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Short Communication

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



Ziad A. Memish^{a,b,*}, Fahad Faqihi^c, Abdulrahman Alharthy^c, Saleh A. Alqahtani^{d,e}, Dimitrios Karakitsos^{c,f}

^a Research and Innovation Center, King Saud Medical City & Faculty of Medicine, Alfaisal University, Riyadh, Saudi Arabia

^b Hubert Department of Global Health, Rollins School of Public Health, Emory University, Atlanta, GA, USA

^c Critical Care Department, King Saud Medical City, Riyadh, Saudi Arabia

^d Liver Transplantation Unit, King Faisal Specialist Hospital & Research Center, Riyadh, Saudi Arabia

^e Division of Gastroenterology and Hepatology, Johns Hopkins University, Baltimore, MD, USA

^f Critical Care Department, Keck School of Medicine, USC, Los Angeles, CA, USA

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ABSTRACT

COVID-19 (coronavirus disease 2019), caused by the novel coronavirus SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2), emerged in Wuhan, China, and has spread worldwide, resulting in over 73 million cases and more than 1 600 000 deaths as of December 2020. Although the disease is asymptomatic in most cases, some patients develop life-threatening disease characterised by acute respiratory distress syndrome, sepsis, multisystem organ failure (MSOF), extrapulmonary 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 and amelioration of microangiopathy, thus preventing the ensuing MSOF. In the course of complicated critical illness due to COVID-19, immune dysregulation may be as important as viral replication itself. Moreover, the natural course of SARS-CoV-2 infection remains obscure, as re-infections and/or recurrently positive real-time PCR results have been reported. Although concerns still exist regarding its potential immunosuppressive effects and safety, TPE shows promise in the management of life-threatening COVID-19 as documented by various pilot studies, which remain to be confirmed by future randomised controlled trials. However, current data suggest that TPE could be an adjunctive rescue therapy in complex COVID-19 critical illness.

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Introduction

COVID-19 (coronavirus disease 2019), caused by the novel coronavirus SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2), emerged in Wuhan, the capital of Hubei Province, China, and has spread worldwide. Most patients infected with SARS-CoV-2 are asymptomatic; however, some patients present with life-threatening disease [1]. One of the main pathophysiological 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 empirical therapies, has been suggested [2]. The pathogenesis of CRS is partially attributed to the hyperinflammation and immune system dysregulation that is observed in COVID-19 [3–5]. Life-threatening COVID-

19 with associated CRS is characterised by refractory acute respiratory distress syndrome (ARDS), sepsis, multisystem organ failure (MSOF), extrapulmonary manifestations and thromboembolic disease [6–9]. The rationale for applying TPE in severe COVID-19 is the suppression of CRS and thromboinflammation and amelioration of microangiopathy, thus preventing 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 [10,11]. This pathobiology was partially attributed to the ability of the virus to bind the angiotensin-converting enzyme 2 (ACE2) receptor, resulting in direct endothelial injury and immune system dysregulation [12]. However, the efficacy of extracorporeal blood purification therapies and TPE aimed at the mitigation of COVID-19-associated thromboinflammation remains questionable.

* Corresponding author. Research and Innovation Center, King Saud Medical City & Faculty of Medicine, Alfaisal University, Riyadh, Saudi Arabia.

E-mail address: zmemish@yahoo.com (Z.A. Memish).

Table 1
Criteria for defining cytokine release syndrome (CRS) in COVID-19

One or more of the following criteria should be present ^a
CRP >100 mg/L or >50 mg/L but doubled in the last 48 h
Lymphocyte count <0.6 × 10 ⁹ /L
Serum IL-6 level ≥3 × ULN
Ferritin >300 µg/L (or surrogate) with doubling within 24 h
Ferritin >600 µg/L at presentation and LDH >250 U/L
Elevated D-dimers (>1 µg/mL)

COVID-19, coronavirus disease 2019; CRP, C-reactive protein; IL, interleukin; ULN, upper limit of normal; LDH, lactate dehydrogenase.

^a The risk of developing CRS was defined as follows: low risk, presence of one criterion; moderate risk, presence of two to three criteria; and high risk, presence of more than three criteria.

Plasma exchange as rescue therapy in severe COVID-19: controversies and perspectives

The use 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 in critically ill patients with COVID-19 and associated CRS [13]. We defined the latter using routine laboratory markers (Table 1). Our clinical observation was that CRS could appear early in the course of severe COVID-19; hence, we aimed to apply TPE within 24–48 h from the development of life-threatening features. Inclusion criteria for the application of TPE as rescue therapy in life-threatening COVID-19 are detailed elsewhere [14]. Briefly, mechanically-ventilated adult 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 (APACHE) 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 using a Spectra Optia™ Apheresis System operating with acid-citrate-dextrose anticoagulant as per Kidney Disease: Improving Global Outcomes (KDIGO) 2019 guidelines [15]. TPE can discreetly remove significant proportions of interferon-gamma, interleukin-3 (IL-3), IL-10, IL-1β, IL-6, IL-8 and tumour necrosis factor-alpha [2,13,14,16]. In our study, all of the following significantly normalised following TPE compared with baseline: Sequential Organ Failure Assessment (SOFA) score; ratio of partial arterial pressure of oxygen to fractional inspired concentration of oxygen (PaO₂/FiO₂); lymphocyte count; and levels of total bilirubin, lactate dehydrogenase, ferritin, C-reactive protein (CRP) and IL-6. The median duration of mechanical ventilation was 9 days, the median length of intensive care unit stay was 15 days and the mortality rate on Day 28 was 10%. No adverse effects such as allergies, infections, coagulopathy, or deterioration of renal or cardiac function were recorded [13]. However, we did not measure SARS-CoV-2 antibody titres in 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 [2,3,17]. Since plasma exchange has a cut-off of 1000 kDa, inflammatory mediators such as CRP (120 kDa), ferritin (474 kDa), lactate dehydrogenase (144 kDa), D-dimers (180 kDa) and IL-6 (21 kDa) can be removed. The extracorporeal reduction of these inflammatory molecules may not correspond to clinical improvement of the septic state per se. Also, TPE could remove immunoglobulins and complement components 3 and 4, thus resulting in immunoparalysis, which could indeed be harmful in viral and bacterial infections [18,19]. Use of several natural and artificial plasma products as replacements in the TPE regimen could effectively counteract the aforementioned concerns by replenishing immunoglobulins and decreasing the risk of coagulopathy and other potential side effects [17–19]. Moreover, in our pilot study, the decrease in inflammatory

biomarkers was associated with a sustained increase in lymphocyte counts [13]. We did not record any significant coagulopathy, apart from elevated D-dimer levels, although levels of ADAMTS-13 activity or other coagulation-related biomarkers were not specifically analysed. Disseminated intravascular coagulation 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 [20]. In our study, we documented CRS rather than macrophage activation syndrome with disseminated intravascular coagulation. Notwithstanding, COVID-19-associated coagulopathy may exhibit overlapping features of haemophagocytic syndrome, antiphospholipid antibodies and thrombotic microangiopathy [20].

TPE was employed for the treatment of sepsis in previous clinical trials with variable results. Recent data support the potential role of TPE in critically ill COVID-19 patients with refractory ARDS [17–20]. Although SARS-CoV-2 is classified as a respiratory virus, the potential severity of its extrapulmonary manifestations cannot be ignored [12]. Suppression of the ensuing CRS in fulminant COVID-19 via blockage of pivotal cytokines (i.e. IL-6) using the monoclonal antibody tocilizumab has also been used but with conflicting results. Preliminary findings of a phase III global tocilizumab versus placebo study (EMPACTA) showed that patients with COVID-19 pneumonia receiving tocilizumab plus standard of care were 44% less likely to progress to mechanical ventilation or death compared with patients who received placebo plus standard of care. However, no significant differences in mortality, time to discharge or time to clinical improvement between the aforementioned groups of patients were observed.

We suggest that applying TPE early in the course of fulminant COVID-19 could mitigate full-blown CRS. At this stage of the disease, dysregulated immune system pathobiology may be equally important as viral replication per se, as also suggested by the RECOVERY trial owing 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 re-infections and/or recurrently positive real-time PCR results were previously reported. Larger studies are required to clarify the optimal TPE regimen as well as the long-term effects of such an immunomodulatory treatment in COVID-19.

Convalescent plasma transfusion has been used as rescue therapy in severe COVID-19; however, no clear survival benefit was recorded. Although the logistics of therapeutic delivery of convalescent plasma at an individual patient level have been overcome, convalescent plasma transfusion is more time-consuming compared with 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 hypothesised to rely mainly on neutralising SARS-CoV-2 antibodies, although the relationship between the neutralising antibody titre and efficacy has not been clearly established. Moreover, this therapeutic modality is not focused directly on immune dysregulation and microangiopathy, which are the main features of the complex disease process in critically ill COVID-19 patients.

TPE presents 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 staff, careful handling of TPE devices, and utilisation of all pertinent disposables as potentially biohazardous materials is deemed necessary [2,13,14,17–20].

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, thus improving the ensuing ARDS, sepsis and MSOF. Larger randomised controlled trials are required to investigate the safety and putative survival benefit of TPE in critically ill COVID-19 patients.

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