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Effectiveness of Coupled Plasma Filtration Adsorption Technique in Cytokine Storm Developing in Critical Covid-19 Patients

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Abstract

Due to its immunopathology, the SARS-Cov-2 virus, which causes COVID-19 disease, leads to an uncontrollable release of cytokines, in which IL-6 plays a role, leading to damage in various organs, especially the lung. In COVID-19 patients, treatment of this cytokine storm is as important and life-saving as antiviral therapy. In this case series, we aimed to present six patients in whom we performed cytokine removal with Coupled Plasma Filtration Adsorption (CPFA) technique in critically ill COVID-19 patients diagnosed with cytokine storm who were hospitalized in the intensive care unit and connected to mechanical ventilator.

Keywords: Coupled plasma filtration adsorption, COVID-19, Cytokine storm, Cytokine removal.

Introduction

The SARS-Cov 2 virus that causes COVID-19 is a new strain of coronavirus that has not been previously isolated from humans or animals. Twenty percent of hospitalized COVID-19 patients have severe illness and need Intensive Care Unit (ICU) treatment [1]. SARS-Cov 2 virus uses ACE2 receptors on host cell membranes to establish infection [2].

Immune abnormality is associated with the pathogenesis of COVID-19 infection [3, 4]. Especially during the cytokine storm, there is excessive and uncontrollable cytokine production in response to infection [3, 4]. These cytokines play an important role in disease progression [4]. Interleukin 6 (IL-6) functions as the core of the cytokine storm. IL-6 is elevated in 52% of these patients [5]. Acute Respiratory Distress Syndrome (ARDS) develops in 50% of patients with cytokine storm [3, 4, 5]. Corticosteroids, intravenous immunoglobulins, cytokine blockade (tacilimuzab, anakinra) and Janus Kinases (JAK) inhibition can be used in this situation [3, 4].

Interleukin 6 and Tumor Necrosis Factor alpha (TNF-alpha) are proinflammatory molecules responsible for effects including tissue damage resulting in vital organ dysfunction [6]. Anti-inflammatory cytokines, such as interleukin 4 and 10, are regulators against proinflammatory mediators [7]. Coupled Plasma Filtration Adsorption (CPFA) is a novel extracorporeal blood purification therapy for sepsis that nonselectively adsorbs both proinflammatory and anti-inflammatory mediators during sepsis [8, 9, 10]. As a result, it reduces the need for inotropes and provides hemodynamic stabilization [11]. It also has an immunomodulatory effect [12]. In the present study, we used CPFA in six COVID-19 cases (2-3 times in each patient). The patients were hemodynamically stable and did not need vasopressors and inotropes. Cytokine storm was diagnosed based on clinical, metabolic, biochemical and endocrine markers and CPFA was used only for cytokine removal.

In this case series, we aimed to present the clinical, metabolic, biochemical and endocrine parameters and mortality status of six COVID-19 patients who developed cytokine storm triggered by *SARS-Cov-2* virus and did not receive vasopressor and inotrope treatment.

Case presentation

The patients were hospitalized either in the COVID-19 ward or directly in the COVID-9 ICU after evaluation of their thoracic CT scans by the radiology specialist. In the ward, all patients were given nasal oxygen therapy at 10L/minute. If SpO_2 was below 85% despite oxygen therapy, the patient was admitted to the ICU. In the ICU, the patient was first started on oxygen therapy

with a free oxygen mask with a reservoir balloon at 10 L/min. If SpO_2 dropped below 85%, the patient was treated with CPAP 4X1 (2 hours) with a non-invasive CPAP mask with PEEP: 8 cmH_2O, pressure above PEEP: 12 cmH_2O and FiO_2: 80% after two hours of treatment. Nasal high-flow oxygen therapy with FiO_2:80% and oxygen flow 60 L/minute was applied between CPAP. As soon as the patients were admitted to the COVID-19 ward, treatment was started in accordance with the current treatment protocol of the WHO and TR Ministry of Health. In **[Tables 1, 2]** days indicated with red were the days when CPFA was performed. In all cases, blood purification (for cytokine removal) was performed with CPFA (HF440, Infomed, Geneva, Switzerland) using a plasma filter polyethersulfone, with surface area 0.45m2 (Plasma filter LF-0.50, Infomed, Geneva, Switzerland) and hemofilter surface area 1.4m2 (Hemofilter DF-140, Infomed, Geneva, Switzerland). Blood flow was set to 100 mL/min. In all cases, if procalcitonin levels were elevated in the ICU, appropriate antibiotics were started according to the culture results. All antibiotic doses were calculated according to daily urea and keratinise values.

Case 1:

59-year-old male patient: The patient was admitted to the emergency department of our hospital with complaints of shortness of breath and high fever. It was found that the patient had previously been diagnosed with type 2 diabetes mellitus and received insulin treatment in our hospital. The patient had no other comorbidities. The patient did not respond to treatment in the COVID-19 ward was hospitalized in the COVID-19 ICU after 10 days. APACHE score at ICU admission was 13 and likelihood of mortality was 16.5%. However, SpO_2 could not be increased above 70% despite five days of treatment in the ICU and CPAP for the last 6 hours. GCS of the patient was 8 and SpO_2 decreased to 40% and the patient was then intubated orotracheally. Ventilation was started with FiO_2:100%, P-SIMV mode, PEEP: 10cmH_2O, pressure above PEEP: 18cmH_2O, Delta-P: 14 cmH_2O and RR: 18/min. On the 5th day of ICU admission, lymphocyte values decreased, urea, keratinise, AST, ALT, creatinkinase, LDH, potassium and CRP values increased, inflammation markers increased **[Table 2]** and ground glass appearance on PA chest radiography became more evident. Cytokine storm was suspected and CPFA was performed twice with 12-hour intervals on the 7th and 8th day. Biochemical, clinical, metabolic and endocrine parameters before and after CPFA administration are shown in **[Table 1, 2].** Blood group On the 7th day of the patient's hospitalization, blood gas levels deteriorated and APRV mode was turned on as T-high:5 sec, Tlow:1 sec, Phigh:29 cmH_2O, Plow:0 cmH_2O with FiO_2:100%. At the end of 6 hours, PCO_2 value was 120 mmHg and the pH was 7.01 and the patient was switched to P-SIMV mode with volume guarantee and given the prone position. After 18 hours in prone position, the patient was moved back to supine position. The patient's RESP score was calculated and the expected survival rate was found to be 33%, so it was decided not to start ECMO. The patient died of bradycardic arrest due to hypoxia and hypotension on the 10th day of hospitalization.

Case 2:

51-year-old female patient: The patient was admitted to the emergency department of our hospital with complaints of shortness of breath and high fever and had been previously treated for hypertension and diabetes mellitus. The patient had no other comorbidities and was using amyloids 10 mg 2x1, cardura 1x4mg, coversyl 1x10mg and insulin. After 5 days of treatment in the COVID-19 ward, the patient was transferred to the COVID-19 ICU. APACHE score at ICU admission was 31 and likelihood of mortality was 73.3%. After admission to the ICU, SpO_2 could not be increased and the patient was intubated after 5 days of CPAP treatment. After intubation, the patient was connected to mechanical ventilator in P-SIMV mode with FiO_2 80%, SS: 18/min, PEEP 10cmH_2O and pressure above PEEP 14 cmH_2O. Cytokine storm was suspected and CPFA was performed on the 6th, 7th and 8th day of ICU admission. Biochemical, clinical, metabolic and endocrine parameters before and after CPFA administration are shown in **[Table 1, 2].** The patient was followed up in the ICU for 58 days and died on the 58th day with MODS due to sepsis and bradycardic arrest due to hypotension.

Case 3:

58-year-old male patient: The patient was admitted to the emergency department of our hospital with complaints of shortness of breath and high fever. The patient had no other comorbidities. When he was admitted to the ICU, he had a tachypnea of 35/minute. The patient was treated in the COVID-19 ward for 5 days. APACHE score at ICU admission was 9 and likelihood of mortality was 9.9%. On the 5th day of ICU admission, the patient was orotracheally intubated because his hypoxia did not improve, respiratory rate did not fall below 30 and GCS was 12. The patient was connected to the mechanical ventilator with FiO_2:100%, SS: 16/min, PEEP: 10cmH_2O and pressure above PEEP: 12 cmH_2O in P-SIMV mode. Cytokine storm was suspected and CPFA was performed for cytokine removal on days 6, 7 and 8 of hospitalization. Biochemical, clinical, metabolic and endocrine parameters before and after CPFA are shown in **[Table 1, 2]**. The patient died on the 12th day of hospitalization with MODS due to sepsis and bradycardic arrest due to hypotension.

Case 4:

76-year-old female patient: The patient was admitted to the emergency department of our hospital with complaints of shortness of breath and high fever. The patient had insulin-dependent diabetes mellitus and was being followed-up. The patient was intubated in the emergency department and taken directly to the ICU. Mechanical ventilator treatment was started in P-SIMV mode with FiO_2 100%, SS: 20/min, PEEP: 10cmH_2O and pressure above PEEP: 16cmH_2O. APACHE score at admission was 29 and likelihood of mortality was 67.2%. CPFA was performed on the 7th, 8th and 9th day of ICU admission with suspected cytokine storm. Biochemical, metabolic, clinical and endocrine parameters before and after CPFA are shown in **[Table 1, 2]**. The patient died on the 9th day of hospitalization with MODS due to septic shock and bradycardic arrest due to hypotension.

Case 5:

64-year-old male patient: The patient was admitted to the emergency department of our hospital with complaints of shortness of breath and high fever. The patient was previously

Tabla 1. Biochemical values of patients, daily change of SOFA and KDIGO values

Case 1	5.Day	6.Day	7.Day	8.Day	9.Day	10.Day
Urea mg/dL	109	129	129	121	103	139
eGFR ml/dk/1,73m^2	25	24	27	1,95	50	22
Creatinine mg/dL	2,70	2,79	2,50	3,7	1,51	2,96
AST U/L	1636	457	684	1425	258	215
ALT U/L	472	320	368	552	330	247
Creatine kinase IU/L	1348	806	580	670	538	1205
LDH U/L	1548	895	1040	1510	1241	952
CRP mg/L	256	190,68	167,30	65,80	44,60	22,20
SOFA score	10	10	10	10	9	15
Case 2	**5.Day**	**6.Day**	**7.Day**	**8.Day**	**9.Day**	**10.Day**
Urea	103	116	115	176	179	204
eGFR	9	10	13	13	15	18
Creatinine	5,16	4,6	3,84	3,82	3,46	22,85
AST	10	19	22	14	14	16
ALT	7	7	7	7	7	9
Creatine kinase	21	104	655	304	228	112
LDH	465	1090	889	782	879	987
CRP	321,7	350	350	149	121,9	56,1
SOFA score	11	10	10	10	10	11
Case 3	**5.Day**	**6.Day**	**7.Day**	**8. Day**	**9.Day**	
Urea	34	56	62	123	143	
eGFR	>90	85	>90	52	22	
Creatinine	0,60	0,98	0,71	1,48	2,98	
AST	67	52	50	74	65	
ALT	41	33	30	27	27	
Creatine kinase	217	169	117	1038	525	
LDH	630	832	598	779	606	
CRP	177,4	-	136	148	161,9	
SOFA score	5	4	6	10	12	
Case 4	**6.Day**	**7.Day**	**8.Day**	**9.Day**	**10.Day**	
Urea	104	119	129	134	118	
eGFR	38	31	29	26	25	
Creatinine	1,36	1,61	1,71	1,85	1,94	0,89
AST	195	128	120	145	167	
ALT	29	28	26	21	20	
Creatine kinase	172	249	495	649	652	
LDH	1815	1296	1280	1756	2110	
Klor	115	115	118	116	119	
CRP	237,8	305,6	>350	>350	>350	
SOFA score	9	9	12	12	13	
Case 5	**6.Day**	**7.Day**	**8.Day**	**9.Day**	**10.Day**	
Urea	98	82	54	55	58	
eGFR	46	51	72	75	62	
Creatinine	1,57	1,43	1,08	1,05	1,23	
AST	42	45	49	57	34	
ALT	31	29	35	49	37	
Creatine kinase	94	62	33	78	46	
LDH	580	883	405	661	590	
CRP	211,7	188,4	156	149,2	223,6	
SOFA score	9	9	9	10	10	
Case 6	**6.Day**	**7.Day**	**8.Day**	**9.Day**		
Urea	63	54	56	71		
eGFR	60	76	84	>90		
Creatinine	0,96	0,79	0,73	0,65		

AST	14	15	26	39		
ALT	15	13	20	17		
Creatine kinase	40	48	54	588		
LDH	750	726	733	751		
CRP	212,8	244,3	248,1	280,4		
SOFA score	7	7	7	7		

AST: Aspartate amino transferase
ALT: Alanine aminotransferase
LDH: Lactic dehydrogenase
eGFR: Estimated glomerular filtration rate
CRP: C-reactive protein
SOFA: Sequential organ failure assesment score

Table 2: Daily variation of patients' ferritin, D-Dimer and procalcitonin values.

Case 1	**6.Day**	**7.Day**	**8.Day**	**9.Day**	**10.Day**		
Ferritin mcg/L	>2000	>2000		>2000	>2000		
D-Dimer ng/mL	529	605			772		
Procalcitonin mcg/mL	18,52			4,93			
Case 2	**4.Day**	**5.Day**	**6.Day**	**7.Day**	**8.Day**	**9.Day**	**10.Day**
Ferritin	169	>2000		>2000		>2000	>2000
D-Dimer	1379			2573		2973	2670
Procalcitonin	18,60						3,32
Case 3	**1.Day**	**6.Day**	**7.Day**	**8.Day**			
Ferritin	>2000	>2000	>2000	>2000			
D-Dimer	307	7061	3614				
Procalcitonin	5,70			2,68			
Case 4	**5.Day**	**6.Day**	**7.Day**	**8.Day**	**9.Day**	**10.Day**	
Ferritin	898	>2000	>2000		>2000	>2000	
D-Dimer	1235			2860		3050	
Procalcitonin	0,76					11,50	
Case 5	**5.Day**	**6.Day**	**7.Day**	**8.Day**	**9.Day**		
Ferritin	>2000		>2000		>2000		
D-Dimer	3947			4200	4480		
Procalcitonin	2,9			6,56	7,80		
Case 6	**5.Day**	**6.Day**	**7.Day**	**8.Day**	**9.Day**		
Ferritin	1200	1350	1355		1376		
D-Dimer	144		1388	814	766		
Procalcitonin	0,75			1,12	1,32		

diagnosed with diabetes mellitus and hypertension. After four days of treatment in the COVID-19 ward, the patient was transferred to the ICU. APACHE score at admission to COVID-19 ICU was 16 and likelihood of mortality was 23.5%. On the 5th day of ICU admission, the patient was orotracheally intubated because hypoxia did not improve, respiratory rate did not fall below 35 and GCS was 7. The patient was connected to mechanical ventilator in P-SIMV mode with FIO_2: 100%, SS: 18/min, PEEP: 10 cmH_2O and pressure above PEEP: 12 cmH_2O. Cytokine storm was suspected and CPFA was performed on days 7, 8 and 9 of hospitalization for cytokine removal. Biochemical, clinical, metabolic and endocrine parameters of the patient before and after CPFA are shown in **[Table 1, 2].** The patient developed MODS due to septic shock on the 9th day of ICU admission and died of bradycardic arrest.

Case 6:

69-year-old female patient: The patient was admitted to the emergency department of our hospital with complaints of shortness of breath and high fever. The patient was previously diagnosed with diabetes mellitus and chronic lymphocytic leukaemia and was on follow-up. The patient was taken directly to the COVID-19 ICU from the emergency department. Oxygen therapy was started with a mask at 10 L/min. APACHE score at hospitalization was 25 and likelihood of mortality was 53.3%. Since the patient's SpO_2 was below 70%, she was orotracheally intubated and connected to mechanical ventilator on the 6th day of ICU admission. Mechanical ventilator treatment was started in P-SIMV mode with FiO_2: 100%, SS: 24/min, PEEP: 10 cmH_2O and pressure above PEEP: 18 cmH_2O. Cytokine storm was suspected and CPFA was performed on the 7th and 8th day of hospitalization. Biochemical, clinical, metabolic and endocrine parameters before and after CPFA are shown in **[Table 1, 2].** The patient developed MODS due to septic shock on the 9th day of hospitalization and died of bradycardic arrest due to hypotension.

Discussion

In this case series, we aimed to evaluate the effects of extracorporeal removal of cytokines, which is one of the ways to eliminate the effect of cytokines that cause cytokine storm, in critical COVID-19 patients with cytokine storm. Cytokine removal has already been practiced in patients with septic shock before the SARS-Cov-2 pandemic. There are numerous applications in the literature [6, 14].

Various extracorporeal systems have been developed for cytokine removal. AN69, Oxiris, HA330, Cytosorb and CPFA are some of these systems [15, 16, 17]. However, cytokine removal is not included in the latest sepsis guideline and there is no specific level of recommendation. CPFA is one of the cytokine removal techniques. In addition to cytokine removal, renal replacement therapy and plasmapheresis can be performed simultaneously. During CPFA, blood cells are separated from plasma and do not cause thrombocytopenia as they do not come into contact with the cytokine-containing resin cartridge. In a single-center study with 25 patients, Cader RA [11]. showed that CPFA can be safely used and tolerated in the treatment of sepsis. In a multicenter study conducted by Livigni S, 91 CPFA-treated patients were compared with 93 control patients and no statistically significant difference was found between the two groups [18]. Hassan J et al. showed that CPFA provided a more permanent and significant hemodynamic stability in patients with severe sepsis, but sepsis biomarkers decreased equally in both SRRT and CPFA [19]. In burn patients with AKI-RRT and sepsis caused by bacterial species that do not respond or respond poorly to treatment, it was shown that mortality rate was lower in patients treated with combined CPFA and RRT compared to patients treated with RRT alone [12]. In a review by Ankawi G [21], it was emphasized that the evidence for the use of extracorporeal techniques in sepsis is still insufficient and clinical studies are needed [20]. In another study, the results of 19 CPFA-treated patients were compared with 30 control patients and no statistically significant difference was found between the groups.

The main site of attack of the SARS-Cov2 virus is the respiratory system, clinically characterized by severe cases with ARDS and MODS and rapidly developing pneumonia [3]. Mortality rate is high in patients hospitalized in ICU and connected to ventilator during respiratory and heart failure complications [3]. All of our patients died in the COVID-19 ICU after CPFA applications. IL-6 is at the core of organ failure caused by a cytokine storm. Studies have shown that CPFA significantly reduces blood levels of IL-6. CPFA also reduces proinflammatory factors other than IL-6, but reduces anti-inflammatory cytokines to the same extent. Because of these effects, we used CPFA for cytokine removal in the six cases we presented. However, SOFA values remained the same or increased after CPFA applications in all of our patients. In other words, organ damage increased or remained at the same level. In cases 4 and 6, there was no bacterial infection before CPFA administration and there was no shock condition. Other cases had bacterial infection before CPFA application. Our patients were not receiving vasopressors or inotropic drugs. In all cases, CVP pressures and vena cava inferior collapsibility indices were against hypervolemia, so there was no circulatory overload. Cases 1 and 2 had acute renal injury but no indication for dialysis. We did not perform CPFA in any of our patients because of CRRT. Only cytokine storm markers were elevated in the patients **[Table 1, 2]**. We performed CPFA for the sole purpose of cytokine removal. All of our patients had a PO_2/FiO_2 ratio below 100 and all of our patients had been orotracheally intubated and were receiving mechanical ventilator treatment at the time of CPFA. After CPFA, there was an increase in aeration on AP-chest radiographs in cases 1-3-4, but SOFA values increased in these cases and KDIGO values also increased in cases 1 and 3. No significant change in PO_2/FiO_2 ratio was observed in any of our patients after CPFA. CRP values decreased after CPFA in cases 1 and 2, but increased in cases 3-4-5-6. Ferritin, D-dimer and procalcitonin values continued to increase after CPFA application in all cases. Again, all of our patients developed septic shock and related hypotensive bradycardic arrest and died within 3 days after CPFA application. In one study, CRRT and removal of inflammatory mediators were recommended in patients with severe COVID-19 [8]. In the Surviving Sepsis Campaign, none of the cytokine removal techniques were included in the guideline in the management of critical COVID-19 patients [13]. Li Weng conducted a review and also included CRRT in the treatment guideline of critical COVID-19 patients, but did not include cytokine removal techniques [22].

We performed CPFA on COVID-19 patients with the hypothesis that the cytokine storm, in which IL-6 plays a major role, will improve with the removal of proinflammatory cytokines and that organ damage will decrease and patients will recover. However, none of the patients responded to CPFA and we saw that the cytokine storm did not abate and organ damage increased even more.

Conclusion

The results obtained in this case series show that CPFA technique should not be used for cytokine removal in the treatment of cytokine storm caused by SARS-Cov-2 virus in intubated and mechanically ventilated critical COVID-19 patients.

Limitations

In this study, we presented a case series of 6 patients and published only these results. The results were not compared with cytokine blockade or techniques inhibiting cytokine production. Furthermore, no investigation was made on when to start cytokine removal. There is a need for further randomized, controlled, double-blind clinical trials comparing cytokine removal techniques with techniques that block cytokines or inhibit cytokine formation and also investigating when to start cytokine removal.

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