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Potential of therapeutic plasmapheresis in treatment of COVID-19 patients: Immunopathogenesis and coagulopathy

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ARTICLE INFO

Keywords:

COVID-19

Coagulopathy

Therapeutic Plasmapheresis

Immunopathogenesis

ABSTRACT

Therapeutic plasmapheresis (TP) is the process of the separation and removal of plasma from other blood components and is considered as an adjunctive treatment strategy to the discarded abnormal agent in the management of respiratory viral pandemics. This article reviews the mechanisms of immunopathogenesis and coagulopathy induced by SARS-CoV-2 and the potential benefits of TP as adjunctive treatment in critically COVID-19 patients.

1. Introduction

The procedure of therapeutic plasmapheresis is based on the fact that removal of abnormal accumulated substances such as cytokines or autoantibodies from the plasma can be therapeutic in certain situations [1]. The American Society for Apheresis 2019 guidelines define sepsis with multi-organ dysfunction (MOD) as category 3 and grade 2B recommendation for TP [2]. This therapeutic potential has caused plasma exchange to be considered as an adjunctive treatment for the management of cytokine storm and coagulopathy in respiratory viral pandemics.

Recently COVID-19 caused by SARS-CoV-2 has become a prominent problem that has affected human health, social and economic relationships. SARS-CoV-2 is a novel human-infecting Betacoronavirus [1]. The structural analysis implies that Spike glycoproteins are the most immunogenic parts of the SARS-CoV-2 which may use receptor angiotensin converting enzyme2 (ACE-2) to enter the host cells [3]. Distribution of the ACE-2 receptor on the surface of alveolar type 2 (AT2) epithelial, cardiac, renal, intestinal, and endothelial cells lead to the target organs involvement and emerging the clinical symptoms in COVID-19 [4].

Symptoms normally occur within a 3-5-day incubation period

(range-2-14 days) of exposure. COVID-19 symptoms vary from mild to severe and may include shortness of breath, cough, myalgia, fever, and extreme pneumonia [1]. SARS-CoV-2 induces excessive and prolonged inflammatory responses in some infected individuals with underlying chronic diseases such as diabetes, cardiovascular, and pulmonary diseases [5]. Also, the highest proportion of severe cases occurs in adult ≥ 60 years. This phenomenon is known as the cytokine storm and causes acute respiratory distress syndrome (ARDS) and multiple organ dysfunction (MOD), which leads to physiological deterioration and death. Timely control of the cytokine storm in its early stage through such means as immunomodulators and cytokine antagonists, as well as the reduction of the burden of cytokine, is the key to the success of treatment and reducing the mortality rate of patients with COVID-19 [6].

In this study, we aimed to review the mechanisms of immunopathogenesis and coagulopathy induced by SARS-CoV-2 and the potential benefits of TP as an adjunctive treatment in critical COVID-19 patients. For this purpose, PubMed and Google Academic were searched. Original data in all studies (including case reports and case series) published in the English language were viewed.

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<https://doi.org/10.1016/j.transci.2020.102993>

2. Immunopathogenesis induced by SARS-CoV-2

Studies have suggested various mechanisms for the immunopathogenesis induced by SARS-CoV-2 and it seems that the overlapping of these mechanisms eventually leads to cytokine storm and the emergence of symptoms in COVID-19.

Actually, in the normal circumstance the response of the immune system to the SARS-CoV2 leads to lysis of infected cells by NK cells of innate immunity and CD8⁺ cytolytic T-cells of the adaptive immunity. This leads to apoptosis of antigen-presenting cells and relevant cytotoxic T cells to avoid unnecessary activation. However, if a defect occurs in lymphocyte cytolytic activity, whether due to genetic problems or acquired conditions, this may lead to the inability of NK and cytolytic CD8 T cells to lysis the infected and activated antigen-presenting cells, resulting in prolonged and exaggerated interactions between innate and adaptive immune cells [4].

Evidence also demonstrates that SARS-CoV-2 may have a similar mechanism of pathogenesis as SARS-CoV. Indeed, in response to SARS-CoV infections, the production of type I interferon (IFN-1) increases to inhibit viral replication [6]. Secretion of Type I interferon including IFN- α / β is the most important response of the natural immune system to viral infections, which plays a very important role in the early stages of viral infection. Delay in production of INF-I in the early stages of SARS-CoV-2 infection prevents an appropriate antiviral response by the immune system [6.] Afterward, the production of cytokines and chemokines increases rapidly and attracts inflammatory cells such as neutrophils and monocytes, resulting in excessive infiltration of inflammatory cells into involved tissue, resulting in tissue damage [6]. To overcome this antiviral activity of interferon, the virus encodes at least 8 viral antagonists that suppress the induction of IFN and cytokines [7]. Studies also showed that rapid replication of SARS-CoV delays IFN- α / β secretion, which is associated with an influx of many macrophages. The collected macrophages receive activation signals through IFN- α / β receptors at their surface and produce more chemotaxis factors (such as CCL2, CCL7, and CCL12), resulting in increased macrophage accumulation [6]. These mononuclear macrophages produce high levels of proinflammatory cytokines (TNF, IL-6, IL1- β , and induced nitric oxide synthetase), resulting in cytokine storms. Besides, macrophage-induced proinflammatory cytokines induce T cell apoptosis, which prevents the clearance of virus-infected cells [8]. Also, Macrophage activation syndrome (MAS), which is associated with the engulfment of blood cells such as red blood cells, leukocytes, or platelets by macrophage cells, may occur in the underlying cytokine storm this phenomenon is also known as secondary hemophagocytic lymphohistocytosis (sHLH) [9].

In another study, in addition to the role of interferon I, impaired viral clearance and increased neutrophil extracellular traps (NET) were also mentioned in the pathogenicity of SARS-CoV-2. SARS-CoV and MERS-CoV can produce dual-membrane vesicles and, by replicating in these vesicles, remain immune to the availability of antiviral immune responses. Transfer of DNA fragments to the extracellular space also occurs following a process known as NETosis, a form of programmed cell death. Viral RNA and proinflammatory cytokines may stimulate the formation of NETs and NETosis and may be involved in the pathogenesis of COVID-19 [4].

Another mechanism that has been proposed is related to antibodies. In this regard, Liu et al. pointed out the importance of antibodies against spike glycoprotein (anti-S-IgG) as a stimulant of proinflammatory monocyte/macrophage accumulation in the lungs. Golonka et al. also speculated that the response of specific antibodies against the virus may be associated with pathological changes in that the glycoprotein S protein on coronaviruses is restructured and enters the host cells through the Fc IgG region. In other words, they proposed a mechanism for antibody-dependent entry of the virus into the host cells [10].

Evidence suggests that in patients with underlying diseases such as diabetes, hypertension, and cardiovascular disease that affect vascular health, flexibility and the capacity to tolerate systemic cytokines are

reduced [11]. This situation creates the conditions for a cytokine storm. Cytokine storm is considered as the sudden production of cytokines such as IL-1, IL-6, IL-2, IL-7, IL-10, G-CSF, MCP 1, MIP-1a, and TNF- α , and is one of the major reasons for ARDS and MOD which leads to exacerbation of the disease.

Patients infected with SARS-CoV-2 are reported to have higher plasma levels of proinflammatory cytokines including IL1, IL-2, IL7, TNF, GSCF, and MCP1 than healthy adults [1]. Importantly, patients in the intensive care unit (ICU) had significantly higher GSCF, IP10, MCP1, and TNF- α levels than non-ICU patients, implying that cytokine storms may be the underlying cause of disease severity [12].

Patients with severe hypoxia and cytokine storm are more likely to develop acute respiratory distress syndrome (ARDS) and multi organ dysfunction syndrome (MOD) [13]. Besides, laboratory findings include lymphopenia [14], prolonged prothrombin time, increased lactate dehydrogenase, high levels of C reactive protein (CRP) and IL-6 are observed in these patients [1]. Also, ICU-admitted patients had more laboratory abnormalities than non-ICU patients [4]. Some of these patients show an increase in aspartate aminotransferase, creatine kinase, creatinine and C-reactive protein, high levels of serum ferritin and D-dimer diffuse intravascular coagulation (DIC), and macrophage activation syndrome (MAS) [4].

3. Coagulopathy induced by SARS-CoV2

ARS-CoV-2-induced coagulopathy may be created by direct viral damage or stimulation of platelet aggregation and thrombosis with increased consumption in lung tissue [15]. Also, the effect of cytokines is not limited to inflammation and is sometimes developed by activation of endothelial cells and spread by microcirculatory thrombosis [15]. A meta-analysis of 1779 COVID-19 patients also proposed thrombocytopenia as a clinical marker of critical disease [16]. Studies also show that the secretion of abnormal von willebrand factor multimers (ULVWF multimers) leads to the deposition of platelet-ULVWF accumulations on injured endothelial cells, leading to endotheliopathy associated vascular microthrombotic disease (EA-VMTD). This condition is associated with consumptive thrombocytopenia, multi-organ dysfunction syndrome (MODS), and DIC [17]. Numerous studies have shown that systemic inflammation can lead to acquired ADAMTS13 deficiency [18]. One study found that platelets were meaningfully reduced in patients with a reduction of more than 30 % of ADAMTS13. The acquired ADAMTS13 deficiency can increase the levels of ULVWF multimers that may already be developed from EA-VMTD in ARDS and MODS [19]. Decreased ADAMTS13 levels correlate with progression to multi-organ failure and have been associated with an increased risk of mortality [18,19].

Coagulopathy seems to play a very important role in the prognosis of COVID-19 patients. D-Dimer levels above 1000 mg/L may recognize COVID-19 patients with poor prognosis at an early stage [20]. Studies show that 18 patients who died of COVID-19 disease revealed significant fibrinogen degradation products and D-dimer levels compared to patients with mild disease [21]. In this regard Wang et al. who studied 138 COVID-19 patients found D-dimer levels of ICU versus non-ICU patients were 414 and 166 mg/L, respectively they also reported that D-dimer levels were higher in non-survivor COVID-19 patients [22]. Moreover, Autopsy findings in COVID-19 patients demonstrate vascular changes, including thickening and pulmonary thrombosis [23].

4. Therapeutic potential of plasma exchange in COVID-19

For blood purification therapy (BPT), various methods such as haemofiltration, haemoperfusion, intermittent or continuous high-volume haemofiltration (HVHF), plasma exchange, or adsorption are used [24].

One of the reasonable methods to reduce the burden of cytokines, aberrant procoagulant agents, and load of viruses in COVID-19 is to physically remove them using plasmapheresis therapy with or without plasma exchange (TPE). Plasmapheresis is performed by two completely

different methods: centrifugation or filtration [25]. A significant advantage of centrifugation is that there is no limit on the size of the molecules being removed. In the filtration method the size of the molecules removed is limited by the pore size of the filter [25].

In this regard, there are reports of the effectiveness of a continuous hemofiltration membrane (CHF) and double filtration plasmapheresis (DFPP) methods in the improvement of COVID-19. It has been reported that using medium/large pore membrane (100/50 KD) continuous hemofiltration membrane (CHF) with albumin replacement may be effective in the removal of IL-6 and IL-23 molecules from COVID-19 patient plasma. [26]

The history of the use of plasmapheresis in the reduction of cytokines and the abnormal agent goes back to its use in sepsis and septic shock. The excessive inflammation, upregulation of procoagulant proteins, and depletion of natural anticoagulants seen in septic shock are associated with MOD and mortality. TP is considered to improve organ function by clearing inflammatory and antifibrinolytic mediators and replenishing anticoagulant proteins to restore hemostasis. Removal of these substances may be helpful, particularly in the early phase of sepsis [27]. In this regard, a prospective, randomized, clinical trial on 106 patients with septic shock showed that the 28-day survival rate was 33.3 % (18/54) in the plasmapheresis group versus 53.8 % (28/52) in the control group [28]. Also, a meta-analysis suggests that the only potentially effective blood purification therapy for the treatment of sepsis is plasma exchange or haemoadsorption particularly with Polymyxin B [29,30].

The efficacy of plasmapheresis as adjunctive therapy in septic shock has led to the development of this method in respiratory virus infections with symptoms similar to septic shock. The purpose of plasmapheresis in the treatment of viral diseases in addition to clearing inflammatory and antifibrinolytic mediators and replenishing anticoagulant proteins can be to reduce the burden of the virus in the blood.

In this regard, there is a report of double filtration plasmapheresis (DFPP) to reduce viral RNA for the hepatitis C virus (HCV) with the reason that HCV particles are large enough (approximate diameter 55–60 nm) to not pass through the membrane so they can be eliminated [2]. Considering the size of the SARS-CoV2 (60–140 nm), the use of DFPP seems to be effective in reducing the virus load due to its ability to remove particles larger than 60 nm [31–33].

However, the main use of plasmapheresis in viral infections is to reduce the load of cytokines and abnormal coagulation factors. In this regard, an artificial-liver blood-purification system was used to treat patients with severe H7N9 influenza infection [34]. Positive results were demonstrated in terms of remarkably reducing the levels of 17 cytokines/chemokines [35]. In another study therapeutic plasma exchange was used for H1N1 influenza during the 2009 global pandemic of the virus. Three children in a pediatric ICU had developed ARDS, cytokine release storm (CRS), and were hemodynamically compromised. Using the filtration exchange method, the patients underwent 2 TPE procedures, which lead to dramatic reductions in oxygen and vasopressor requirements and significant drops in their pediatric organ dysfunction scores. All 3 patients tolerated TPE procedures without any adverse effects and ultimately survived with a good functional status at discharge. This study also showed that TPE is still effective even in the later stages of a cytokine storms [36].

In patients with SARS-CoV2 associated with ARDS and MOD, cytokine storm targeted therapy was suggested to treat severe pulmonary failure secondary to an extreme inflammatory cytokine. Some studies showed that cytokine/chemokine clearance was obtained using therapeutic plasmapheresis [37]. TPE was proposed by Keith et al. as a potential treatment targeting the mitigation of a cytokine storm, inflammation, endothelial dysfunction and coagulation dysfunction in critically COVID-19 patients [38]. According to FDA's recent approval, TPE can be used based on the same guidelines that are recommended for investigational COVID-19 convalescent plasma [39].

In this regard, Lu et al. studied the relationship between IL-6 levels in

COVID-19 patients and the effect of plasma exchange on these values. In this study, various parameters such as CRP and IL-6 level of 6 critically COVID-19 patients were assessed. Prior to plasma exchange; the test group (3 patients) had IL-6 values of 12.14, 12.20, and 142.90 pg/L, respectively. The result showed that after the plasma exchange, IL-6 values decreased to 4.33, 2.55, and 6.48 pg/L, respectively [40].

In a study conducted by Hua Shi and colleague, plasma exchange with fresh frozen plasma as replacement fluid, followed by administration of 20 g of IVIG was done from day 14–17, the patient's symptoms decreased after three courses of plasma exchange, the oxygenation index increased with an oxygen saturation of 96 %, and the blood pressure was recovered on Day16. Vasopressor and antibiotic therapy was stopped. Concurrently, levels of serum transaminase enzymes and creatinine improved. However, diarrhea continued on Day16 and the patient was prescribed intravenous anisodamine (10 mg daily). After a fourth plasma exchange followed by IVIG on Day17, the patient made an immediate improvement with no further diarrhea. Her PaO₂ /FiO₂ increased to 302 mmHg, coinciding with improving chest radiographic evidence on Day 18, the patient received the sixth IVIG treatment, with the dose of methylprednisolone divided to 20 mg and discontinued on Day 19. Supplementary oxygen was discontinued on Day 20, with the O₂ saturation improved to 95 % on room air. Swab samples collected on days 16, 18, and 20 from the patient's throat were negative for SARS-CoV-2. The patient was discharged from the hospital on Day 23 with noticeable improvement of chest radiographic evidence after 15 days of hospitalization. this study reveals that timely initiation of PE treatment followed by IVIG protected the patient from progression to ARDS and MOD. Significantly, the patient made a prompt recovery following PE treatment without the need for mechanical ventilation or any side effects [41].

In another study to assess the effectiveness of therapeutic plasmapheresis in COVID-19 patients a case series of critically ill patients, with laboratory-confirmed SARS-CoV2 was investigated at the Royal Hospital, Oman. A total of 31 COVID-19 patients were included with an overall mean age of 51.15 years (range: 27–76 years); 90 % (n = 28) were males, and 35 % (n = 11) of the patients had undergone TPE. The study was performed on patients admitted to the intensive care unit (ICU) Nearly all of the patients in the plasma group (10/11) presented with moderate to severe ARDS, while severe pneumonia was the main presentation in the control group. The results demonstrated that the TPE group was associated with higher extubation rates than the control (73 % versus 20 %; p = 0.018). Additionally, patients on TPE had a lower 14 days (0 versus 35 %; p = 0.033) and 28 days (0 versus 35 %; p = 0.033) post plasma exchange mortality compared to patients in the control group. However, this difference was not significant (9.1 % versus 45 %; p = 0.055; power = 66 %). Also, laboratory and ventilatory parameters also improved post-TPE (n = 11). This study revealed that the use of TPE in critically COVID-19 patients has been associated with improved outcome and the clinical evidence were favorable in terms of extubation and mortality benefit with TPE [42].

In the following case report by Philip Keith on a 65-year-old female with septic shock and multi-organ failure with multiple comorbidities demonstrated notable clinical improvement after therapeutic plasma exchange. She was found to be SARS-CoV-2 positive with pneumonia and developed progressive hypoxemia and shock requiring vasopressors, cardioversion, and non-invasive positive pressure ventilation. She experienced 4.5-L TPE using fresh frozen plasma (FFP) as replacement fluid. She showed rapid improvement and was weaned off vasopressors within 24 h. She had improved respiratory status and was able to alternate between NIPPV and high-flow nasal cannula. She reverted back to afib with rapid ventricular response (RVR). Her hypoxemia improved daily, and she was slowly weaned to room air. A repeat echocardiogram on day 9 showed return of her EF to baseline. She was discharged home on hospital day 13. This case supports the theory that plasma exchange may help decrease the "cytokine storm" induced endotheliopathy and microthrombosis associated with COVID-19 [15].

The level of cytokine, coagulation agent, and viral load is the most important parameter to determine the outcome of COVID-19. It seems that a correctly timed combination therapy includes interferon, antiviral drugs, corticosteroids, and physical elimination of aberrant agent should be considered in disease management. TP seems to be a reasonable approach to decrease the viral burden and especially to remove circulating cytokines. Also, convalescent plasma as a replacement fluid during the TP procedure can be most beneficial among the COVID-19 patients due to its having specific antibodies and normal coagulation factors [31].

Another important point regarding the efficiency of therapeutic plasmapheresis is to start in the early stages of SARS-CoV-2 infection, when proinflammatory cytokines are probably high [43]. In COVID-19 patients, it has been reported that the cytokine storm with severe disease was significantly higher around 7–14 days after the disease emerged. [44]. Thus, early initiation of plasmapheresis within this period could be related to better outcomes. It is also necessary to administer TP for the correct duration and quantity to monitor the possible drug removal of specific therapies and to follow the treatment outcome. The investigation effect of plasmapheresis in sepsis has shown that both the timing and disease severity are important for the beneficial effect of TP [43]. Routinely, for reducing the effects of the cytokine storm and coagulopathy in patients with viral infections and septic shock plasma exchange is performed 5–7 TP s daily and it is noted that respiratory improvements were only seen after completing the a course of TP [42].

5. Adverse event and complication

In a study conducted by Dr. Norda and the Swedish Apheresis Group the observations of over 20,000 therapeutic apheresis procedures were reported. The results showed that the incidence of adverse events was low (Grade I: mild 1.5 %, Grade II: moderate 2.8 %, Grade III: severe 0.8 %, and Grade IV: fatal events 0%). Although the occurrence of these side effects is very low, various factors may impact the incidence of adverse events including (1) the anticoagulation type, (2) the replacement fluid type, (3) the vascular access type, and (4) the underlying disease state [45].

FFP as a replacement fluid is associated with a two-fold higher risk of albumin. The most common side effects related to FFP are anaphylactoid shock other complications include fever, rigors, urticaria, wheezing, pruritus, hypotension, and laryngeal edema. Also, the side effects can be associated with a low concentration of ionized calcium and magnesium and metabolic alkalosis due to the presence of citrate anticoagulants in FFP (14 % per unit). Another rare but potential complication is the possibility of viral transmission [45]. Also, if convalescent plasma is used in COVID patients as a replacement fluid, the phenomenon of increased antibody-dependent enhancement of infection (ADE) may occur. Previous studies have shown that the antibodies target one serotype of the virus but only subneutralize another, leading to ADE. ADE can make symptoms worse in secondary virus infection [46]. The use of albumin as an alternative fluid, especially in COVID-19 patients, can be associated with some complications. Importantly, the use of this alternative fluid reduces the concentration of immunoglobulins, and due to the 22-day half-life of IgG, this reduction may persist for a long time after TP [45]. Also, critical COVID-19 patients have a high incidence of coagulopathy, and TP procedures with the use of albumin may result in depletion of procoagulant factors and increased bleeding risk [39].

Another potential complication associated with plasmapheresis is the removal or dilution of the antiviral or corticosteroid drugs. Since treatment with these drugs overlaps with TP and possesses anti-inflammatory effects, it is suggested that the drugs be prescribe after TP [45].

Despite the potential of TP for an adverse event, no severe side effects have yet been reported in COVID-19 patients undergoing plasmapheresis. In this regard, in one study in COVID-19 patients, five TP daily

were performed, and it was noted that all patients in this case study tolerated TP except for one hypotension episode, which resolved after normal saline bolus and hydrocortisone injection and did not recur with subsequent procedures [42].

6. Conclusion

Immunopathogenesis and coagulopathy induced by SARS-CoV2 in susceptible patients leads to cytokine storms and aberrant coagulation responses that can lead to high mortality due to the occurrence of ARDS and MOD. Reducing the burden of cytokines and abnormal coagulation agents by plasmapheresis can be very helpful in the management of COVID-19.

The main factor in the success of plasmapheresis is to start in the early stages of inflammation, in which there is a very high concentration of inflammatory cytokines. Also, the frequency of plasmapheresis is very important in controlling the disease. In this regard, evidence shows that just after completing treatment, a significant improvement is observed. Although this therapeutic method can potentially be associated with complications, in studies performed in COVID-19 patients, this method was well tolerated by patients. However, the restricted low availability to the plasmapheresis devices in all areas and the need for professional personnel are the limitations of this therapeutic method.

Declaration of Competing Interest

The authors report no declarations of interest.

Acknowledgment

The study was supported by the Iranian blood transfusion organization.

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