Journal of Current Hematology & Oncology Research

Original Article

DOI: 10.51271/JCHOR-0041

The role of therapeutic plasma exchange in the treatment of patients with septic shock- single center experience

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Cite this article: Çelik S, Erkurt MA, Sarıcı A, et al. The role of therapeutic plasma exchange in the treatment of patients with septic shock- single center experience. *J Curr Hematol Oncol Res.* 2024;2(3):67-71.

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Received: 12/01/2024 ◆ **Accepted**: 17/04/2024 ◆ **Published**: 01/08/2024

ABSTRACT

Aims: Sepsis is a life-threatening organ dysfunction resulting from an excessive inflammatory response in the host due to infection. Due to the activation of the coagulation system in sepsis, the search for treatment has shifted in this direction and therapeutic plasma exchange (TPE). This study, it was aimed to compare the hemogram and biochemical values and inflammatory markers of patients who underwent TPE before and after TPE.

Methods: The research data were obtained retrospectively from the records on the hospital system of the patients who were hospitalized in Malatya İnönü University Faculty of Medicine Intensive Care Clinic and were treated with TPE.

Results: A total of 25 patients were included. It was observed that platelet count (p=0.427), hemoglobin (p=0.545), leukocyte (p=0.527) and neutrophil (p=0.657) counts decreased statistically after TPE. It was observed that C-reactive protein (p=0.065) and procalcitonin (p=0.267) values also decreased after TPE procedure. Among the direct bilirubin (p=0.326), total bilirubin (p=0.397), AST (p=0.840) and alanine transferase (ALT) (p=0.122) values, it was determined that the aspartate transferase (AST) value increased after the TPE procedure and the others decreased. It was observed that the blood urea nitrogen (p=0.326) value increased after TPE procedure, while creatinine (p=0.677) value decreased.

Conclusion: TPE process can reduce harmful components in plasma. Since it is of vital importance to reduce harmful components in the plasma in sepsis, TPE can be applied by evaluating patient-specifically. Our study is important in terms of showing that TPE can be an alternative treatment modality in patients with sepsis and septic shock.

Keywords: Sepsis, septic shock, therapeutic plasma exchange, inflammatory markers

INTRODUCTION

Sepsis is a life-threatening organ dysfunction as a result of an excessive inflammatory response observed in the host because of infection.[1] Despite the identification of the factors leading to sepsis and the administration of specific antibiotic treatment, the death rate due to sepsis in intensive care patients is still quite high.[2,3] This increases the tendency to try new therapies and develop novel methods in the treatment of sepsis.[4]

Bacterial toxins and cytokines released as a result of sepsis may cause endothelial dysfunction. Disseminated intravascular coagulation and multiple organ failure syndrome may also develop. It is thought that reducing the level of these toxic substances in blood will affect the prognosis of sepsis positively.[1]

The quest for new treatments has shifted towards the coagulation system which is activated in sepsis, and therapeutic plasma exchange (TPE), a procedure followed for the treatment of sepsis, has been highlighted. The said procedure is based on the principle of removing the plasma and replacing it with albumin or plasma.[5]

TPE has been thought to be a treatment alternative that could be used in the treatment of patients with sepsis and septic shock, and this study aimed to compare the pre- and post-

TPE whole blood counts (WBC), biochemical values, and inflammatory markers of patients.

METHODS

The study was carried out with the permission of The study was carried out with the permission of the Malatya İnönü University Faculty of Medicine Ethics Committe (Date: 09.02.2021, Decision No: 2021-1607). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. The research data were obtained retrospectively from the hospital records of the inpatients in Malatya İnönü University Faculty of Medicine Intensive Care Clinic who were treated with TPE. This is a cross-sectional study conducted between January 2021 and October 2021 by way of evaluating the data of 25 patients who were determined to meet the study inclusion criteria between January 2019 and June 2021.Patients that presented with sepsis criteria, patients with septic shock or severe sepsis, and patients admitted to intensive care were included in the study. Exclusion criteria included end-stage malignant disease, liver cirrhosis, use of medication that may alter blood coagulation, previously known coagulopathy, pregnancy, and nephrotic syndrome.Therapeutic plasma exchange procedures were performed using a Fresenius AS 204TM automatic apheresis machine and veno-venous access. Acid-citrate dextrose solution was used as an anticoagulant. In the plasmapheresis process, fresh frozen plasma was used as replacement fluid in accordance with the blood groups of the patients, and the fresh frozen plasma volume was set as 1-1.5 times the total plasma volume calculated for each patient.

All of the replacement fluid was made with FFP. No sepsis column was used for TPE. Steroid premedication may change leukocyte levels. Extra avil was applied as premedication.

Study Variables

In this study, we compared the patients' pre- and post-TPE platelet counts, C-reactive protein (CRP), hemoglobulin (HB), WBC, neutrophil, procalcitonin, PT, APTT, INR, fibrinogen, total bilirubin, direct bilirubin, blood gas lactate, BUN (blood urea nitrogen), creatinine, AST (Aspartate Aminotransferase test), and ALT (Alanine aminotransferase) values.

SPSS version 22.0 was used to perform the statistical analyses. Descriptive statistics were expressed as numbers and percentages, and the Shapiro-Wilk normality test showed that the quantitative variables did not follow a normal distribution. The Wilcoxon test was used to compare the medians of the dependent group. Mann-Whitney U test was used to compare the medians in independent groups p <0.05 was accepted as statistically significant.Before the TPE procedure, 52% of the patients had not undergone any surgical operation. Prior to the procedure, inotropes were administered to all patients, and they were given anticoagulants and fresh frozen plasma (FFP). 60% of the patients were not mechanically ventilated before TPE.

RESULTS

A total of 25 patients were included in the study. 10 (%40) of them died.Of the patients included in the study, 68% were male, 56% were hospitalized in the organ transplant intensive care unit, and it was found that sepsis was a hospital-acquired infection in 87.5% of the patients. Demographic data of the study participants are provided in Table 1. The clinical characteristics of the study participants are given in Table 2.

Table 1. Patients' sociodemographic and infection details

Variable		Number of participants (n)	Percentage (%)
Gender	Female	8	32.0
	Male	17	68.0
The intensive care clinic the patient is admitted to	Reanimation	2	8.0
	Hematology	9	36.0
	Organ transplant	14	56.0
Presence of septicshock	Yes	14	56
	No	11	44
Site of infection	Urological	1	4.0
	Unknown	1	4.0
	Skin and soft tissue	2	8.0
	Other endocarditis	2	8.0
	Abdominal	6	24.0
	Lungs	13	52.0
Sepsis source	Community-acquired	3	12.0
	Hospital-acquired	21	84.0
	Unknown	1	4.0
Pathogenic feature	Bacterial gram positive	8	32.0
	Bacterial gram negative	5	20.0
	Fungal	1	4.0
	Mix	9	36.0
	Undefined	2	8.0

Table 2. Patients' age, body mass index, APACHE2 score, TPE session quantity, post-TPE follow-up days

Variable	Median ± SD	Minimum-Maximum
Age	42,80±18,48	18-80
Body mass index	23,66±3,56	13,4-30,5
APACHE 2 score	14,48±4,64	7-23
Number of TPE sessions	3,76±1,98	1-10
Number of post-TPE follow-up days	22,68±28,95	1-104

SD: Standard deviation, APACHE: Acute physiology and chronic health evaluationscoring, TPE: Therapeutic plasma exchange

Although the findings of the study are statistically non-significant, the following were the observations after the TPE procedure: The number of platelets (p:0.427), hemoglobin (p: 0.545), WBC (p:0.527), and neutrophils (p:0.657) in the blood, which are the formed elements of blood, decreased. CRP (p:0.065) and procalcitonin (p:0.267) levels beneficial in infection follow-up also diminished after the TPE procedure. PT (p:0.333), aPTT (p:0.367), INR (p:0.319) and fibrinogen (p:0.123) levels used to examine coagulation dropped after the procedure.From among direct bilirubin (p:0.326), total bilirubin (p:0.397), AST (p:0.840), and ALT (p:0.122), the AST level elevated following the procedure while the others declined. On the other hand, BUN (p:0.326) increased after TPE whereas creatinine (p:0.677) lessened.It would be appropriate to monitor and evaluate more patients with a

prospective study plan in order to determine the statistically significant difference. Table 3 provides changes in laboratory values before and after the TPE procedure. The changes in kidney functions before and after TPE are given in Table 4. The limitations of the study are that it is retrospective and the number of patients is small

Table 3. Comparison of the median values of pre- and post-TPE platelet count, CRP, hemoglobin, WBC, neutrophil count, procalcitonin, PT, aPTT, INR (International Normalized Ratio), fibrinogen, direct bilirubin, indirect bilirubin, AST, and ALT

Variable	Mean±SD	Median	Min-Max	p
Pre-TPE CRP	12.10±9.99	10.58	0.7-0.3	0.065
Post-TPE CRP	8.68±7.29	6.89	0.3-22.8	
Pre-TPE procalcitonin	17.66±29.68	3.70	0.03-100.10	0.277
Post-TPE procalcitonin	8.17±17.22	1.47	0.47-73.76	
Pre-TPE platelet count	94.00±135.65	42.00	3-647	0.427
Post-TPE platelet count	78.92±103.71	38.00	2-368	
Pre-TPE HB	12.95±19.03	9.60	5.9-104.0	0.545
Post-TPE HB	9.07±1.82	9.20	5.5-13.5	
Pre-TPE WBC	8.94±11.53	4.82	0.02-51.7	0.527
Post-TPE WBC	6.67±8.25	4.30	0.14-37.30	
Pre-TPE neutrophil	7.16±10.54	4.03	0.00-46.60	0.657
Post-TP Eneutrophil	5.17±7.52	3.23	0.05-35.76	
Pre-TPE PT	18.27±8.01	16.5	10.2-41.4	0.333
Post-TPE PT	16.36±4.26	15.7	11.5-28.1	
Pre-TPE aPTT	34.26±23.58	27.2	20.8-142.0	0.367
Post-TPE aPTT	28.1±5.28	26.3	22.1-44.6	
Pre-TPE INR	1.55±0.72	1.41	0.8-3.7	0.319
Post-TPE INR	1.38±0.40	1.28	0.95-2.57	
Pre-TPE fibrinogen	356.79±204.86	336.00	51.6-791.0	0.123
Post-TPE fibrinogen	251.18±78.45	242.15	72.0-392.7	
Pre-TPE total bilirubin	7.56±7.08	6.40	0.44-33.74	0.397
Post-TPE total bilirubin	6.13±5.40	4.99	0.69-19.87	
Pre-TPE direct bilirubin	5.10±5.08	4.60	0.18-23.99	0.326
Post-TPE direct bilirubin	4.02±3.60	3.32	0.34-13.99	
Pre-TPE lactate	3.37±2.50	2.30	1.1-12.1	0.884
Post-TPE lactate	4.70±5.75	3.00	0.7-27.0	
Pre-TPE AST	80.32±82.40	47.0	9-315	0.840
Post-TPE AST	97.48±145.37	57.0	6-704	
Pre-TPE ALT	90.40±111.88	57.0	8-501	0.122
Post-TPE ALT	63.68±64.67	41.0	5-241	

TPE: Therapeutic plasma exchange, CRP: C-reactive protein, HB: Hemoglobulin, WBC: White blood cell, PT:Prothrombin Time,aPTT:Activated partial thromboplastin Time, INR:International normalized ratio, AST:Aspartate aminotransferase ALT: Alanine aminotransferase

Table 4. Comparison of the median values of pre- and post-TPE BUN and serum creatinine

Variable	Mean ± Standard Deviation	Median Value	Minimum-Maximum	p value
Pre-TPE BUN	36.80±26.13	29.90	8.07-119.80	0.326
Post-TPE BUN	42.68±32.77	33.33	3.2-124.0	
Pre-TPE creatinine	1.16±0.94	0.83	0.43-4.67	0.677
Post-TPE creatinine	1.23±0.93	0.84	0.45-3.65	

TPD: Therapeutic Plasma Exchange, BUN: Blood urea nitrogen

DISCUSSION

Caused by the dysregulated inflammatory response by the host, sepsis is defined as a clinical condition that progresses with the development of cytokine storm and organ dysfunctions in the host.[1] Sepsis is one of the most common causes of death in intensive care units. This illustrates the importance of sepsis treatment approaches aiming to reduce ICU mortality rates.[6] Whilesepsis and septic shock mortality rates vary across countries, the international literature shows that these rates are around 30-50%.[7,8]

It was determined that sepsis and septic shock mortality rates in Türkiye are higher than the mentioned figures. This paves the way for the review of the currently implemented treatments for sepsis and the trial of new therapies.[9,10]

The TPE procedure allows reducing the harmful components in the plasma and performing a large-volume plasma replacement without causing a volume load.[11] Since the reduction of harmful components in the plasma is of vital importance in sepsis, the TPE procedure is implemented in a patient-specific manner. TPE is known as a treatment method used to removetoxic materials from the plasma in sepsis.[12]

The research which cannot be generalized represents only its own sample. The retrospective nature of the study allowed for the evaluation of only certain variables. Prospective furtherstudies will enable a more comprehensive evaluation and follow-up.

In this study, the mortality rate following the TPE procedure was 40%. In a study performed at another center, on the other hand, the rate was 36.4%.[13] This difference may be due to the fact that in that center, TPE was performed in Category I and Category II patients in accordance with the American Society for Apheresis (ASFA) indication classification. In our study, sepsis patients in Category III according to ASFA plasmapheresis indication classification underwent the TPE procedure. It is crucial to perform a therapeutic plasmapheresis procedure by adopting a case-specific approach in category III diseases.

Although TPE is a procedure with a certain level of risk, the rate of its fatal side effects is quite low. Common side effects after TPE are anaphylactoid reactions such as urticaria and shivering; hypocalcemia symptoms such as headache, hypotension, hypovolemia, nausea, vomiting, muscle twitching, and paresthesia may also be observed.[14,15,16]

It was determined that 72% of the patients included in our study did not develop any complications after the TPE procedure. 1 person developed an allergic reaction, 1 person had decreased HB, 2 people had hypocalcemia, and 3 people developed serious reactions that could lead to life-threatening risks. In a study in another center, it was observed that the patients who underwent the TPE procedure most commonly developed catheter site-related complications, hypocalcemia, chills and shivering.[17] This difference in the frequency of complications may be due to the procedures performed.

Calculated according to the APACHE II scoring system in which body temperature, mean arterial pressure, heart rate, respiratory rate, oxygenation, arterial pH, venous HCO3, sodium, potassium, serum creatinine, hematocrit, leukocytes, and glasgow coma score were evaluated as physiological variables, the mean score of the patients in our study was 14.48±4.64. It was determined that in the APACHE II scoring

which is a way to evaluate acute physiology, age, and chronic health, mortality was 25.0% when the total score was 25 but it rose to 80% once the total score was 35 and above.[18] A crucial weakness of the said scoring system employed in this study is the inability to evaluate hemodynamic support therapy and mechanical ventilation; these two variables can be analyzed in further studies.

Although the findings of the study are statistically non-significant, it demonstrated that platelets, hemoglobin, WBC, and neutrophils, which are the formed elements of blood, decreased following the TPE procedure. In another study, the number of platelets in patients who underwent TPE due to multiple organ failure and sepsis showed a statistically significant increase. Our study might not have provided the same results because we did not examine patients only with multiple organ failure and sepsis but evaluated patients with sepsis and septic shock altogether.[19] It was seen that there was a drop in platelet and WBC counts of patients who had TPE as part of another study; however, similar to our study, the decrease was not statistically significant.[20]

It was also detected that CRP and procalcitonin levels used in infection follow-up also diminished after the TPE procedure. A study compared procalcitonin and CRP levels in 21 patients before and after 42 TPE procedures and showed a 31.0% and 64.0% decrease in procalcitonin and CRP levels respectively.[21]

Similar to previous research, our study exposed a drop in CRP and PCT levels. A 48.0% and 28.2% decrease in procalcitonin and CRP levels respectively were found after the TPE procedure in the present study. In another research, survival following the TPE procedure in sepsis and septic shock patients was compared, and it was seen that the surviving group had higher levels of procalcitonin. This result suggests that the decrease in procalcitonin levels following the TPE procedure also has an effect on survival.[22] Nevertheless, a comparison of mortality and procalcitonin levels in our study did not provide statistically significant results while the mean of procalcitonin levels of patients who died was found to be higher than those who survived. It would be appropriate to perform further research to evaluate survival using a larger sample. PT, aPTT, INR, and fibrinogen levels used to evaluate coagulation were also observed to have dropped at a statistically non-significant rate after the TPE procedure. From among direct bilirubin, total bilirubin, AST, ALT, and blood gas lactate, the AST level was found to have elevated following the procedure while the others declined. In another study, patients'total bilirubin, AST, and ALT levels decreased statistically significantly after the TPE procedure. This difference may be due to dissimilarities in study samples.[19]It was seen that BUN increased after TPE whereas creatinine lessened. In a different study, patients' BUN and creatinine levels were found to have reduced statistically significantly after the TPE procedure.[19] Another study, on the other hand, demonstrated that BUN and creatinine levels rose but statistically significantly, unlike the resultsof our study.[20] It would be appropriate to monitor and evaluate more patients with a prospective study plan in order to determine the statistically significant difference.

CONCLUSION

The TPE procedure performed in the clinical course of the patients provided longer-term antibiotic use with improvement in survival. It is predicted to provide an advantage in agent control.

A total of 25 patients were included. It was observed that platelet count (p=0.427), hemoglobulin (p=0.545), WBC (p=0.527) and neutrophil (p=0.657) counts decreased statistically after TPE. It was observed that CRP (p=0.065) and procalcitonin (p=0.267) values also decreased after TPE procedure. Among the direct bilirubin (p=0.326), total bilirubin (p=0.397), AST (p=0.840) and ALT (p=0.122) values, it was determined that the AST value increased after the TPE procedure and the others decreased. It was observed that BUN (p=0.326) value increased after TPE procedure, while creatinine (p=0.677) value decreased.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Malatya İnönü University Faculty of Medicine Ethics Committe (Date: 09.02.2021, Decision No: 2021-1607).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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