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CASE REPORT

Modified Double Filtration Plasmapheresis Exchange for Managing Sepsis-Induced Shock

Lei Zhang [1], Guan Wang [1], Yan-Rui Chen [2], Xin-Yu Zhao [1], Jian Jiang [1], Yi-bing Weng [1]

[1] *Department of Critical Care, Beijing Luhe Hospital, Capital Medical University, Beijing, China*
[2] *Department of Anesthesiology, Beijing Luhe Hospital, Capital Medical University, Beijing, China*

SUMMARY

Background: **This research primarily concentrated on investigating the impact of plasma exchange, especially the modified double filtration plasmapheresis (M-DFPP), in cases of septic shock (SS). Different from traditional plasma exchange which simply removes some macromolecular pathogenic solutes and protein-binding solutes, M-DFPP, based on DFPP, switches the return and discard ports to remove inflammatory mediators more accurately with less plasma used.**

Methods: **A 67-year-old male patient suffered a right femoral neck fracture in a road accident and underwent right hemiarthroplasty. Twelve days post-surgery, he developed persistent lower abdominal pain and fever. Emergency surgical exploration revealed a retroperitoneal abscess caused by sigmoid colon perforation. Subsequently, the patient was admitted to the ICU for SS treatment. The treatment plan included fluid resuscitation, vasoactive medications, antibiotics, ventilator support, and M-DFPP. Each M-DFPP session exchanged 400 mL of plasma, which accounted for approximately 15% of the patient's total plasma volume. The patient underwent two M-DFPP sessions on the first and second days of admission, with a cumulative treatment time of 4 hours. The long treatment time was due to the need to ensure the stability of the patient's condition during the procedure. Slow-flow operation was adopted to minimize the risk of adverse reactions, such as hypotensive episodes or electrolyte imbalances.**

Results: **After two rounds of plasma exchange, there was a significant decline in plasma inflammatory factors related to SS, such as a decrease in TNF-α from 76.5 to 25.4 pg/mL, IL-6 from 1,000 to 178 pg/mL, and IL-8 from 7,500 to 512 pg/mL. The patient's hemodynamic condition improved remarkably, with heart rate decreasing from 128 to 95 beats per minute, blood pressure rising from 80/40 to 127/64 mmHg, and urine output increasing from 20 to 125 mL/hour. The dosage of vasoactive medications was gradually reduced until they were no longer required. However, due to ineffective management of the retroperitoneal infection, the patient's sepsis deteriorated on the 38th day of ICU admission, and the patient passed away on the 41st day.**

Conclusions: **Compared with traditional continuous renal replacement therapies, M-DFPP is more efficient in eliminating inflammatory substances, simplifying the management of SS. It is a safe, user-friendly, and easily implementable method. Early application of M-DFPP can potentially reduce the damage of the body's inflammatory response to organs and lower the risk of organ failure. Future research is expected to further explore its effectiveness and optimal application strategies.**

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Correspondence:
Yi-Bing Weng
Department of Critical Care
Beijing Luhe Hospital
Capital Medical University
No. 82 Xinhuanan Road
Tongzhou District
Beijing, 101149
China
Phone: + 86 695439012128
Email: yibingweng@ccmu.edu.cn

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KEYWORDS

hemodynamic improvement, inflammatory factors (IL-6, IL-8, TNF-α), modified double filtration plasmapheresis, plasma exchange, septic shock

LIST OF ABBREVIATIONS

SS - Septic Shock
EN - Norepinephrine Bitartrate
DFPP - Double filtration plasmapheresis
ICU - Intensive care unit
DFPP - Double filtration plasmapheresis
MAP - Mean arterial pressure
SOFA - Sequential Organ Failure Assessment

INTRODUCTION

Despite the considerable efforts made by healthcare professionals following the 2002 "Declaration of Barcelona", the treatment of septic shock (SS) remains largely ineffective. One of the most detrimental outcomes of SS is a clinically persistent hypotension**.** Sepsis and septic shock are important drivers of death in critically ill patients. In China, the incidence of septic shock ranges from 25.9% to 41.3%, and the mortality rate ranges from 28.6% to 46.0% [1]. A number of previous studies have shown the importance of plasma purification in SS management, which can effectively reduce mortality [2-4]. The therapeutic principle of traditional plasma exchange (PE) is to remove some macromolecular pathogenic solutes and protein-binding solutes from circulating blood through effective plasma separation methods, while supplementing replacement fluids such as exogenous plasma. Dual filtration plasmapheresis (DFPP) involves separating plasma using a plasma separator (model plasma separator Plasmaflo OP) and passing it through a plasma component separator with a smaller membrane aperture (membrane plasma separator Cascadeflo EC). Based on DFPP, modified double filtration plasmapheresis (M-DFPP) switches the return and discard ports to remove inflammatory mediators more accurately. Specifically, after separating plasma from a plasma separator (model plasma separator Plasmaflo OP) as in DFPP, in M-DFPP, the plasma passes through a plasma component separator with a smaller membrane aperture (membrane plasma separator Cascadeflo EC) in a more optimized way (Figure 1). This adjustment enables more precise elimination of inflammatory mediators while using less plasma and without changing the amount and speed of return and discard. In this article, we present a case study involving a patient who developed retroperitoneal abscess and SS due to a post-traumatic perforation of the posterior wall of the sigmoid colon [5,6]. The patient received palliative surgery and intensive care in the ICU.

CASE REPORT

A 67-year-old man who recently experienced injuries from a traffic accident resulting in a fracture of his right femur neck underwent a surgical procedure for right hemixtherapeutic replacement at a local hospital. After 12 days, he developed persistent lower abdominal pain and fever, leading to concerns about gastrointestinal perforation. Consequently, the patient was transferred to our hospital. He denies having a history of conditions such as hypertension, diabetes, coronary heart disease, or chronic lung disease. There is also no history of infectious diseases like hepatitis or tuberculosis, major traumas, blood transfusions, drug allergies, or food allergies.

During the specialist examination, the patient displayed abdominal distension, the absence of normal gastrointestinal shape and peristalsis waves, abdominal breathing, a normal umbilicus, no protrusions or secretions, no varicose veins in the abdominal wall, a flat abdomen upon palpation, full abdominal tenderness in the left lower quadrant, rebound pain, muscle tension, the absence of a fluid wave sensation and water vibration, no palpation under the ribs of the liver, and no percussion pain. The gallbladder remained unaffected, and there was a negative Murphy sign. The subcostal spleen, kidney, and ureteral tender points were also unaffected, with normal hepatic dullness and a negative mobile dullness. Upon auscultation, there were four intestinal sounds per minute, no metallic or high-pitched tones, clear percussive pain in both kidney locations, and no vascular murmurs. The laboratory results showed WBC: 27.58×10^9/L, Neut (neutrophil granulocyte): 95.40%, HGB: 110 g/L, HCT: 32.8%, PLT: 90×10^9/L. Abdominal CT scans revealed thickening of the descending colon, sigmoid colon, and rectal wall, suggesting potential inflammatory changes. Cloudiness in the surrounding fat gap and gas accumulation were observed.

An emergency surgical examination verified the presence of a retroperitoneal abscess caused by a perforation in the sigmoid colon. Upon creating an incision and drainage in the proximal stoma, rectal, and sigmoid mesenteric regions, a significant volume of infected fluid was observed to discharge. Additionally, a rupture measuring 1.5 cm in diameter was identified in the mesosteroid sigmoid membrane. There were indications of heightened acute and chronic inflammatory cell infiltration, expanded small blood vessels, increased blood flow, and congestion, as well as the formation of an acute inflammatory exudate and an abscess around the incision and serous membrane.

Following surgery, the patient developed septic shock, necessitating his admission to the intensive care unit (ICU). In the ICU, the patient received a comprehensive treatment regimen involving plasmapheresis, antibiotics, vasoactive medications, and fluid resuscitation. Notably, we employed a modified double filtration plasmapheresis (M-DFPP) approach using the Asahi Kasei ACH-10 system for plasma exchange. Our modified

Table 1. Observed indicators.

ICU day	0	1	2	3	4	5	6	7
Blood purification		M-DFPP	M-DFPP					
T (high, ℃)	36.7	36.9	38.7	38.5	38.1	38.4	38.7	38.3
HR (high)	128	100	102	95	93	107	99	97
BP (low, mmHg)	80/40	109/59	99/48	127/64	113/61	125/63	123/61	110/50
Mean arterial pressure	53.33	75.67	65.00	85.00	78.33	83.67	81.67	70.00
RR (high)	15	15	15	15	15	20	19	19
PaO_2/FiO_2 (mmHg)	≥ 200	≥ 200	≥ 200	≥ 300				
SpO_2 (low, %)	97	100	96	99	100	100	98	98
WBC (high, 10^9/L)	7.25	7.07	3.7	5.6	6.7	5.65	4.79	7.13
N % (high)	93.8	92.27	92.6	86.7	81.73	75.48	83.4	88.06
Hb (low, g/L)	105	80	74	74	80	80	68	68
PLT (low, 10^9/L)	63	29	48	55	86	102	100	106
Hs-CRP (mg/L)	202.17	196.8	203.42	173.48	169.17	186.99	154.87	119.45
TNF-α (pg/mL)	76.5	35.1	74.6	25.4	23	15	--	15.9
IL-6 (pg/mL)	1,000	360	1,000	178	246	106	--	142
IL-8 (pg/mL)	7,500	7,500	1,526	512	359	282	--	244
GLU (high, mmol/L)	9.08	10.27	12.99	17.53	4.93	9.75	14.59	9.37
ALT (high, U/L)	17	92	50	37	29	21	18	32
AST (high, U/L)	20	226	58	43	35	24	22	55
ALB (low, g/L)	26.5	19.1	24.8	27.2	25.4	25.3	27.1	26.2
CHE (low, U/L)	1,757	1,313		2,306				
T-Bil (μmol/L)	12.1	21.7	25.8	40.9	55.1	92.9	80.6	86.5
D-Bil (μmol/L)	7.5	16.5	20.3	29.8	43	68.8	63.7	68.1
Cr (high, μmol/L)	172	189	143	115	107	106	101	96
Ventilation mode	A/C	A/C	A/C	A/C	A/C	A/C	A/C - SIMV	SIMV - CPAP
PEEP (cmH_2O)	6	6	6	7	7	7	6/12	6/12
FiO_2 (%)	100 - 60	60	60	60 - 50	50	50	50 - 40	40
NE (high, μg/kg/minute)	0.2	0.2↓	--	--	0.06↓	--	--	--
DA (high, μg/kg/minute)	4	4	0.5	0.5	0.3	0.4↓	--	--
Total input (mL)	3,800	4,400	4,240	3,490	3,150	3,770	3,200	3,430
Total output (mL)	740	2,210	2,470	2,635	3,975	4,280	2,910	3,260
Urine output (mL)	500	1,810	2,200	2,465	3,705	3,940	2,650	2,780
Paracolic drainage volume (mL)	10	50	20	20	20	20	20	20
Drainage of pelvic abscess (mL)	230	150	210	110	30	220	20	380
Day balance (mL)	+ 3,060	+ 2,190	+ 1,770	+ 855	- 825	- 510	+ 290	+ 170
Total balance (mL)	+ 3,060	+ 5,250	+ 7,020	+ 7,875	+ 7,050	+ 6540	+ 6,830	+ 7,000
GCS rating	8	8	10	10	--	--	--	--
SOFA rating	11	13	10	9	--	--	--	5
Lac	4.6	1.8	3.0	1.9	3.2	2.3	2.3	2.0

T temperature, HR heart rate, BP blood pressure, RR respiratory rate, PaO_2 oxygen partial pressure, FiO_2 oxygen concentration, SpO_2 oxygen saturation, WBC white blood cell, Hb hemoglobin, PLT platelet, Hs-CRP hypersensitive C-reactive protein, TNF-α tumor necrosis factor α, IL-6 interleukin 6, IL-8 interleukin 8, GLU glucose, ALT alanine aminotransferase, AST aspartate aminotransferase, ALB albumin, CHE cholinesterase, T-Bil total bilirubin, D-Bil direct bilirubin, Cr creatinine, PEEP positive end-expiratory pressure, NE norepinephrine, DA dopamine, GCS Glasgow, SOFA sequential organ failure assessment, Lac lactic acid.

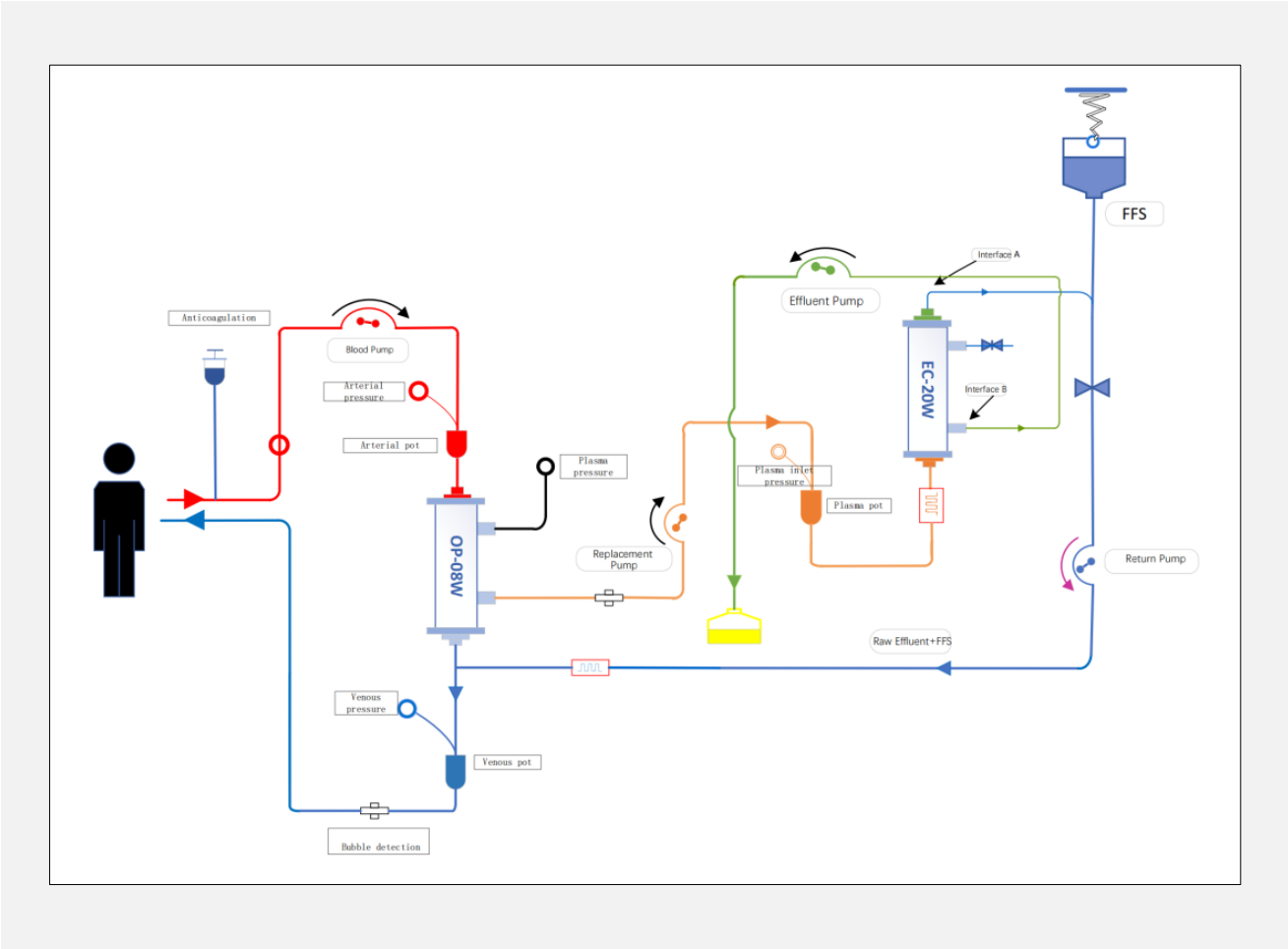

Figure 1. M-DFPP flow chart.

method involved eliminating small and medium-sized molecular substances while reintroducing previously removed macromolecular materials through a secondary membrane.

During his ICU stay, the patient underwent two M-DFPP sessions on the first and second days of admission, each session consisted of a 400 mL plasma exchange over 2 hours, costing RMB 1,560. These procedures were carried out in strict adherence to infection control and shock management principles.

The level of inflammatory factors decreased rapidly, with notable reductions in IL-6, IL-8, and TNF-α concentrations. Specifically, NF-α decreased from 76.5 to 25.4 pg/mL, IL-6 from 1,000 to 178 pg/mL, IL-8 from 7,500 to 512 pg/mL. Additionally, the dosage of vasoactive drugs was adjusted: norepinephrine (NE) was tapered from 0.2 μg/kg/minute to discontinuation, dopamine (DA) was adjusted from 4 to 0.5 μg/kg/minute and discontinued on the fifth day. Heart rate (HR) decreased from 128 to 95 beats per minute, blood pressure (BP) rose from 110/70 to 127/64 mmHg, and urine output increased from 20 to 125 mL/hour. The sequential organ failure assessment (SOFA) rating decreased from 11 to 5 within a week. (Table 1).

After M-DFPP treatment, the dose of vasoactive drugs was significantly reduced, and the use of vasoactive drugs was eventually stopped with the significant improvement of the hemodynamic status of patients. However, the abdominal wound of the patient had not healed and, due to long-term bed rest complicated with lung infection, symptomatic treatment such as anti-infection, anti-shock with fluid, acid inhibition, atomization of phlegm, wound dressing change was actively administered. The patient's sepsis worsened 38 days after admission to ICU, and he died on the 41st day.

DISCUSSION

ICUs commonly encounter SS, which is a leading cause of mortality in these settings [7]. The imbalances in pro-inflammatory and anti-inflammatory cytokine levels, believed to be triggered by pathogen-associated molecular patterns (PAMPs) associated with bacterial cell wall

components and damage-related molecular patterns (DAMP) associated with host cell damage, are considered contributory factors to the development of life-threatening organ dysfunction in SS. However, the primary mechanism of death in SS is presently understood as a dysregulation of the immune response to infection [8,9]. This dysregulation can, in turn, lead to various severe complications, such as dysfunction in the coagulation system, acute respiratory distress syndrome, acute kidney injury, and cardiomyopathy. The treatment of SS comprises three essential elements: managing the infection, stabilizing hemodynamics, and regulating the body's response to sepsis [10].

The former two aspects have gained broad consensus within the hour-1-bundle approach [11], and managing sepsis responses involves addressing PAMPs and immune imbalances induced by DAMPs. Many interventions and strategies explored in these studies, such as corticosteroids, vasopressin, monoclonal antibodies, lipid emulsions, bactericidal peptides, adhesins, soluble phospholipase A2 inhibitors, PAF antagonists, statins, and blood purification, have shown limited effectiveness in treating organ dysfunction caused by SS. Notably, bactericidal peptides appear to have some potential efficacy in prospective RCTs.

In recent years, there has been a growing focus on blood purification, particularly the role of plasma exchange in SS treatment. Plasmapheresis is an in vitro procedure that eliminates harmful components from the blood using separation techniques [12]. Vladimir et al. found that adjunctive TPE can provide a potential survival benefit for adult patients with sepsis, resulting in a significant reduction in short-term mortality compared to the standard of care. The majority of inflammatory mediators, including endotoxins, cytokines, chemokines, activated complements (C3a, C5a), coagulation factors, arachidonic acid, and leukotrienes, can theoretically be removed through plasmapheresis [13]. Consequently, plasma exchange techniques can be clinically applied to specifically eliminate various inflammatory mediators, reduce both pro-inflammatory and anti-inflammatory responses, and restore "immune homeostasis" [14].

Previous studies have compared traditional plasma exchange and double filtration plasma exchange in sepsis treatment [15]. These studies have shown that traditional plasma exchange can remove some harmful substances, but DFPP has the advantage of more precisely separating plasma components. M-DFPP further optimizes this process. By switching the return and discard ports, it can more effectively remove inflammatory mediators related to sepsis, such as endotoxins, cytokines, and activated complements. This not only reduces the body's excessive inflammatory response but also helps to restore immune homeostasis to a certain extent. Compared with traditional methods, M-DFPP shows potential in better managing septic shock and reducing the risk of organ failure.

In this study, after the application of M-DFPP, the levels of inflammatory factors in the body were significantly reduced, and the blood pressure, heart rate, urine volume and SOFA score were significantly improved. Usually, there is a rebound effect on inflammatory factors after plasma exchange because it simply mechanically removes the cytokines. In this study, the lack of a significant rebound effect of these inflammatory cytokine markers may be due to the continued elimination of cytokine sources by the body's autoimmune response during the treatment interval, or the long-term inhibition of cytokine production by M-DFPP. However, this needs to be further validated in more clinical cases. Platelet count initially dropped from 90×10^9/L to 29×10^9/L, but then gradually recovered. The decrease in platelets may be related to platelet adhesion to the filter membrane during the plasma exchange process or an immune-mediated reaction. However, it is not clear whether this is a common adverse event of M-DFPP, and further research is needed.

This study shows that M-DFPP has certain effects in reducing the level of inflammatory factors and improving the hemodynamic status of patients, which provides a new idea and method for the treatment of septic shock. Early application of M-DFPP may reduce the damage of the body's inflammatory response to organs and reduce the risk of organ failure, but more clinical studies are needed to verify it. This study has some reference significance for the future development of treatment strategies for septic shock. However, the source of infection persists, which leads to the failure of treatment. At the same time, we are considering whether continuous M-DFPP treatment can be carried out to continuously control inflammatory factors in patients, avoid the formation of inflammatory storms in the body, and surgically clear retroperitoneal infection under continuous M-DFPP support, which may have a favorable impact on patient prognosis. We will conduct such research in subsequent clinical practice and research.

Ethics Approval and Consent to Participate:

This study was conducted in accordance with the Declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Beijing Luhe hospital of Capital Medical University (2022-LHKY-005-02). A written informed consent was obtained from the participant.

Data Availability:

Data will be made available on request.

Declaration of Interest:

None of the authors have any financial disclosure or conflict of interest.

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