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Original Article / Özgün Araştırma

Results of Coupled Plasma Filtration Adsorption (CPFA) Treatment Applied to Critical COVID-19 Patients in Intensive Care Unit

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Abstract

Objective: The novel coronavirus, called SARS-CoV-2, causes COVID-19 disease and began a pandemic on a global scale. Uncontrolled cytokine production is observed especially in COVID-19 cases with severe progression and this situation is thought to be one of the causes of more severe disease progression and increased mortality.

In our study, we aimed to assess the efficacy of Coupled Plasma Filtration Adsorption (CPFA) treatment in situations with severe disease progression like sepsis, septic shock and multiple organ failure, considered to be secondary to cytokine storm, in COVID-19 disease.

Methods: Our study retrospectively screened data from 20 patients admitted to our intensive care unit and administered CPFA. CPFA was administered as 10 hours each session and 2 sessions with 12 hours interval.

Results: After our CPFA treatment, there were statistically significant ameliorations in clinical and laboratory findings like SOFA scores, mainly, Horowitz values, fever and IL-6 values.

Conclusion: The CPFA treatment removes the uncontrolled production of harmful cytokines/chemokines and toxic substances from the blood and shows promise in the treatment of the cytokine storm that develops in COVID-19 disease.

Keywords: Coronavirus, Coupled Plasma Filtration Adsorption, COVID-19 disease, cytokine release syndrome, cytokine storm

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Yoğun Bakımdaki Kritik COVID-19 Hastalarına Uygulanan Coupled Plasma Filtration Adsorption (CPFA) Tedavisi Sonuçları

Öz

Amaç: SARS-CoV-2 olarak adlandırılan yeni tip koronavirüs, COVID-19 hastalığına sebep olmuş ve küresel ölçekte bir pandemi başlatmıştır. Özellikle ağır seyreden Covid-19 hastalarında kontrolsüz bir sitokin üretimi gözlenmiş ve bu durum hastalık seyrinin ağırlaşmasının ve mortalite artışının önemli bir nedeni olarak düşünülmüştür.

Çalışmamızda Covid-19 hastalarında, sitokin fırtınasına sekonder olduğu düşünülen sepsis, septik şok ve çoklu organ yetmezliği gibi hastalığın ağır seyrettiği durumlarda uygulanan Coupled Plasma Filtration Adsorption (CPFA) tedavisinin etkinliğinin değerlendirilmesini amaçlıyoruz.

Yöntemler: Çalışmamız yoğun bakım ünitemizde yatan ve CPFA uygulanmış 20 hastanın verileri retrospektif taranarak gerçekleştirilmiştir. CPFA uygulamaları, her seans 10 saat olacak şekilde ve 12 saat ara verilmek suretiyle 2 seans olarak yapılmıştır.

Bulgular: CPFA uygulamalarımız sonrası SOFA skorları, Horowitz değerleri, ateş, IL-6 değerleri gibi klinik ve laboratuvar bulgularında istatistiksel olarak anlamlı iyileşmeler gözlenmiştir.

Sonuç: CPFA tedavisi kontrolsüz üretimi olan zararlı sitokinleri/kemokinleri ve toksik maddeleri kandan temizlemekte ve COVID-19 hastalığında gelişen sitokin fırtınasının tedavisinde umut vadetmektedir.

Anahtar kelimeler: Koronavirus, Coupled Plasma Filtration Adsorption, COVID-19 hastalığı, sitokin salınım sendromu, sitokin fırtınası.

INTRODUCTION

The novel coronavirus, called SARS-CoV-2 by the World Health Organization (WHO) on 11 February 2020, causes COVID-19 disease and began to be observed from the beginning of December 2019 in Wuhan city in China[1]. The virus which causes COVID-19 disease infected 284 million people around the world by 30 December 2021 and caused the death of nearly 5,4 million people[2].

In the disease that develops due to Covid-19; in order to control viral replication and clean virus-infected cells, it is necessary to produce proinflammatory cytokines stimulated by natural immunity and to activate T lymphocyte cells[3].

Cytokine Storm (CS, Cytokine Storm) develops after tissue damage caused by the virus, excessive activation of macrophages and granulocytes, and excessive production of proinflammatory cytokines. Data obtained from patients with COVID-19 infection show that in serious cases characterized by cytokine storm, it inevitably progresses to acute respiratory distress syndrome (ARDS)[4-6].

Guidelines for use in diagnosis and treatment of pneumonia caused by SARS-CoV-2 virus were first published on 30 January 2020. This guideline recommended monitoring cytokines to increase amelioration rates and reduce mortality[7,8].

Currently, there are methods ensuring immune homeostasis by providing extracorporeal non-selective cleaning of soluble mediators and bacterial toxins in blood[9]. Treatments used in situations with development of CS include methods like passive antibody treatment called convalescent plasma use, anti-IL-6 monoclonal antibody use (tocilizumab, siltuximab), use of antibodies produced against interferon (IFN) subtypes (sifalimumab), continuous renal replacement treatment (CRRT) and coupled plasma filtration adsorption (CPFA).

CPFA treatment, one of these techniques, has been used among intensive care patients with indications such as ARDS, sepsis and septic

shock since the early 2000s. One of the biggest advantages of this method is that in addition to removing particulate parts, cytokines and mediators from the blood by plasmapheresis method, hemodiofiltration can be applied together or afterwards[10].

OBJECTİVE

The aim of our study is to evaluate the effectiveness of CPFA treatment in patients with severe COVID-19 disease such as sepsis, septic shock and multi-organ failure, which are thought to be secondary to cytokine storm.

METHODS

This study was written with the permission of Health Sciences University Hamidiye Clinical Research Ethics Committee (ethics committee: 17/06/2020-18521 no). Data from 20 patients admitted to Health Sciences University of Health Sciences Sultan 2. Abdülhamid Han Training and Research Hospital, Department of Anesthesiology Intensive Care Unit, from March to June 2020, due to COVID-19 and developing ARDS were retrospectively screened. Written informed consent was obtained from each patient or their relatives.

Patients not requiring renal replacement treatment, not considered to have cytokine release syndrome (CRS) in line with present clinical findings, aged younger than 18 years, older than 90 years, without consent from legal heirs to perform the procedure, with severe coagulation disorder or contraindicated anticoagulant use and with untreated cancer or linked metastasis were not administered CPFA treatment and were not included in the study.

The decision to apply CPFA was made for patients admitted to our intensive care unit with COVID-19 ARDS diagnosis or developing ARDS in later periods. Clinical and laboratory findings such as desaturation, increase in respiratory rate, refractory high fever (>390C), liver enzyme elevations such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), International normalized ratio (INR) and Bilirubin, C-reactive protein (CRP)-Procalcitonin elevation, increased lymphopenia, increased Ferritin and D-dimer, severe deterioration in arterial blood gas (Horovitz value <200), deterioration in microcirculation, increased need for inotropic agents, low SOFA scores (Sequential Organ Failure Assessment> 6%), sepsis, septic shock in these patients were evaluated. CPFA treatment was performed by anesthetists experienced in extracorporeal renal replacement therapies.

The procedure was completed with a polyether sulfone plasma filter (0.5 m2, MPS 05), synthetic resin cartridge (surface area 700 m^2/g, MediasorbTM type resin sterilized with 140 g steam), a polyphenylene hemodialyzer (1.4 m2, HFT 12) and 180-200 ml/min blood flow (Qb) with 30-40 ml/min plasma flow (Qp) in a plasma adsorption device (CPFA, Medtronic Bellco Amplya, Italy). In situations with arterial hypotension developing during the procedure (<65 mmHg), both plasma flow and blood flow were reduced and fluid replacement and noradrenaline infusion were administered to return to normotensive status. The procedure was performed through 11.5-13.5-gauge width, double lumen femoral central venous catheter. If required, hourly 40 ml/kg/hr intermittent hemofiltration was included with each session of CPFA planned for 10 hours. Unfractionated heparin or citrate was used as anticoagulant. CPFA treatment was performed in 2 sessions with a 12-hour interval according to the hemodynamic status of patients.

Immediately before beginning CPFA treatment, in the 24^{th} and 48^{th} hour afterward and on the 7^{th} day measured and/or calculated SOFA values, Horowitz index values (PaO2/FiO2 ratio, partial pressure of oxygen in blood / the fraction of oxygen in the inhaled air), presence of fever, noradrenaline requirements for hypotension, SpO2, heart rate and a range of

related laboratory values (IL-6, lymphocyte count, CRP, procalcitonin, AST, ALT, d-dimer, Hb, total and indirect bilirubin) were obtained from files and system data.

Statistical Analysis

Descriptive statistics of data used mean, standard deviation, median, minimum, maximum, frequency and percentage values. Distribution of variables was measured with the Kolmogorov Smirnov test. Analysis of dependent quantitative data used the Wilcoxon test. Analysis of dependent qualitative data used the McNemar test. Analyses used the SPSS 26.0 program. Statistical analyses were performed using the Statistical Package for the Social Sciences 10.1 for Windows (SPSS Inc., Chicago, IL, USA).

RESULTS

Our study was completed with retrospective data from a total of 20 patients, 12 male and 8 female, monitored and treated with intubation and mechanical ventilator with indications like ARDS, sepsis, septic shock and multiple organ failure due to COVID-19 in our intensive care unit. Mean SOFA scores were 10 before CPFA treatment (0-24 interval, higher scores indicate increasing risk), while mean values fell to 8 in the 24th hour and 7 on the 7th day and significant improvement was observed in the patients (Table I). Statistically significant falls were observed in SOFA scores in the 48th hour and 7th day after CPFA treatment compared to before CPFA ($p<0.05$) (Table III).

Table I: Demographic data, clinical and laboratory values

		Min-Max	Median	Mean±ss.	n / %
Age		43.0 – 72.0	51.0	52.8 ± 10.0	
Sex	Female Male			8 12	40.0 % 60.0 %
Weight (kg.)		75.0 – 124.0	94.5	95.1 ± 13.3	
Blood group	A + AB + B – 0 +				6 30.0 % 6 30.0 % 4 20.0 % 4 20.0 %
Comorbidity	(-) (+)				8 40.0 % 12 60.0 %
Fever (°C)		36.5 – 39.5	38.6	38.7 ± 0.9	
SpO_2		56.0 – 88.0	84.5	82.2 ± 9.4	
Heart rate (BPM)		86.0 – 130.0	103.5	104.6 ± 11.7	
Horovitz score		55.0 – 118.0	81.0	79.1 ± 21.1	
Lymphocyte (mcL)		270.0 – 1850.0	525.0	789.0 ± 553.2	
IL-6 (pg/ml)		33.2 – 339.2	103.0	140.6 ± 117.4	
Procalcitonin (ng/ml)		0.7 – 18.3	2.5	4.6 ± 5.4	
CRP (mg/L)		27.4 – 268.0	135.4	138.7 ± 83.4	
D-dimer (µ/L)		627.0 – 8850.0	2085.0	3181.7 ± 2851.8	
AST (IU/L)		47.0 – 941.0	88.0	185.5 ± 270.7	
ALT (IU/L)		56.0 – 596.0	84.0	157.1 ± 173.9	
Hb (gr/dL)		9.2 – 13.7	10.5	10.9 ± 1.5	
T-Bb (mg/dL)		0.51 – 3.00	1.42	1.52 ± 0.75	
ID-Bb (mg/dL)		0.18 – 0.86	0.66	0.64 ± 0.20	
SOFA		6.0 – 17.0	10.0	11.0 ± 3.65	
Discharged Exitus					14 70.0 % 6 30.0 %

SpO2 : Saturation, IL-6 : Interleukin-6, CRP: C-reactive protein, AST: aspartate aminotransferase, ALT: alanine aminotransferase, Hb: haemoglobin, T-Bb: total bilirubin, ID-Bb: indirect bilirubin,
SOFA: Sequential Organ Failure Assessment, BPM: beats per minute

After CPFA treatment, fever was assessed in the 24th hour, 48th hour and 7th day and a significant fall was observed compared to before CPFA ($p<0.05$). There was no significant change in SpO_2 values in the 24th and 48th hour after CPFA compared to before CPFA ($p>0.05$). However, on the 7th day SpO_2 values were statistically significantly increased compared to before CPFA ($p<0.05$). Heart rate assessment in the 24th hour and 7th day after CPFA treatment did not observe any significant variation compared to before CPFA ($p>0.05$). There was a significant increase in Horowitz index values in the 24th hour, 48th hour and 7th day compared to before CPFA ($p<0.05$). In the 24th hour, 48th hour and 7th day after CPFA treatment, lymphocyte values increased from 525 103/µL to 1150 103/µL; however, this was not found to be statistically significant compared to before CPFA ($p>0.05$) (Table II).

Table II: Fever, SpO2, Heart Rate, Horowitz Scores, Lymphocyte values

	Min-Max	Median	Mean±ss.	P*	P**
Fever					
Before CPFA	36.5 - 39.5	38.6	38.7 ± 0.9		
After CPFA, 24th hour	36.2 - 38.5	37.1	37.2 ± 0.8	**0.008**w	
After CPFA, 48th hour	36.0 – 38.1	36.9	36.9 ± 0.7	**0.008**w	0.514w
After CPFA, 7th day	36.2 – 38.1	36.5	36.8 ± 0.7	**0.018**w	0.399w
SpO_2					
Before CPFA	56.0 – 88.0	84.5	82.2 ± 9.4		
After CPFA, 24th hour	47.0 - 94.0	90.5	86.4 ± 14.1	0.066w	
After CPFA, 48th hour	66.0 - 96.0	93.0	90.4 ± 9.4	0.109w	0.312w
After CPFA, 7th day	93.0 – 99.0	96.0	96.0 ± 2.4	**0.018**w	**0.041**w
Heart Rate					
Before CPFA	86.0 - 130.0	103.5	104.6 ± 11.7		
After CPFA, 24th hour	68.0 - 121.0	91.5	91.8 ± 16.2	0.066w	
After CPFA, 48th hour	73.0 - 99.0	91.0	88.7 ± 7.9	**0.011**w	0.859w
After CPFA, 7th day	75.0 - 111.0	90.0	90.6 ± 11.6	0.091w	0.670w
Horovitz score					
Before CPFA	55.0 - 118.0	81.0	79.1 ± 21.1		
After CPFA, 24th hour	30.0 - 337.0	107.5	125.2 ± 82.5	**0.024**w	
After CPFA, 48th hour	43.0 - 350.0	125.0	139.6 ± 85.0	**0.013**w	0.477w
After CPFA, 7th day	121.0 - 337.0	150.0	187.9 ± 78.0	**0.018**w	**0.042w**
Lymphocyte					
Before CPFA	270.0 – 1850.0	525.0	789.0 ± 553.2		
After CPFA, 24th hour	440.0 - 2370.0	830.0	1041.0 ± 706.1	0.169w	
After CPFA, 48th hour	207.0 - 1760.0	920.0	1044.1 ± 581.9	0.260w	0.374w
After CPFA, 7th day	285.0 – 2480.0	1150.0	1226.4 ± 807.3	0.237w	0.398w

w Wilcoxon test
p Compare to CPFA before / p** Compare to previous measurement*
SpO2 : Saturation

Statistically significant falls were observed in IL-6 values in the 24th hour, 48th hour and 7th day after CPFA treatment compared to before CPFA ($p<0.05$). In the 48th hour after CPFA, IL-6 values showed no significant change compared to the 24th hour ($p>0.05$), while values on the 7th day showed a significant fall compared to 48th hour values ($p<0.05$). For procalcitonin values, a statistically significant fall was observed in the 24th hour, 48th hour and 7th day after CPFA compared to before CPFA ($p<0.05$). In the 24th hour, 48th hour and 7th day after CPFA, CRP values were observed to have significant falls compared to before CPFA ($p<0.03$) (Table III). After CPFA treatment, D-dimer values in the 24th hour, 48th hour and 7th day displayed a significant fall compared to values before CPFA ($p<0.05$). The D-dimer values on the 7th day after CPFA treatment did not show a significant change compared to 48th hour values ($p>0.05$). AST values in the 24th hour after CPFA did not show significant variation compared to before CPFA ($p>0.05$).

However, in the 48th hour and 7th day after CPFA, there was a significant fall in AST values compared to before CPFA ($p<0.05$). There was no significant change in ALT values in the 24th hour after CPFA compared to before CPFA. In the 48th hour and 7th day, ALT values displayed a significant fall compared to before CPFA ($p<0.05$) (Table III).

Table III: IL-6, Procalcitonin, CRP, D-dimer, AST-ALT, Haemoglobin values, SOFA Scores

	Min-Max	Median	Mean±ss.	P*	P**
IL-6					
Before CPFA	33.2 - 339.2	103.0	140.6 ± 117.4		
After CPFA, 24th hour	6.1 - 293.7	18.8	78.2 ± 106.7	**0.005**[w]	
After CPFA, 48th hour	2.9 - 201.3	9.2	46.3 ± 77.5	**0.008**[w]	0.086[w]
After CPFA, 7th day	5.9 - 29.3	7.3	14.1 ± 9.8	**0.018**[w]	**0.043**[w]
Procalcitonin					
Before CPFA	0.7 - 18.3	2.5	4.6 ± 5.4		
After CPFA, 24th hour	0.0 - 13.0	0.4	2.1 ± 4.0	**0.005**[w]	
After CPFA, 48th hour	0.0 - 2.0	0.3	0.6 ± 0.7	**0.008**[w]	0.128[w]
After CPFA, 7th day	0.2 - 0.7	0.4	0.4 ± 0.2	**0.018**[w]	0.498[w]
CRP					
Before CPFA	27.4 - 268.0	135.4	138.7 ± 83.4		
After CPFA, 24th hour	2.2 - 191.0	77.8	78.6 ± 60.0	**0.013**[w]	
After CPFA, 48th hour	2.0 - 195.0	40.7	65.6 ± 65.4	**0.008**[w]	**0.038**[w]
After CPFA, 7th day	2.5 - 130.0	16.0	56.0 ± 58.5	**0.018**[w]	0.499[w]
D-dimer					
Before CPFA	627.0 - 8850.0	2085.0	3181.7 ± 2851.8		
After CPFA, 24th hour	440.0 - 4300.0	1945.0	1882.0 ± 1302.5	**0.047**[w]	
After CPFA, 48th hour	330.0 - 3130.0	960.0	1179.4 ± 885.5	**0.038**[w]	**0.015**[w]
After CPFA, 7th day	310.0 - 2430.0	760.0	902.1 ± 734.1	**0.018**[w]	0.063[w]
AST					
Before CPFA	47.0 – 941.0	88.0	185.5 ± 270.7		
After CPFA, 24th hour	29.0 - 297.0	58.5	82.0 ± 77.7	0.074[w]	
After CPFA, 48th hour	21.0 - 189.0	52.0	64.2 ± 51.7	**0.012**[w]	0.123[w]
After CPFA, 7th day	23.0 – 47.0	32.0	34.7 ± 8.9	**0.018**[w]	0.398[w]
ALT					
Before CPFA	56.0 – 596.0	84.0	157.1 ± 173.9		
After CPFA, 24th hour	33.0 - 410.0	69.0	105.6 ± 112.5	0.059[w]	
After CPFA, 48th hour	25.0 - 101.0	69.0	63.9 ± 28.5	**0.008**[w]	0.260[w]
After CPFA, 7th day	31.0 – 70.0	46.0	48.3 ± 14.3	**0.018**[w]	0.128[w]
Hb					
Before CPFA	9.2 – 13.7	10.5	10.9 ± 1.5		
After CPFA, 24th hour	9.3 – 16.3	10.8	11.3 ± 2.1	0.441[w]	
After CPFA, 48th hour	9.2 – 13.6	10.5	10.9 ± 1.5	0.553[w]	0.722[w]
After CPFA, 7th day	9.2 – 12.3	10.0	10.2 ± 1.0	0.237[w]	0.395[w]
T-Bb					
Before CPFA	0.51 – 3.00	1.42	1.52 ± 0.75		
After CPFA, 24th hour	0.58 – 2.70	1.04	1.28 ± 0.65	0.059[w]	
After CPFA, 48th hour	0.64 – 1.78	0.90	1.02 ± 0.41	**0.049[w]**	0.080[w]
After CPFA, 7th day	0.42 – 1.47	0.70	0.87 ± 0.39	**0.028[w]**	0.236[w]
ID-Bb					
Before CPFA	0.18 – 0.86	0.66	0.64 ± 0.20		
After CPFA, 24th hour	0.27 – 0.72	0.48	0.51 ± 0.15	**0.028[w]**	
After CPFA, 48th hour	0.27 – 0.73	0.49	0.47 ± 0.16	0.110[w]	0.342[w]
After CPFA, 7th day	0.27 – 0.68	0.44	0.46 ± 0.13	**0.018[w]**	0.866[w]
SOFA					
Before CPFA	6.00 – 17.00	10.00	11.00 ± 3.65		
After CPFA, 24th hour	5.00 – 19.00	8.00	10.10 ± 4.53	0.066[w]	
After CPFA, 48th hour	3.00 – 16.00	8.00	8.44 ± 4.33	**0.031[w]**	0.336[w]
After CPFA, 7th day	4.00 – 7.00	7.00	6.14 ± 1.21	**0.018[w]**	0.317[w]

w Wilcoxon test

p Compare to CPFA before / p** Compare to previous measurement*

In the 24th hour, 48th hour and 7th day, there was no significant change in Hb values compared to before CPFA that would lead to consideration of clear hemolysis (Table III). The total bilirubin (T-Bb) value in the 24th hour after CPFA treatment did not show significant change compared to before CPFA (p>0.05). However, in the 48th hour and 7th day after CPFA, T-Bb values displayed a significant fall compared to before CPFA (48th hour p: 0.031, 7th day p: 0.018). In the 24th hour and 7th day after CPFA, indirect bilirubin (ID-Bb) values were observed to be statistically significantly reduced compared to before CPFA (24th hour p: 0.028, 7th day p: 0.018).

A significant decrease was observed in the use of noradrenaline, especially on the 7th day after CPFA administration. However, these results were not statistically significant (Table IV).

Table IV: Noradrenaline use

		n	%	P*	P**
Noradrenaline					
Before CPFA	(-) (+)	14 6	70.0 % 30.0 %		
After CPFA, 24th hour	(-) (+)	12 8	60.0 % 40.0 %	1.000 N	
After CPFA, 48th hour	(-) (+)	16 4	80.0 % 20.0 %	1.000 N	1.000 N
After CPFA, 7th day	(-) (+)	18 2	90.0 % 10.0 %	1.000 N	1.000 N

N McNemar test
p Compare to CPFA before / p** Compare to previous measurement*

DISCUSSION

In our study, we retrospectively scanned the effects of CPFA therapy on our intensive care patients who were thought to have developed CS from their files and archives. As a result of our study, significant improvements were observed in the clinical and laboratory findings of the patients who underwent CPFA. Particularly, improvements in oxygenation and improvements in mortality scores were observed.

SARS-CoV-2 is attacked by immune cells, including mast cells found mainly in the respiratory tract and nasal cavity. When the virus infects the respiratory tract, it causes a respiratory syndrome with the release of cytokines such as interleukin IL-1 and IL-6. These mediators cause more lung inflammation, fever, and fibrosis[11]. Induced hypercytokinemia caused by pathogenic human coronaviruses (HCoV) leads to uncontrolled excessive production of proinflammatory and anti-inflammatory cytokines[12]. This situation may contribute to the development of severe clinical findings like acute pulmonary injury, ARDS, sepsis, septic shock and multiple organ failure[12,13]. The release of different cytokines called CRS is closely associated with development of a range of clinical symptoms.

CRRT may benefit critical patients by removing potentially harmful components from blood while preserving hemodynamic and metabolic status. In addition to conventional application to improve kidney functions, it may benefit patients developing sepsis by regulation of circulating inflammatory cytokines and complement factors (TNFα, IL-1, IL-6 etc) and targeting removal from blood[14,15]. CPFA was developed as an extracorporeal cycle comprising a plasma filter, resin cartridge and high smart dialyzer for the non-specific removal of inflammatory mediators during systemic inflammation. Plasma filtration and hemofiltration are performed with the CPFA treatment. Additionally, if required, hemodialysis can be performed or connected to an extracorporeal membrane oxygenation (ECMO) device. The CPFA system may be used together with continuous venovenous hemofiltration (CVVH) like renal replacement treatment, it can be operated in standard CVVH modality by stopping the plasma filter, and does not require use of an additional CRRT set[16,17].

We performed the CPFA treatment to our patients with severe COVID-19 due to these advantages of use. First of all, positive changes occurred in laboratory values and this also contributed to clinical improvement.

COVID-19 first emerged as an acute respiratory tract disease characterized by interstitial and alveolar pneumonia; however, it was later reported to affect many organs like kidneys, heart, digestive system and nervous system[18]. Kidneys are one of the organs with difficult treatment and management in critically ill patients with COVID-19 infection. In SARS and MERS-CoV infections, 5-15% of cases developed acute kidney injury (AKI) and it was reported to involve high mortality (60-90%) rates[19]. A study of 59 patients infected with SARS-CoV-2 showed that 63% of patients (32/51) displayed proteinuria, 19% (11/59) had high plasma creatinine levels and 27% (16.59) had high urea nitrogen levels[20]. After CPFA procedure mean potassium levels were 6,4 mEq/L and regressed to 4,1 mEq/L and mean creatinine values fell from 2.8 mg/dL to 0.7 mg/dL. After this, a remarkable improvement in kidney function was observed. Additionally, the hydrophobic resin cartridge in the CPFA system ensures removal of toxic molecules like cytokines, bilirubin and myoglobin without causing loss of albumin[21]. After the CPFA procedure was finished, only one of our patients continued with systemic standard CVVH.

IL-6 has pronounced pro-inflammatory properties. It displays pleiotropic effects on two signal paths called cis and trans in the acquired immune system (B and T cells) and on the natural immune system (neutrophils, macrophages, natural killer cells). The cis signal pathway causes clinical findings like fever, cough, fatigue, muscle and joint pains and laboratory findings like normal or reduced lymphocyte count and elevated CRP. In SARS-CoV-2 infection, elevated CRP values are observed both due to infection and secondarily elevated by IL-6[22]. The trans signaling pathway induces cytokine release and affects endothelial cells. Consequently, increased vascular permeability leads to hypotension and ARDS formation[23]. In our study, the need for inotropic agents decreased after the CPFA procedure, but no statistically significant change was observed. After the CPFA procedure, which is one of the methods that provides non-selective removal of soluble mediators and bacterial toxins, significant decreases in IL-6 levels occurred at 24th hour, 48th hour and 7th day compared to before CPFA procedure. 24 hours after the procedure, IL-6 values decreased from 160 pg / mL to 80 pg / mL, then it was observed that it was 20 pg / mL 7 days after procedure. A statistically significant decrease in CRP values from 135 mg / L to 16 mg / L occurred 7 days after the CPFA procedure. In situations secondary to IL-6 increase, procalcitonin values may be normal if there is no secondary bacterial infection. Elevated procalcitonin values are observed in the presence of coinfection[24]. After the CPFA procedure, the mean procalcitonin values decreased from 4.5 pg / mL to 0.5 pg / mL.

Overall, lymphopenia and increased levels of certain cytokines, such as IL-6, have been closely associated with the disease severity. A remarkable decrease in T cell counts is almost always observed in severe cases. Patients admitted to ICU show a dramatic decrease in T cells, especially CD8+ T cell counts[25].

A study observed that among patients admitted to intensive care due to COVID-19, 98% had high fever, 63% had lymphocytopenia and the d-dimer levels of patients in intensive care were higher compared to those not monitored in intensive care[25]. High fever, one of the clinical signs of SARS-CoV-2 infection and negatively affecting the progression of the disease, was recorded in our intensive care unit with high d-dimer levels and lymphocytopenia in laboratory tests during the progression of the disease. After the CPFA procedure, body temperature values decreased from an average of 38.6 to 36.5 °C, and significant improvements were observed in body thermoregulation. After the CPFA procedure, an increase in the mean lymphocyte

count from 525 103/μL levels to 1150 103/μL levels was observed.

Liver dysfunction may be common in patients admitted for COVID-19. Elevated ALT and AST levels were reported in 16–53% of patients. Patients with severe COVID-19 seem to have higher rates of liver dysfunction[26]. The pooled analysis study results of P Paliogiannis and A Zinellu[27] on 6 articles show that bilirubin levels increase significantly in severe COVID-19 patients. In our study after CPFA procedure, ALT and AST mean values decreased from 80 units/L to 30 units/L, total bilirubin mean values decreased from 1,4 mg/dL to 0,7 mg/dL and indirect bilirubin mean values decreased from 0,66 mg/dL to 0,44 mg/dL.

After CPFA procedure positive changes occurred in almost all clinical and laboratory findings of patients. This situation positively affected the Horowitz scores (PaO2/FiO2) we used to evaluate the respiratory capacity and oxygenation of the patients. The Horowitz score varies with age, but is approximately 350-405 in people with healthy lungs. A value below 300 is the threshold for mild lung injury, and 200 is indicative of a moderately severe lung injury. A value below 100 as a criterion for a severe injury. The Horowitz index plays a major role in the diagnosis of ARDS[28]. Before the procedure, 8 patients had Horowitz values below 100 and had serious oxygenation problems. While the mean Horowitz values before the procedure was 80, after the CPFA procedure the mean Horowitz values increased to 180. As a result, serious improvements were observed in respiratory parameters and oxygen saturation. In addition, these clinical and laboratory changes positively affected the SOFA scores. SOFA score is a good diagnostic marker for sepsis and septic shock. The SOFA score evaluates six organ systems: respiratory, cardiovascular, hepatic, coagulation, renal, and neurological[29]. Before the CPFA procedure, the mean SOFA score of our patients was 10, this value decreased to 7 a week later after CPFA procedure. Some studies have noted long-term predicted mortality rates of 40-50% when SOFA scores are in the 10-12 range[30]. In our study, the mortality rate was found to be 30% in our patients with an average SOFA score of 10 and who underwent CPFA.

There are some limitations of our study. The most significant is that our study is a retrospective study. The difficulty of designing a prospective randomized study while dealing with the pandemic in intensive care conditions should not be ignored. Another limitation is the low number of cases administered CPFA. This study rapidly presents our experience related to CPFA showing that it may be an alternative COVID-19 treatment. It will guide more comprehensive, larger and prospective studies to be performed in the future about this topic.

CONCLUSION

Both the virus particle and the excessive immune response stimulated by the virus play an important role in the immunopathogenesis of infection developing linked to COVID-19. CS developing as a result of uncontrolled production of proinflammatory and anti-inflammatory cytokines/chemokines due to the disrupted immune system cause progression of the disease to severe stages, organ injury, complete disruption of physiology and death.

CPFA treatment removes inflammatory cytokines / chemokines and potentially harmful compounds from the blood, caused by COVID-19 disease. Therefore, significant improvements were observed in the clinical and laboratory values of our patients. In particular, promising improvements were achieved in the oxygenation marker Horowitz scores and mortality marker SOFA scores. Another advantage is; Hemodiafiltration can be applied during treatment or after the procedure is completed.

In conclusion, we have demonstrated that CPFA is a safe and well tolerated procedure and can be particularly beneficial if initiated in the early

phase of the cytokine storm associated with COVID-19.

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