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CONCISE REVIEW

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The use of therapeutic plasma exchange as adjunctive therapy in the treatment of coronavirus disease 2019: A critical appraisal of the current evidence

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Abstract

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has led to a major pandemic. While vaccine development moves forward, optimal treatment continues to be explored. Efforts include an ever-expanding number of clinical trials along with newly proposed experimental and off-label investigational therapies; one of which is therapeutic plasma exchange (TPE). There have been a number of publications on TPE use as adjunctive therapy for coronavirus disease 2019 (COVID-19), but no prospective randomized controlled trials (RCTs) have been completed. This article critically appraises the current available evidence on TPE as a treatment modality for SARS-CoV-2 infection.

KEYWORDS

COVID-19, plasma exchange, SARS-CoV-2

1 | BACKGROUND

In December 2019, a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was reported in Wuhan, China. SARS-CoV-2 is a RNA virus that belongs to the beta coronavirus genus.[1] In humans, the entry receptor is angiotensin-converting enzyme 2 (ACE2).[1,2] ACE2 is expressed on epithelial and endothelial cells throughout the body (eg, lung, kidney, and gastrointestinal tract), which may in part explain the ability of SARS-CoV-2 to cause systemic coronavirus disease 2019 (COVID-19). As of 27 September 2020, 32.7 million infections and over 991 000 deaths have been reported to the World Health Organization.[3]

In adults, SARS-CoV-2 primarily causes respiratory illness, but can lead to cardiovascular, gastrointestinal, hematologic, neurologic, and other manifestations. Approximately 5% of patients develop severe COVID-19, which is characterized by acute respiratory distress syndrome (ARDS), multi-organ failure (MOF), and septic shock that require intensive supportive care and often lead to poor prognosis.[2] Early on, elevations in ferritin, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), lactate dehydrogenase (LD), tumor necrosis factor alpha (TNF-α), interleukin-1 (IL-1), IL-6, and other cytokines were reported in critically ill COVID-19 patients.[2,4,5] Those with severe disease also had elevated D-dimer and thrombocytopenia.[6] Autopsy findings of patients who did not survive SARS-CoV-2 infection demonstrated microthrombosis and fibrin clots throughout the lung.[7] These findings led to the association of cytokine release syndrome (CRS) and hypercoagulability with disease progression and poor prognosis.[4] Hyperviscosity has also been proposed to contribute to COVID-19 coagulopathy and thrombosis.[8,9] These suggested mechanisms of disease, however, have not been proven. The role of CRS in COVID-19, in particular, has even come into question.[10,11] It has been noted that while the median value of IL-6 in patients with COVID-19 ARDS is high, non-COVID-19 ARDS patients have IL-6 levels 10- to 200-fold higher than COVID-19 ARDS patients. Even more striking, peak IL-6 level in patients who develop CRS after chimeric antigen receptor T (CAR-T) cells infusion is almost 1000-fold higher than that reported in severe COVID-19.[11] The pathogenic mechanism in severe COVID-19, whether it is due to direct viral damage or cytokine mediated injury and hypoperfusion injury due to microthrombosis, remains unclear at this time.

In pediatric patients, an illness with features akin to Kawasaki shock syndrome (KSS) has been reported in the aftermath of COVID-19; this condition is sometimes known as COVID-19 associated multisystem inflammatory syndrome.[12] These patients present with persistent fever, evidence of inflammation (high ferritin, procalcitonin, CRP, triglycerides, and D-dimer), cardiac involvement, and/or MOF in the absence of other known infections.[12] They test positive for SARS-CoV-2 antibodies consistent with evidence of humoral immune response, but not all test positive for SARS-CoV-2 by molecular testing.[13] Furthermore, these patients display evidence of elevated markers of inflammation and thus, this hyperinflammatory syndrome is likely due to a postinfectious immune-mediated pathogenesis (and not from a direct viral damage).[13]

The mortality in patients with COVID-19 depends on multiple factors, such as age, gender, comorbidities, and even location. Nonetheless, the mortality can be high in a subgroup of patients with severe COVID-19[2] despite intense supportive care. Therefore, therapeutic plasma exchange (TPE) has been proposed and tried as adjunctive therapy. The theoretical rationale of this strategy will be discussed and the experience of using TPE in the treatment of this disease thus far will be appraised. Given the novel nature of SARS-CoV-2, the use of TPE to treat other similar viral infection will also be reviewed. In addition, hemadsorption devices compatible with TPE will be discussed briefly. Finally, additional considerations regarding the provision of TPE during the COVID-19 pandemic will be highlighted.

2 | COVID-19 AND THERAPEUTIC PLASMA EXCHANGE

2.1 | Rationale for therapeutic plasma exchange

Therapeutic plasma exchange involves the removal of whole blood from the patient, its separation into components, followed by the removal of the patient's plasma, and the return of the patient's other blood components along with replacement fluid such as 5% albumin, fresh frozen plasma (FFP). The procedure can reduce plasma components, such as auto and alloantibodies, plasma proteins, and inflammatory mediators and thus, TPE has been proposed as an adjunctive therapy for the treatment of COVID-19.[4,14,15] It is theorized that TPE could attenuate CRS, stabilize the endothelial membrane, and adjust aberrations in the coagulation pathway.[4,14,15] This is not a new hypothesis; the peak concentration hypothesis proposed that an imbalance between pro- and anti-inflammatory mediators, coupled with endothelial dysfunction and aberrations in the coagulation cascade, is the pathogenic mechanism of acute kidney injury (AKI).[16] This further led to the theory that AKI can be treated with continuous renal replacement therapy (CRRT). Since then, these ideas have been expanded to include the use of TPE to treat CRS mediated sepsis and now COVID-19.[17]

In addition to removing cytokines, it has been proposed that TPE may reduce viral burden, clear antifibrinolytic mediators and fibrin degradation products, decrease the levels of injurious free radicals and viscous components leading to hyperviscosity.[8,9,18-20] It has been postulated that using plasma rather than albumin as the replacement fluid may replenish consumed protective factors that maintain microcirculatory flow (such as a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 [ADAMTS-13] and protein C) and prevent vascular leakage (angiopoietin-1).[21-23]

These theoretical benefits of TPE have been challenged for several reasons. First, while hypercytokinemia

is present, the actual contribution of CRS to the progression of severe COVID-19 has not been established. Second, the efficacy of TPE to treat CRS has been questioned because of the incredibly short half-life of cytokines (approximately 5 min) and the continued production of cytokines.[24] Third, TPE does not only remove cytokines, but also nonselectively removes other plasma proteins. Pro-inflammatory as well as anti-inflammatory mediators are reduced along with anti-viral immune factors, such as immunoglobulins and complement. These components may clear SARS-CoV-2 and protect against secondary infections.[21,25] Fourth, as with hypercytokinemia, antifibrinolytic mediators, free radical damage, and hyperviscosity have yet to be established as part of the pathologic process of severe COVID-19. Finally, there is no published data to support the claim that TPE is able to decrease SARS-CoV-2 viral burden.

2.2 | Available applicable guidelines for the use of therapeutic plasma exchange

A number of neurologic conditions have been suspected to be associated or exacerbated with COVID-19, including Guillain Barre syndrome (GBS)[26] and myathenia gravis (MG).[27-29] According to the most recent 2019 American Society for Apheresis (ASFA) Guidelines, GBS and acute exacerbation of MG are category I indications for TPE (ie, apheresis is accepted as a first line therapy, either as a standalone or in conjunction with other modes of modality).[30] The treatment of other neurologic complications of COVID-19 remains unclear. Evidence for whether TPE is beneficial in sepsis and MOF is limited. Specifically, the ASFA Guidelines states that the optimum role of apheresis therapy in the treatment of sepsis and MOF is not established (category III) based on the moderate-quality evidence available (grade 2B).[30] The role of hyperviscosity in severe COVID-19 is also currently speculative. Nonetheless, TPE has been suggested as an intervention to treat COVID-19 hyperviscosity.[8,9] Of note, TPE is only indicated for the treatment of hyperviscosity in the context of hypergammaglobulinemia according to ASFA Guidelines.[30] Additional ASFA Guidelines for indications such as viremia and ARDS are not available.

2.3 | Reported experience of therapeutic plasma exchange to treat COVID-19

There have been case reports, case series, and case-controlled studies on the use of TPE in patients with COVID-19, which are discussed below and summarized in the Table S1.

Therapeutic plasma exchange has been used to treat COVID-19 patients who had various degrees of respiratory involvement ranging from nonintubated patients with pneumonia[22] to those with ARDS[15,31-33] required to be in the intensive care unit (ICU).[19] Patients reportedly demonstrated clinical improvement after TPE.[15,22] For example, a retrospective study involving five tertiary centers identified 91 COVID-19 ICU patients with pneumonia and included 73 of these patients in their analysis. Of the 53 patients with elevated D-dimer (>2 mg/L), 18 received TPE and 35 did not. In this subgroup analysis, a statistically significant difference in (unspecified) mortality was observed in the TPE treated group (3/18 [16.7%] vs 16/35 [45.7%], $P = .037$), and this difference in mortality remained after propensity score matching (PSM) was performed (1/12 [8.3%] vs 7/12 [58.3%], $P = .009$).[19]

Therapeutic plasma exchange has not only been provided as therapy for COVID-19 respiratory disease, but other manifestations as well, such as neurological or gastrointestinal complications. In one case, Shi et al[34] reported the use of TPE and intravenous immunoglobulin (IVIG) in a COVID-19 patient with respiratory failure, shock, and persistent diarrhea with report of clinical improvement. Ma et al[35] managed a COVID-19 patient with respiratory failure required mechanical ventilation, cerebral infarct, and antiphospholipid syndrome (APS) with TPE. The patient was successfully weaned off mechanical ventilation but remained hospitalized. Fernandez et al[36] provided TPE to one COVID-19 patient with pneumonia and APS, who then became stable for discharge. A number of neurologic conditions have been suspected to be associated with COVID-19. The use of TPE, usually in combination with methylprednisolone or IVIG, with clinical improvement has been reported in rare cases of COVID-19 associated meningoencephalitis, acute necrotizing encephalopathy (ANE), acute transverse myelitis, acute necrotizing myelitis (ANM), and acute motor axonal neuropathy (AMAN).[37-42] Seven TPEs were performed in a pediatric COVID-19 patient with postviral quadriplegia and transverse myelitis who requiring mechanical ventilation and did not respond to IVIG and methylprednisolone treatment. However, this patient did not have any clinical improvement.[41] More data is needed to assess the utility of TPE for COVID-19-associated neurologic conditions outside of GBS and acute MG.

Therapeutic plasma exchange has additionally been used to treat severe COVID-19 with ARDS accompanied by MOF and/or septic shock.[23,43-47] Keith et al[43] reported a single patient experience with COVID-19 positive pneumonia who developed MOF and septic shock requiring cardioversion and mechanical ventilation. The patient was treated with TPE and weaned off vasopressors within 24 h. Khamis et al[23] compared 11 COVID-19 patients

with severe pneumonia or ARDS, MOF, and septic shock treated with TPE with 20 patients who did not receive TPE. Although those who received TPE had a longer ICU length of stay than those who did not (14 vs 6 days; $P = .028$), the all-cause mortality was not statistically different between these groups (9.1% vs 45%; $P = .055$). An unpublished retrospective observational study comparing 40 patients with COVID-19 complicated by MOF and septic shock who received adjunct TPE with 40 propensity matched controls who received supportive care without TPE found no difference in PaO2/FiO2 (P/F) ratio between the two groups at 48 h after TPE ($P = .84$). After subgroup analysis, the 28-day mortality benefit (47.8% vs 81.3%; $P = .05$) may be present for patients with pneumonia as the primary source of sepsis treated with TPE.[47]

Many reports claimed that patient improvement after TPE demonstrated its efficacy as COVID-19 therapy by removing cytokines, without reporting cytokine levels.[43,45,47] When laboratory and clinical information were available, data was limited and inconsistent. Ma et al[35] reported decreased CRP and IL-6 after TPE and IVIG in one patient. In a cohort of six patients critically ill with COVID-19 ARDS followed by progression to meningoencephalitis who received TPE, reversal of magnetic resonance imaging (MRI) findings was reported in all patients. However, decreased ferritin was only observed in four of six patients.[37] Morath et al[46] treated five COVID-19 ICU patients with ARDS, MOF, and vasopressor-dependent circulatory shock with TPE. Biomarkers, such as CRP, IL-6, ferritin, and D-dimer, were reported to have decreased after TPE in all patients, but only three of five survived. Khamis et al[23] found reductions in D-dimer, ferritin, CRP, and IL-6 after TPE, but all-cause mortality was not significantly different between TPE treated and non-TPE treated patients. In a subgroup analysis of patients with COVID-19 pneumonia and elevated D-dimer, after PSM, Gucyetmez et al[19] reported a statistically significantly lower unspecified mortality in the group treated with TPE compared to the group not treated with TPE, but the reduction in IL-6 was not significantly different ($P = .933$).

The ability of TPE to provide survival benefit to patients with severe COVID-19 by attenuating cytokine mediated inflammation is not established. An experience with TPE in a critically ill COVID-19 patient reported detection of SARS-CoV-2 specific IgG and IgA antibodies in the waste bag, as well as a one log reduction in the circulating antibodies in the patient. Given the importance of humoral immunity in clearing SARS-CoV-2, these findings provide cause for concern.[21]

In the absence of sufficient data and proven efficacy, TPE protocols as part of the treatment regimens in patients with COVID-19 have been quite heterogenous (Table S1). In brief, the treatment schedules ranged from one to nine procedures, usually provided daily, but sometimes every other day. Fresh frozen plasma was specified as the replacement fluid for many, but not all studies. The duration of the procedure and plasma volume exchanged were also variable.

3 | THERAPEUTIC PLASMA EXCHANGE TO TREAT OTHER VIRAL ILLNESSES

Therapeutic plasma exchange has previously been used in patients with other viral infections (influenza virus, adenovirus, Epstein-Barr virus [EBV], severe fever with thrombocytopenia syndrome [SFTS] virus) who have failed conventional antiviral therapy. In these viral diseases, instead of targeting the viruses themselves, TPE has typically been used to manage complications associated with the infections.

The most widely reported use of TPE in a respiratory viral infection is with influenza. Liu et al[48] managed 16 patients with ARDS due to avian influenza A (hemagglutinin 7 neuraminidases 9 [H7N9]) with TPE and tandem continuous veno-venous hemofiltration. Of 16 patients, 10 survived. The survival benefit from this combination of TPE and continuous veno-venous hemofiltration was attributed to management of fluid overload, metabolic disturbance, and removal of inflammatory mediators. Seventeen of 27 cytokines and chemokines measured decreased significantly after TPE. Two additional studies have attributed the benefit of TPE in the treatment of critically ill patients with H1N1 to a reduction in circulating cytokines. Kawashima et al[49] reported using TPE and methylprednisolone to treat influenza-associated encephalopathy in three patients. IL-6 decreased after TPE, and the patients recovered without severe sequela. Patel et al[50] utilized TPE in three children with acute lung injury in the setting of H1N1 influenza. The patients reportedly had features of CRS which were attenuated by daily TPEs (for three consecutive days), but cytokine levels were not provided. Other complications such as thrombotic thrombocytopenic purpura (TTP),[51] hemophagocytic lymphohistiocytosis (HLH),[52] GBS,[52,53] and other neurologic conditions[54] presumably triggered by H1N1 were also reported to be treated with TPE.

Therapeutic plasma exchange has also been studied in SFTS virus, a tick-borne illness. It can cause symptoms including fever, thrombocytopenia, leukocytopenia, MOF, coagulopathy, and neurological abnormalities with an approximate mortality rate of 30%.[55] A cytokine-mediated inflammatory response has been reported to play an important role in the pathogenesis of SFTS. A retrospective

cohort study was conducted in nine hospitals in Korea with 53 patients, comparing those treated with TPE (n = 24) with those who were not treated with TPE (n = 29). The inpatient mortality rate of the TPE treated group did not differ from that of the non-TPE treated group (29.3% vs 34.5%, $P = .68$).[55]

Therapeutic plasma exchange has also been studied in neurologic complications associated with adenovirus[56] and EBV.[57] There is one case report of using TPE to treat disseminated adenovirus and acute encephalitis in the setting of allogeneic stem cell transplantation.[56] There is also a single report of postinfectious cerebellitis associated with EBV with improved outcomes after TPE.[57]

The data on patient outcomes after TPE in other viral infections is sparse and variable. Due to multiple concurrent treatment modalities, reports of favorable outcomes cannot be attributed to TPE alone. Furthermore, the pathogenesis of COVID-19 may or may not be the same as the other viruses discussed above.

4 | HEMADSORPTION DEVICES COMPATIBLE WITH THERAPEUTIC PLASMA EXCHANGE

While yet to be proven, the primary theoretical rationale for using TPE to treat COVID-19 is to reduce pro-inflammatory cytokines. However, TPE removes plasma proteins non-selectively, raising concern that removal of protective host defense proteins and anti-inflammatory mediators may lead to worse rather than better outcomes. To address this concern, hemadsorption has been proposed.[4]

Hemadsorption is performed using adsorption columns made of porous polymer that bind to compounds typically ranging from 5 to 60 kDa, the size of most cytokines.[58,59] Blood is placed in direct contact with the adsorbent in an extracorporeal circuit. Different circuit options include hemodialysis, CRRT, extracorporeal membrane oxygenation (ECMO), and TPE.[59] Four devices have received emergency use authorization (EUA) from the Food and Drug Administration (FDA) for patients at least 18 years old with COVID-19 admitted to the ICU with confirmed or imminent respiratory failure: the Seraph 100 Microbind Affinity Blood Filter (ExThera Medical Corporation, Martinez, CA)[60]; the oXiris Set (Baxter Healthcare Corportation, Deerfield, IL)[61]; the CytoSorb device (CytoSorbents Inc., Monmouth Junction, NJ),[62] and the Depuro D2000 Adsorption Cartridge (Marker Therapeutics Inc., Houston, TX).[63,64] The availability of these products under EUA (section 564 of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. §360bbb-3) is not approval, licensure, or clearance of the device by the FDA.[65]

Only the Depuro D2000 Adsorption Cartridge (D2000) is used in conjunction with TPE, as it operates with the Spectra Optia (Terumo BCT, Lakewood, CO). The separated plasma is filtered through a proprietary adsorption material (consisting of a blend of activated uncoated coconut shell charcoal, the nonionic resins Amberlite XAD-7HP and Amberchrom GC300C) to remove IL-3, IFN-gamma, IL-10, IL-1B, IL-6, IL-8, MCP-1, and TNF-alpha.[64] The D2000 is Conformitè Europëenne (CE) marked for reduction of inflammatory cytokines. There is one available case report[66] and two trials registered on clinicaltrials.gov aiming to evaluate the D2000 in the treatment of patients with COVID-19.[67] The pilot study of one of these trials reported treatment of 10 ICU patients with life-threatening COVID-19 ARDS, at least one CRS defining criteria, sepsis/septic shock, and/or MOF. Nine of 10 were extubated successfully and discharged without complications, while one of 10 expired.[68]

The oXiris Set is CE marked to help remove excessive levels of cytokines, endotoxin, and other inflammatory mediators from the patient's blood.[69] CytoSorb is CE marked for the removal of cytokines from circulation, as well as the removal of ticagrelor.[62] The Seraph 100 Microbind Affinity Blood Filter is neither CE marked nor FDA approved. These three hemadsorption devices allowed under EUA are used with hemodialysis, CRRT, or ECMO circuits. Thus, further discussion is beyond the scope of this article. Apart from the EUA, the FDA approved an Investigational Device Exemption for Toraymyxin B PMX adsorber (Spectral Medical Inc., Toronto, Canada), a device developed to adsorb circulating endotoxins.[70] In addition, adsorptive granulocyte and monocyte apheresis (using Adacolumn, which is an adsorptive type leukocytapheresis column containing cellulose acetate beads bathed in saline to selectively remove granulocytes and monocytes/macrophages) was used to treat COVID-19 in a patient with a history of ulcerative colitis.[71] A single COVID-19 patient experience using C-reactive protein apheresis (PentraSorb, Pentracor GmbH, Germany), which selectively removes plasma CRP, has also been published.[72]

At present, hemadsorption is not a standardized strategy and there are no randomized controlled trials proving its efficacy in achieving improved clinical outcomes or survival benefits in patients with COVID-19. Additional studies, some of which are currently in progress, are required to determine if hemadsorption is therapeutically effective.[73]

5 | ADDITIONAL CONSIDERATIONS

Medical management of COVID-19 is not the only challenge posed to healthcare workers and the healthcare

system by this pandemic. SARS-CoV-2 infections can be completely asymptomatic and respiratory droplets may travel up to six feet causing person-to-person transmission. The virus may also persist on surfaces for several days.[74] Therefore, equipment management as well as protection of other patients and medical personnel are essential. Personal protective equipment guidelines for COVID-19 must be followed. Apheresis staff should don N95 masks, goggles, gloves, gowns, head, and shoe covers when providing care for patients with suspected or confirmed COVID-19 infection. Use of electronic records is ideal. Any paper documents, such as consent forms or apheresis worksheets, should be protected by plastic covers that allow for decontamination. Large private rooms that allow as much distance as possible between COVID-19 patients and healthcare providers is ideal. Instrument setup outside of the patient's room[33] and having unit nurses already caring for the patient perform vascular access[41] have been reported. After the procedure, the apheresis machine should be thoroughly decontaminated. Another precaution may be designating a COVID-19 instrument and quarantining it for 96 h after exposure,[75] if possible and not limited by the availability of apheresis machines.

Routine complications of TPE associated with central line placement, line infection, and hypocalcemia apply for COVID-19 patients.[76] TPE may also be technically challenging to perform in COVID-19 patients who are routinely placed in prone position.[77] An additional consideration is risk of clotting during the procedure which may prematurely interrupt the procedure and lead to acute blood loss in a patient who is already critically ill with hypotension or shock. Given that these patients with COVID-19 are hypercoagulable, adjustments in the anticoagulant must be performed with extreme care to avoid the risk of clotting the circuit while at the same time not placing the patient at increased risk for bleeding. The cost and resources necessary for TPE are not trivial and must be evaluated carefully when the healthcare system is overburdened with pandemic response. Finally, during the ongoing COVID-19 pandemic, scientific rigor remains indispensable. The release of results in nonpeer reviewed, prepublication status, may confuse the practice of evidence-based medicine.

6 | CONCLUSION

The potential benefit of TPE as adjunctive therapy for COVID-19 by controlling cytokine-mediated inflammation remains theoretical. The causal relationship between CRS and the development and progression of ARDS, MOF, and septic shock still remains to be proven. TPE not only removes pro-inflammatory cytokines, but also anti-inflammatory mediators and host defense factors. It is unknown whether TPE is capable of curbing CRS while maintaining an adequate anti-viral immune response. There is no published data in support of the claim that TPE can diminish SARS-CoV-2 viral load. Given the novel nature of this virus, clinical studies are limited, but studies evaluating the role of TPE in other viral illnesses are also inconclusive. TPE and adsorption devices compatible with TPE have not been appropriately and adequately studied as adjunctive therapy for COVID-19. The LEOSS (Lean European Open Survey on SARS-CoV-2 Infected Patients) registry is an open, international, anonymous registry covering all aspects of COVID-19 including treatment using TPE.[78] As of August 2020, the trial registry site clinicaltrials.gov listed almost 3000 COVID-19 trials, nearly 10 studying the use of TPE or extracorporeal methods in COVID-19.[73] With these clinical trials underway, new evidence may come to light in the future that will provide stronger recommendations.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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