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CASE REPORT / *OLGU SUNUMU*

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Alternative Treatment Method for Crimean Congo Hemorrhagic Fever: Coupled Plasma Filtration and Adsorption

Kırım Kongo Kanamalı Ateşi için Alternatif Tedavi Yöntemi: Birleştirilmiş Plazma Filtrasyonu ve Adsorpsiyon

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ABSTRACT Crimean-Congo hemorrhagic fever (CCHF) is a viral hemorrhagic fever syndrome that can cause multi-organ failure with hyperactivation of the immune system. There is no proven treatment for CCHF, supportive care is essential for management. Extracorporeal depurative techniques have been used to remove inflammatory mediators from the bloodstream. This report aims to present the use of coupled plasma filtration and adsorption (CPFA) in CCHF patients. We performed CPFA on three patients with CCHF, all of which were confirmed with polymerase chain reaction. A 35-year-old female was admitted one week after tick-exposure. Despite supportive treatment, patient developed mucosal and gastrointestinal bleeding due to disseminated intravascular coagulation (DIC). After CFPA, her clinic situation and laboratory results improved. A 54-year-old female was admitted to the intensive care unit due to severe bleeding and had a history of tick bite nine-days-ago. She had multiple organ failure with DIC, we started CPFA. Patient didn't respond to the treatment and died. A 69-year-old male was admitted to the hospital on the seventh-day of exposure to tick. He had diabetes, hypertension and coronary artery disease. Next day, patient developed alveolar hemorrhage and his liver enzymes, coagulation parameters deteriorated. We performed CFPA, however, the patient didn't respond to treatment and died. We suggested that CPFA may have positive effects on the outcome and prognosis of critically ill CCHF patients. Only one patient responded well which can be a result of being young, early admission to the hospital and lack of comorbidity. CPFA may be an option to treat severe CCHF infection with cytokine storm. However,there is a need for further studies on when we should apply this treatment and whether early application prevents mortality.
Keywords: Crimean-Congo hemorrhagic fever, therapeutic plasma adsorption, therapeutic plasmapheresis

ÖZ Kırım-Kongo kanamalı ateşi (KKKA), bağışıklık sisteminin hiperaktivasyonu ile çoklu organ yetmezliğine neden olabilen viral bir hemorajik ateş sendromudur. KKKA için kanıtlanmış bir tedavi yoktur, yönetim için destek tedavisi şarttır. Ekstrakorporeal depuratif teknikler enflamatuvar mediyatörleri kan dolaşımından uzaklaştırmak için kullanılır. Bu rapor, KKKA hastalarında birleştirilmiş plazma filtrasyon ve adsorpsiyon (BPFA) kullanımını sunmayı amaçlamaktadır. Polimeraz zincir reaksiyonu ile tanısı doğrulanmış üç hastaya BPFA uygulandı. Otuz beş yaşında kadın hasta kene temasından bir hafta sonra başvurdu. Destek tedavisine rağmen hastada yaygın damar içi kanama (YİK) nedeniyle mukozal ve gastrointestinal kanama gelişti. BPFA sonrası klinik durumu ve laboratuvar sonuçları düzeldi. Dokuz gün önce kene ısırması öyküsü olan 54 yaşında kadın hasta mukozal kanama ve hipotansiyon nedeniyle yoğun bakıma alındı. YİK'nin eşlik ettiği çoklu organ yetmezliği vardı, BPFA tedavisine rağmen hasta tedaviye yanıt vermedi ve eksitus oldu. Altmış dokuz yaşında erkek hasta kene maruziyetinden bir hafta sonra hastaneye başvurdu. Eşlik eden diabetes mellitus, hipertansiyon ve koroner arter hastalığı vardı. Ertesi gün hastada alveoler hemoraji gelişti, karaciğer enzimleri yükseldi ve pıhtılaşma parametreleri bozuldu. BPFA uygulandı ancak tedaviye yanıt vermeyen hasta öldü. BPFA'ya yalnızca bir hasta olumlu yanıt verdi, bu durum genç olmak, hastaneye erken başvurmuş olmak ve komorbidite olmaması ile ilişkili olabilir. Şiddetli KKKA hastalarında sitokin fırtınasını tedavi etmek için BPFA iyi bir seçenek olabilir. Ancak bu tedaviyi ne zaman uygulamamız gerektiği ve erken uygulamanın mortaliteyi önleyip önlemediği konusunda ileri çalışmalara ihtiyaç vardır.
Anahtar Kelimeler: Kırım-Kongo kanamalı ateşi, terapötik plazma adsorpsiyonu, terapötik plazmaferez

Introduction

Crimean-Congo hemorrhagic fever (CCHF) is a viral hemorrhagic fever syndrome caused by a tick-borne virus from the genus Nairovirus and the family Bunyaviridae. The clinical progression occurs in four phases: incubation, pre-hemorrhagic, hemorrhagic and convalescent period. In severe cases, hemorrhagic manifestations develop 3-6 days after the onset of the disease. Thrombocytopenia, leukopenia, elevated liver enzymes and prolonged coagulation times are the main laboratory features. Endothelial cells damaged by virus and virus-derived mediators play a role in the immunopathogenesis of CCHF (1,2). Pro-inflammatory cytokines released from damaged endothelial cells activate immune cells. Cytokines cause releasing of procoagulant factors, endothelial cell dysfunction and increased vascular permeability resulting in disseminated intravascular coagulation (DIC) and multiple organ failure. Rapid and severe activation of the inflammatory cascade autoamplificate cytokine production,which is called cytokine storm (3). There is no recommended antiviral treatment for CCHF. The clinical and laboratory effect of ribavirin is controversial (4). Supportive therapy is recommended in the management of the disease. Different extracorporeal depurative techniques have been developed to remove inflammatory mediators from the bloodstream thus restore immune homeostasis. Plasmapheresis, one of these techniques, has been shown to have a positive effect on the clinical course of severe CCHF patients (5-7). Coupled plasma filtration and adsorption (CPFA), another depurative technique, is used in intensive care patients with indications such as sepsis, septic shock and multiorgan failure (8). We present the the use of CFPA in management of three patients with CCHF.

Case Reports

CPFA was applied to three patients followed in the intensive care unit (ICU). All of the patients lived in rural areas and were engaged in animal husbandry. The diagnosis of CCHF was confirmed by polymerase chain reaction. Informed consent was obtained for this study.

Case 1

A 35-year-old female patient presented to the emergency department with complaints of fever, malaise and nausea. The patient was biten by a tick seven-days before her admission. Her symptoms started three-days after exposure. She was conscious, cooperative and oriented. She had fever (38 °C), other vitals were normal. She had bilateral conjunctivitis and vaginal bleeding. The laboratory blood results at the admission were as follows: leukocyte count: 810/μL, hemoglobin: 11.4 gr/dL, platelet: 33,000/μL, alanine aminotransferase (ALT): 55U/L, aspartate aminotransferase (AST): 239U/L, lactate dehydrogenase (LDH): 1670U/L, international normalized ratio (INR) 1 and D-dimer >36.2 mg/L. The severity grading score (SGS) was nine (9). On the 4th day of hospitalization, despite supportive treatment refractory thrombocytopenia developed, and intravenous immunoglobulin (IVIG) was administered. The patient whose vaginal bleeding continued had hematochezia. Hemoglobin value decreased (6.6 g/dL). Laboratory values of the patient are given in Table 1. She developed severe mucosal bleeding,

Table 1. Laboratory parameters of Patient-1 during the clinical course

Days after tick exposure	7	9	11	13	15	17	19	25
	Admission to hospital		1st session of CPFA	2nd session of CPFA				Day of discharge
WBC (x10^3/μL)	0.81	0.85	0.91	9.5	8.3	7	7.4	4
Hb (gr/dL)	11.4	9	7.5	7.1	8.7	8.7	8.9	9
Plt (x10^3/μL)	33	14	8	101	67	131	251	235
FIB (mg/dL)	238	230	380	214	375	571	340	300
INR	0.9	1	1.2	0.86	0.8	0.82	0.9	0.9
aPTT (sec)	42	50	50	38	25	20	-	22
D-dimer (mg/L)	>36	1.93	3.26	2.2	2.1	-	2.1	-
ALT (U/L)	55	171	430	275	168	100	92	24
AST (U/L)	239	431	1280	667	230	90	40	21
LDH (U/L)	1670	2160	2250	1057	620	543	483	120

WBC: White blood cells, Hb: hemoglobin, Plt: platelet, FIB: fibrinogen, INR: international normalized ratio, aPTT: activated partial thromboplastin time, ALT: alanine aminotransferase, AST: aspartate aminotransferase, LDH: lactate dehydrogenase, CPFA: coupled plasma filtration and adsorption

tachycardia (n=140/min) and hypotension (90/50 mm/Hg). After the patient became desaturated (SpO_2: 85%) and chest X-ray was consistent with interstitial edema, she transferred to the ICU with oxygen support. By calculating the patient's plasma volume, the total plasma volume was passed through the absorbent (Medisorb, Bellco, Medtronic, IT) once, the blood flow was 100-120 mL/min, and CPFA (Bellco, Medtronic, IT) was administered with heparin infusion for approximately 10-12 hours. The target activated partial thromboplastin time value in heparin infusion was between 45-65 seconds. After nine days in ICU, patient's leukocyte and thrombocyte values returned to normal and bleeding stopped. On the 25th day of admission, her vitals were stable and she was discharged healthy.

Case 2

A 54-year-old female was brought to the hospital with complaints of widespread muscle-joint pain, fever and nausea that started three days after a tick bite. There was no known comorbidities. The patient, who was hospitalized in another center for five days, was referred to our ICU because of increased liver enzymes and deterioration in coagulation parameters. Ten days after tick exposure, the laboratory blood parameters at admission to the hospital were as follows: leukocyte: 5910/µL, hemoglobin: 11.4 gr/dL, platelet: 61,000/µL, ALT: 2153 U/L, AST: 239 U/L, LDH: 116890 U/L, INR: 1, D-dimer: 1.9 mg/L. SGS was nine. When admitted to the ICU, the patient required mechanical ventilation. Patient was treated with CPFA for two days. On the 2nd day at the ICU, she died due to septic shock.

Case 3

A 69-year-old male was admitted to the emergency department with the complaints of chills, fatigue and weakness. He had a history of tick exposure seven days prior to the admission. He had hypertension, diabetes mellitus and coronary artery diseases with the use of anticoagulants. The laboratory blood parameters were as follows: leukocyte: 2510/µL, hemoglobin: 16 gr/dL, platelet: 19,000/µL, ALT: 185 U/L, AST: 390 U/L, LDH: 1120 U/L, INR: 0.9, D-dimer: 0.89 mg/L. SGS was ten. Supportive treatment was started. The patient desaturated on the 2nd day of hospitalization, chest X-ray was consistent with alveolar hemorrhage. The patient was intubated and transferred to the ICU. Patient was treated with CFPA on the 2nd day of his admission for two days. The desaturated, hypotensive patient died on the 5th day of admission.

Discussion

CCHF incidence is increasing due to changes in agricultural and animal practices as well as the effects of global warming on climate. CCHF is among the most fatal zoonotic diseases. There is a need for new treatment modalities to manage severe patients.

All of the three patients presented to clinic one week after the tick exposure were found to have SGS >9, which is a high risk for mortality (9). Case-based management of CCHF patients is required therefore checking complete blood count, coagulation parameters daily to replace blood products such as platelets, fresh frozen plasma (FFP) and erythrocyte preparations is essential. As presented in these cases, vital signs and examination are important since the clinical course of patients can change very rapidly. We did not use ribavirin because there are controversial findings regarding the use of this antiviral in CCHF patients (4).

Clinical progress of all three cases worsened in hemorrhagic period. One of the reasons for this rapid deterioration is cytokine storm. Cytokine storm triggers development of hemophagocytic lymphohistiocytosis, characterized by an overactivation of macrophages causing DIC, liver dysfunction, and endothelial damage. To manage cytokine storm in this particular phase will be effective for decreasing mortality. In a study, methylprednisolone, FFP and IVIG have been shown to be beneficial in the treatment of DIC-associated thrombocytopenia in CCHF patients with hemophagocytosis (10). In patient-1, IVIG was started due to refractory thrombocytopenia, but other patients' vitals were not stable enough to administer IVIG. To fight with overactive immune system, extracorporeal depurative techniques have been developed. Removing inflammatory mediators from the bloodstream restore immune homeostasis. CPFA is a hybrid system combining plasma filtration and adsorption with a resin cartridge that removes cytokines.There are case-based publications on the use of extracorporeal depurative techniques in CCHF patients.A positive effect of plasmapheresis on the prognosis of a pediatric CCHF patient was reported (6). In another study, 119 adult CCHF patients were examined, mortality was significantly reduced in the plasmapheresis group, but the effect on the prognosis could not be demonstrated (5). We performed CPFA to patients with CCHF who had cytokine storm causing multiple organ failure. In average ten days after tick exposure and seven days after onset of symptoms, when patients were in hemorrhagic period, first CPFA session done.Primary goal

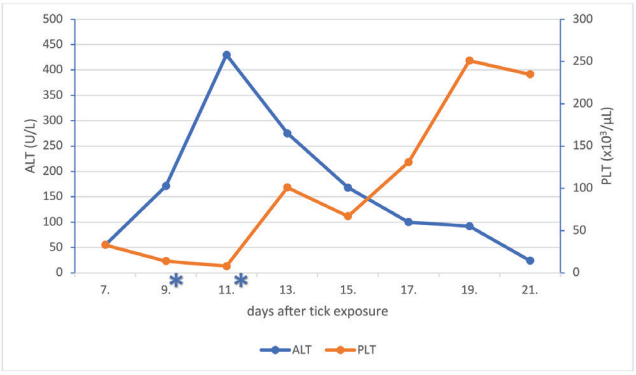

Figure 1. ALT and platelet values of patient-1 during the clinical course
*Indicate days of coupled plasma filtration and adsorption sessions
ALT: Alanine aminotransferase, PLT: platelet

for using CFPA is to reduce overactive inflammation and hemorrhagic complications. The number of CPFA sessions was determined according to the clinical and laboratory improvement. CFPA was used with heparin, considering that there may be an increase in liver toxicity when used with citrate as an anticoagulant. Despite severe thrombocytopenia in patient-1, elimination of inflammatory mediators resulted in rapid improvement in white blood cells and platelet counts (Figure 1). This promising result may indicate that endothelial damage can be prevented by controlling the underlying hyperinflammation with CPFA. Overall, only one patient responded well, which can be a result of being young, early admission to the hospital and lack of comorbidity. Since these treatments were applied to ICU patients improvement of symptoms or decreasing severity of clinical symptoms cannot be optimally assessed. The main question we face is when to apply CFPA. It is not possible to comment on the effect of the early application of CPFA on mortality and which patient should be administered early with small number of patients. Further studies are needed on the indications, application time and duration of CPFA in CCHF patients.

In this case series, for the first time, use of CFPA in CCHF patients and its positive effect on prognosis were demonstrated. More studies are needed using CFPA in CCHF to understand its effect on disease management.

Ethics

Informed Consent: Informed consent was obtained for this study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: D.T., G.Y., Design: D.T., M.P.K., Data Collection and/or Processing: D.T., Analysis and/or Interpretation: A.O.K., M.P.K., Literature Search: D.T., G.Y., Writing: D.T., G.Y., A.O.K., M.P.K.

Conflict of Interest: No conflict of interest was declared by the authors.

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