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Prospective Evaluation of Critically ill Patients With Therapeutic Plasma Exchange in Medical Intensive Care Unit

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Abstract

Background: Therapeutic plasma exchange (TPD) is the separation of the patient's plasma for treatment purposes and the replacement of another fluid. Therapeutic plasma exchange, the use of which has expanded in recent years, is a treatment method that cleans the blood extra-corporeally and is used in many immunological and toxicological diseases. The aim of this study is to prospectively examine critical patients who are followed up in the intensive care unit and undergo therapeutic plasma exchange.

Materials and methods: Patients who were hospitalized in the Intensive Care Unit of Erciyes University, Faculty of Medicine, older than 18, and whose therapeutic plasma exchange (TPD) indication were included in the study. Demographic information of the patients, indication for admission to intensive care unit, and TPD indication were recorded before the procedure. Patients who were indicated for plasmapheresis were observed for side effects during the procedure.

Result: A total of 31 patients were included in the study. The mean age of the patients was 46 ± 18 years. 52% of the patients were female and 48% were male. The hospitalization medyan APACHE II score (min-max: 5-40) of the patients was 20. When the patients were evaluated in terms of TPD indications in intensive care, the most common causes were 56% microangiopathic hemolytic anemia (MAHA), 13% Crimean Congo Hemorrhagic Fever (KKKA) and 10% Guillen Barre Syndrome.

Conclusion: The frequency of TPD indications of patients included in the study is compatible with the literature, and TPD was applied most frequently because of MAHA. The patients were younger than the normal intensive care population. This study provides clinicians with some helpful information about the intensive care clinical course before patients undergo TPD.

Keywords: Therapeutic plasma exchange, intensive care unit, mortality, critical disease.

Introduction

Therapeutic Plasma Exchange (TPE) is the removal of pathological substances from the blood and reinfusion of the remaining components (such as erythrocytes, leukocytes, platelets) in the replacement fluid [1, 2]. In TPE, blood is separated from the plasma by an extracorporeal technique and the high molecular weight substances in the plasma are removed, while 5% albumin, fresh frozen plasma (FFP) or colloidal solutions are given to the patient as a replacement fluid [3]. TPE procedure aims to reduce the plasma components acting on the pathogenesis of several diseases (i.e., immune complexes, toxins, auto-allo antibodies, lipoproteins, monoclonal proteins and cryoglobulins) and thereby to prevent the related morbidity caused by pathogenic substance in the blood [4].

TPE is primarily used in treatment of hematological diseases such as thrombotic thrombocytopenic purpura (TTP), atypical hemolytic uremic Syndrome (aHUS) and hyper-viscosity syndrome caused by multiple myeloma and Waldenström'smacroglobulinemia (WM).The primary treatment in Good Pasture disease is TPE combined with immunosuppressive therapy[5]. Plasma exchange is also considered a life-saving treatment option in fatal pathologies such as immune activated conditions, sepsis, macrophage activation syndrome, thrombotic microangiopathic and disseminated intravascular coagulopathy (DIC) in intensive care unit (ICU) patients[6, 7].

This study aimed to evaluate the demographic, clinical and laboratory data of critically ill patients who werefollowed up in the ICU with TPE indication.

Materials and methods

A total of 31 adult (aged >18 years)patients who were referred to ICU with TPE indication during their hospitalization at a tertiary care were included in thisprospective observational study conducted between July 2018 and July 2019. All

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patients were categorized according to The American Society for Apheresis (ASFA) [8]. Written informed consent was obtained from each subject or their relatives following a detailed explanation of the objectives and protocol of the study which was conducted in accordance with the ethical principles stated in the "Declaration of Helsinki" and approved by the institutional ethics committee (Date of approval 15/01/2020, Decision no.: 2020/03).

2.1. Study Plan and Data Collection

Data on patient demographics (age, gender), indications for initial hospital admission, ICU admission and TPE, APACHE II scores, Glasgow Coma Scores (GCS) and the referral service (emergency room or a department in internal medicine) were recorded at initial ICU admission. In the daily follow-up of the patients, GCS, SOFA score, the amount of FFP or albumin used in the TPE procedure, whole blood count, biochemistry and coagulation tests were recorded on the days before and after the TPE procedure. The adverse effects during the TPE procedure, the length of ICU stay and patients' final status were also recorded.

2.2. Plasmapheresis device

TPE Procedure was performed by Fresenius-COMTEC 204 from July 2018 to March 2019 and by SpectraOptia® ApheresisSystem device after March 2019.

2.3. Statistics

Statistical analysis was made using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, NY). Chi-square ($\chi 2$) test was used for the comparison of categorical data. Mann-Whitney U test and independent sample t-test were used for the parametric variables. Data were expressed as mean±standard deviation (SD), minimum-maximum and percent (%) where appropriate. $p<0.05$ was considered statistically significant

Results

A total of 207 TPE sessions were applied to 31patients. The mean±SD age of the patients was 46±18 years and 52% of patients were females. The respiratory failure (35% and 42%, respectively) and somnolence (16% and 26%, respectively) were the two most common indications for the initial hospital admission and ICU referral. The most commonly noted TPE indications were included microangiopathic hemolytic anemia (MAHA, 56%) and Crimean Congo hemorrhagic fever (CCHF, 13%).The median GCS was 11 (range, 3 to 15), SOFA score was 8 (range, 2 to 16) and APACHE II score was 20 (range, 5 to 40). Replacement fluids used during plasmapheresis were FFP in 84% of patients and albumin in 16% of patients. The length of ICU stay was median 12 days (range, 1 to 86 days), while ICU mortality rate was 48%. Detailed results are presented in Table 1.

Table 1: Demographic and clinical features of critically ill patients with therapeutic plasma change in medical ICU

Variable	Value (n = 31)
Age (year),mean±SD	46±18
Gender, n (%) Male Female	 15(48) 16 (52)
Initial hospitalization, n (%)	
Emergency service	14 (45)
Hematology ward	10 (32)
Nephrology ward	3 (10)
Gastroenterology ward	2 (7)
General surgery ward	1 (3)
Other	1 (3)
Reasons for hospitalization, n (%)	
• Respiratory failure	11 (35)
• Loss of consciousness	5 (16)
• CCHF	4 (13)
• Acute kidney failure	3 (10)
• Sepsis	3 (10)
• MAHA	3 (10)
• Pneumonia	2 (7)
Reason for ICU admission, n (%)	
• Respiratory Failure	13 (42)
• Loss of consciousness	8 (26)
• Pneumonia	3 (10)
• CCHF	3 (10)
• Multiple organ failure	2 (6)
• Liver failure	1 (3)
• Acute kidney failure	1 (3)
GCS, (min-max)	11(3-15)
SOFA score, (min-max)	8 (2-16)
APACHE II score, (min-max)	20 (5-40)
Replacement fluid used in plasmapheresis, n (%)	
• Fresh frozen plasma (FFP)	26(84)
• Albumin	5 (16)
Length of ICU stay (day) median (min-max)	12 (1-86)
ICU mortality, n (%)	15 (48)

MAHA: Microangiopathic Hemolytic Anemia; CCHF: Crimean Congo Hemorrhagic Fever; GCS: Glasgow Coma Score; ICU: Intensive Care Unit

The detailed TPE indications in patients withMAHA were TTP in 4 (13%) patients, aHUS in 3(10%) patients and other indications in 10(33%) patients. Overall, 121 TPE sessions were applied to patients with MAHA and 32 TPE sessions were applied to those with CCHF patients. One of the patients has improved to DIC syndrome. Guillain-Barre Syndrome (GBS) patients who had undergone TPE procedure constitute 10% of all patients (n=3) in the study. Detailed results are presented in Table 2.

The survivors vs. non-survivors had significantly higher GCS scores (median(min-max) 12 (3-15)vs. 8

Table 2: Indications for TPD application by the number of patients, ASFA category and mortality

Indications	Number of patients	ASFA Category	Mortality (n)	Cause of death
Microangiopathic Hemolytic Anemia				
TTP	**17**			
a-HUS	4	I	1	sepsis
other	3	III	3	sepsis and cardiovascular diseases
	10	III		
Crimean Congo Hemorrhagic Fever	**4**		1	DIC
Gullian- Barre Syndrome	**3**	I	2	sepsis
Systemic Lupus Erythematosus	**2**			
Nephritis	1	IV	0	
Alveolar hemorrhage	2	II	0	
Multiple Myeloma	**2**	I	2	sepsis
ANCA-associated vasculitis	**1**			
Alveolar hemorrhage	1	I	1	sepsis

TTP: Thrombotic Thrombocytopenic Purpura; a-HUS: Atypical Hemolytic Uremic Syndrome, DIC: Disseminated Intravascular Coagulation; ASFA: American Society for Apheresis

(3-15), p=0.008) and significantly lower APACHE II scores (mean±SD 17±7 vs. 25±9, p=0.02). No significant difference was noted between survivors and non-survivors in terms of age (mean±SD 43±17 vs. 50±18 years), SOFA scores (median(min-max) 7 (3-12) vs. 10(2-16) and length of ICU stay (median(min-max) 13(4-40) vs. 8 (1-86) days). Detailed results are presented in Table 3.

Of 31 patients who underwent TPE, 4 patients experienced adverse effects during plasmapheresis, including anaphylaxis (n=2), hypotension (n=1) and bleeding (n=1). The anaphylaxis in one patient resulted in mortality.

Discussion

Patients who underwent TPE were examined prospectively and observationally. MAHA was the most common cause of TPE indication among these patients. When MAHA is evaluated, it was observed that TPE is an effective treatment in TTP patients. It was observed that the mean age of patients who underwent TPE in intensive care was smaller than the mean age of patients who were followed in intensive care. Our study showed that mortality was high in patients with low hospitalization GCS and high hospitalization APACHE II scores.

Table 3: Patient's demographic and clinical outcomes of critically ill survivor and non-survivor patients with therapeutic plasma exchange in medical ICU.

	Survivor (n=16)	Non-survivor (n=15)	pvalue
Age (year), mean±SD	43±17	50±18	0.342
Gender, n (%)			
Male	6(38)	9(60)	0.210
Female	10 (62)	6(40)	
GCS, (min-max)	12(3-15)	8(3-15)	**0.008**
SOFA score, (min-max)	7(3-12)	10(2-16)	0.064
APACHE II score, ±SD	17±7	25±9	**0.020**
Length of ICU stay, day (min-max)	13(4-40)	8(1-86)	0.470

GCS: Glasgow Coma Score; ICU: Intensive Care Unit

In the current study a total of 207 TPE sessions were applied to 31 patients in a medical ICU. The mean age of the patients was 46±18 years. In a previous study performed by Gündoğan et al. in 2011 at the same unit, the mean age of the patients wasreported to be 61±19 years[9]. The smaller age of patients in our study seems to be associated with the fact that TPE diseases are autoimmune diseases commonly observed in middle age. In our study, 52% of patients were female and 48% were male. Consistent with patient demographics reported in our study, in anICU study by Ranganathan et al. in India in 2017, the authors reported the mean age of patients who required TPE to be 43.08±16.84 years, while 59% of patientswere males and 41% were females[6].

In a10-year retrospective ICU study by Paton et al. in 2014 in Australia, total of 30 patients had undergone 135 TPE procedures, while the TPE indication included TTP in 11(36.7%) patients, liver transplantation rejection in 4(13.3%) patients, MG in 3(10%) patients, GBS in 2(6.7%) patients, anti-GBM disease in 3(10%) patients, ANCA-induced vasculitis in 2(6.7%) patients and other diseases in 5 patients[7]. In another ICU study performed by Lemaire et al. in 2017[10], 50 patients had undergone 260 TPE procedures, while TPE indications included MAHA in 29(58%) patients [TTP: 18(36%), aHUS: 10(20%) and drug induced TMA: 1(2%)], hyperviscositysyndromein 12(24%) patients, ANCA induced vasculitis in 4(8%) patients, humoral rejection after kidney transplant in 3(6%) patients, severe cryoglobulinemia in 1(2%) patients and catastrophic antiphospholipid syndrome in 1(%2) patient. In this regard, our findings support the consideration of MAHA as the more prevalent TPE indication in ICU patients [7,10].

Considering the TTP, a type of MAHA, France and Canadian reports in the recent years showed that TPE use is increasing especially in hematological diseases since TPE

is used more commonly used for TTP [11]. TTP commonly manifests with fever, thrombocytopenia, MAHA, renal failure, and neurological findings[12, 13]. The introduction of treatments such as plasma infusion and plasma exchange, immunosuppressive treatment and antiplatelet agents cased dramatic reduction in mortality rates among TTP patients, which were about 100% by the 1960s[14, 15, 16]. The literature showed that TPE is an effective treatment for TTP and decreases mortality significantly. Likewise, our study also showed that TPE is an effective treatment for TTP.

Several studies showed that the high interleukin-10, interleukin-6, gamma interferon and tumor necrosis factor alpha levels are associated with poor prognosis[17]. TPE reduces cytokines and toxic components in the patients with CCHF[18]. It was observed that TPE is useful on survival in the critical patients with severe sepsis, and several diseases with known or suspected immune etiology[19, 20]. Few studies in the literature investigated the utility of TPE in CCHF, and TPE was considered effective for CCHFin these studies. The favorable results of TPE were also seen in our study.

In a multicentered retrospective study by Kaynar et al. in 2008, 41 GBS patients and 11 myasthenia gravis patients were evaluated by Hughes score for outcome before and after TPE[19]. The authors reported significant improvement in GBS patients after TPE [19]. However, in our study, the number of GBS patients was small and the mortality scores of the patients were high (APACHE II), therefore the results were not in line with the literature.

In a prospective study on 86 SLE patients performed by Lewis et al., 46 patients received treatment and 40 patients underwent TPE 3 times per week for 4 weeks[21]. When mortality rates of the two groups were compared, it was 13% in the treatment group, and 20% in TPE group. The decrease in serum creatinine rates was reported to be similar in both groups, however, the decrease in antibody level wasfaster in the TPE group. Similar to our findings, TPE was reported to be an effective treatment in the alveolar hemorrhage patients with SLE [21].

GCS and APACHE score systems are used to evaluate the treatment efficacy and to identify the mortality rate in ICU. APACHE II score is the modified version of APACHE and based on the worst values within the first 24 hours of 12 different physiological variables. The calculated score is used to predict the mortality and morbidity of the patient in the ICU [22, 23]. When these two scoring systems are evaluated togetherbefore the TPE procedure, they seem to offer a valuable data on the likelihood of post-procedure outcome in these patients.

In a 10-year retrospective ICU study by Paton et al. in 2014 in Australia, total of 30 patients had undergone 135 TPE procedures, and the authors reported that mean hospitalization period in ICU was 9.5 (3-17) days and mortality was 20%(n=6)[13].In another ICU study performed by Lemaire et al., 50 patients had undergone 260 TPE procedures and the authors reported that the mean hospitalization period in ICU was 6(3-9) days and mortality was 6% (n=3)[10]. When our study is compared with these two ICU studies, ICU hospitalization is longer, and mortality is higher. Small number of patients and high mortality scores of hospitalizations (APACHE II) were considered to be associated with delayed ICU hospitalization and delayed TPE initiation.

TPE procedure is a well-tolerated procedure without common adverse effects. The most common adverse effect is hypocalcemia induced by citrate use, paresthesia, cramps and these are minor adverse effects. However, adverse effects that show a mortal course may also occur. Approximately 50 fatal reactions during TPE were reported worldwide between 1978 and 1983, while16 of them were cardiac and 14 were respiratory[24]. Mortality is associated with anaphylaxis, sepsis and DIC. In an ICU study performed in 2017 by Ranganathan et al. with 56 patients, TPE procedure was reported to be interrupted in 3 patients, due to transfusion-induced acute lung injury (TRALI), clinically significant hypotension and cardiac arrest[6]. The authors also indicated that the reported complications were TRALI in one patient with myasthenia gravis, hypotension induced by allergic reaction in one patient with possible vasculitis, and termination of the procedures because of cardiac arrest in one patient with mixed connective tissue disease. The adverse effects in our study were in line with the literature.

Conclusion

In conclusion, our findings revealed the microangiopathic hemolytic anemia, Crimean Congo hemorrhagic fever and Guillain-Barre syndrome to be the most frequent TPE indications in a medical ICU. Plasma exchange is a safe and generally well-tolerated procedure in ICU.

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