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Coupled Plasma Filtration Adsorption as a Potential Therapy for Critically III Covid-19 Patients

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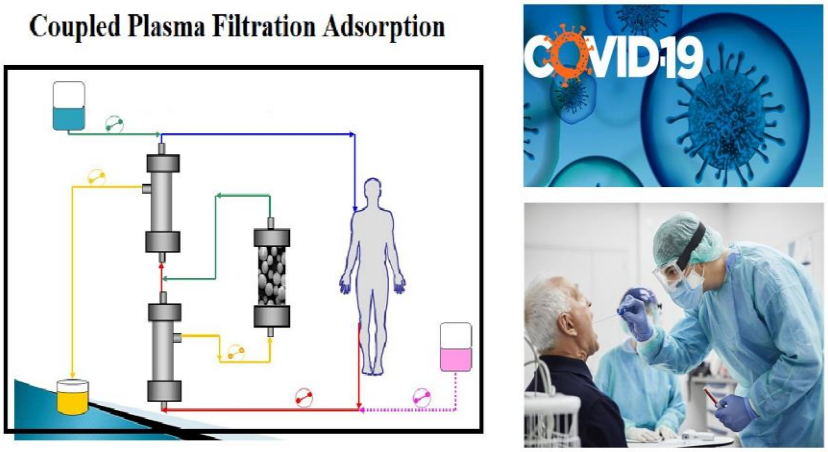
ABSTRACT

The Corona-19 virus disease (Covid-19) continues to cause an increasing number of deaths, mainly due to acute respiratory disorders. The high pandemic mortality and morbidity prompted clinicians to seek suitable adjunctive therapeutic methods to eliminate high cytokine levels effectively. This study aimed to review the combined plasma filtration adsorption (CPFA) technology and its potential efficacy in treating critically ill Covid-19. CPFA combines plasma separation, adsorption, and hemofiltration techniques that meet the need to remove substances such as cytokines. Findings from the report suggest an immune dysregulation known as cytokine storm syndrome plays a role in severe and critically ill Covid-19 patients. Extracorporeal blood purification targets cytokine elimination and is preferred as a bridging strategy to improve survival. Combined adsorption plasma filtration (CPFA) can remove various substances, including cytokines, without depleting physiologically essential proteins. CPFA can be considered and assessed in clinical trials to treat critically ill Covid-19 patients. Paired Plasma Filtration Adsorption (PPFA) can be viewed as a potentially effective therapy in treating Covid-19 patients in critical condition.

GRAPHICAL ABSTRACT



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Introduction

Since its appearance in Wuhan, China, in December 2019, the corona-19 virus (Covid-19) has rapidly spread globally [1-3]. There have not been adequate studies on the immunological response to COVID-19 infection, and it is unclear if people who have recovered from the virus will become infected again. Young children and the elderly were among the most susceptible populations since they were at high risk of becoming infected with COVID-19 [4, 5]. Those who have recovered from these infections must continue to improve and maintain their quality of life. There is, however, minimal evidence that exercise and physical activity aid in the maintenance of general physical functioning [6]. The Covid-19 virus became a pandemic and affected an estimated 63,965,092 people, and more than one million deaths increased exponentially (World Health Organization (WHO), 2020) [7]. Approximately 5% to 14% of Covid-19 patients developed multiple organ dysfunction syndromes (MODS) [8–11]. The current Covid-19 management strategy is preventive and supportive [12]. Practical use of various pharmacological interventions has not been proven for Covid-19.

Severe Covid-19 did cause diffuse alveolar injury and respiratory failure and attacked other organs such as the gastrointestinal, coagulation system, and the kidneys. Immune dysfunction contributes to coagulation dysfunction that promotes thrombotic vascular events in severe Covid-19 patients with poor prognoses [13]. Early studies on Covid-19 found that 60% of patients with extreme conditions had lower platelet counts than patients with the mild-to-moderate disease and higher D-dimer levels [14]. Furthermore, 71.4% of Covid-19 non-survivors fulfilled DIC criteria with a significantly elevated level of D-dimer and fibrin degradation products, prolonged prothrombin time, and activated partial thromboplastin time (APTT) [15]. Furthermore, acute kidney injury can be found in approximately 29% of patients with severe and critically ill Covid-19, contributing to high mortality [16]. Renal dysfunction during hyper inflammation is caused by reduced microcirculation flow to the kidney and destruction of renal tubular epithelial cells via apoptosis or epithelial-mesenchymal transition. Studying 701 covid-19 patients has reported that the presence of AKI stage III is correlated with 4.72 times [17].

The most important part of the main countermeasures against viral infections includes Cytokines, which are produced by immune cells. This induces a signaling cascade by binding pattern recognition receptors (PRRs) to viral pathogen-associated molecular patterns (PAMPs). The induction will stimulate the inflammatory response needed to clear the virus [18]. The virus SARS-CoV-2 can evade the immune system via various non-structural proteins, the conformational change of viral mRNA, and indirect lymphocyte damage. It led to lymphopenia, allowing rapidly unopposed viral replication [19]. There were lower T lymphocytes and major subsets (CD3+, CD+4, and CD8+ T cells) in severe Covid-19 cases than moderate cases [20]. Covid-19 infection is associated with an aggressive inflammatory reaction, known as the "cytokine storm syndrome" (CSS) that is directly correlated with acute respiratory distress syndrome (ARDS), sepsis, disseminated intravascular coagulation (DIC), and poor prognosis in severe Covid-19 [20]. This phenomenon of CSS has been reported previously in other viral infections, including influenza H5N1, H1N1, MERS-CoV, and SARS-CoV [21].

Therapeutic options such as non-invasive ventilation and high-flow nasal cannula are options [22]. Severely ill and critically ill Covid-19 patients have immune dysregulation. This dysregulation underlies cytokine storm syndrome and endothelial dysfunction [23]. Based on this rationale, a modality such as extracorporeal blood purification that targeted eliminating inflammatory mediators could represent an option as a bridging strategy to improve survival. Coupled-plasma adsorption filtration (CPFA) was developed in the mid-1990s. This development of plasma adsorption, separation, and hemofiltration techniques is effectively removed by conventional RRT and fulfills the need to remove unnecessary

substances [24]. This review discussed the available technology and its potential efficacy in treating critically ill Covid-19 patients. This study aimed to review the combined plasma filtration adsorption (CPFA) technology and its potential effectiveness in treating critically ill Covid-19. CPFA combines plasma separation, adsorption, and hemofiltration techniques that meet the need to remove substances such as cytokines

Material and Methods

Immune dysregulation in critically Ill Covid-19

The excessive viral load of SARS-CoV-2 drives the differentiation of Th1 cells responsible for releasing pro-inflammatory cytokines such as interleukin (IL)-1 and -6. Granulocyte-macrophage colony-stimulating factor (GM-CSF), interferon (IFN)-γ, and tumor necrosis factor (TNF)-α. This cytokine (CD14+ and CD16+) releases more IL-6, the key mediator in the pathophysiology of CSS, whose level is found three times higher in Covid-19 non-survivors. In a study with 69 Covid-19 patients in China, it was found that those with less than 90% oxygen saturations had increased IL-6, IL-10, lactate dehydrogenase, and C-reactive protein [25]. Cytokine profile analysis in 41 patients admitted to the ICU showed elevated levels of interleukins, GM-CSF, IFN-γ, TNF-α, monocyte chemoattractant proteins (MCP), macrophage inflammatory protein (MIP), fibroblast growth factors (FGF), vascular endothelial growth factor (VEGF), and platelet-derived growth factor (PDGF).

Adsorption coupled-plasma filtration

An extracorporeal blood purification technique that can remove important cytokines and mediators, which functions beyond traditional RRT that provides only renal support and volume control, is called Adsorption-coupled plasma filtration (CPFA). It was first used in the 1990s to remove inflammatory mediators in the treatment of sepsis [26]. CPFA combines principles of plasma separation through a plasma filter. It was being returned into the blood through a sorbent cartridge and flowed through a hemofilter or hemodialyzed. The plasma filter possesses a larger pore size of 0.45 m2 allowing passage of major cytokines. Inflammatory mediators and toxins cannot be removed by traditional hemodialysis (HD)/hemodiafiltration (HDF). Treatment Adsorption filtration technology (CPFA) can be seen in Figure 1.

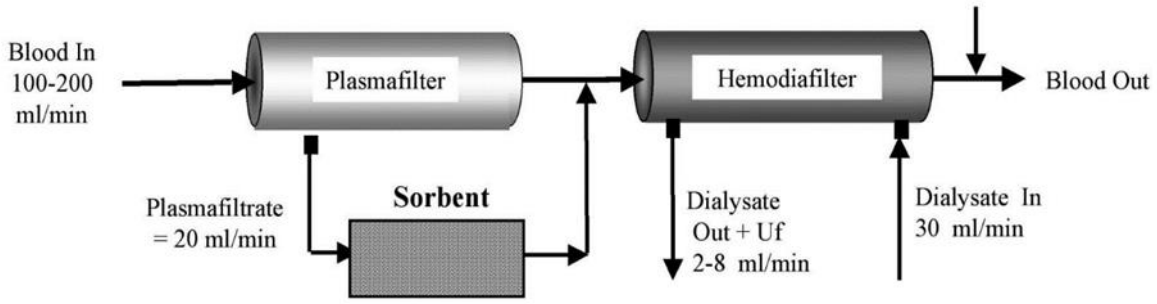

Figure 1: Schematic diagram of CPFA

Purification plasma passes through a resin cartridge before being returned into the blood. This resin allows adsorption of various inflammatory mediators using a non-specific adsorption technique, targeting pro- and anti-inflammatory mediators with considerable molecular weight.

The adsorptive cartridge used in CPFA contains a hydrophobic styrene resin. A large area of the adsorptive matrix (700-1,000m2/g) allows binding various mediators or toxins via hydrophobicity. The rationale for choosing plasma filtration rather than hemoperfusion in the current CPFA technique is that some cytokines bind better to the resin at lower flow rates. Higher blood flow rate (Qb) in hemoperfusion (150-200mL/min) yields higher blood volume to be treated but limits the adsorption capability as the increased blood flow pulled some molecules. Also, direct blood contact leads to protein or resin surfaces. A low plasma flow rate (usually 10-20% of Qb) at 20-40mL/min permits a longer contact time between molecules and the resin, giving the

optimum adsorption capability [24]. The hemofiltration is applied in the last stage of CPFA to remove small-to-middle molecules with a maximum ultrafiltration rate of 2,500ml/hour. A typical CPFA session uses a minimum of 0.2L plasma/kg/day that runs for approximately 10-12 hours, at which saturation of the sorbent starts to be noticeable. The CPFA has dose-dependent efficacy, where plasma volume >0.2-0.22L/kg/day is correlated with improved survival 6 [27].

Results and discussion

Clinical use of CPFA

CPFA therapy aims to target an excess of circulating inflammatory mediators in patients with impaired immune function. We analyzed 35 severe septic shock patients and found decreased IL-6, IL-8, IL-10, TNF-α, and CRP in patients treated with a 10-hour CPFA session compared with conservative management. CPFA also reduced lipopolysaccharide in the circulation. This led to improved proteinuria and albuminuria in these patients [28]. In septic patients with MODS, we found a marked reduction in the acute physiology and chronic health evaluation (APACHE) II and the sequential organ failure assessment (SOFA) scores after treatment with CPFA compared with high-volume hemofiltration, with a significant decline in adhesion molecule-1 (ICAM-1) and the level of TNF-α elevated intercellular space in sepsis and systemic inflammatory response syndrome. A similar finding was also reported in burn patients [29]. In the case of a 43-year-old male who developed ARDS secondary to pneumonia accompanied by AKI, critically ill Covid-19 patients were found, also, CPFA reduced serum pro-inflammatory cytokines, specifically IL-6 and TNF-α, with a parallel decrease in serum CRP and PCT. The patients also showed rapid improvement in clinical condition and a reduction in APACHE II score.

An early clinical pilot study on CPFA was performed on ten patients with septic shock compared with continuous venovenous hemodiafiltration (CVVHDF). CPFA had better hemodynamic improvement, reducing the need for vasopressor. Comparable results on improved hemodynamic parameters with CPFA have also been previously reported [30]. When combined with continuous venovenous hemofiltration (CVVH), CPFA+CVVH is superior. CVVH improves oxygenation index and means arterial pressure (MAP). In addition, they are significantly reducing cytokines, procalcitonin, and CRP in patients with severe sepsis.

In a multicenter randomized clinical study (RCT), we compared COMPACT and mortality in 350 hospital patients treated with CPFA to standard management. Nearly half of the patients had a coagulation circuit that prevented the patient from reaching the expected plasma target amount, leading to the closure of the immature trial. Although CPFA was not found to reduce in-hospital mortality, it was observed that patients receiving 0.2 L/day plasma had better survival. Another multicenter RCT called ROMPA also had to face a premature closure and showed no significant statistical difference in mortality reduction of septic shock patients between CPFA and control [31].

The resin in the sorbent cartridge can remove inflammatory cytokines and various toxins, myoglobin, free fatty acids, bile acids, and bilirubin. CPFA plus CVVH can reduce serum amylase and blood urea nitrogen without significantly affecting the electrolyte. The use of CPFA was studied in a case series of traumatic rhabdomyolysis with AKI. Three 10-hour CPFA treatments reduced creatinine kinase and myoglobin and improved overall renal function [32]. The application of CPFA in removing toxins and protein-bound bilirubin has also been reported in cases of hyperbilirubinemia due to acute liver failure [33], severe intra-abdominal infections [34], and transplantation rejection.

CPFA in Critically Ill Covid-19

Early recognition and prompt treatment of CSS can lead to improved outcomes for Covid-19 patients. A recombinant humanized IL-6 receptor antagonist, Tocilizumab, emerged as a promising drug to manage CSS in Covid-19. However, despite a clinical study showing improvement in symptoms, oxygen saturation, and pulmonary opacity after treatment with Tocilizumab [35], recent RCT revealed no reduction in 28-day

mortality [36]. Therefore, we propose that CPFA may have a potential role in improving patients' clinical condition due to the following rationales: 1) The capacity for removal of a wide range of substances with different molecular weights, such as pro-and anti-inflammatory mediators, without losing critical physiological substances, 2) Promoting hemostasis needed in patients with underlying coagulopathy, 3) management of AKI from the addition of hemofiltration and 4) the advantage of having hemodynamic stability with the improvement of oxygenation index, thus decreasing the need of vasopressors and reducing hospitalization days in the ICU.

Most of the cytokines are implicated in the pathophysiology of CSF. Even in the presence of high convective volumes, it is still too large to be efficiently expelled through the hemodialyzer pores with conventional HD or HDF [20]. Therefore, plasma exchange therapy (TPE) has been proposed for critically ill Covid-19 patients [37]. Studies have found improved clinical outcomes and higher extubation rates in hospitalized Covid-19 patients with ARDS in the ICU. In addition, they provided anti-coagulant properties in patients presented with DIC, thrombotic microangiopathy, and MODS [38]. Hypotension is the most common adverse effect of TPE. Added hemofiltration in CPFA offers the extra benefit. It has volume control to provide hemodynamic stability.

Furthermore, a highly porous dialyzer in TPE allows the removal of more prominent cytokines but has the disadvantage of immunoglobulin. In some TPE procedures, 5% albumin might be used as a replacement fluid. However, the use of albumin may deplete procoagulant factors and worsen. It was the underlying coagulopathy in critically ill Covid-19 patients [39]. As CPFA offers an advantage over TPE in that it loses less protein, albumin, and other physiologically essential components; these molecules are not absorbed by the resin and can be reinfused into the patient.

CPFA is one of the various extracorporeal therapies. It uses the principle of adsorption besides hemoperfusion and plasma perfusion. Cytosorb contains highly absorbent coated beads that provide better biocompatibility [40]. Sorbents offer clear advantages compared with other extracorporeal techniques in managing Covid-19 patients [41]. CPFA may be superior to hemoperfusion due to the low plasma flow rate that provides optimum adsorption capability.

Conclusion

Covid-19 is a novel disease that may develop severe symptoms complicated with the presence of cytokine storm syndrome. Medical interventions under current investigations may provide effective early management for Covid-19. The search for adjunctive therapies continues for those with severe and critical cases. CPFA combines the benefit of plasma filtration, adsorption, and conventional dialysis to optimize the efficacy of cytokine removal with minimal risks and could be a potential therapeutic strategy to reduce mortality in patients. The absence of CPFA benefits and randomized clinical trials on CPFA is direly needed to determine its efficacy.

The results of therapeutic use suggest an underlying immune dysregulation known as cytokine storm syndrome plays a role. Extracorporeal blood purification targets cytokine elimination and is preferred as a linking strategy to improve survival. Combined adsorption plasma filtration (CPFA) can remove various substances, including cytokines, without depleting physiologically essential proteins. CPFA can be considered and assessed in clinical trials to treat critically ill Covid-19 patients. Coupled Plasma Filtration Adsorption should be regarded as an effective potential therapy in treating critically ill Covid-19 patients.

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Authors' contributions

All authors contributed toward data analysis, drafting and revising the paper and agreed to be responsible for all the aspects of this work.

Conflict of Interest

The authors declare that they have no competing interests.

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