) and hemoadsorption have been used; however, their role remains still controversial [6]. This is due to the fact that the evidence available so far comes from single-center reports and case series. In addition, there is a heterogeneity of data that can be attributed to differences either in technical matters like cartridges and replacement solutions, or modality prescription like frequency and length of session [6]. Furthermore, it should be noted that currently the most relevant variant is Omicron that causes less severe symptoms and fewer admissions to hospital and especially to intensive care units [7]. This creates difficulties in designing and implementing large randomized studies in the future.

Therapeutic plasma exchange (TPE) was one of the first methods studied as a rescue therapy in severe ARDS due to COVID-19, demonstrating better survival, reduced hospitalization rate and duration on mechanical ventilation, and improved cytokine and coagulation marker levels immediately after the procedure [8-13]. The main rationale is that TPE has a cutoff of 1.000 kDa which can remove easily inflammatory proteins, such as IL-6 (21 kDa) and CRP (120 kDa) [14]. However, the opposite opinion claims that the reduced levels of inflammatory proteins are simply an artificial reduction and is not necessarily associated with an amelioration of the septic status of the patient [15]. Furthermore, TPE could be potentially harmful by removing protective autoantibodies, immunoglobulins, and complement 3 and 4, attenuating the immune response against the infection. The removal of medicines received for treatment of Coronavirus like tocilizumab, prednisolone, and remdesivir may also be deleterious [15].

Hemoperfusion methods through different hemoadsorbers are widely used for critically ill COVID-19 patients. The most common device is Cytosorb whose emergency use was approved by the FDA since April 2020 and is included in the Italian guidelines [7,16]. It is a highly porous biocompatible polymer that can bind and remove from the blood hydrophobic substances with molecular weight of up to 55 kDa, like cytokines and other inflammatory mediators, without affecting larger beneficial substances like albumin, immunoglobulin, and coagulator factors. Differently, hydrophobic drugs may be removed by the device based on their molecular weight [17]. However, tocilizumab is not expected to be removed due to its large molecular weight (148 kDa) [16]. An important advantage of the method is its ability to install either as stand-alone hemoperfusion method, or integrated with another extracorporeal circuit as continuous replacement therapy (CRRT) or extracorporeal membrane oxygenation (ECMO), unlike Hemoperfusion HA330 whose compatibility with other methods is limited [7,17]. On the other hand, it is twice as expensive as other hemoadsorbers like HA330 cartridge [18]. Even if Cytosorb is considered the most clinically recommended apheresis method [19], data from randomized trials have shown that it was not associated with better survival [20] and had even higher mortality when used in combination with ECMO [21].

In addition to the aforementioned hemoperfusion methods, Seraph-100 Microbind Affinity Blood Filter column (Seraph 100) has been successfully used during the pandemic; however, to a lesser degree [7]. It received Emergency Use Authorization by FDA for the treatment of COVID-19 patients with severe respiratory failure that were admitted to an ICU. This filter differs from the other absorption devices because it is designed to remove various pathogens, including bacteria, viruses, fungi from the blood [22]. Its functional basis is an adsorption substrate of polyethylene beads coated with immobilized heparin where various pathogens have been shown to bind irreversibly and thereby removed from the bloodstream [23]. Recently, it has been demonstrated that Seraph 100 removes the nucleocapsid protein of Sars-CoV-2 in critically ill COVID-19 patients [24]. This is an important advantage of the method because there is strong evidence that existence of SARS-CoV-2 viral RNA in the blood is related to disease severity and is a significant risk factor for mortality, ICU admission, invasive mechanical ventilation and multiorgan failure [25,26]. Jacobs et al. demonstrated that viral RNA was present in the plasma of 100% of ICU COVID-19 patients and to a lesser extent in non-ICU hospitalized patients (52.6%) and outpatients (11%). Although viral RNA levels decreased over time among survivors, they have continued to be high among non survivors [27]. It is believed that SARS-CoV-2 viremia may contribute to worse outcome by allowing broad metastasis of viral invasion into non pulmonary organs [22]. Data from case reports [28] and a registry of 82 patients treated with Seraph 100 [23] demonstrated that it is a safe and well tolerated method, associated with lower mortality when initiated early after admission to a ICU. In addition, it seems that the filter does not bind to drugs [29]. On the contrary, Chitty et al., in a retrospective cohort study, failed to demonstrate survival benefit [22]. Randomized prospective studies could possibly evaluate the benefit of Seraph 100 in critical COVID-19 illness.

Four years after the outbreak of the pandemic, the medical community is faced with the Long COVID or post- COVID syndrome (PCS). It is estimated that 5 to 21% of patients develop PCS after recovery from acute infection [30], presenting a variety of nonspecific symptoms including fatigue, shortness of breath, cognitive impairment, sleep disturbance, myalgia, and neuropathy [31]. There is strong evidence suggesting a pathophysiological correlation between PCS and Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME-CFS) [32]. Several mechanisms have been proposed to explain PCS, as reduced tissue perfusion, viral infiltration of tissues, ongoing inflammation, persistence of SARS-CoV-2 spike proteins, microvascular blood clotting with endothelial dysfunction and reactivation of other infectious agents including Epstein-Barr Virus and CMV [33-35]. Furthermore, there is strong evidence that a great variety of autoantibodies play a crucial role in severe forms of COVID-19 disease and in PCS [36,37]. Additionally, Long COVID correlates with elevated lipid levels, causing long term risk for cardiovascular disease [33]. The management of patients diagnosed with PCS focuses on symptomatic therapy and psychiatric support, although there is evidence that propose EBP treatments, especially absorption methods, as an alternative therapeutic option [38]. Their advantage in relation to specific medication is its ability to remove a broad range of toxins, inflammatory proteins, lipids, and autoantibodies from human blood [33,39]. Achleitner et al., demonstrated a significant reduction of neurotransmitter autoantibodies, lipids, fibrinogen and inflammatory markers, with concomitant clinical improvement in 27 Long COVID patients following two cycles of therapeutic apheresis [33]. Currently, data are scarce and there is need for large randomized controlled trials. However, the design of a large scale research study seems to

be difficult given the heterogeneity of clinical symptoms and the complexity of the pathophysiological mechanisms of the syndrome. Individualized trials with different treatment protocols for patients with severe symptoms have been proposed as an adjuvant alternative [33].

In conclusion, during the pandemic, several extracorporeal apheresis methods have been proposed as safe and efficient adjuvant treatment in severe forms of the COVID-19 disease. However, there is not enough clinical data to fully understand their role in the survival and the outcome of COVID-19 patients. This is due to lack of large randomized trials. In addition, we have to take into account that as these treatments are costly and require special equipment and highly skilled stuff, they have low availability. Therefore, weighting costs and benefit and making selection of the appropriate patient and modality is of paramount importance. Furthermore, as the pandemic is evolving to less virulent variants with reduced mortality rate and to an increasing number of Long COVID patients, extracorporeal apheresis methods might be a therapeutic option for PCS. Randomized clinical trials are required to accurately assess the effects of extracorporeal apheresis methods especially in Long COVID patients.

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