ImmunoAnalysis, 2022, 2, 10
doi:10.34172/ia.2022.10
https://ia.tbzmed.ac.ir/

Original Research

Hemoperfusion Therapy's Efficiency in Reducing Serum IL-6 Levels and Disease Severity in COVID-19 Patients

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ARTICLE INFO

Article History:
Received: August 25, 2022
Accepted: November 24, 2022
ePublished: December 26, 2022

Keywords:
COVID-19, Severe respiratory failure, Acute respiratory distress syndrome, Cytokine storm, IL-6, Hemoperfusion

Abstract

Background: Interleukin (IL)-6, one of the inflammatory mediators involved in severe cases of coronavirus disease-19 (COVID-19), has been implicated in the pathogenesis of this disease. Extracorporeal blood purification has been suggested as one of the therapeutic strategies for COVID-19 patients, due to its favorable effect on the removal of inflammatory cytokines. Here, we investigated the impact of hemoperfusion (HP), a type of extracorporeal blood purification, in serum IL-6 levels and disease severity in COVID-19 patients.

Methods: 35 patients with severe COVID-19 were enrolled in this study at the Imam-Reza Hospital, Tabriz University of Medical Sciences, between April 2020 and June 2020. The HA330 disposable HP cartridge was utilized (Jafron Biomedical Company, China). After a hemodialysis catheter was placed, patients underwent HP for at least three days in a row.

Results: Our results indicated that COVID-19 patients' serum levels of IL-6 significantly diminished following HP (P value ≤ 0.001). Furthermore, a decrease in IL-6 levels following HP demonstrated the effectiveness of this approach (area under the curve [AUC] = 0.7102 and $P = 0.0025$).

Conclusion: Taken together, our findings suggest HP as a promising therapeutic option in COVID-19. However, a detailed evaluation of HP's efficacy is required in large prospective multicenter trials.

Introduction

The coronavirus disease 2019 (COVID-19) pandemic has been caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) around the world.[1-4] Patients with COVID-19 frequently have mild to moderate symptoms, however; severe respiratory failure and acute respiratory distress syndrome (ARDS) have also been reported.[5] The virus's ability to evade the primary immune response and the generation of excessive immune responses in infected tissues are crucial for the progression of severe COVID-19 disease.[5-8] As a result, inflammatory chemokines and cytokines are overproduced, contributing to the disease pathogenesis.[9-11] Increased levels of inflammatory markers, e.g., C-reactive protein (CRP), ferritin, and D-dimer, as well as a high ratio of neutrophils to lymphocytes,[12-15] and elevated levels of inflammatory cytokines and chemokines, are detected in severe cases of COVID-19.[12,15-17] Various studies have shown that excessive inflammation in the severe form of COVID-19 may be due to high serum levels of CRP and interleukin (IL)-6.[16,18,19] As a result of the uncontrolled infection in COVID-19 disease, a phenomenon known as the cytokine storm develops. In this condition, numerous cytokines, i.e., tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and IL-6 are overproduced and cause damage to multiple organs.[20] In line with this, according to Huang et al, hospitalized patients in both intensive care unit (ICU) and non-ICU wards exhibited increased serum inflammatory cytokine levels compared with healthy individuals.[5] Additionally, it was shown that ICU patients showed increased concentrations of cytokines than non-ICU patients, including IL-2, IL-7, and TNF-α, which were

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found to have a more central role in the inflammation process.[5,21] It has been demonstrated that quantities of pro- and anti-inflammatory cytokines are positively correlated with mortality rate.[22] This findings show that cytokine storm affects patient outcomes and disease severity.[23] Management of this disease is mainly proactive, and several antiviral and immunomodulatory therapies have been recommended.[24-26] No curative therapies for COVID-19 are currently available, emphasizing the need to enhance the current understanding of SARS-CoV-2 pathogenesis to develop effective therapeutic strategies.[27] The pathophysiology of COVID-19 suggests that sequential extracorporeal therapies may help remove extra inflammatory mediators.[28] In this regard, hemoperfusion (HP), one of the extracorporeal blood purification techniques, removes particular compounds from bloodstream using a particular sorbent.[29] In this process, anticoagulated blood is circulated via a sorbent-containing cartridge (or column) and depending on the sorbent type (i.e., pure resins, polymyxin-coated resins, or heparin-coated resins), large endogenous and exogenous molecules such as targeted cytokines, endotoxins, and virus particles are removed.[30,31] Besides, as a result of this process, pro-inflammatory and anti-inflammatory cytokines are effectively removed from the bloodstream.[28] In line with this, De Vriese and colleagues have indicated that in patients with septic shock and acute kidney injury, the levels of pro-inflammatory and anti-inflammatory cytokines were significantly diminished after continuous venovenous hemofiltration.[32] Since there is evidence of an association between cytokine storm, septic shock, and ARDS,[33,34] we hypothesized that the removal of inflammatory cytokines like IL-6 can potentially diminish the severity of COVID-19. Accordingly, we evaluate the efficacy of HP in removing IL-6 from the bloodstream of patients with COVID-19 and its correlation with disease severity. In this study, we showed that serum levels of IL-6 in COVID-19 patients significantly decreased after HP. Additionally, a diminishment in IL-6 levels after HP confirmed the efficacy of this approach. Overall, these findings illustrate that HP is an appealing option for the successful management of COVID-19.

Materials and Methods

Patients and study design

This study has been performed on 35 patients with severe COVID-19 disease were recruited in the Imam-Reza Hospital, Tabriz University of medical sciences, between April 2020 to June 2020. Patients who had been admitted in ICU with radiologic findings or laboratory confirmation by testing of the oropharyngeal specimen, using real-time PCR in addition to PaO2/FiO2 ratio less than 200 mmHg were included. Patients that did not completely follow the criteria, who had evidence of coagulation abnormalities, plasma platelets count less than 50000/μL or any other viral or bacterial infections, or patients with multiple organs failure, malignancy, and shock status were excluded from this study. Patients underwent HP in addition to the routine treatment protocol for COVID-19 recommended by the Iranian Ministry of Health, which included ribavirine, lopinavir-ritonavir (Kaletra), and hydroxychloroquine. We utilized the HA330 disposable HP cartridge manufactured by Jafron Biomedical Company, China. Patients underwent HP for at least three consecutive days following the placement of a hemodialysis catheter. Each session was conducted for 4 hours of HP. During the HP procedure, the blood flow rate was 180 to 250 mL/min and a heparin dosage was 10-12 units/kg/h.

IL-6 quantification

After HP, 3 to 5 mL of peripheral blood was collected from patients who had undergone HP, and serum samples were separated by centrifugation at 2000 rpm/20 minutes. The serum was collected and stored at -80°C after centrifugation. According to the manufacturer's recommendations, IL-6 was evaluated using an ELISA kit manufactured by Karmania Pars Gene (Iran). Regarding the requirement of a marker for evaluation of HP efficacy during the treatment of COVID-19, the receiver operating characteristic (ROC) analysis was done to find the sensitivity and specificity of IL-6 serum level before and after HP to assess the serum level of IL-6 as an efficacy marker.

Statistical analysis

All the raw data were analyzed with GraphPad Prism v8.0.2 (GraphPad Software, San Diego, California USA) and paired *t* test. Also, the results have been shown as mean ± SD with the significance cut-off of $P \leq 0.05$.

Results

HP could decrease the serum level of IL-6 in COVID-19 patients

Upon the HP of the COVID-19 patient, the serum of each individual was collected and analyzed to measure the level of IL-6 before and after the HP. The data indicated that the level of IL-6 could be significantly reduced after the HP and this treatment approach might be effective in the reduction of COVID-19 severity (Figure 1).

Serum level of IL-6, as a marker for the efficacy of HP

ROC analysis of IL-6 serum level in COVID-19 patients before and after HP showed that the reduced level of IL-6 upon the HP could be a marker for the efficacy of this therapeutic approach (area under the curve [AUC] = 0.7102 and $P = 0.0025$) (Figure 2).

Discussion

SARS-CoV-2 was initially identified in China and caused a worldwide public health emergency.[35] Like many pandemics caused by other viral infections, there is no definitive cure for the disease, and most treatments are supportive.[36,37] Various potential mechanisms have been

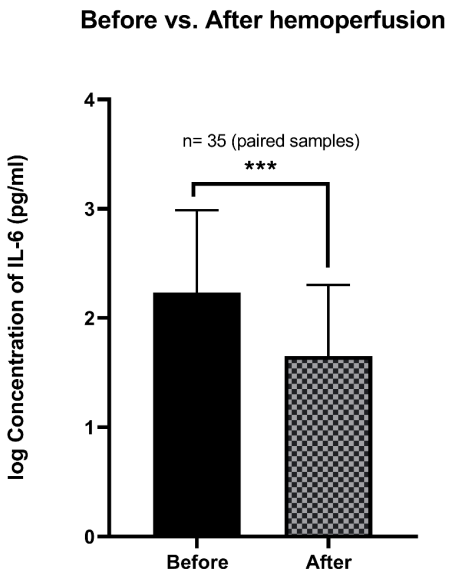

Figure 1. Comparison of serum IL-6 levels of COVID-19 patients before and after HP (***$P \leq 0.001$)

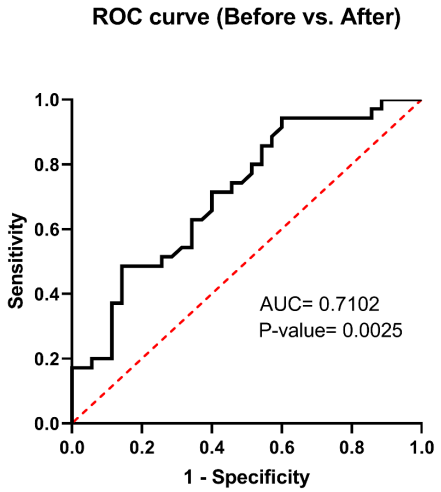

Figure 2. ROC analysis of IL-6 serum level in COVID-19 patients

reported to cause organ damage and disease severity in COVID-19 patients.[5] The cytokine storm is regarded as one of the most fundamental mechanisms that can be lethal.[34,38] This phenomenon is defined by a high stimulation of immune cells and an excessive generation of inflammatory mediators and chemical mediators.[39] In this regard, it has been reported that increased levels of inflammatory mediators, i.e., TNF-α, CRP, D-dimer, ferritin, and lactate dehydrogenase (LDH) are associated with the higher mortality rate in COVID-19 patients.[5,40-42] Furthermore, elevated CRP levels may be related to severe lung complications such as ARDS in the early stages of COVID-19.[43] Besides, 67% of patients with COVID-19 may suffer organ failure due to a sepsis-like syndrome triggered by elevated circulating cytokine levels.[44] Although, high production of various pro-inflammatory mediators is present in the cytokine storm in COVID-19, however; elevated levels of IL-1, TNF-α, and notably, IL-6 are hallmarks of this phenomenon.[39,45] In line with this, in comparison with cases with mild COVID-19, severe COVID-19 patients have significantly higher levels of IL-6.[5,39] Furthermore, it has been demonstrated that IL-6 is primarily responsible for COVID-19 patient's mortality and disease severity.[46] Liu et al have indicated that the maximum body temperature during hospitalization and the higher baseline levels of CRP, LDH, ferritin, and D-dimer were all positively associated with the elevation in baseline IL-6.[47] Additionally, they have demonstrated an association between elevated baseline IL-6 and more advanced chest computed tomography (CT) findings.[47] Since inflammatory factors such as IL-6 correlate with mortality rate and COVID-19 severity, it is possible to reduce the complications of this disease by removing these inflammatory factors from the blood. In this regard, extracorporeal blood purification, is one of the approaches that can remove inflammatory factors from the bloodstream.[30,48-50] HP is an extracorporeal procedure in which blood is passed through a cartridge containing sorbent material in order to remove molecules directly from the blood.[30,48-50] HP functions by an adsorption mechanism associated with the several cartridges that are present in its structure.[30,48-50] The efficacy of HP to remove inflammatory mediators in H1N1 influenza-related antibiotic-resistant septic shock and ARDS has been reported.[51,52] Since the application of HP has been shown to have beneficial outcomes for influenza patients, HP appears to be a promising therapeutic strategy for the management of COVID-19 patients' complications. Herein, we aimed to investigate the effect of HP in serum IL-6 levels and disease severity in patients with COVID-19. Our findings demonstrated that HP considerably reduced the serum levels of IL-6 in COVID-19 patients. Furthermore, a decrease in IL-6 levels following HP demonstrated the effectiveness of this approach. Various investigators have attempted to evaluate the effect of HP on the serum levels of inflammatory cytokine and mortality rate in COVID-19 disease. In accordance to our study, Asgharpour et al have demonstrated a substantial decrease in serum IL-6 levels following HP in COVID-19 patients.[53] In a case report study by Dastan et al, a significant decrease in the serum levels of IL-6 in a 54-year-old man with COVID-19 was shown, which was consistent with our findings.[54] In another case report study, it was found that the application of HP diminished IL-6 levels and improved acute kidney injury and chest X-ray imaging.[55] Furthermore, 12 COVID-19 patients with PaO2/FiO2 levels less than 300 underwent HP for two days by Katagiri et al.[56] They have demonstrated that in 58.3% of patients, disease severity was decreased, and the PaO2/FiO2 level was improved.[56] Additionally, it has been demonstrated that using HP can decrease mortality rates and increase SPO2 and PaCO2 levels.[57] HP has been shown to reduce organ failure and inflammatory markers, i.e., LDH and CRP in COVID-19 patients.[29] Besides, punctual and early utilization of HP/continuous

renal replacement therapies in the treatment of ARDS in patients with COVID-19 decreased respiratory distress and the patient's dependence on oxygen, prevented the progression of ARDS and patient intubation.[58] Our findings demonstrated that HP is an effective approach in removing IL-6 in COVID-19 patients, implying a promising therapeutic option for SARS-CoV-2 infection.

Conclusion

This study has implied that HP significantly decreased the serum levels of IL-6 in patients with COVID-19. Moreover, a reduction in IL-6 levels after HP confirmed the efficacy of this approach. As a result of these findings, it is suggested that HP be investigated further in large prospective multicenter trials.

Author Contributions

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Funding Sources

This study was supported by the Tuberculosis and Lung Diseases Research Center, Tabriz University of Medical Sciences, Tabriz, Iran (Grant number: 65332).

Data Availability Statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethical Issues

All procedures were conducted in compliance with the ethical principles of Tabriz University of Medical Science, Tabriz, Iran and approved by the regional ethical committee for medical research (Ethical code: IR.TBZMED.REC.1399.023).

Conflict of Interest

The authors certify that there is no potential conflict of interest in relation to this article.

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