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Short Communication

Plasma exchange in the treatment of complex COVID-19 related critical illness: controversies and perspectives

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ABSTRACT

SARS-CoV-2 disease (COVID-19) emerged in Wuhan, China, and spread worldwide resulting in over 73 million cases and more than 1 million 600 thousand death toll as of December 2020. Although the disease is asymptomatic in most cases, several patients can develop life-threatening disease, which is characterized by acute respiratory distress syndrome, sepsis, multi-system organ failure, extra-pulmonary manifestations, thromboembolic disease, and associated cytokine release syndrome. The rationale for applying therapeutic plasma exchange (TPE) early in the course of fulminant COVID-19 is the suppression of thromboinflammation, ameliorating the microangiopathy, and the ensuing multi-system organ failure. In the course of complicated critical illness due to COVID-19, dysregulated immune system pathology may be as important as the viral replication itself. Moreover, the natural course of SARS-CoV-2 infection remains obscure as reinfections and/or recurrently positive real-time-polymerase-chain-reaction results were reported. Although concerns still exist regarding its potential immunosuppressive effects and safety, TPE showed promise in the management of life-threatening COVID-19 as documented by various pilot studies, which eventually remains to be confirmed by future randomized-control trials. Current data suggest though that TPE could be an adjunctive rescue therapy in complex COVID-19 critical illness.

1. Introduction

The novel SARS-CoV-2 disease (COVID-19) emerged in Wuhan, capital of Hubei province, in China and spread worldwide. Most patients infected with COVID-19 are asymptomatic; however, a few of these patients can present with life-threatening disease [1]. One of the main pathophysiologic characteristics of life-threatening COVID-19 is cytokine release syndrome (CRS); hence, the putative role of therapeutic plasma exchange (TPE) in its management, in conjunction with other empiric therapies was suggested [1,2]. The pathogenesis of CRS was partially attributed to the hyperinflammation and immune system dysregulation that is observed in COVID-19 [2-3]. Life-threatening COVID-19 with associated CRS is characterized by refractory acute respiratory distress syndrome (ARDS), sepsis, multi-system organ failure (MSOF), extra-pulmonary manifestations, and thromboembolic disease [4-5]. The rationale for applying TPE on severe COVID-19 is the suppression of CRS, thromboinflammation, and amelioration of microangiopathy, preventing thus the development of MSOF. The latter was further documented by the increased incidence of microthrombosis and end-organ injury in post-mortem examinations of COVID-19 patients [6-7].This pathobiology was partially attributed to the ability of the virus in binding with the ACE2 receptor, resulting in direct endothelial injury and immune system dysregulation [8]. However, the efficacy of extracorporeal blood purification therapies and TPE aiming on the mitigation of COVID-19 associated thromboinflammation remains questionable. The role of TPE in altering the natural course of severe COVID-19 with associated CRS appears to be a rational strategy. Recently, our group applied TPE on critically ill patients with COVID-19 and associated CRS [5].We defined the latter using routine laboratory markers (Table 1). Our clinical ob-

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Table 1
Criteria for defining CRS in COVID-19.

One or more of the following criteria should be present*
C-reactive protein > 100 or > 50 mg/L but doubled in the past 48 hours
lymphocyte count < 0.6 × 10^9/L
Serum Interleukin-6 (IL-6) ≥ 3x upper normal limit
Ferritin > 300 ug/L (or surrogate) with doubling within 24 hours
Ferritin > 600 ug/L at presentation and LDH >250 U/L
Elevated D-dimer (> 1 mcg/mL)

Abbreviations: CRS = cytokine release syndrome, LDH = lactate dehydrogenase.
* We define as low risk for developing CRS the presence of one criterion, moderate risk the presence of two to three criteria, and high risk the presence of more than three criteria.

servation was that CRS could appear early in the course of severe COVID-19; hence, we aimed on applying TPE within 24 to 48 hours from the development of life-threatening features. The inclusion criteria for the application of TPE as rescue therapy in life-threatening COVID-19 are detailed elsewhere [9]. Briefly, adult mechanically ventilated patients with confirmed SARS-CoV-2 infection and life threatening features such as ARDS (according to the Berlin criteria), Acute Physiology and Chronic Health Evaluation II score ≥ 20, severe sepsis/septic shock, MSOF, and one or more inflammatory biomarkers defining CRS were enrolled in our feasibility study. We performed TPE by means of the Spectra Optia ™ Apheresis System operating with acid-citrate dextrose anticoagulant as per Kidney Disease Improving Global Outcomes 2019 guidelines [9]. TPE can discreetly remove significant proportions of interferon-gamma, interleukins -3, -10, -1B, -6, -8, and tumor necrosis factor-alpha [5,10-11]. In our study, all of the following significantly normalized following TPE, when compared to baseline: Sequential Organ Function Assessment score, partial arterial pressure of oxygen to fractional inspired concentration of oxygen ratio, levels of lymphocytes, total bilirubin, lactate dehydrogenase, ferritin, C-reactive protein and interleukin-6. The median duration of mechanical ventilation was 9 days, the median intensive care unit length of stay was 15 days, and the mortality on day-28 was 10%. No adverse effects such as allergies, infections, coagulopathy, and deterioration of renal or cardiac function were recorded [5]. However, we did not measure SARS-CoV2 antibody titers on pre- and post- TPE samples as these were not available during the study period. Plasma exchange associated immunosuppression could be possible, but this was not documented in previous studies [5-11]. Since PE has a cutoff of 1.000.000 Daltons (Da), inflammatory mediators such as C-reactive protein (120.000 Da), ferritin (474.000 Da), lactate dehydrogenase (144.000 Da), D-dimers (180.000 Da), and interleukin-6 (21.000 Da) can be removed. The extracorporeal reduction of these inflammatory molecules may not correspond to the clinical improvement of the septic status per se. Also, TPE could remove immunoglobulins and complement components 3 and 4 resulting thus in immunoparalysis, which could be indeed harmful in viral and bacterial infections [12-13]. The use of several natural and artificial plasma products as replacements in the TPE regime could effectively counteract the aforementioned concerns by replenishing immunoglobulins and decreasing the risk of coagulopathy and other potential side effects [5,11,14-15]. Moreover, in our pilot study, the decrease in inflammatory biomarkers was associated with a sustained increase of lymphocyte counts [5]. We did not record any significant coagulopathy apart from elevated levels of D-dimer; although levels of ADAMTS 13 activity or other coagulation related biomarkers were not specifically analyzed. Disseminated intravascular coagulation (DIC) is a well-known feature of sepsis and decreased levels of ADAMTS 13 were reported to correlate with progression to MSOF and a poor prognosis [16]. In our study, we documented CRS rather than macrophage activation syndrome with DIC as others previously reported [17]. Notwithstanding, COVID-19 associated coagulopathy may exhibit overlapping features of hemophagocytic syndrome, antiphospholipid antibodies, and thrombotic microangiopathy. TPE was employed for the treatment of sepsis in previous clinical trials with variable results. Recent data support the potential role of TPE [18] and extracorporeal blood purification therapies [19] in critically ill COVID-19 patients with refractory ARDS. Although SARS-CoV-2 is a classified respiratory virus, the potential severity of its extra-pulmonary manifestations cannot be ignored [8].The suppression of the ensuing CRS in fulminant COVID-19, via the blockage of pivotal cytokines (i.e., interleukin-6) by the monoclonal antibody tocilizumab was also used but with conflicting results. Preliminary findings of a phase III global tocilizumab versus placebo study (EMPACTA) showed that the administration of tocilizumab in patients with COVID-19 pneumonia plus standard of care were 44% less likely to progress to mechanical ventilation or death compared to patients who received placebo plus standard of care [20]. However, no significant differences in mortality, time to discharge, or in time to clinical improvement between the aforementioned groups of patients were observed [20]. We suggest that applying TPE early in the course of fulminant COVID-19 could mitigate a full-blown CRS. At this stage of the disease, dysregulated immune system pathobiology may be equally important as viral replication per se as the RECOVERY trial also suggested due to the observed beneficial effect of the administration of low-dose dexamethasone in mechanically ventilated critically ill COVID-19 patients.The natural course of SARS-CoV-2 infection remains obscure as reinfections and/or recurrently positive real-time-polymerase-chain-reaction results were previously reported. Larger studies are required to clarify the optimal TPE regime, and the long-term effects of such an immunomodulatory treatment in COVID-19. Convalescent plasma transfusion was used as rescue therapy in severe COVID-19; however, no clear survival benefit was recorded. Although the logistics of producing therapeutic delivery of convalescent plasma at an individual patient level have been overcome, convalescent plasma transfusion is more time consuming compared to TPE as the former integrates the process of collecting convalescent plasma from recovered donors. Moreover, unlike TPE, convalescent plasma transfusions may carry the risk of antibody-dependent infection enhancement. This could suppress innate immunity, and thus facilitate intracellular viral growth. In that sense, TPE may be a less complex therapeutic option in life-threatening COVID-19, especially if natural immunity does not arise. Convalescent plasma transfusion has been hypothesized to rely mainly on neutralizing SARS-CoV-2 antibodies, although the relationship between neutralizing antibodies' titer and efficacy has not been clearly established. Moreover, this therapeutic modality is not focusing directly on the immune dysregulation and microangiopathy, which are main features of the complex disease process in critically ill COVID-19 patients. TPE bares its own logistical concerns as the availability of equipment and trained staff varies globally. The safety of TPE requires close monitoring, preferably in a high-dependency unit. TPE still carries the risk of exposure to a highly transmissible virus. In that sense, proper application of personal protective equipment by the staff, careful handling of the TPE devices, and utilization of all pertinent disposables as potentially biohazardous materials is deemed to be necessary [5,11,14-15, 18].

2. Conclusion

TPE is a promising adjunctive rescue therapy in critically ill COVID-19 patients, although concerns still exist regarding its immunosuppressive effects and safety. TPE can discreetly mitigate the hyperinflammation of life-threatening COVID-19, improving thus the ensuing ARDS, sepsis, and MSOF. Larger randomized control

trials are required to investigate TPE's safety and putative survival benefit in critically ill COVID-19 patients.

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Competing Interests

The authors declare that they have no competing interests.

Ethical Approval

The study was approved by our Institutional Review Board (protocol/serial number: H-01-R-053, IORG0010374, H1R1-29-20-01). This study was registered at ISRCTN21363594; doi.10.1186/ ISRCTN21363594.

Authors' contributions

All authors contributed equally in data collection/analysis, and in drafting this manuscript. All authors reviewed the final version of the manuscript and agreed for its submission to the journal.

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