Received: 6 April 2022 | Revised: 4 July 2022 | Accepted: 4 August 2022

DOI: 10.1002/jca.22006

RESEARCH ARTICLE

Journal of Clinical Apheresis ASFA WILEY

Can charcoal hemoperfusion treatment be an option for pediatric MIS-C patients? A single-center experience in a tertiary pediatric intensive care unit

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Abstract

Introduction: Multisystem inflammatory syndrome in children (MIS-C) is a hyper-inflammatory disorder that develops following SARS-CoV-2 infection and has clinical signs that overlap with Kawasaki disease. Immunomodulatory treatments can be used in these patients. One of the alternative treatments reported in the literature is hemoperfusion therapy. In this study, we aim to evaluate our experience of charcoal hemoperfusion therapy in children admitted and followed up with a diagnosis of MIS-C at our Pediatric Intensive Care Unit (PICU).

Material and Methods: We performed a retrospective evaluation of children diagnosed with MIS-C and children treated with charcoal hemoperfusion who are admitted to our PICU.

Results: Among 49 MIS-C patients, hemoperfusion therapy was performed on 14 patients. Duration of hospitalization, duration of invasive/non-invasive ventilation, VIS, OFI, PRİSM 3 scores, and mortality rates were significantly higher in the charcoal hemoperfusion group before treatment. In patients who did not respond to conventional therapies, we observed a statistically significant decrease in the need for inotrope and invasive mechanical ventilation support and statistically significant improvements in clinical indicators after hemoperfusion therapy.

Discussion: In our study, we observed a significant clinical and laboratory improvement by charcoal hemoperfusion in our MIS-C patients who had a severe clinical course and multiple organ failure.

Conclusion: In our opinion, this study is the first report regarding the use of charcoal hemoperfusion therapy in MIS-C patients, and the choice of charcoal hemoperfusion as an initial or rescue therapy is needed to be investigated in large patient groups both in children and adults who are diagnosed with COVID-19 and MIS-C.

KEYWORDS
charcoal hemoperfusion, MIS-C, pediatric intensive care

1 | INTRODUCTION

The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes coronavirus disease 2019 (COVID-19), was declared by the World Health Organization (WHO) as a global pandemic on March 11, 2020. Children and newborns are generally asymptomatic, or they can present with atypical symptoms, such as mild fever, vomiting, diarrhea, and mild fatigue without any signs of pneumonia. As the presentation is atypical, patients may attend many healthcare centers without being a confirmed COVID-19 case, so they contribute to the spread of the virus.[1-5] Severe patients develop dyspnea and hypoxia, and critical patients may deteriorate rapidly through acute respiratory distress syndrome (ARDS), sepsis, and multi-organ failure.[2] Multisystem inflammatory syndrome (MIS-C) is defined by multisystem involvement including mucocutaneous, cardiac, gastrointestinal, and respiratory systems, and has clinical findings similar to Kawasaki disease. It was reported by the National Health Service (NHS) in the UK on April 27, 2020 for the first time.[6] Children diagnosed shortly after the beginning of the SARS-CoV-2 pandemic manifest evidence of immune response against the virus, and they had features of macrophage activation syndrome (MAS) with a higher rate of cardiac involvement.[7] The current clinical characteristics of MIS-C were defined by the Centers for Disease Control and Prevention in May 2020. Diagnosis criteria include fever for 24 h, laboratory evidence of inflammation, and necessary evidence for hospitalization with multiple system involvement of>2 organs (cardiac, renal, respiratory, hematological, gastrointestinal, dermatological, or neurological), and no alternative diagnosis to explain the clinical findings.

Although MIS-C is generally observed with a mild clinical course, patients with cardiac dysfunction, hypotension, and respiratory failure need to be followed up in the pediatric intensive care unit, as they need inotropic support and noninvasive or invasive mechanical ventilation support. Moreover, in the literature, a very small proportion of patients needed extracorporeal membrane oxygenation support. Hyponatremia, markers of acute kidney injury, hypoalbuminemia, high troponin levels, hematologic abnormalities including neutrophilia, lymphopenia, low to normal platelet levels, elevated D-dimer, elevated interleukin (IL) 6 levels, and low fibrinogen levels have been reported as common laboratory markers along with acute phase reactants such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), procalcitonin, and ferritin.[8-12] In the literature, intravenous immunoglobulin (IVIG), steroid, and high-dose steroid therapies are reported to lead to successful outcomes in patients diagnosed with MIS-C. On the other hand, there are case reports regarding the use of immunomodulatory therapies such as anakinra (recombinant IL-1 antagonist), a second dose of IVIG, tocilizumab, and plasmapheresis in patients with MIS-C.[6,10,13]

Charcoal hemoperfusion (CHP) is an extracorporeal elimination method in which blood circulates in a closed circuit through a cartridge containing activated charcoal through a hemodialysis machine. CHP is a preferred method for extracorporeal extraction of toxins adsorbed with activated charcoal.[14] Like hemodialysis, CHP is effective mostly on toxins that have a small volume of distribution. Unlike hemodialysis, it also can effectively remove toxins that are bound to plasma proteins.[14] Although CHD is generally used to remove toxic substances from the body, there are studies in the literature declaring its use in inflammatory conditions like sepsis, by efficiently removing cytokines with large molecular weight such as TNF alpha.[15] In a study by Nagaki M et al., it is reported that charcoal hemoperfusion is effective in removing cytokines such as TNF-alpha, IFN-y, IL-1, and IL-6 from the body.[16] Shixiang Zheng et al. reported that the early use of charcoal hemoperfusion in patients with sepsis may cause upregulation of serum High Mobility Group Box-1 (HMGB1), leading to increased urinary excretion of HMGB1 and improving the prognosis of sepsis.[17]

In this study, we aim to evaluate our experience with charcoal hemoperfusion therapy in children admitted to our pediatric intensive care unit (PICU) and followed up with a diagnosis of MIS-C.

2 | MATERIALS AND METHODS

2.1 | Study design

We performed a retrospective evaluation of children diagnosed with MIS-C and treated with charcoal hemoperfusion after being admitted to the PICU at Sancaktepe Training and Research Hospital. Informed consent was obtained from all parents before hospitalization and during all procedures. Noninvasive Clinical Research Ethics Committee approval was received from Hospital at Health Science University institution (B.10.1. TKH.4.34.H.GP.0.0.1/139). MIS-C was diagnosed based on the Centers for Disease Control and Prevention criteria. Hemoperfusion therapy was applied through hemodialysis catheters which were placed in the subclavian vein, femoral veins, and internal jugular veins of one, three, and 10 of our patients, respectively. Heparin infusion was the first choice as an anticoagulant strategy due to the hypercoagulability in COVID-19 patients, ongoing ECMO therapy, or contraindication for citrate

anticoagulation, like liver failure. Heparin infusion continued in the dose range of 10-30 U/kg/hour during ECMO; activated clotting time (ACT) or aPTT was monitored throughout this infusion. Targeted intervals for several parameters were as follows: ACT between 170-220 seconds, aPTT between 60-80 seconds. Citrate anticoagulation was preferred in patients with severe thrombocytopenia or bleeding risk. Patient and filter ionized calcium values were monitored during citrate anticoagulation. Data were collected using a detailed form involving the patient's age, gender, Pediatric Risk of Mortality (PRISM) score, Pediatric Logistic Organ Dysfunction (PELOD) score, Organ Failure Index (OFI) score, length of stay in PICU, duration of use of inotropes, Vasoactive Inotropic Score (VIS) before and after hemoperfusion therapy, duration of mechanical ventilation, mechanical ventilation parameters such as positive end-expiratory pressure (PEEP)/peak inspiratory pressure (PIP), echocardiographic findings, treatments, treatment complications, treatment outcomes, and mortality. We recorded patients who received charcoal hemoperfusion with other extracorporeal treatments such as continuous renal replacement treatment (CRRT), therapeutic plasma exchange (TPE), and extracorporeal membrane oxygenation (ECMO). Also, complete blood count, blood biochemistry, biomarkers of infection, coagulation parameters, serum ferritin levels, serum IL-6 levels, and serum troponin levels were obtained retrospectively from our digital records and patient forms filled upon admission. Charcoal hemoperfusion therapy was applied with Adsorba 300C (Baxter, Gambro) hemoperfusion cartridge. Hemoperfusion therapy with Adsorba 300 cartridge was applied by serial connection to the ECMO circuit in two patients and by using a dialysis catheter in 12 patients. By connecting to the Oxiris filter in series in 10 of 12 patients and with its own HPX set in two patients. During the hemoperfusion procedures, blood flow was adjusted to 2 to 6 mL/min/kg. One cartridge was used for 8 hours. No cartridge occlusion or bleeding complications were observed in any of the patients. Two cartridges were used in four of the patients followed up in ECMO and one cartridge was used in the remaining 10 patients. In the clinical and laboratory evaluations of the patients before and after hemoperfusion, the values just before the hemoperfusion and 24 h after the start of the hemoperfusion therapy were used (Table 3, Table 4). Blood investigations including blood culture and procalcitonin (PCT) were used in the differential diagnosis of secondary bacterial infections. Nasopharyngeal swab real-time reverse-transcriptase-polymerase-chain-reaction (RT-PCR) assay for detection of SARS-CoV-2 was performed according to the guidelines established by the WHO.

2.2 | Outcomes

We described demographic/clinical characteristics and disease severity of patients admitted to our pediatric intensive care with MIS-C diagnosis, and we compared the clinical and laboratory parameters and outcomes of these patients before and after the hemoperfusion treatment.

2.3 | Statistical analysis

SPSS v.21 (SPSS Inc., Chicago, Illinois) was used for statistical analysis. Kolmogorov-Smirnov or Shapiro-Wilk tests were used to assess normality, where appropriate. Results were presented as median (minimum-maximum) for non-normally distributed variables. Categorical variables were presented with frequency and percentage. Comparisons of the groups for continuous variables were made by the Mann-Whitney *U* test. The chi-square test or Fisher's exact test was used to analyze categorical variables, where appropriate. All tests are two-sided, and the significance level was accepted as $P < .05$.

3 | RESULTS

Among 49 patients diagnosed with MIS-C, hemoperfusion therapy was performed on 14 patients. Duration of hospitalization, duration of invasive/non-invasive ventilation, VIS, OFI, PRİSM 3 scores, and mortality rates were significantly higher in the charcoal hemoperfusion group before treatment (Table 1). Of 14 patients, eight were female, and six were male. The mean age of 14 patients was 149.9 ± 46.1 months, and the mean equal length of stay was 23.8 ± 12.2 days. All our patients needed intubation and invasive mechanical ventilation, also 11 of them needed vasoactive inotrope support due to severe circulatory failure in the hemoperfusion group. IVIG therapy, as suggested in MIS-C treatment, was given to all our patients before hemoperfusion therapy. IVIG, steroid, and plasmapheresis therapies were applied to seven patients before hemoperfusion therapy. Three patients were treated with IVIG and steroids before hemoperfusion therapy. In four of our patients, we could not exclude sepsis, and they were initially treated not with steroids but with IVIG and plasmapheresis therapies before hemoperfusion (Table 2). In most of the patients (n:11) heparin infusion was used as an anticoagulant, as in some of them (n:3) citrate anticoagulation was selected.

Patients treated with hemoperfusion therapy had findings of two or more organ failures, as their median

TABLE 1 Comparison of clinical features of MIS-C patients with or without charcoal hemoperfusion

Features	Hemoperfusion		*P* value
	Yes ($n = 14$)	No ($n = 35$)	
Hospitalization day, median (IQR)	24.5 (21.0)	7.0 (4.0)	<.001
Mortality, n (%)			
Yes	3 (21.4)	0 (0)	.020
No	11 (78.6)	35 (100)	
Mechanical ventilation, n (%)			
Yes	14 (100)	3 (8.6)	<.001
No	0 (0)	32 (91.4)	
Mechanical ventilation day, median (IQR)	9.0 (13.0)	0.0 (0.0)	<.001
Noninvasive ventilation day, median (IQR)	2.0 (2.25)	0.0 (3.0)	.001
OFI score, median (IQR)	3.0 (2.0)	1.0 (2.0)	<.001
VIS, median (IQR)	32.0 (61.0)	0.0 (12.0)	<.001
PRISM, median (IQR)	17.0 (9.25)	2.0 (4.0)	<.001

Abbreviations: IQR, inter quantile range; OFI, organ failure index; PRISM, pediatric risk of mortality; VIS, vasoactive inotropic score.

PRISM score was 17 (9), and the median PELOD score was 9 (4). Through the clinical course, ECMO therapy was applied to four and one patient in veno-arterial and venovenous ways, respectively. After the ending of ECMO therapy, hemoperfusion therapy was applied to every patient who had received ECMO support. Ten patients had hemodiafiltration and hemoperfusion therapies simultaneously with a hemoperfusion cartridge connected to an Oxiris cytokine filter, while eight had hemodiafiltration treatment with an Oxiris (Baxter, Gambro) cytokine filter before hemoperfusion.

In patients who did not respond to conventional therapies, we observed a statistically significant decrease in the need for inotrope and invasive mechanical ventilation support after hemoperfusion therapy. As seen in Table 3, we observed statistically significant improvements in clinical indicators such as the highest heart rate, vasoactive inotrope need, number of failed organs and positive end-expiratory pressure, mean airway pressure, and peak inspiratory pressure parameters in mechanical ventilation. Also, a decrease in blood levels of important indicators of inflammation such as ferritin and IL-6 was statistically significant. On the other hand, improvements in prognostic parameters like serum lactate, serum lactate/albumin ratio, serum creatinine, lactate dehydrogenase, and international normalized ratio levels were statistically significant (Table 4).

Through the clinical course, one patient supported with veno-arterial ECMO died, and the mortality rate was 7.14% among patients treated with hemoperfusion.

4 | DISCUSSION

Previous studies demonstrated that both primary infection and multisystem inflammatory syndrome, which were described in children, may cause critical illnesses.[18] In a previous review, 68%, 40%, 15%, and 2.7% of MIS-C patients needed intensive care, inotropic support, mechanical ventilation, and ECMO, respectively.[19] Immunological mechanisms, cytokine storms, and hyperinflammation occur in the clinical course of critical disease. In addition, multi-organ failure in adults with severe SARS-COV-2 infection has similar pathophysiology to MIS-C.[18,20-22]

The main purpose of MIS-C therapy is to reduce mortality and morbidity by controlling cytokine storms, hyper-inflammatory responses, and organ dysfunctions by using immunomodulatory therapies. The use of IVIG, aspirin, and corticosteroids is suggested in treatment.[18,19,23] In the treatment of refractory patients, high-dose corticosteroids, a second dose of IVIG, tocilizumab (IL-6 receptor antagonist), anakinra (IL-1 receptor antagonist), infliximab (monoclonal antibodies to tumor necrosis factor), or convalescent plasma therapy may be considered.[6,18]

There are many blood purification methods such as CRRT, plasmapheresis, hemofiltration, hemoperfusion, and immunoadsorption, which are useful in controlling the development of cytokine storms by possibly restoring a balance of immune response and eliminating/deactivating inflammatory mediators.[24,25] On the other hand, these treatment modalities may have important

TABLE 2 Clinical features of the patients treated with charcoal hemoperfusion

Case	Age (month)	Sex	Length of stay (days)	Duration of use of inotropes (days)	Duration of use of IMV(days)	IVIG use[a]	Steroid use[a]	Plasmapheresis[a]	PRISM score	OFI score	PELOD score
1	188	Female	7	–	3	Yes	Yes	–	6	2	6
2	176	Female	13	7	5	Yes	–	Yes	14	3	9
3	210	Female	25	10	8	Yes	Yes	Yes	36	6	15
4	120	Female	29	11	14	Yes	Yes	Yes	24	6	21
5	180	Male	29	20	29	Yes	Yes	Yes	33	6	22
6	85	Male	15	5	5	Yes	Yes	Yes	13	3	9
7	171	Female	24	2	12	Yes	Yes		11	3	10
8	147	Female	50	45	45	Yes		Yes	16	4	9
9	176	Female	11	–	6	Yes	–	Yes	11	3	7
10	121	Male	35	20	35	Yes	Yes	Yes	19	4	10
11	137	Male	34	2	10	Yes	–	Yes	14	3	8
12	153	Male	14	2	2	Yes	Yes	–	21	2	7
13	193	Male	34	–	11	Yes	Yes	Yes	9	2	6
14	41	Female	13	8	8	Yes	Yes	Yes	18	3	7

Abbreviations: IMV, invasive mechanical ventilation; IVIG, intravenous immunoglobulin; OFI, organ failure index; PELOD, pediatric logistic organ dysfunction; PRISM, pediatric risk of mortality.
[a]Prior to hemoperfusion.

TABLE 3 Clinical parameters of patients treated with charcoal hemoperfusion

	Median (IQR)	*P* value
Pre-Hearth rate	142.0 (36.0)	.001*
Post-Hearth rate	81.0 (12.5)	
Pre-MAP	55.0 (24.0)	.012*
Post-MAP	82.0 (10.75)	
Pre-VIS	32.0 (61.0)	.005*
Post-VIS	0.0 (8.0)	
Pre-MOF	3 (1.0)	.001*
Post-MOF	0.5 (2.0)	
Pre-PEEP	8.0 (5.0)	.007*
Post-PEEP	5.0 (2.0)	
Pre-Ppeak	32.5 (5.0)	.001*
Post-Ppeak	19.5 (3.0)	
Pre-PaO_2/CO_2	3.15 (2.83)	.046*
Post-PaO_2/CO_2	5.20 (2.78)	

Note: *P values < .05.
Abbreviations: IQR, inter quantile range; MAP, mean arterial pressure; MOF, multi-organ failure; $PaCO_2$, partial pressure of carbon dioxide in arterial blood; PaO_2, partial pressure of oxygen in arterial blood; PEEP, positive end-expiratory pressure; Post, after hemoperfusion therapy; Ppeak, peak pressure; Pre, before hemoperfusion therapy; VIS, vasoactive inotropic score.

TABLE 4 Laboratory features of patients treated with charcoal hemoperfusion

	Median (IQR)	*P* value
Pre-lactate (mmol/L)	2.20 (2.23)	.001*
Post-lactate (mmol/L)	1.20 (0.65)	
Pre-lactate/Albumin ratio	0.80 (1.11)	.001*
Post-lactate/Albumin ratio	0.28 (0.20)	
Pre-ferritin (ng/ml)	1169 (2590.0)	.010*
Post-ferritin (ng/ml)	303.0 (625.0)	
Pre-platelet	45 500.0 (120 434.0)	.235
Post-platelet	128 000.0 (170500)	
Pre-IL-6 (pg/ml)	121.5 (665.0)	.011*
Post-IL-6 (pg/ml)	25.0 (89.0)	
Pre-creatinine (mg/dL)	0.84 (1.96)	.003*
Post-creatinine (mg/dL)	0.49 (0.67)	
Pre-LDH (U/L)	363.5 (1624.0)	.001*
Post-LDH (U/L)	246.5 (70.0)	
Pre-INR	1.62 (0.45)	.002*
Post-INR	1.21 (0.17)	
Pre-troponin (ng/mL)	0.037 (214.81)	.311
Post-troponin (ng/mL)	0.056 (32.56)	
Pre-EF (%)	64.0 (36.0)	.012*
Post-EF (%)	70.0 (12.0)	

Note: *P values < .05.
Abbreviations: EF, ejection fraction ratio; IL-6, interleukin 6; INR, international normalized ratio; IQR, inter quantile range; LDH, lactate dehydrogenase; Post, after hemoperfusion therapy; Pre, before hemoperfusion therapy.

adverse effects and complications such as loss of electrolytes, nutrients, and drugs, including antibiotics.[24] Also, complications due to vascular access and anticoagulation may be seen.[24] Based on the previous experience with these effects on cytokine storms in sepsis and septic shock, in recent studies, CRRT and plasma exchange therapies were preferred mostly among blood purification methods in COVID-19 patients.[24-28]

There are two major types of adsorbent materials, including activated charcoal and resins. Charcoal has a greater affinity for hydrophilic molecules, whereas resins have a higher affinity for hydrophobic molecules.[29] Although it is known that hemoperfusion can be used classically to remove drugs and chemicals, limited evidence studies are declaring its beneficial impact on the removal of inflammatory mediators from the bloodstream in inflammatory responses such as cytokine storms.[30] In the review of SanFilippo F et al. on hemoperfusion therapy in COVID-19 patients, it was emphasized that hemoperfusion therapy was effective in reducing IL-6 levels; however, more randomized controlled studies are needed on this subject.[31] A recent study, in which HA330 Disposable Hemoperfusion Cartridge (Jafron Biomedical Co., Ltd. China) was used, suggested that the early initiation of hemoperfusion significantly reduced mortality in critically ill COVID-19 adult patients.[32] Another study with HA resin hemoperfusion cartridge (Model HA 280, Jafron Biomedical Co., Ltd.) reported that hemoperfusion at the inflammatory phase of the disease, especially before the intubation, reduced the need for mechanical ventilation, but hemoperfusion did not have any impacts on the duration of hospital and intensive care unit stay.[33] Similarly, in a report of a 54-year-old male COVID-19 case, the application of CRRT/HP in the early stages of ARDS prevented the progression of the disease from moderate to severe ARDS, stabilizing and gradually enhancing the oxygen saturation, thus, removing the need for invasive mechanical ventilation.[34] In a report including eight cases, Shadvar K et al. recorded that hemoperfusion could reduce the level of inflammation and organ dysfunction in critically ill patients with COVID-19.[35]

There are more limited reports investigating the use of these extracorporeal therapies in MIS-C patients. In the case of a 14-year-old MIS-C patient, it is reported that

hemoadsorption with Cytosorb filter achieved a safe and rapid reduction of cytokine levels and improvement in multiorgan dysfunction parameters.[36] The authors suggested that hemoadsorption with Cytosorb filter provided a safe and rapid reduction of cytokine levels in another case report of a 17-year-old male patient with a diagnosis of acute myocarditis secondary to MIS-C.[37] In this study, we observed a significant clinical and laboratory improvement by charcoal hemoperfusion in our MIS-C patients who had a severe clinical course and multi-organ failure.

5 | CONCLUSION

Despite some older studies showing the effectiveness of charcoal hemoperfusion in removing cytokines such as TNF-alpha, IFN-y, IL-1, and IL-6, in the recent studies, we did not find the usage of charcoal hemoperfusion in patients with cytokine storms. In this study, patients treated with one or more conventional therapies such as IVIG, steroid, and plasmapheresis, clinical indicators such as mechanical ventilation need, vasoactive inotrope need, and prognostic laboratory parameters such as ferritin, serum lactate, international normalized ratio, lactate dehydrogenase, and creatinine levels were statistically significantly improved after hemoperfusion therapy. After the start of charcoal hemoperfusion, there was a rapid and progressive recovery in cardiac functions and hemodynamic parameters.

Despite our low patient count, due to the statistical significance of clinical and laboratory parameters, we think the use of hemoperfusion therapy as an initial or rescue therapy in COVID-19 and MIS-C should be investigated in large patient groups both in children and adults.

AUTHOR CONTRIBUTIONS

Fatih Varol and Ebru Sahin had a role in the patient's diagnosis. Fatih Varol, Aziz Kilic, and Mehmet Cengiz had a role in data collection. Sirin Guven and Halit Çam had a role in literature overview. Fatih Varol, Aziz Kilic, and Zeynep Meva Altas played a role in the study documentation and table preparation.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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How to cite this article: Varol F, Guney Sahin E, Cengiz M, et al. Can charcoal hemoperfusion treatment be an option for pediatric MIS-C patients? A single-center experience in a tertiary pediatric intensive care unit. *J Clin Apher*. 2022;1-8. doi:10.1002/jca.22006