REVIEW

J Crit Intensive Care 2020;11(Suppl. 1):32–35
https://doi.org/10.37678/dcybd.2020.2436

Blood Purification Treatments in COVID-19

Sahin TEMEL[1], Murat SUNGUR[1]

[1]Erciyes University, Department of Internal Medicine, Division of Critical Care, Kayseri, Turkey

Cite this article as: Temel S, Sungur M. Blood Purification Treatments in COVID-19. J Crit Intensive Care 2020; 11(Suppl. 1):32–35.

Corresponding Author: Sahin Temel
E mail: dr.sahintemel@gmail.com

Received: Jun 17, 2020
Accepted: Jun 18, 2020
Available online: Jun 22, 2020

ABSTRACT

Severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) emerged for the first time in Wuhan, China, in December 2019. These viruses mainly cause respiratory and intestinal infections and induce a variety of clinical manifestations (1, 2). High virus titer and the subsequent strong inflammatory cytokine and chemokine responses are related to the high morbidity and mortality observed during the pathogenic HCoV infection. Blood purification system including plasma exchange, adsorption, perfusion, blood/plasma filtration, etc., can remove inflammatory factors, block the "cytokine storm", to reduce the damage of inflammatory response to the body. This therapy can be used for severe and critical patients in the early and middle stages of the disease (3). We recommend not using Extracorporeal treatments based on cytokine and / or endotoxin removal routinely in patients infected with COVID-19 due to insufficient studies (4).

Keywords: COVID-19, Blood purification therapy, sepsis, SARS-CoV-2

Introduction

Coronaviruses (CoVs) are single-stranded, positive-strand RNA viruses belonging to the Coronaviridae family, Nidovirales order. The International Committee on Taxonomy of Viruses (ICTV) classifies the CoVs into four categories: α, β, γ, and δ. under the electron microscope, the virus particles display a rough spherical or multi-faceted crystal shape. The surface of the viruses has prominent club-shaped projections composed of its spike protein. Inside the virus particle is the viral genome wrapped in a nucleocapsid. The viral genome contains approximately 26000 to 32000 bases. CoVs are the largest known RNA viruses. CoVs can infect a variety of host species, including birds, humans and some other vertebrates. These viruses mainly cause respiratory and intestinal infections and induce a variety of clinical manifestations (1, 2).

Severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) emerged for the first time in Wuhan, China, in December 2019. It is a type of highly pathogenic human coronavirus (HCoV) that causes zoonotic diseases and poses a major threat to public health. The vast majority of patients with the coronavirus disease 2019 (COVID-19) have had a good prognosis, but there were still some critical individuals and even deaths (5).

Pathogenesis of cytokine storm in COVID-19

The pathophysiology of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-induced ARDS has similarities to that of severe community-acquired pneumonia caused by other viruses or bacteria(6). The relevant evidences from severely ill patients with HCoVs suggest that pro-inflammatory responses play a role in the pathogenesis of HCoVs. The first step of the infectious process is the recognition of the pathogen by the immune system. All pathogens exhibit on their surface specific components, known as pathogen-associated molecular patterns (PAMPs), such as the endotoxins expressed by Gram-negative bacteria. During infection, PAMPs are recognized by the pattern recognition receptor expressed at the surface of immune cells. This signal activates the leukocytes and induces the synthesis of pro- and anti-inflammatory cytokines, including tumor necrosis factor-alpha, interleukin-1 (IL-1), IL-6, IL-8, and IL-10(7, 8). *In vitro* cell experiments show that delayed release of cytokines and chemokines

occurs in respiratory epithelial cells, dendritic cells (DCs), and macrophages at the early stage of SARS-CoV infection. Later, the cells secrete low levels of the antiviral factors interferons (IFNs) and high levels of proinflammatory cytokines (interleukin (IL)-1 β, IL-6, and tumor necrosis factor(TNF)) and chemokines (C-C motif chemokine ligand (CCL)-2,CCL-3, and CCL-5) (9). The overproduction of early response proinflammatory cytokines (tumor necrosis factor [TNF], IL-6, and IL-1β) results in what has been described as a cytokine storm, leading to an increased risk of vascular hyperpermeability, multiorgan failure, and eventually death when the high cytokine concentrations are unabated over time (10).

The theory of blood purification with inflammatory cytokine storm

High virus titer and the subsequent strong inflammatory cytokine and chemokine responses are related to the high morbidity and mortality observed during the pathogenic HCoV infection. The experience from treating SARS and MERS shows that reducing viral load through interventions in the early stages of the disease and controlling inflammatory responses through immunomodulators are effective measures to improve the prognosis of HCoV infection (11).

Extracorporeal Blood Purification Therapies

In addition, the blood purification treatments currently used in clinic practice can remove inflammatory factors to a certain extent. Blood purification system including plasma exchange, adsorption, perfusion, blood/plasma filtration, etc., can remove inflammatory factors, block the "cytokine storm", to reduce the damage of inflammatory response to the body. This therapy can be used for severe and critical patients in the early and middle stages of the disease (3).

1-Therapeutic plasma exchange

Therapeutic plasma exchange (TPE) refers to the extracorporeal technique performed in an apheresis device were patient's plasma is separated from whole blood and removed, while the cellular blood components are returned to the patient together with a replacement fluid. The separation of blood can be performed either by centrifugation or by filtration (12).

According to American Society for Apheresis (ASFA) guidelines, over 30 diseases may be treated with TPE. In all of them, the rational for TPE is the removal of a pathological substance in plasma that is responsible for the disease, i.e. autoantibodies, immune complexes, cryoglobulins, toxins or lipids (13).

In a single TPE procedure the amount of plasma removed varies according to the volumes of plasma (PV) exchanged following an exponential function. Thus, usually 1–1.5 PV is exchanged, because larger volumes do not add much benefit but increase the risk of side-effects. The removal of the pathogenic substance also depends on its distribution between the intravascular and extravascular compartment. For example, in the case of IgM antibodies, which are predominantly in the intravascular space, a significant decrease is achieved after one or two consecutive procedures. On the contrary, IgG antibodies that are distributed in both the intravascular and extravascular compartments, require multiple exchanges to decrease total body stores, and are usually performed every other day to allow redistribution between both compartments. Lastly, TPE efficiency is also influenced by the speed of production and clearance of the pathogenic substance. Therefore, in immune-mediated diseases, immunosuppressive treatment should be given together with TPE in order to obtain a sustained response (14).

Hemophagocytic lymphohistiocytosis and macrophage activating syndrome

Hemophagocytic lymphohistiocytosis (HLH) is a life-threating immune mediated disease caused by genetic defects or reactive to some triggers. This results in an acute cytokine storm triggering an avalanche of hyperinflammation with a severe sepsis-like clinical picture. Macrophage activating syndrome refers to the same picture secondary to juvenile idiopathic arthritis. The basis of treatment of HLH is supportive intensive care, the elimination of the trigger, and the suppression of inflammatory response and cell proliferation or both with immunosuppressive and cytotoxic drugs. Although TPE benefits controversial, extracorporeal removal of cytokines with daily TPE with 5% albumin (or other methods) may be part of the supportive care used to stabilize organ function in severe patients (15).

Therapeutic plasma exchange can affect many steps such as clearing cytokines, stabilization of endothelial membranes, and correction of hypercoagulable condition in sepsis patients (16). It has been claimed in a limited number of small studies that therapeutic plasma exchange may reduce mortality in patients with sepsis (17). We recommend not routinely using therapeutic plasma exchange in patients infected with COVID-19 due to insufficient studies.

2-Removing Cytokines and Endotoxins

AN69 Membrane

It is composed of a copolymer combining acrylonitrile and sodium methallylsulfonate molecules. Due to the sulfonate groups, the membrane is highly negatively charged and able to adsorb the cytokines via their cationic residues. This membrane exhibits a symmetric microporous architecture with a hydrogel structure. The latter allows cytokine adsorption within the entire bulk of the membrane, enhancing the overall adsorption capacity. This membrane has been claimed to heal hemodynamically, but studies are inadequate (18, 19).

The oXiris® Membrane

The improvement of industrial processes led to the development of the oXiris® membrane, a heparin-grafted membrane specifically designed for cytokine and endotoxin adsorption, alongside RRT. More recently, Malard et al. conducted an in vitro experiment, comparing endotoxin and cytokine adsorption with 3 different devices: oXiris®, CytoSorb®, and Toraymyxin®; oXiris® was found to combine high endotoxin adsorption capacity, similar to Toraymyxin®, with a removal rate of inflammatory mediators comparable to CytoSorb® (20)

Toraymyxin® Membrane

One of the most widely used endotoxin removal therapiesis adsorption with polymyxin B-immobilised fiber column (Toraymyxin®; Toray, Tokyo, Japan). Numerous RCTs comparing polymyxin B adsorption toa standard treatment found conflicting results, suggesting that the positive effect of Toraymyxin® could be greater in particular subgroups of patients such as severe patients, patients with endotoxin activity levels (as evaluated by the endotoxin activity assay) between 0.6 and 0.9, or those presenting a particular genetic profile (21, 22).

The Alteco® LPS adsorber

The Alteco® LPS adsorber (Alteco Medical AB; Lund,Sweden) contains a synthetic peptide developed for endotoxin adsorption. The peptide covers the surface of a porous polyethylene matrix designed to provide an optimal binding surface. A few case series in critically ill adults have reported a decrease in endotoxin levels and a hemodynamic improvement (23, 24). However, the ASSET (abdominal septic shock – endotoxin adsorption treatment) multicenter RCT evaluating the feasibility of Alteco® LPS adsorber was terminated early because of patient recruitment issues (25).

High-volume hemofiltration (HVHF)

High-volume hemofiltration (HVHF) is a continuous renal replacement therapy (CRRT) with a high ultrafiltration rate (> 50 mL·kg–1·h–1) offering an enhanced removal of hydrophilic middle molecular weight molecules (26).

The IVOIRE (high volume in intensive care) RCT failed to find a significant difference in mortality between the high-volume group (70 mL·kg–1·h–1) and the standard volume group (35mL·kg–1·h–1), but also it could not find an improvement in secondary outcomes such as hemodynamic parameters, severity scores and length of stay (27). This absence of beneficial effects was confirmed by 2 recent meta-analyses (28, 29).

Conclusion

We recommend not using Extracorporeal treatments based on cytokine and / or endotoxin removal routinely in patients infected with COVID-19 due to insufficient studies (4).

References

1. Peck KM, Burch CL, Heise MT et al: Coronavirus Host Range Expansion and Middle East Respiratory Syndrome Coronavirus Emergence: Biochemical Mechanisms and Evolutionary Perspectives. Annu Rev Virol 2015, 2:95-117.
2. Su S, Wong G, Shi W et al: Epidemiology, Genetic Recombination, and Pathogenesis of Coronaviruses. Trends Microbiol 2016, 24:490-502.
3. Xu K, Cai H, Shen Y et al: [Management of corona virus disease-19 (COVID-19): the Zhejiang experience]. Zhejiang Da Xue Xue Bao Yi Xue Ban 2020, 49:0.
4. Monard C, Rimmele T, Ronco C et al: Extracorporeal Blood Purification Therapies for Sepsis. Blood Purif 2019, 47 Suppl 3:1-14.
5. Lai CC, Shih TP, Ko WC et al: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): The epidemic and the challenges. Int J Antimicrob Agents 2020, 55:105924.
6. D'Elia RV, Harrison K, Oyston PC et al: Targeting the "cytokine storm" for therapeutic benefit. Clin Vaccine Immunol 2013, 20:319-327.
7. Prince LR, Whyte MK, Sabroe I et al: The role of TLRs in neutrophil activation. Curr Opin Pharmacol 2011, 11:397-403.
8. Angus DC, van der Poll T: Severe sepsis and septic shock. N Engl J Med 2013, 369:840-851.
9. Law HK, Cheung CY, Ng HY et al: Chemokine up-regulation in SARS-coronavirus-infected, monocyte-derived human dendritic cells. Blood 2005, 106:2366-2374.
10. Meduri GU, Kohler G, Headley S et al: Inflammatory cytokines in the BAL of patients with ARDS. Persistent elevation over time predicts poor outcome. Chest 1995, 108:1303-1314.
11. Ye Q, Wang B, Mao J: The pathogenesis and treatment of the `Cytokine Storm' in COVID-19. J Infect 2020, 80:607-613.
12. Fernandez-Zarzoso M, Gomez-Segui I, de la Rubia J: Therapeutic plasma exchange: Review of current indications. Transfus Apher Sci 2019, 58:247-253.
13. Schwartz J, Padmanabhan A, Aqui N et al: Guidelines on the Use of Therapeutic Apheresis in Clinical Practice-Evidence-Based Approach from the Writing Committee of the American Society for Apheresis: The Seventh Special Issue. J Clin Apher 2016, 31:149-162.
14. Karr EG, Neyrinck, M.M. et al : Therapeutic apheresis procedures. Principles of apheresis technology 2017:53-63.
15. Kinjo N, Hamada K, Hirayama C et al: Role of plasma exchange, leukocytapheresis, and plasma diafiltration in management of refractory macrophage activation syndrome. J Clin Apher 2018, 33:117-120.
16. Knaup H, Stahl K, Schmidt BMW et al: Early therapeutic plasma exchange in septic shock: a prospective open-label nonrandomized pilot study focusing on safety, hemodynamics, vascular barrier function, and biologic markers. Crit Care 2018, 22:285.
17. Busund R, Koukline V, Utrobin U et al : Plasmapheresis in severe sepsis and septic shock: a prospective, randomised, controlled trial. Intensive Care Med 2002, 28:1434-1439.
18. Shiga H, Hirasawa H, Nishida O et al : Continuous hemodiafiltration with a cytokine-adsorbing hemofilter in patients with septic shock: a preliminary report. Blood Purif 2014, 38:211-218.
19. Kobashi S, Maruhashi T, Nakamura T et al : The 28-day survival rates of two cytokine-adsorbing hemofilters for continuous renal replacement therapy: a single-center retrospective comparative study. Acute Med Surg 2019, 6:60-67.
20. Malard B, Lambert C, Kellum JA: In vitro comparison of the adsorption of inflammatory mediators by blood purification devices. Intensive Care Med Exp 2018, 6:12.
21. Klein DJ, Foster D, Walker PM et al : Polymyxin B hemoperfusion in endotoxemic septic shock patients without extreme endotoxemia: a post hoc analysis of the EUPHRATES trial. Intensive Care Med 2018, 44:2205-2212.
22. Chang T, Tu YK, Lee CT et al : Effects of Polymyxin B Hemoperfusion on Mortality in Patients With Severe Sepsis and Septic Shock: A Systemic Review, Meta-Analysis Update, and Disease Severity Subgroup Meta-Analysis. Crit Care Med 2017, 45:e858-e864.

23. Adamik B, Zielinski S, Smiechowicz J et al : Endotoxin Elimination in Patients with Septic Shock: An Observation Study. Arch Immunol Ther Exp (Warsz) 2015, 63:475-483.
24. Yaroustovsky M, Abramyan M, Popok Z et al : Preliminary report regarding the use of selective sorbents in complex cardiac surgery patients with extensive sepsis and prolonged intensive care stay. Blood Purif 2009, 28:227-233.
25. Lipcsey M, Tenhunen J, Sjolin J et al : Abdominal Septic Shock - Endotoxin Adsorption Treatment (ASSET) - endotoxin removal in abdominal and urogenital septic shock with the Alteco(R) LPS Adsorber: study protocol for a double-blinded, randomized placebo-controlled trial. Trials 2016, 17:587.
26. Kellum JA, Johnson JP, Kramer D et al : Diffusive vs. convective therapy: effects on mediators of inflammation in patient with severe systemic inflammatory response syndrome. Crit Care Med 1998, 26:1995-2000.
27. Joannes-Boyau O, Honore PM, Perez P et al: High-volume versus standard-volume haemofiltration for septic shock patients with acute kidney injury (IVOIRE study): a multicentre randomized controlled trial. Intensive Care Med 2013, 39:1535-1546.
28. Borthwick EM, Hill CJ, Rabindranath KS et al : High-volume haemofiltration for sepsis in adults. Cochrane Database Syst Rev 2017, 1:CD008075.
29. Clark E, Molnar AO, Joannes-Boyau O et al : High-volume hemofiltration for septic acute kidney injury: a systematic review and meta-analysis. Crit Care 2014, 18:R7.