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Therapeutic plasma exchange in adult critically ill patients with life-threatening SARS-CoV-2 disease: A pilot study

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Abstract

Keywords:
Life-threatening COVID-19
Acute respiratory distress syndrome
Cytokine release syndrome
Therapeutic plasma exchange
Intensive care unit

Purpose: We investigated the effect of therapeutic plasma exchange (TPE) on life-threatening COVID-19; presenting as acute respiratory distress syndrome (ARDS) plus multi-system organ failure and cytokine release syndrome (CRS).

Materials and methods: We prospectively enrolled ten consecutive adult intensive care unit (ICU) subjects [7 males; median age: 51 interquartile range (IQR): 45.1–55.9 years old] with life-threatening COVID-19 infection. All had ARDS [PaO2/FiO2 ratio: 110 (IQR): 95.5–135.5], septic shock, CRS and deteriorated within 24 h of ICU admission despite fluid resuscitation, antibiotics, hydroxychloroquine, ARDS-net and prone position mechanical ventilation. All received 5–7 TPE sessions (dosed as 1.0 to 1.5 plasma volumes).

Results: All of the following significantly normalized (p < 0.05) following the TPE completion, when compared to baseline: Sequential Organ Function Assessment score, PaO2/FiO2 ratio, levels of lymphocytes, total bilirubin, lactate dehydrogenase, ferritin, C-reactive protein and interleukin-6. No adverse effects from TPE were observed.

Acute kidney injury and pulmonary embolism were observed in 10% and 20% of patients, respectively. The duration of mechanical ventilation was 9 (IQR: 7 to 12) days, the ICU length of stay was 15 (IQR: 13.2 to 19.6) days and the mortality on day-28 was 10%.

Conclusion: TPE demonstrates a potential survival benefit and low risk in life-threatening COVID-19, albeit in a small pilot study.

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1. Introduction

Coronaviruses (CoV) can cause infections ranging from the common cold to severe disorders such as the Middle East Respiratory Syndrome and the Severe Acute Respiratory Syndrome (SARS-CoV) [1,2]. In December 2019 in Wuhan city, China, a novel coronavirus was identified and subsequently named the Severe Acute Respiratory Syndrome Corona Virus-2 (SARS-CoV-2) [3]. It is responsible for a pandemic that has threatened the world’s health, economy and way of life. Hyperbole aside, treatments are desperately needed. A minority of patients develop fulminant (life-threatening) SARS-CoV-2 disease (COVID-19): defined by acute respiratory failure/acute respiratory distress syndrome (ARF/ARDS), septic shock and/or multi-system organ failure (MSOF) [4-6]. While antiviral agents, such as remdesivir, and convalescent plasma transfusion (CPT) containing a high concentration of neutralizing antibodies, show promise, there is currently no treatment supported by robust evidence [7-15]. Moreover COVID-19 antibodies titers in infected cases can vary and decrease over time [14,15]. Therapeutic plasma exchange (TPE), without protective antibodies, has been previously used with success in patients with severe sepsis, MSOF and fulminant SARS-CoV; although its benefit is unclear in severe ARDS [16,17]. This is a pilot study using TPE as rescue therapy in ten adult intensive care unit (ICU) patients with fulminant COVID-19.

2. Materials and methods

2.1. Subjects

We prospectively enrolled ten consecutive subjects with life-threatening COVID-19 who were admitted to King Saud Medical City...
We primarily evaluated 28-day mortality, and the safety of TPE in life-threatening COVID-19. Secondary outcomes were: improvement in Sequential Organ Function Assessment (SOFA) score [18], changes in inflammation markers, days on mechanical ventilation and ICU length of stay. Inclusion criteria were: 1) Age ≥ 18 years old; 2) Intubation and ICU admission; and 3) Life-threatening COVID-19 [4-6,12,13,15,19-22] defined as: i) ARDS (according to the Berlin criteria) [23,24], ii) Acute Physiology and Chronic Health Evaluation II (APACHE II) score ≥ 20 upon ICU admission [25], or iii) Presence of severe sepsis/septic shock, and/or multi-system organ failure (MSOF) [26,27], and one or more criteria for defining cytokine release syndrome (CRS). The criteria for CRS are fully outlined in Table 1 [12,13,19,20,28,29]. SARS-CoV-2 infection was confirmed by Real-Time-Polymerase-Chain-Reaction (RT-PCR) assays using QuantiNova Probe RT-PCR kit (Qiagen) in a Light-Cycler 480 real-time PCR system (Roche, Basel, Switzerland) [30-35]. Exclusion criteria were: 1) previous allergic reaction to plasma exchange or its ingredients (i.e., sodium citrate) and 2) two consecutive negative RT-PCR tests for SARS-CoV-2 taken at least 24 h apart. The study was conducted according to the principles of the Declaration of Helsinki and approved by our Institutional Review Board [36]. Written informed consent was obtained from patients or legal representatives. Therapeutic Plasma Exchange TPE was initiated using the Spectra Optia™ Apheresis System equipped with the Depuro D2000 Adsorption Cartridge (Terumo BCT Inc., USA) [37]. Spectra Optia™ Apheresis System operates with acid-citrate dextrose anticoagulant (ACDA) as per Kidney System equipped with the Depuro D2000 Adsorption Cartridge containing activated uncoated coconut shell (carbon granules) charcoal (100 g), and the nonionic resins Amberlite XAD-7HP and Amberchrom GC300C [37]. These adsorption materials could remove significant proportions of interferon-gamma, interleukins −3, −10, −1β, −6, −8, and tumor necrosis factor-alpha [39-47]. A dose of 1.5 plasma volumes was used for the first dose then one plasma volume daily for five to seven doses per clinical case. Plasma was replaced with albumin 5% or fresh frozen plasma in patients with coagulopathy (prothrombin time > 37 s; international normalized ratio > 3; activated partial thromboplastin time > 100 or fibrinogen level < 100 mg/dl) [48]. TPE sessions were performed daily over four hours and laboratory markers were measured daily [4-6,12,13,37,38]. To evaluate the effect of TPE in removing inflammatory mediators known to be increased in COVID-19 patients [4-6,12,13,28,29], we measured serum levels of C-reactive protein (CRP), d-dimers, LDH, ferritin and IL-6 prior to the initiation of TPE and after the last TPE session. CRP was defined as elevated if it was >5.0 mg/l and IL-6 if >7.0 μg/ml [49].

### 2.2. Statistical analysis

Continuous variables were expressed as medians with interquartile ranges (IQR) and categorical variables were expressed as absolute numbers and proportions. We utilized the Wilcoxon signed rank test for non-parametric data to compare parameters before and after TPE. All tests were two-tailed and considered significant when the p value was <0.05. Statistical analysis was performed using SPSS, version 23.0.

### 3. Results

#### 3.1. Patients and therapeutic interventions

Out of one hundred and sixty-five consecutive patients who were admitted to the ICU between March 22 and May 11, 2020, eighteen COVID-19 patients were eligible for the study. Out of these eighteen cases, five patients expired upon ICU admission and could not be recruited. For three patients the legal representatives did not provide their informed consent for participation in the study. Finally, ten consented patients were enrolled in this pilot study (please, refer to the flow diagram Fig. S1 suppl. of the Appendix). All enrolled patients had ARDS and septic shock, within 24 h of ICU admission, and all had more than three risk factors for CRS (Table 1). All received empiric treatment (see below) for COVID-19 along with standard ICU support [4-6,12,13,15,19-27]. All deteriorated within 24 h of ICU admission despite recruitment maneuvers, low tidal volume and prone position mechanical ventilation resulting in a PaO2/FiO2 ratio of 110 (IQ5.95 to 135.5) and increasing norepinephrine requirements [norepinephrine (1.9 μg/kg/min; IQ5.1 to 2.8 μg/kg/min)]. After the administration of vasopressin (infusion rate: 0.07 units/min; IQR: 0.05 to 0.09 units/min) the dose of norepinephrine was reduced to 0.9 μg/kg/min (IQR: 0.7 to 1 μg/kg/min). Co-interventions included, lung recruitment, prone positioning, and empiric hydroxychloroquine (400 mg twice daily on day 1, followed by 200 mg twice daily on days 2–5) [4-6,9,10,50,51], broad spectrum antibiotics, intravenous hydrocortisone (200 mg daily for 3 days) [26,27], and prophylactic anticoagulation (enoxaparin 40 mg subcutaneously once daily and intermittent pneumatic compression) in all patients [52-58]. Plasma exchange was administered as rescue therapy to all patients and extracorporeal membrane oxygenation (ECMO) was added in one patient who exhibited a PaO2/FiO2 ratio < 80 for 26 h (case number 8, Table 2). Baseline features are presented in Table 2 (also, please, refer to Table S1 suppl. of the Appendix). Median patient age was 51 (IQ5.1 to 55.9) years old and body mass index (BMI) 24.9 (IQ5.2 to 29.8) kg/m². Time of symptom onset to ICU admission was 6.5 (IQ5.3 to 7.4) days. All cases were enrolled approximately 24 h post ICU admission. Their most common symptoms were: cough (10/10 cases), fever (8/10 cases), and dyspnea (5/10 cases); while less common symptoms included sputum production (4/10 cases), vomiting and nausea (4/10 cases), diarrhea, altered level of consciousness and anosmia (2/10 cases). Six patients had underlying chronic diseases: diabetes mellitus (60%), essential hypertension (50%) and cardiovascular disease (10%). Pulmonary embolism (PE) was ruled out in 8/10 cases and confirmed in 2/10 following contrast chest computed tomography (CT). The two positives (patients 8 and 9, Table 2) exhibited subsegmental PE without hemodynamic compromise and received therapeutic anticoagulation. Baseline point-of-care cardiac ultrasonography showed no significant cardiac dysfunction in any of our ten patients; while, their cardiac enzymes were within normal limits. Acute kidney injury, which was defined per the “risk,” “injury,” and “failure” (RIFLE) criteria [59], was observed in 10% of cases (Table S1 suppl., Appendix). In all cases, chest (CT) scans, performed upon ICU admission, showed bilateral ground-glass opacities and variable pulmonary parenchymal consolidations consistent with COVID-19 pneumonia (Fig. 1 and Fig. S2 suppl., Fig. S3 suppl. of the Appendix) [60-62]. Five patients had multi-lobe involvement and two had chronic lung parenchymal changes. Effects of TPE All TPE patients had an increase in their PaO2/FiO2 ratio above 250 following the 3rd or later treatment. Radiologic findings showed variable degrees of improvement after the completion of five or more TPE sessions (Fig. 1 and Fig. S2, Fig. S3 of the Appendix). Nine of ten patients were successfully liberated.
from mechanical ventilation and extubated, survived and were discharged from the hospital to home isolation after 20 days (IQR: 17.6 to 22.6), and without complications. A comparison of parameters in COVID-19 patients prior to and after TPE is outlined in Table 3.

All patients were weaned off vasopressors following TPE completion. There was a significant improvement of all laboratory parameters related to the CRS, the PaO2/FiO2 ratio and SOFA scores (all \( p < 0.05 \); Table 3). The duration of mechanical ventilation was 9 (IQR: 7 to 12) days, the ICU length of stay was 15 (IQR: 13.2 to 19.6) days, the hospital discharge rate was 90\% and the mortality on day-28 was 10\% (Table S1 suppl. Appendix). One patient had a secondary infection from a Gram negative bacterium (case 7). The expired patient (case 8, Table 2) developed cardiac arrest after completing all TPE sessions, and while undergoing weaning trials. No patient had any severe coagulopathy apart from elevated D-dimer levels (Table 3). No arrhythmias and/or other cardiac events that might have been linked to hydroxychloroquine were identified [63-66]. No adverse effects (i.e., transfusion/allergic reactions, line complications) from the TPE were observed in this case-series. Screening for other viral infections and systemic disorders was negative. SARSCoV-2 RNA, assayed by RT-PCR, became negative in all discharged cases after 18 (16 to 20) days.

4. Discussion

The use of TPE, with a variety of adsorption cartridges, has been the subject of cohort studies and clinical trials [39-47]. The putative benefit is assumed to come from reducing inflammatory cytokines such as IL-6 and endotoxins [27,28,39-47,67,68]. The objective of our small pilot study was to determine if using TPE in critically ill COVID-19 patients could ameliorate inflammatory mediators and potentially rescue extremely sick patients. In brief, we demonstrated that the use TPE for life-threatening COVID-19 infection appears safe and feasible, and may be associated with improved survival.

When compared to other studies [4-15], our cohort, of COVID-19 patients who received TPE had acceptable and better survival, hospital discharge rates, days on mechanical ventilation and ICU length of stay compared to other clinical studies [4-15]. CRS could be a unique feature of life-threatening COVID-19, as previously described [27,28,67-69]. Elevated levels of inflammation markers and lymphopenia are early predictors of severe COVID-19 and death [4-15]. In all of our TPE patients, serum C-RP, d-dimers, ferritin, LDH and IL-6 were markedly increased; hence all patients had more than three risk factors for CRS (Table 1). We demonstrated that all of these acute inflammatory

Table 2
Baseline features of the TPE patients (\( n = 10 \)).

| Patient no. | Sex       | Age (Years) | Classification of disease severity | Days of symptom onset to ICU admission | Number of TPE sessions | Clustering infection* | Main symptoms prior to hospital admission | Comorbidities                        |
|------------|-----------|-------------|------------------------------------|----------------------------------------|-------------------------|-----------------------|------------------------------------------|--------------------------------------|
| 1          | Male      | 45          | Life-threatening                    | 5                                      | 5                       | Yes                   | Fever, cough, dyspnea, sputum production | None                                 |
| 2          | Female    | 51          | Life-threatening                    | 6                                      | 5                       | No                    | Fever, cough, dyspnea, vomiting           | None                                 |
| 3          | Male      | 38          | Life-threatening                    | 7                                      | 5                       | No                    | Cough, dyspnea, chest pain, anosmia       | None                                 |
| 4          | Female    | 52          | Life-threatening                    | 2                                      | 5                       | Yes                   | Cough, nausea, vomiting, altered level of consciousness | Diabetes                             |
| 5          | Male      | 61          | Life-threatening                    | 3                                      | 5                       | No                    | Fever, cough, dyspnea, sputum production | Hypertension, diabetes                |
| 6          | Female    | 48          | Life-threatening                    | 2                                      | 5                       | No                    | Fever, cough, dyspnea, chest pain, diarrhea | Hypertension, diabetes                |
| 7          | Male      | 55          | Life-threatening                    | 8                                      | 7                       | No                    | Fever, cough, sputum production, anosmia | Hypertension, diabetes                |
| 8          | Male      | 58          | Life-threatening                    | 7                                      | 7                       | No                    | Fever, cough, sputum production, anosmia | Hypertension, diabetes                |
| 9          | Male      | 65          | Life-threatening                    | 7                                      | 6                       | No                    | Fever, cough, sputum production, anosmia | Hypertension, diabetes                |
| 10         | Male      | 51          | Life-threatening                    | 7                                      | 6                       | No                    | Fever, cough, chest pain                  | Cardio-vascular disease               |

Abbreviations: TPE = therapeutic plasma exchange; ICU = intensive care unit. *clustering infection means that these patients were infected in an area where several other cases were discovered at the same time (cluster).
markers decreased after five to seven TPE sessions. However, it is important to acknowledge that these markers might have decreased over time in patients not treated with TPE. It is believed that IL-6 is central to CRS, and accordingly, a new monoclonal antibody against IL-6 was initiated for life-threatening COVID-19, the better for our patients. Conceivably, patients could have recovered without TPE. Research to compare TPE to CPT, the time from onset of symptoms to initiation of TPE was shorter compared to that reported in CPT trials (6.5 vs. 16.5 days) [12,13]. Notably, the natural course of SARS-CoV-2’s viremia is not well established. Hence, it is difficult to know the relationship between viral RNA reduction and TPE, or the optimal TPE regime. Instead, we intuited that the sooner that TPE was started de novo or refined to therapy. Although no myocardial injury was documented, we cannot exclude the possibility of sudden cardiac arrest due to the development of arrhythmias related to the virus per se and/or the administration of hydroxychloroquine as previously reported [74–78]. Notably, in the revised version of Saudi MOH guidelines for COVID-19 ICU management, which was released after the completion of this study, hydroxychloroquine is no longer included as an optional empiric therapy [20]. Hence, if it was the initiating event then at least we are not using the medication in the ICU anymore. It is also noteworthy that our PE observed prevalence was 20% and that there is an increased incidence of microthrombi and PE in serious COVID-19 [52–58]. The suggested pathophysiological mechanism of microthrombosis and vascular dysfunction associated with COVID-19 may differ from macrophage activation syndrome with disseminated intravascular coagulation (DIC) [72,73]. Importantly, in this case-series, we confirmed CRS rather than just DIC [27,28,67–69]. Study limitations This pilot study has limitations which confines its generalizability. Apart from TPE, patients received other empiric medications and supportive interventions despite uncertainty as to their effectiveness. As these were not controlled for, we are uncertain of their effects on inflammatory mediator levels and survival. All patients received 200 mg of hydrocortisone (40 mg prednisone equivalent), and hence steroids might have affected the immune response or viral clearance. Also, the median initial dose of norepinephrine was higher than in septic shock trials; however, we believe this reflected how sick patients were and was part of our justification for rescue TPE. While our study did not set out to compare TPE to CPT, the time from onset of symptoms to initiation of TPE was shorter compared to that reported in CPT trials (6.5 vs. 16.5 days) [12,13]. Notably, the natural course of SARS-CoV-2’s viremia is not well established. Hence, it is difficult to know the relationship between viral RNA reduction and TPE, or the optimal TPE regime. Instead, we intuited that the sooner that TPE was initiated for life-threatening COVID-19, the better for our patients. Conceivably, patients could have recovered without TPE. Resource limitations restricted us from measuring a full panel of cytokines but those measured are comparable to published literature [12–14,39–47,67–70]. Our patient sample was too small to draw definitive conclusions and/or perform meaningful subgroup analysis. Despite the aforementioned limitations, our preliminary work suggests that TPE is associated with discrete improvement in the biochemical markers of CRS, ARDS, septic shock and MOF related to fulminant COVID-19. TPE also appeared to be low risk despite the high illness severity of our patients. Larger randomized control trials are required to confirm or refute our findings and we are working towards that end.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2020.07.001.

Table 3

| Parameters                          | Before TPE | After 5 to 7 TPE sessions |
|-------------------------------------|------------|---------------------------|
| Sequential Organ Function Assessment score | 11 (8.9 to 11.5) | 2 (1.4 to 3.6) * |
| PaO2/FiO2 ratio                     | 110 (95.5 to 135.5) | 340 (310.5 to 370.6) * |
| Lymphocyte count                    | 0.6 (0.45 to 0.8) | 1.15 (0.8 to 1.4) * |
| C-reactive protein                  | 71.3 (51.3 to 89.7) | 13.2 (7.2 to 26.4) * |
| Total bilirubin                     | 28.2 (17.7 to 33.4) | 11.6 (8.2 to 15.8) * |
| Alanine aminotransferase            | 66.5 (52.3 to 91.2) | 42.5 (22.7 to 53.6) * |
| Aspartate aminotransferase          | 45.9 (39.2 to 78.3) | 33.2 (30.9 to 41.6) * |
| Creatinine                          | 1.2 (0.9 to 1.4) | 1.1 (0.8 to 1.2) |
| Serum lactate                       | 5.5 (3.4 to 8.9) | 1.7 (1.2 to 2.6) * |
| Lactate dehydrogenase               | 576.5 (378.4 to 673.4) | 199.5 (156.1 to 232.3) * |
| Ferritin                            | 1233 (799 to 1758) | 290 (201 to 322) * |
| D-dimers                            | 7.4 (4.9 to 11.7) | 0.9 (0.7 to 1.2) * |
| Interleukin-6 (>200 pg/ml)          | 1595 (889.9 to 1823) | 31.2 (15.4 to 49.8) * |

Abbreviations: TPE = therapeutic plasma exchange; PaO2/FiO2 = partial arterial pressure of oxygen to fractional inspired concentration of oxygen; values are medians with interquartile range; the median time between the baseline data and the data after 5–7 TPE sessions was 5 days; * p values <0.05 were statistically significant by Wilcoxon signed rank test for non-parametric data. The value for creatinine did not reach statistical significance (p = 0.56).

Declarations authors’ contributions

All authors contributed to data acquisition, analysis, and interpretation. All authors reviewed and approved the final version.

Ethics approval and consent to participate

The study was approved by the Institutional Review Board of King Saud Medical City, Riyadh, Kingdom of Saudi Arabia [H-01-R-053, IORG0010374#, serial number: H1-R-20-00]. Written informed consent was obtained by all eligible patients or their legal representatives.

Funding

No financial support was received for this preliminary study.
