Clinical and Applied Thrombosis/Hemostasis
Volume 27: 1-10

DOI: 10.1177/10760296211053313
journals.sagepub.com/home/cat
SAGE

Therapeutic Plasma Exchange Protects Patients with Sepsis-Associated Disseminated Intravascular Coagulation by Improving Endothelial Function

Junting Weng, MD, Min Chen, MD, Dexiang Fang, MD, Danjuan Liu, PhD, Rongjie Guo, MD, and Shuzhen Yang, MD

Abstract

The mortality rate of sepsis-associated disseminated intravascular coagulation (DIC) is high. This study aimed to explore the efficacy of therapeutic plasma exchange (TPE) in sepsis-associated DIC patients by improving endothelial function. A total of 112 sepsis-associated DIC patients were randomly divided into the TPE group (n = 40), the heparin (HP) group (n = 36), and the SHAM group (n = 36). The SHAM group received conventional treatment; the HP group was treated with HP based on conventional treatment; and the TPE group received conventional treatment plus TPE. The differences in thromboelastogram (TEG), platelet (PLT), coagulation function, and the endothelial cell (EC) injury biomarkers at 6 h, 24 h, 48 h, 72 h, and 7 days after TPE were compared among the three groups, and the three groups were compared in terms of Acute Physiology and Chronic Health Evaluation II (APACHE II) score, Sepsis-Related Organ Failure Assessment (SOFA) score, the length of intensive care unit (ICU) hospitalization, 28-day mortality rate, 28-day cumulative survival rate, the incidence of bleeding events, the incidence of acute kidney injury (AKI), and acute respiratory distress syndrome (ARDS). The efficacy of TPE is superior to the HP in increasing PLT, improving coagulation function, increasing the 28-day cumulative survival rate, and reducing the length of ICU hospitalization, 28-day mortality, and the incidence of bleeding events, AKI, and ARDS with statistically significant differences ($P < .05$). Moreover, the effect of TPE outperforms HP on the EC injury biomarkers with statistically significant differences ($P < .05$). Our results suggest that TPE may be more effective than HP in the treatment of patients with sepsis-associated DIC. The possible mechanism is via improving endothelial function.

Keywords

therapeutic plasma exchange, sepsis, disseminated intravascular coagulation, endothelial function

Date received: 12 July 2021; revised: 12 September 2021; accepted: 27 September 2021.

Introduction

In recent years, sepsis has become a major public health problem due to its increasing incidence and high cost. Sepsis in 30% to 50% of sepsis patients can cause disseminated intravascular coagulation (DIC), which accounts for approximately 50% of the total No. of DIC patients.[1] Currently, there is no effective therapy for sepsis-associated DIC; thus, the mortality rate of sepsis-associated DIC is as high as 28% to 43%.[2] The features of sepsis are an uncontrollable nonspecific inflammatory response mediated by mononuclear cells and coagulation disorders triggered by endothelial cell (EC) damage. Inflammation and coagulation disorders interact and aggravate each other, which can result in DIC, eventually leading to multiple organ failure and death.[3] The pathophysiological mechanism of sepsis-associated DIC involves the stimulation of

Affiliated Hospital of Putian University, Putian, China

Corresponding Author:
Junting Weng, Department of Critical Care Medicine, Affiliated Hospital of Putian University, No. 999 Dongzhen East Road, Licheng District, Putian, Fujian 351100, China.
Email: 503072428@qq.com

inflammatory cytokines, which increase the expression of tissue factor (TF) and initiate the exogenous coagulation pathway; this pathway has been shown to promote a hypercoagulable state and fibrinolysis inhibition. Then, the specific hypercoagulable state leads to microvascular thrombosis in the systemic circulation. At the same time, inflammatory cytokines act on ECs, activate or damage ECs, and interact with activated white blood cells. Finally, coagulation and inflammation occur and form a vicious cycle, which ultimately leads to microvascular obstruction, microcirculation bleeding, and deterioration of the circulatory state of the organism.[4] Therefore, for sepsis-associated DIC patients, the keys to treatment are removing inflammatory cytokines, removing abnormal coagulation and fibrinolytic substances, supplementing coagulation factors to rebuild the normal coagulation mechanism, inhibiting endothelial activation, and protecting endothelial function.[5] At present, domestic and foreign studies on DIC caused by sepsis are intervention treatments for low-dose heparin (HP). The overall efficacy of HP in the treatment of sepsis and sepsis-associated DIC patients has not yet been determined, and there is a trend to reduce the mortality rate, but there is also an increased risk of bleeding.[6]

Reports in recent years have shown that therapeutic plasma exchange (TPE) has a good effect on the treatment of DIC.[7] TPE takes the patient's blood out of the body and separates and discards the patient's plasma from the whole blood through a membrane plasma separation method to remove various metabolic toxins and other pathogenic factors from the patient's body and then replenishes fresh frozen plasma, coagulation factors, and other beneficial substances, which can rebuild the normal coagulation mechanism, and regulate the body's immune balance and hemodynamic status.[8] Plasmapheresis in treating DIC in patients stung by Hemiscorpius lepturus stings can prevent death and encourage recovery.[9] Studies have shown that DIC patients have significant clinical efficacy after plasma exchange treatment.[10] Trung et al.[11] used TPE in 10 children with multiple organ dysfunction syndrome (MODS) (including DIC) to decrease the severity of the disease and increase the survival rate of the patients. In the treatment of a patient with meningococcemia with DIC, TPE can eliminate the activation of complement, coagulation factors, and lysosomal enzymes rather than reduce the concentration of endotoxin in the patient's blood, thereby restoring the normal coagulation mechanism and correcting the abnormality of DIC and coagulation index.[12] However, the protective mechanism of TPE in sepsis-associated DIC patients is still unclear, and it is worthy of further study.

ECs have a high degree of biological activity and participate in a variety of physiological processes in the body, including regulating the tension of vascular smooth muscle, completing the exchange of cells and nutrients, maintaining blood fluidity, and forming a barrier between blood and tissues. It also has important roles in inflammation, immune regulation, coagulation and anticoagulation, fibrinolysis, and regulation of vascular tension and permeability.[13] Sepsis can induce phenotypic regulation of ECs through many different mechanisms. In particular, components of bacterial cell walls such as lipopolysaccharide (LPS) can activate structural recognition receptors on the surface of ECs, resulting in EC activation and functional damage.[14] EC activation, damage, and dysfunction are important features of Sepsis and MODS. EC has potential diagnostic, therapeutic, and prognostic value in sepsis and MODS, and may become a potential therapeutic target for the treatment of sepsis.[15] Studies have emphasized the importance of endothelial function to the pathophysiological process of sepsis-associated DIC patients. Endothelial dysfunction is closely related to the mortality and severity of sepsis-associated DIC patients. Therefore, endothelial function is a new target for the diagnosis and treatment of sepsis-associated DIC.[16] The biomarkers reflecting endothelial function are as follows: tissue factor pathway inhibitor (TFPI), Protein C, high-mobility group box 1 (HMGB-1), Endocan, angiopoietin 2 (Ang-2), von Willebrand factor (vWF), and others.[16–19]

In this investigation, we hypothesized that TPE might protect patients with sepsis-associated DIC by improving their endothelial function.

Materials and Methods

Patient Samples

A total of 112 sepsis-associated DIC patients in the intensive care unit (ICU) of the Affiliated Hospital of Putian University were analyzed from January 2015 to December 2020. They were randomly divided into 40 cases in the TPE group, 36 cases in the HP group, and 36 cases in the control (SHAM) group. Patient baseline characteristics and coagulation indices were collected before treatment, including demographic characteristics, International Society on Thrombosis and Hemostasis (ISTH) score, Sepsis-Related Organ Failure Assessment (SOFA) score, and Acute Physiology and Chronic Health Evaluation II (APACHE II) score. HP is used for anticoagulation during TPE. To eliminate the influence of HP on blood coagulation function, the study established a TPE group, HP group, and SHAM group. This study was discussed and approved by the Ethics Committee of the Affiliated Hospital of Putian University, and all patients signed an "Informed Consent in Clinical Research" form.

Inclusion and Exclusion Criteria

Inclusion criteria included (1) the diagnostic criteria for sepsis in the "Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock"[20] and (2) according to the "Scientific Subcommittee on DIC of the International Society on Thrombosis and Hemostasis (ISTH)", a score ≥ 5 points was diagnosed as DIC.[21]

Exclusion criteria included (1) having a history of severe allergies to plasma, HP, etc., (2) pregnant women, and (3) presence of intracranial hemorrhage or severe cerebral edema accompanied by brain herniation.

Methods

The three groups of patients were treated with conventional treatments such as etiological treatment, coagulation factor supplementation, anti-shock, platelet (PLT) increase, nutritional support, and anti-infective treatment. The SHAM group received conventional treatment; the HP group was treated with low-dose HP anticoagulant based on conventional treatment and continuously pumped for 24 h every day at a dosage of 50 mg every 24 h. The TPE group received conventional treatment plus TPE treatment.

Plasma exchange method: A femoral vein puncture double-lumen hemofiltration tube was inserted to establish vascular access, and 2000 mL of plasma was exchanged every day (using the PRISMAFLEX system of the Jinbao Company). The replacement time was 3 h, once a day, and the No. of replacements was three times. When plasma exchange was performed, a small dose of HP sodium was used for anticoagulation, which was continuously pumped for 24 h, and the dosage was 50 mg every 24 h.

Observation Index

Assessment of the protective effect of therapeutic plasma exchange on sepsis-associated disseminated intravascular coagulation patients. The differences in thromboelastogram (TEG), PLT count, and coagulation function at 6 h, 24 h, 48 h, 72 h, and 7 days after TPE were compared among the three groups, and the three groups were compared in terms of APACHE II score, SOFA score, length of ICU hospitalization, 28-day mortality rate, 28-day cumulative survival rate, the incidence of bleeding events, the incidence of acute kidney injury (AKI) and acute respiratory distress syndrome (ARDS).

Evaluation of the effect of therapeutic plasma exchange on the improvement of endothelial function in patients with sepsis-associated disseminated intravascular coagulation. At 6 h, 24 h, 48 h, 72 h, and 7 days after TPE, the differences in EC injury biomarkers were compared between the three groups.

Detection of Indicators

The coagulation function indicators included the PLT counts, activated partial thromboplastin time (APTT), prothrombin time (PT), fibrinogen level (FIB), and D-dimer level. TEG detection: the coagulation reaction time (R value), blood clot formation time (K value), blood clot formation rate (α angle), maximum width value (MA value), percentage of blood clot lysis 30 min after the MA value is determined (LY30), etc., (using the TEG5000 coagulation analyzer and TEG detection box provided by the Hemoscope Company). Biomarkers of EC damage: TFPI, Protein C, HMGB-1, Endocan, Ang-2, and vWF.

Statistical Analyses

Measurement data are expressed as the mean ± standard deviation. Differences between all groups were assessed through one-way analysis of variance (ANOVA) followed by Tukey's *post hoc* test. $P < .05$ was considered statistically significant. Counting data were using [n (%)] according to the χ^2 test. Survival curves were analyzed using the Kaplan–Meier log-rank test. All statistical analyses were performed in GraphPad Prism software version 8.0 (GraphPad Software, Inc.).

Results

Comparing Baseline Characteristics Between the Three Groups Before Treatment

There was no significant difference in demographic characteristics, SOFA score, APACHE II score, and ISTH score between the three groups before treatment ($P > .05$), as shown in Table 1.

Protective Effect of therapeutic plasma exchange in Sepsis-Associated Disseminated Intravascular Coagulation Patients

Effect of therapeutic plasma exchange on platelet in sepsis-associated disseminated intravascular coagulation patients. At 48 h and 72 h after TPE, the PLT count of the TPE group was higher than that of the SHAM group, and the difference between the two groups was statistically significant ($P < .05$); Seven days after TPE, the PLT count of the TPE group was significantly higher than that of the SHAM group, and the difference between the two groups was statistically significant ($P < .01$); Seventy-two hours and 7 days after TPE, the PLT count in the TPE group was higher than that in the HP group, and the difference between the two groups was statistically significant ($P < .05$) (Figure 1).

Table 1. Comparing Baseline Characteristics Between the Three Groups Before Treatment.

Parameters	TPE (n = 40)	HP (n = 36)	SHAM (n = 36)
Age (years)	50.07 ± 2.09	47.92 ± 2.58	49.73 ± 2.50
Male patients (%)	31 (77.5)	28 (77.7)	27 (75.0)
SOFA score	11.00 ± 1.31	10.61 ± 1.39	11.09 ± 1.41
APACHE II score	20.29 ± 1.29	19.17 ± 1.69	21.09 ± 1.73
ISTH score	6.38 ± .45	6.42 ± .47	6.02 ± .51

The results are expressed as the mean ± standard deviation. There was no significant difference in demographic characteristics, SOFA score, APACHE II score, and ISTH score between the three groups before treatment ($P > .05$).
Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; HP, heparin; ISTH, International Society on Thrombosis and Hemostasis; SOFA, Sepsis-Related Organ Failure Assessment; TPE, therapeutic plasma exchange.

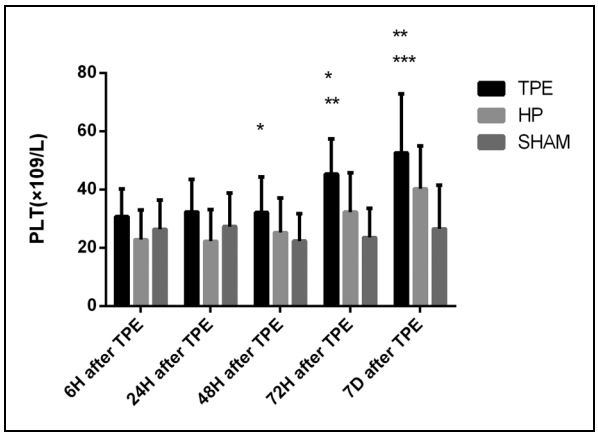

Figure 1. Effect of TPE on platelets (PLT) in sepsis-associated DIC patients. The results are expressed as the mean ± standard deviation. *$P < .05$ versus SHAM, **$P < .01$ versus SHAM, ***$P < .05$ versus HP.
Abbreviations: DIC, disseminated intravascular coagulation; HP, heparin; TPE, therapeutic plasma exchange.

Effect of therapeutic plasma exchange on the coagulation function in sepsis-associated disseminated intravascular coagulation patients. At 24 h and 72 h after TPE, the PT of the TPE group was lower than that of the SHAM group, and the difference between the two groups was statistically significant ($P < .05$); at 48 h and 7 days after TPE, the PT of the TPE group was significantly lower than that of the SHAM group, and the difference between the two groups was statistically significant ($P < .01$). Then, 7 days after TPE, the PT of the TPE group was lower than that of the HP group, and the difference between the two groups was statistically significant ($P < .05$) (Figure 2A). At 6 h, 24 h, 48 h, and 7 days after TPE, the APTT of the TPE group was lower than that of the SHAM group, and the difference between the two groups was statistically significant ($P < .05$). Then, 72 h after TPE, the APTT of the TPE group was significantly lower than that of the control group, and the difference between the two groups was statistically significant. Academic significance ($P < .01$); 6 h, 24 h, 48 h, 72 h, and 7 days after TPE, APTT in the TPE group was lower than that in the HP group, and the difference between the two groups was statistically significant ($P < .05$) (Figure 2B). At 48 h, 72 h, and 7 days after TPE, the FIB of the TPE group was higher than that of the SHAM group, and the difference between the two groups was statistically significant ($P < .05$). Then, at 48 h, 72 h, and 7 days after TPE, the FIB of the TPE group was higher than that of the HP group, and there was a difference between the two groups There was statistical significance ($P < .05$) (Figure 2C). At 24 h after TPE, the D-dimer in the TPE group was lower than that in the SHAM

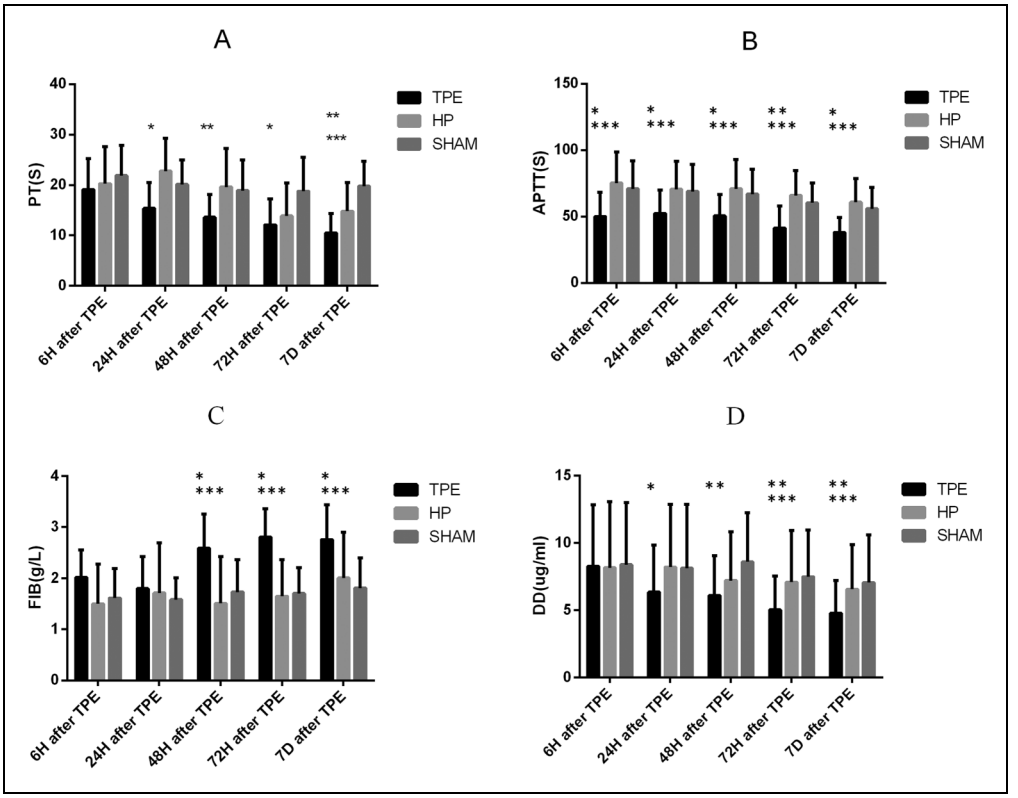

Figure 2. Effect of TPE on coagulation function in sepsis-associated DIC patients. A: Effect of TPE on PT, B: Effect of TPE on APTT, C: Effect of TPE on FIB, D: Effect of TPE on DD. The results are expressed as the mean ± standard deviation. *$P < .05$ versus SHAM, **$P < .01$ versus SHAM, ***$P < .05$ versus HP.
Abbreviations: DIC, disseminated intravascular coagulation; HP, heparin; TPE, therapeutic plasma exchange.

group, and the difference between the two groups was statistically significant ($P < .05$). Then, at 48 h, 72 h, and 7 days after TPE, the D-dimer in the TPE group was significantly lower than that in the SHAM group. The difference between the two groups was statistically significant ($P < .01$). Additionally,72 h and 7 days after TPE, the D-dimer in the TPE group was lower than that in the HP group, and the difference between the two groups was statistically significant ($P < .05$)(Figure 2D).

Effect of therapeutic plasma exchange on thromboelastogram in sepsis-associated disseminated intravascular coagulation patients. First, 72 h after TPE, the R-value of the TPE group was lower than that of the SHAM group, and the difference between the two groups was statistically significant ($P < .05$). Then, 7 days after TPE, the R value of the TPE group was significantly lower than that of the SHAM group, and the difference between the two groups was statistically significant ($P < .01$). Additionally, 72 h and 7 days after TPE, the R value of the TPE group was lower than that of the HP group, and the difference between the two groups was statistically significant ($P < .05$) (Figure 3A). At 48 h and 72 h after TPE, the K value of the TPE group was lower than that of the SHAM group, and the difference between the two groups was statistically significant ($P < .05$). Moreover, 7 days after TPE, the K value of the TPE group was significantly lower than that of the control group, and the difference between the two groups was statistically significant ($P < .01$); then, 48 h, 72 h, and 7 days after TPE, the K value of the TPE group was lower than that of the HP group, and the difference between the two groups was statistically significant ($P < .05$) (Figure 3B). At 48 h and 72 h after TPE, α angle in the TPE group was higher than that in the SHAM group, and the difference between the two groups was statistically significant ($P < .05$). Then, 7 days after TPE, α angle in the TPE group was significantly higher than that in the SHAM group, and the difference between the two groups was statistically significant ($P < .01$); At 48 h, 72 h, and 7 days after TPE, α angle in the TPE group was higher than that in the HP group, and the difference between the two groups was statistically significant ($P < .05$) (Figure 3C). At 72 h after TPE, the MA of the TPE group was higher than that of the SHAM group, and the difference between the two groups was statistically significant ($P < .05$). Moreover, 7 days after TPE, the MA of the TPE group was significantly higher than that of the SHAM group, and the difference between the two groups was statistically significant ($P < .01$). After TPE, 72 h and 7 days, the MA of the TPE group was higher than that of the HP group, and the difference between the two groups was statistically significant ($P < .05$) (Figure 3D). Then, 72 h after TPE, LY30 in the TPE group was lower than in the SHAM group, and the difference between the two groups was statistically significant ($P < .05$). Additionally, 7 days after TPE, The LY30 in the TPE group was significantly lower than in the SHAM group, and the difference between the two groups was statistically significant ($P < .01$). Finally, 72 h and 7 days after TPE, the LY30 of the TPE group was lower than that in the HP group, and the difference between the two groups was statistically significant ($P < .05$) (Figure 3E).

Effects of therapeutic plasma exchange on the Acute Physiology and Chronic Health Evaluation II score and the Sepsis-Related Organ Failure Assessment score of sepsis-associated disseminated intravascular coagulation patients. Forty-eight hours after TPE, the APACHE II score of the TPE group was lower than that of the SHAM group, and the difference between the two groups was statistically significant ($P < .05$). At 72 h and 7 days after TPE, the APACHE II score of the TPE group was significantly lower than that of the SHAM group, and the difference between the two groups was statistically significant ($P < .01$). At 48 h, 72 h, and 7 days after TPE, the APACHE II score of the TPE group was lower than that of the HP group, and the difference between the two groups was statistically significant ($P < .05$) (Figure 4A). At 48 h after TPE, the SOFA score of the TPE group was lower than that of the SHAM group, and the difference between the two groups was statistically significant ($P < .05$). At 72 h and 7 days after TPE, the SOFA score of the TPE group was significantly lower than that of the SHAM group, and the difference between the two groups was statistically significant. ($P < .01$). At 48 h, 72 h, and 7 days after TPE, the SOFA score of the TPE group was lower than that of the HP group, and the difference between the two groups was statistically significant ($P < .05$)(Figure 4B).

Effect of therapeutic plasma exchange on the prognosis of patients with sepsis-related disseminated intravascular coagulation. The length of ICU hospitalization and 28-day mortality in the TPE group were lower than those in the SHAM and HP groups, and the difference between the two groups was statistically significant ($P < .05$) (Figure 5, Table 2). The 28-day cumulative survival rate in the TPE group was higher than that in the SHAM and HP groups, and the difference between the two groups was statistically significant ($P < .05$) (Figure 6).

Effect of therapeutic plasma exchange on complications in sepsis-associated disseminated intravascular coagulation patients. The incidences of bleeding events, AKI, and ARDS in the TPE group were lower than those in the SHAM and HP groups. The difference between the two groups was statistically significant ($P < .05$) (Table 3).

Effect of Therapeutic Plasma Exchange on Endothelial Function in Sepsis-Associated Disseminated Intravascular Coagulation Patients

At 48 h and 72 h after TPE, the TFPI of the TPE group was higher than that of the SHAM group, and the difference between the two groups was statistically significant ($P < .05$); at 7 days after TPE, the TFPI of the TPE group was significantly higher than that of the SHAM group, and the difference between the two groups was statistically significant ($P < .01$);

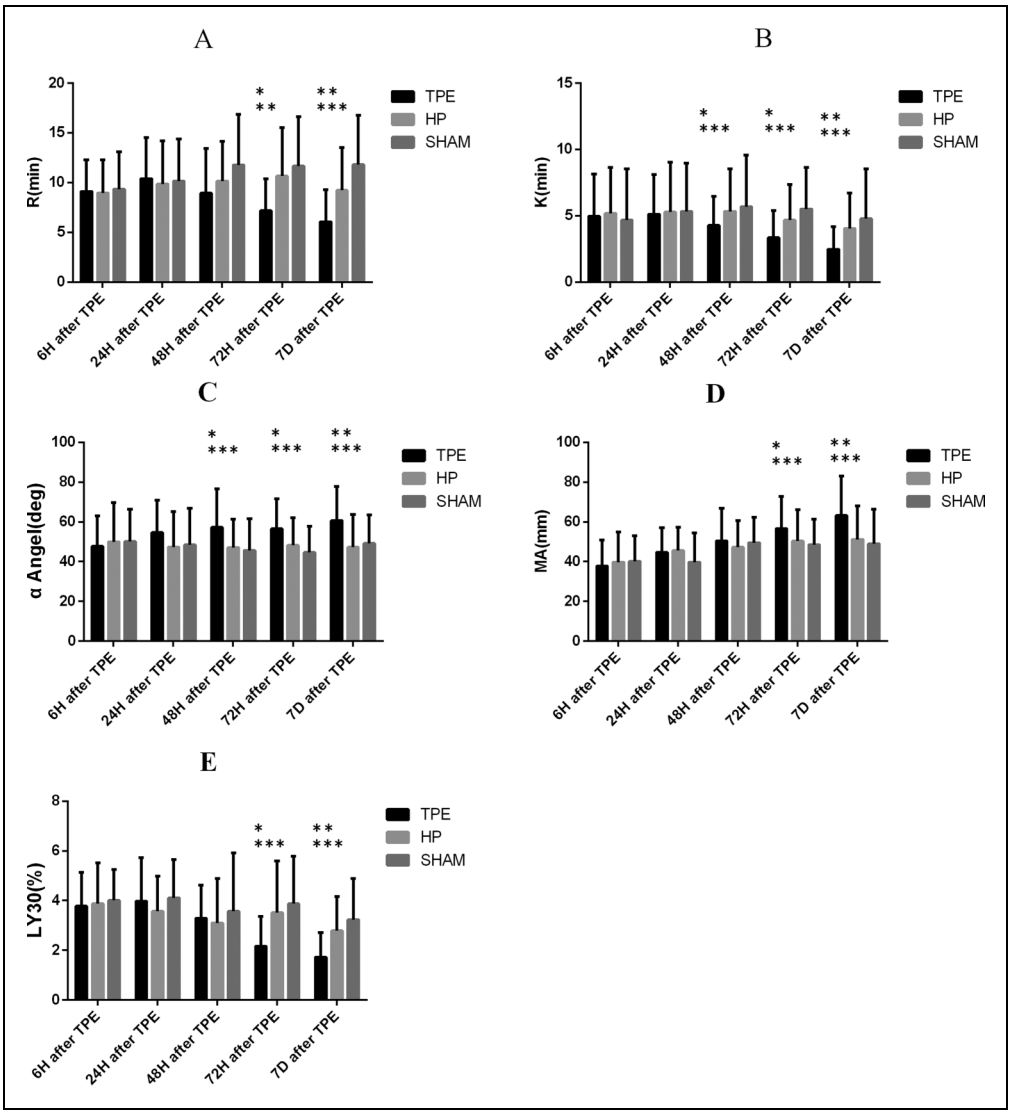

Figure 3. Effect of TPE on TEG in sepsis-associated DIC patients. A: Effect of TPE on R, B: Effect of TPE on K, C: Effect of TPE on α angel, D: Effect of TPE on MA, E: Effect of TPE on LY30. The results are expressed as the mean ± standard deviation. *$P < .05$ versus SHAM, **$P < .01$ versus SHAM, ***$P < .05$ versus HP.

Abbreviations: DIC, disseminated intravascular coagulation; HP, heparin; TEG, DIC, disseminated intravascular coagulation; HP, heparin; TPE, therapeutic plasma exchange; TPE, therapeutic plasma exchange.

at 72 h and 7 days after TPE, the TFPI of the TPE group was higher than that of the HP group, and the difference between the two groups was statistically significant ($P < .05$) (Figure 7A). At 48 h and 72 h after TPE, protein C of the TPE group was higher than that of the SHAM group, and the difference between the two groups was statistically significant ($P < .05$). At 7 days after TPE, protein C of the TPE group was significantly higher than that of the control group, and the difference between the two groups was statistically significant ($P < .01$). At 48 h and 7 days after TPE, Protein C in the TPE group was higher than that in the HP group, and the difference between the two groups was statistically significant ($P < .05$) (Figure 7B). At 48 h and 72 h after TPE, the HMGB-1 of the TPE group was lower than that of the SHAM group, and the difference between the two groups was statistically significant ($P < .05$); at 7 days after TPE, the HMGB-1 of the TPE group was significantly lower than that of the SHAM group, and the difference between the two groups was statistically significant($P < .01$). At 48 h, 72 h, and 7 days after TPE, the HMGB-1 of the TPE group was higher than that of the HP group, and the difference between the two groups was statistically significant ($P < .05$) (Figure 7C). At 72 h after TPE, Endocan in the TPE group was lower than that in the SHAM group, the difference between the two groups was statistically significant ($P < .05$). At 7 days after TPE, Endocan in the TPE group was significantly lower than that in the SHAM group, and the difference between the two groups was statistically significant ($P < .01$); 72 h and 7 days after TPE, Endocan in the TPE group was lower than that in the HP group, and the difference between the two groups was

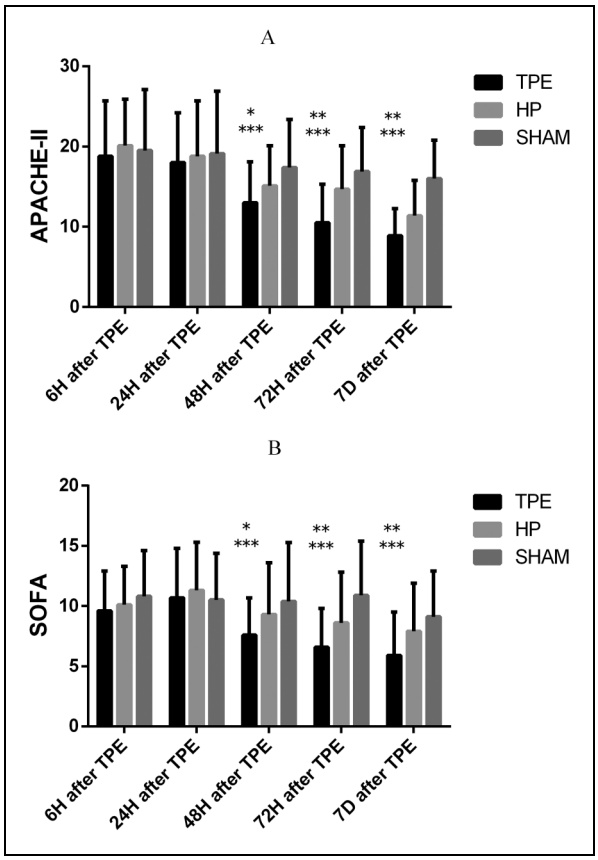

Figure 4. Effect of TPE on the APACHE II score and SOFA score of sepsis-associated DIC patients. A: Effect of TPE on APACHE II score, B: Effect of TPE on SOFA score. The results are expressed as the mean ± standard deviation. *$P < .05$ versus SHAM, **$P < .01$ versus SHAM, ***$P < .05$ versus HP.
Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; DIC, disseminated intravascular coagulation; SOFA, Sepsis-Related Organ Failure Assessment; TPE, therapeutic plasma exchange.

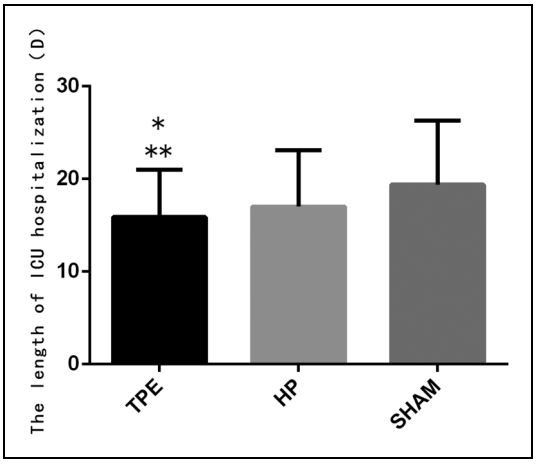

Figure 5. Effect of TPE on the length of ICU hospitalization of sepsis-associated DIC patients. The results are expressed as the mean ± standard deviation. *$P < .05$ versus SHAM, **$P < .05$ versus HP.
Abbreviations: DIC, disseminated intravascular coagulation; HP, heparin; ICU, intensive care unit; TPE, therapeutic plasma exchange.

Table 2. Effect of TPE on 28-Day Mortality in Sepsis-Associated DIC Patients.

Indicators	TPE	HP	SHAM
n	40	36	36
28-day mortality	15.0*,**	33.3	38.9

*$P < .05$ versus SHAM, ** $P < .05$ versus HP.
Abbreviations: DIC, disseminated intravascular coagulation; HP, heparin; TPE, therapeutic plasma exchange.

statistically significant ($P < .05$) (Figure 7D). At 72 h after TPE, the vWF of the TPE group was lower than that of the SHAM group, and the difference between the two groups was statistically significant ($P < .05$). At 7 days after TPE, the vWF of the TPE group was significantly lower than that of the SHAM group, and the difference between the two groups was statistically significant ($P < .01$). At 72 h and 7 days after TPE, the vWF of the TPE group was lower than that of the HP group, and the difference between the two groups was statistically significant ($P < .05$) (Figure 7E). At 48 h and 72 h after TPE, the Ang-2 of the TPE group was lower than that of the SHAM group, and the difference between the two groups was statistically significant ($P < .05$). Then, at 7 days after TPE, the Ang-2 of the TPE group was significantly lower than that of the SHAM group, and the difference between the two groups was statistically significant ($P < .01$). Moreover, at 48 h, 72 h, and 7 days after TPE, Ang-2 in the TPE group was higher than that in the HP group, and the difference between the two groups was statistically significant ($P < .05$) (Figure 7F).

Discussion

The pathophysiological process of sepsis-associated DIC involves inflammatory cytokines activating or damaging ECs

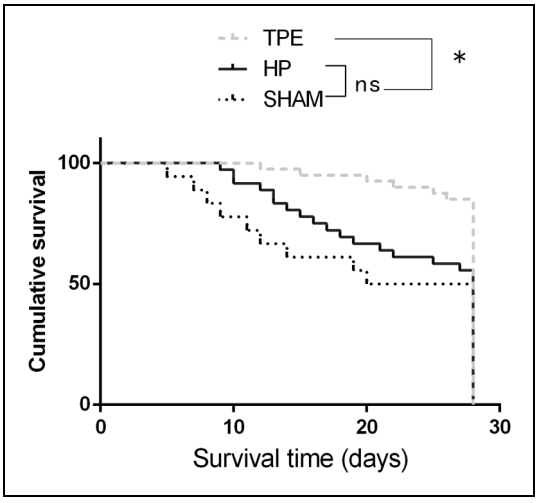

Figure 6. Effect of TPE on the 28-day cumulative survival rate of sepsis-associated DIC patients. The results are expressed as the mean ± standard deviation. *$P < .05$ versus SHAM and HP.
Abbreviations: DIC, disseminated intravascular coagulation; HP, heparin; TPE, therapeutic plasma exchange.

Table 3. Effect of TPE on Complications in Sepsis-Associated DIC Patients.

Indicators	TPE	HP	SHAM
n	40	36	36
Incidence of bleeding events%	45.0	20.0*,**	44.4
Incidence of AKI%	30.0*,**	44.4	55.6
Incidence of ARDS%	35.0*,**	50.0	61.1

*$P < .05$ versus SHAM, **$P < .05$ versus HP.
Abbreviations: AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; DIC, disseminated intravascular coagulation; HP, heparin; DIC, TPE, therapeutic plasma exchange.

and triggering coagulation disorders, and then inflammation and coagulation disorders interact and aggravate each other. Therefore, vascular ECs are a potential therapeutic target of sepsis-associated DIC.[16]

Protective Effect of Therapeutic Plasma Exchange in Sepsis-Associated Disseminated Intravascular Coagulation Patients

It is currently known that thrombocytopenia is one of the independent risk factors in the ICU.[22] The causes of

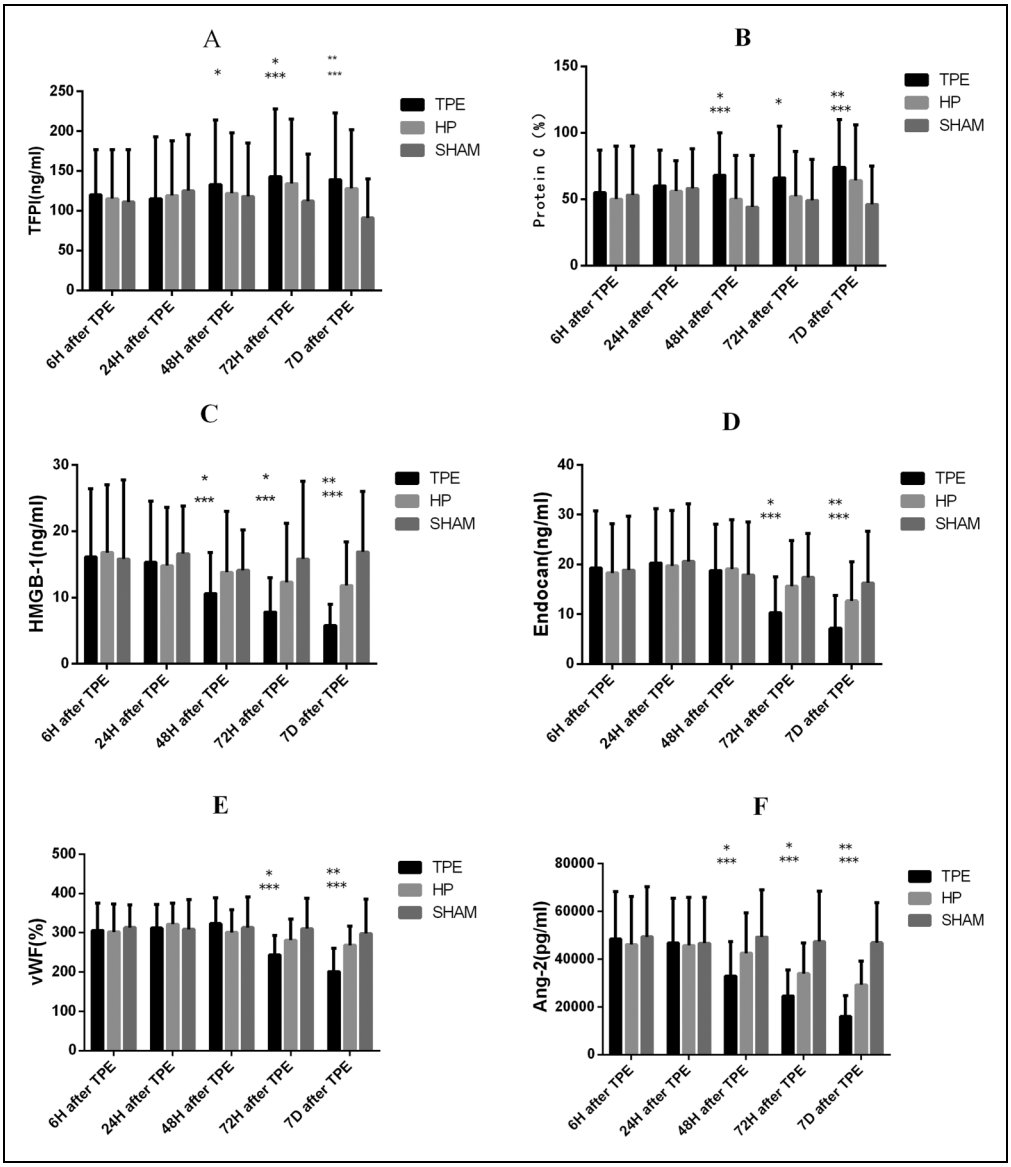

Figure 7. Effect of TPE on endothelial function in sepsis-associated DIC patients. A: Effect of TPE on TFPI, B: Effect of TPE on Protein C, C: Effect of TPE on HMGB-1, D: Effect of TPE on Endocan, E: Effect of TPE on vWF, F: Effect of TPE on Ang-2. The results are expressed as the mean ± standard deviation. *$P < .05$ versus SHAM, **$P < .01$ versus SHAM, ***$P < .05$ versus HP.
Abbreviations: DIC, disseminated intravascular coagulation; HP, heparin; TPE, therapeutic plasma exchange.

thrombocytopenia in sepsis-associated DIC patients include (1) toxins produced by infection inhibit the hematopoietic function of bone marrow, (2) excessive PLT consumption due to thrombosis, and (3) production of a large No. of autoimmune antibodies, leading to a reduction in PLT.[23,24] The results of this study showed that after TPE, the PLT count of the TPE group was higher than that of the SHAM group, and the PLT count of the TPE group was higher than that of the HP group. The MA value in TEG is an index reflecting the function of PLT, and MA decreases in sepsis-related DIC patients. After TPE, the MA of the TPE group was higher than that of the SHAM and HP groups. Because plasma exchange can clear patients' inflammatory cytokines, micro thrombosis, and immune antibodies,[8] it affects increasing PLT in sepsis-associated DIC patients.

When sepsis-associated DIC occurs, due to the release of a large No. of inflammatory cytokines, the coagulation system is activated, micro thrombosis and thrombosis are formed, and a large number of coagulation factors are consumed, which leads to prolonged PT, APTT, and R time. At the same time, the fibrinolytic system is activated, which leads to reduced FIB, elevated D-dimer, prolonged K time, expanded α angle and elevated LY30. At this time, plasma exchange can not only remove the patient's inflammatory cytokines, micro thrombosis, and immune antibodies but also enter normal plasma and can also retain coagulation factors and ATIII, which are lacking in DIC.[8] This study showed that the PT, APTT, and D-dimers in the TPE group were lower than those in the SHAM and HP groups after TPE. After TPE, the FIB of the TPE group was higher than that in the SHAM group and HP group. After TPE, the R value, K value, and LY30 of the TPE group were lower than those of the SHAM and HP groups. After TPE, α angle in the TPE group was higher than that in the SHAM and HP groups. Therefore, it is inferred that TPE can help correct coagulation disorders in patients with sepsis-related DIC and restore the normal coagulation mechanism.

The APACHE II and SOFA scores are important indicators to assess the severity of the disease and are closely related to the prognosis of patients. According to domestic and foreign literature reports,[25] the mortality rate of sepsis patients increases as the APACHE II and SOFA scores rise. The results of this study showed that after TPE, the APACHE II and SOFA scores of the TPE group were lower than those of the SHAM group and the HP group. According to one study, TPE combined with conventional treatment can significantly improve the survival rate of patients with DIC and MODS.[7] Our results showed that TPE reduced the length of ICU hospitalization and 28-day mortality, and increased the 28-day cumulative survival while reducing the incidence of ARDS, AKI, bleeding events, and other complications. As mentioned above, the mortality of septic patients increases with increases in the APACHE II and SOFA scores, while plasma exchange can reduce APACHE II and SOFA scores and improves disease severity, thus reducing ICU stay, AKI, and ARDS, and increased the 28-day survival rate. TPE can improve blood coagulation and increase PLT, and it can reduce the incidence of bleeding events. Therefore, combining plasma exchange based on conventional treatment can improve the condition and prognosis of patients with sepsis-associated DIC.

Therapeutic Plasma Exchange Protects Sepsis-Associated Disseminated Intravascular Coagulation Patients by Improving Endothelial Function

In sepsis, both the infection and the host's response to the infection can lead to activation, damage, or dysfunction of ECs. This is helpful to the development of DIC. Patients with sepsis-associated DIC have endothelial damage and dysfunction, and vascular endothelial damage and dysfunction are associated with the severity of coagulopathy and mortality in DIC patients. From the perspective of pathophysiology, endothelial injury is considered one of the necessary conditions for thrombosis. Biomarkers reflecting endothelial function include TFPI, Protein C, HMGB-1, Endocan, Ang-2, and vWF. In sepsis-associated DIC patients, HMGB-1, Endocan, Ang-2, and vWF increase, while TFPI and protein C decrease.[16] After TPE, HMGB-1, Endocan, Ang-2, and vWF in the TPE group decreased, and TFPI and Protein C increased in this study. Therefore, TPE can improve the endothelial function of patients with sepsis and DIC.

Recent studies have reported the beneficial effects of HP on the morbidity and mortality of patients with sepsis-associated DIC, but it increases the risk of bleeding.[6] Because HP was used for anticoagulation during TPE, to exclude the influence of HP on the results, the HP group was established in this study. The results showed that the TPE group was better than the HP group at protecting the blood coagulation function, PLT, APACHE II score, SOFA score, length of ICU stay, 28-day mortality, rate of AKI, ARDS, and bleeding events, and endothelial function.

This trial is a single-center prospective study with a relatively small number of cases. A large, multicenter, randomized controlled trial is still needed to validate the efficacy of TPE in the treatment of patients with sepsis-associated DIC.

Conclusion

The efficacy of TPE is superior to the HP in increasing PLT, improving coagulation function, increasing the 28-day cumulative survival rate and reducing the length of ICU hospitalization, 28-day mortality, and the incidence of bleeding events, AKI, and ARDS. Moreover, the effect of TPE outperforms HP on endothelial function in sepsis-associated DIC patients. Our results suggest that TPE may be more effective than HP in the treatment of patients with sepsis-associated DIC. The possible mechanism is via improving endothelial function.

Author's Contribution

Junting Weng: conception, design, analysis, and interpretation of data; writing the manuscript. Min Chen: conception, design, analysis, and interpretation of data; writing the manuscript. Dexiang Fang: conception, design, analysis, and interpretation of data; writing the manuscript. Danjuan Liu: conception, design, analysis, and interpretation

of data; writing the manuscript. Rongjie Guo: analysis and interpretation of data; writing the manuscript. Shuzhen Yang: analysis and interpretation of data; writing the manuscript.

Financial Support

This study was supported by the Natural Science Foundation of Fujian Province of China (grant number 2020J011253) and the Scientific Research Project of Putian University of Fujian Province (grant number 2019077).

Highlights

TPE protects patients with sepsis-associated DIC. TPE protects patients with sepsis-associated DIC by improving endothelial function

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

ORCID iD

Junting Weng https://orcid.org/0000-0001-8820-0960

References

1. Iba T, Thachil J. Present and future of anticoagulant therapy using antithrombin and thrombomodulin for sepsis-associated disseminated intravascular coagulation: a perspective from Japan. *International Journal of Hematology*. 2016;103(3):253-261.
2. Iba T, Yamada A, Hashiguchi N, et al. New therapeutic options for patients with sepsis and disseminated intravascular coagulation. *Polskie Archiwum Medycyny Wewnetrznej*. 2014;124(6):321-328.
3. Okamoto K, Tamura T, Sawatsubashi Y. Sepsis and disseminated intravascular coagulation. *J Intensive Care*. 2016;4(1):23.
4. Walborn A, Hoppensteadt D, Syed D, et al. Biomarker profile of sepsis-associated coagulopathy using biochip assay for inflammatory cytokines. *Clinical and Applied Thrombosis/Hemostasis: Official Journal of the International Academy of Clinical and Applied Thrombosis/Hemostasis*. 2018;24(4):625-632.
5. Blaisdell FW. Causes, prevention, and treatment of intravascular coagulation and disseminated intravascular coagulation(article). *Journal of Trauma and Acute Care Surgery*. 2012;72(6):1719-1722.
6. Zarychanski R, Abou-Setta AM, Kanji S, et al. The efficacy and safety of heparin in patients with sepsis: a systematic review and meta-analysis. *CRITICAL CARE MEDICINE*. 2015:1):123..
7. Stegmayr BG, Banga R, Berggren L, et al. Plasma exchange as rescue therapy in multiple organ failure including acute renal failure. *Critical Care Medicine*. 2003;31(6):1730-1736.
8. Winters JL. Plasma exchange: concepts, mechanisms, and an overview of the American society for apheresis guidelines. *Hematology American Society of Hematology Education Program*. 2012;2012(1):7-12.
9. Mostafazadeh B, Gorbani A, Mogaddaspour M, et al. The effect of plasmapheresis on treating disseminated intravascular coagulation (DIC) caused by a hemiscorpius lepturus (gadim) sting. *Clinical Toxicology*. 2017;55(8):902-907.
10. Negi G, Ahuja R, Gupta V, et al. Therapeutic plasma exchange: a study of indications and efficacy. *Global Journal of Transfusion Medicine*. 2018;3(2):136-139.
11. Nguyen TC, Han YY, Kiss JE, et al. Intensive plasma exchange increases a disintegrin and metalloprotease with thrombospondin motifs-13 activity and reverses organ dysfunction in children with thrombocytopenia-associated multiple organ failure. *Critical Care Medicine*. 2008;36(10):2878-2887.
12. Grigorakos L, Moles A, Alexopoulou A, et al. The role of plasmapheresis in adult respiratory distressed syndrome due to meningococcemia with disseminated intravascular coagulation - a case report. *Case Reports in Internal Medicine*. 2015;2(4):1.
13. Aird WC. Endothelium as an organ system. *Critical Care Medicine*. 2004;32(5, Suppl):S271-S279.
14. Volk T, Kox WJ. Endothelium function in sepsis. *Inflammation Research: Official Journal of the European Histamine Research Society*. 2000;49(5):185-198.
15. Aird WC. The role of the endothelium in severe sepsis and multiple organ dysfunction syndromes. *Blood*. 2003;101(10):3765-3777.
16. Walborn A, Rondina M, Mosier M, et al. Endothelial dysfunction Is associated with mortality and severity of coagulopathy in patients with sepsis and disseminated intravascular coagulation. *Clinical and Applied Thrombosis/Hemostasis: Official Journal of the International Academy of Clinical and Applied Thrombosis/Hemostasis*. 2019:1–9.
17. Goon PKY, Boos CJ, Lip GYH. Circulating endothelial cells: markers of vascular dysfunction. *Clinical Laboratory*. 2005;51(9–10):531-538.
18. Reinhart K, Bayer O, Brunkhorst F, et al. Markers of endothelial damage in organ dysfunction and sepsis. *Critical Care Medicine*. 2002;30(5, Suppl):S302-S312.
19. Scherpereel A, Depontieu F, Grigoriu B, et al. Endocan, a new endothelial marker in human sepsis. *Critical Care Medicine*. 2006;34(2):532-537.
20. Dellinger RP, Levy MM, Rhodes A. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock, 2012. *Intensive Care Medicine*. 2013;39(2):165-228.
21. Taylor FB, Toh CH, Hoots WK, et al. Towards definition, clinical and laboratory criteria, and a scoring system for disseminated intravascular coagulation. *Thrombosis and Hemostasis*. 2001;86(5):1327-1330.
22. Strauss R, Wehler M, Mehler K, et al. Thrombocytopenia in patients in the medical intensive care unit: bleeding prevalence, transfusion requirements, and outcome. *Critical Care Medicine*. 2002;30(8):1765-1771.
23. Marder E, Kirschke D, Robbins D, et al. Thrombotic thrombocytopenic purpura (TTP)--like illness associated with intravenous opana ER abuse -- Tennessee, 2012. (cover story). *Morbidity & Mortality Weekly Report*. 2013;62(1):1-4.
24. Brichacek M, Blake P, Kao R. Capnocytophaga canimorsus infection presenting with complete splenic infarction and thrombotic thrombocytopenic purpura: a case report. *BMC Research Notes*. 2012(1):695.
25. Sharma BMD, Sharma MMD, Majumder MMD, et al. Thrombocytopenia in septic shock patients-A prospective observational study of incidence, risk factors and correlation with clinical outcome. *Anaesthesia & Intensive Care*. 2007;35(6):874-880.