

Investigation of the Effects of Blood Product Replacement and Type on Mortality in Patients with Sepsis and Septic Shock

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Abstract

Objective: Anaemia, thrombocytopenia, leucopenia, disseminated intravascular coagulation (DIC) and functional deficiencies of coagulation factors are all common in patients with severe sepsis or septic shock. There is no standard protocol for blood and blood product transfusion for this disease. The aim of this study is to evaluate prospectively the blood and blood products transfusion in patients who are diagnosed with sepsis and septic shock.

Material and Methods: This prospective descriptive study was performed on patients who are 18 years of age and over, with septic/septic shock who stay for 48 hours or more in the intensive care unit.

Results: One hundred three patients were enrolled in this study. Fifty six percent of the patients were male and forty four percent were female. The mean age was 60.9±17.2 years. APACHE II score of the patients was 23.2±4.1. Patients were included in study in 6 (1-22) hours after being diagnosed with sepsis or septic shock in the intensive care unit. Patients were monitored for 6 (3-26) days as sepsis or septic shock. Blood and blood products were transfused to the 67 patients (65%). The most frequently transfused blood product was red blood cell suspension and the second most frequently transfused blood product was platelet suspension. Red blood cell suspension was transfused to 56% of the patients. The pre-transfusion Hb values of patients transfused erythrocyte suspension was 8.6±1.5 g/dL. A total of 167 units of red blood cell suspension were transfused. Hemoglobin decrease was the most common cause of red blood cell transfusion. A part of 94.8% patients who received red blood cell transfusion died. The mortality rate was statistically higher in the group of red blood cell transfusion compared to the group without transfusion (p=0.005). Platelet suspension was transfused to 30% of the patients. The pre-transfusion platelet values of patients transfused platelet suspension was 23000 (6000-191000) 10³/µL. A total of 163 units of platelet suspension were transfused. Thrombocytopenia was the most common cause of platelet transfusion. All of patients who received platelet transfusion died. Patients mortality rate was 86% in intensive care unit.

Conclusion: Patients with sepsis and septic shock who are followed up in intensive care unit are transfused high percent blood and blood products. The most transfused blood products were red blood cell and platelet suspensions. The mortality was higher in patients transfused blood and blood products.

Keywords: Blood transfusion, intensive care, platelet, red blood cell, sepsis, septic shock

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Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Erciyes University Clinical Research (Approval Date: 12.08.2016 / Decision No: 2016/477).

Informed Consent: Written informed consent was obtained from patients or patients' parents who participated in this study.

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Introduction

Cell damage may occur when the immune response becomes widespread in sepsis, cellular damage

is the precursor of organ dysfunction. The exact mechanism of cell damage is not understood. The mechanisms proposed to explain cell damage include tissue ischemia (oxygen deficiency in the face of

oxygen demand), cytopathic damage (direct cell damage by proinflammatory mediators and/or other inflammatory products), and change in the rate of apoptosis (programmed cell death).

Abnormalities in blood cell series, coagulation factors, and antithrombotic proteins are frequently observed in patients with sepsis and septic shock. Among these, anemia, thrombocytopenia, leukopenia, diffuse intravascular coagulation (DIC), functional deficits of coagulation factors are frequently observed in septic shock and severe sepsis (1). In such cases, it is indicated that support for treatment can be provided by blood and blood product transfusion (2).

Anemia is a common problem in patients with sepsis. As well as reduced production of erythrocytes due to systemic inflammatory response, the increase in erythrocyte destruction due to hemolysis and hemorrhage causes an acute decrease in hemoglobin (Hg) levels in patients with sepsis. Sepsis-induced oxygen consumption may increase deterioration of tissue oxygenation (3). In case of anemia, it can be supplemented by erythrocyte suspension (ES) transfusion to maintain adequate oxygen delivery (4). In patients with sepsis and septic shock, the ES transfusion threshold is still controversial (5). According to the Surviving Sepsis Campaign (SCC) 2016, in adults without indications such as myocardial ischemia, severe hypoxemia, acute hemorrhage, ES transfusion is recommended when only the Hg level is below 7.0 g/dL (6). If there is no hemorrhage or invasive procedure plan, according to the SCC 2016, it is recommended not to use FFP (Fresh Frozen Plasma) to correct coagulation abnormalities (6). According to the SCC 2016, prophylactic platelet suspension (PS) transfusion is recommended at a limit of 10,000/mm³ if there is no certain hemorrhage and at a limit of 20,000/mm³ if the patient has hemorrhage risk. Higher levels of 50,000/mm³ are recommended for active hemorrhage, surgical or invasive procedures (6).

This study aimed to evaluate prospectively the blood and blood products given to patients followed up with sepsis and septic shock diagnoses in the Internal Medicine Intensive Care Unit (ICU).

Material and Methods

Determination of Patient Population

Sepsis/septic shock patients who were followed in the Medical Intensive Care Unit between 15.08.2016 and 15.04.2017, who were 18 years of age and over, who were examined and treated in the ICU for 48 hours or more were included in this prospective descriptive study, after receiving their or their first-degree relatives' approval. All patients under 18 years of age with active hemorrhage and patients hospitalized in the ICU for less than 48 hours were excluded from the study. The approval of Erciyes University Ethics Committee (Ethics Committee no:2016/477 Date:12.08.16) was obtained for the study.

Definitions

For the diagnosis of sepsis and septic shock, the criteria defined in the SCC 2016 guidelines were used. Treatment of sepsis was performed following the SCC 2016 guidelines (6). Indications for patients receiving ES transfusion were determined as hypotension, tachycardia, low Hg level, reduced need for vasopressors and other indications. For PS transfusion, indications were determined as thrombocytopenia, thrombocytopenia accompanied by fever, the possibility of hemorrhage, before an invasive procedure and other indications. For FFP transfusion, indications were determined as PT, aPTT International Normalized Ratio (INR) elevation, hemorrhage probability, before an invasive procedure, massive transfusion, plasma exchange, liver disease, factor deficiency, antithrombin III

deficiency, and other indications. For cryoprecipitate transfusion, they were determined as PT, aPTT, INR elevation, the possibility of hemorrhage, before an invasive procedure, massive transfusion, hypofibrinogenemia, and other indications.

Hypotension: Mean arterial pressure less than 65 mmHg.

Tachycardia: Heart rate above 120/min.

Low hemoglobin level: Hg level lower than 7 g/dL.

Vasopressor requirement: In patients with sepsis, mean arterial pressure less than 65 mmHg despite 1000 cc of physiological saline solution loading.

Indications for platelet suspension: Platelet value below 10x10⁹/L, or platelet value below 20x10⁹/L in febrile or septic condition.

Thrombocytopenia: Platelet value below 150x10⁹/L.

PT elevation: PT more than 13 seconds.

aPTT elevation: aPTT more than 35 seconds.

INR elevation: INR value above 1.5.

Massive Transfusion:

- Over 10 packed ES transfusions within 24 hours,
- Transfusion of more than four packaged ESs in 1 hour when ongoing need can be foreseen,
- Transfusion of 50% of the total blood volume within 3 hours.

Hypofibrinogenemia: Fibrinogen level below 200 mg/dL.

Data Collection

Age, gender, height, weight, body mass index (BMI), hospitalization dates, comorbid diseases, the reasons for ICU admission, and laboratory values were recorded in the first 24 hours during which the patients were diagnosed with sepsis/septic shock. Transfusion indications of the patients in this patient group, who received blood and blood product transfusion, were recorded.

The places of ICU admission of the patients were recorded as emergency service, service, and another hospital. After the diagnosis of sepsis or septic shock was made, the hour they were included in the study and the number of days they stayed in the study were recorded. The sepsis status of the patients when they were included in the study was recorded as sepsis or septic shock.

As laboratory findings, Hg, white blood cell count, platelet count, PT, aPTT, INR, blood gas values were recorded. Patients receiving blood and blood product transfusion and their indications were recorded. The APACHE II score was calculated on admission of patients, the daily SOFA (Sequential Organ Failure Assessment), GCS (Glasgow Coma Scale), sepsis conditions (such as sepsis, septic shock) were recorded.

The number of days of ICU stay of patients, number of days of hospital stay and intensive care mortality were recorded.

Statistical Analysis

All analyses were performed using the Statistical Package for Social Sciences for Windows 22.0. (IBM Corp. Armonk, NY, USA). The median values, minimum and maximum values, mean and standard deviations of

quantitative variables with normal distribution were calculated, and the results were expressed as mean \pm standard deviation (SD) and median (min-max). Qualitative variables were defined as frequency and percentage. The "chi-square test" was used to compare categorical variables, and the "independent samples t-test" and "Mann-Whitney U test" were used to compare continuous variables; $p < 0.05$ was considered statistically significant.

Results

A total of 103 patients were included in this study. Fifty six percent of the patients (58) were male, and 44% (45) were female. The average age of the patients was 60.9 ± 17.2 years. The most common causes of ICU admission were sepsis (53.6%) and respiratory failure (50.5%). The average APACHE II score of the patients was 23.2 ± 4.1 . The average GCS on the 1st day of the patients in the ICU was 10.2 ± 5.0 , and the average SOFA value was 9.0 ± 3.4 . The demographic and clinical data of the patients are presented in Table 1.

The laboratory values of the patients taken on the day they were included in the study are presented in detail in Table 2.

After admitting to the ICU and diagnosing with sepsis or septic shock, the patients were included in the study after median 6 (1-22) hours. The patients were followed up for 6 (3-26) days as sepsis or septic shock. When the patients included in the study were evaluated, 63% (65) of them were diagnosed with sepsis at the time of the initial study, and 37% (38) were diagnosed with septic shock.

Blood and blood product transfusion was given to 65% (67) of the patients included in the study. Fifty five percent (37) of the patients receiving blood and blood product transfusion were male, and 45% (30) were female. The most common blood product given was ES (167 units). While the second most common transfusion product was 163 units of PS, a total of 37 units of FFP and 17 units of cryoprecipitate were given.

ES was given to 56% of the patients (58). ES transfusion was given to pa-

tients most frequently due to low Hg level (165 times). ES transfusion was given to patients 138 times due to hypotension. A total of 167 units of ES transfusion were given to 58 patients included in the study. The median ES amount per patient was 2 (range: 1-14). The average pre-transfusion Hg values of the patients who received ES transfusion were 8.6 ± 1.5 g/dL. The average Hg values of the patients not receiving ES transfusion were 11.8 ± 2.0 g/dL. The average SOFA score of the patients who received ES transfusion was 9.47 ± 2.9 , and the average SOFA score of the patients not receiving transfusion was 8.13 ± 3.8 ($p = 0.047$). The average APACHE-II score of the patients who received ES transfusion was 23.4 ± 3.8 , and of the patients who did not receive transfusion was 22.9 ± 4.3 ($p = 0.59$). Ninety four point eight percent of the patients receiving ES transfusion lost their lives, and mortality was significantly higher in the ES transfusion group ($p = 0.005$).

PS transfusion was given to 30% (31) of the patients. PS transfusion was given to the patients most frequently due to thrombocytopenia (163 times). When thrombocytopenia was accompanied by fever, PS transfusion was given to the patients 125 times. A total of 163 units of PS were given to 31 patients included in the study. The median PS per patient was 3 (range: 1-28). Before the transfusion, the platelet values of the patients who received PS transfusion were 23000 (6000- 191000) $10^3/\mu\text{L}$. The platelet values of the patients who did not receive transfusion were 159000 (16500-743000) $10^3/\mu\text{L}$. All of the patients who received PS transfusion lost their lives.

FFP was given to 15% (15) of the patients. FFP transfusion was given to the patients most frequently due to PT, aPTT INR elevation (14 times). FFP transfusion was given eight times to the patients before an invasive procedure. A total of 37 units of FFP transfusion were given. The median FFP per patient was 2 (1-8) units. Before the transfusion, the average PT was 21.2 ± 7.4 sec, aPTT 40 ± 14.2 sec, and INR 1.7 ± 0.5 in patients who received FFP transfusion. The average PT was 19.3 ± 14 sec, aPTT 43.7 ± 24.6 sec, INR 1.6 ± 0.9 in the patients who did not receive FFP transfusion. Eighty six point seven percent of the patients who received FFP transfusion lost their lives.

Table 1. Laboratory values of the patients

Variable	General	Erythrocytes transfused	Erythrocytes not transfused	p
White Blood Cell Count, (min-max), $10^3/\mu\text{L}$	11000 (50 -98000)	8130 (50-98000)	13650 (2100-82000)	0.001
Hemoglobin \pm SD, g/dL	10.0 ± 2.3	8.6 ± 1.5	11.8 ± 2	0.001
Platelet Count, (min-max), $10^3/\mu\text{L}$	135000 (6000-743000)	85000 (6000-569000)	155000 (20300-743000)	0.001
PT \pm SD, sec	19.6 ± 13.2	19.99 ± 13.01	19.20 ± 13.65	0.766
aPTT \pm SD, sec	43.1 ± 23.3	45.87 ± 39.66	39.66 ± 17.65	0.182
INR \pm SD, INR	1.6 ± 0.8	1.65 ± 0.79	1.62 ± 1.01	0.901

Table 2. Laboratory Values of the Patients

Variable	General	Platelets transfused	Platelets not transfused	p
White Blood Cell Count, (min-max), $10^3/\mu\text{L}$	11000 (50 -98000)	1000 (50-98000)	12550 (630-82000)	0.001
Hemoglobin \pm SD, g/dL	10.0 ± 2.3	8.7 ± 1.7	10.6 ± 2.3	0.001
Platelet Count, (min-max), $10^3/\mu\text{L}$	135000 (6000-743000)	23000 (6000-191000)	159000 (16500-743000)	0.001
PT \pm SD, sec	19.6 ± 13.2	18.7 ± 5.5	20.0 ± 15.4	0.637
aPTT \pm SD, sec	43.1 ± 23.3	40.8 ± 21.8	44.1 ± 24.0	0.510
INR \pm SD, INR	1.6 ± 0.8	1.6 ± 0.4	1.6 ± 1.0	0.901

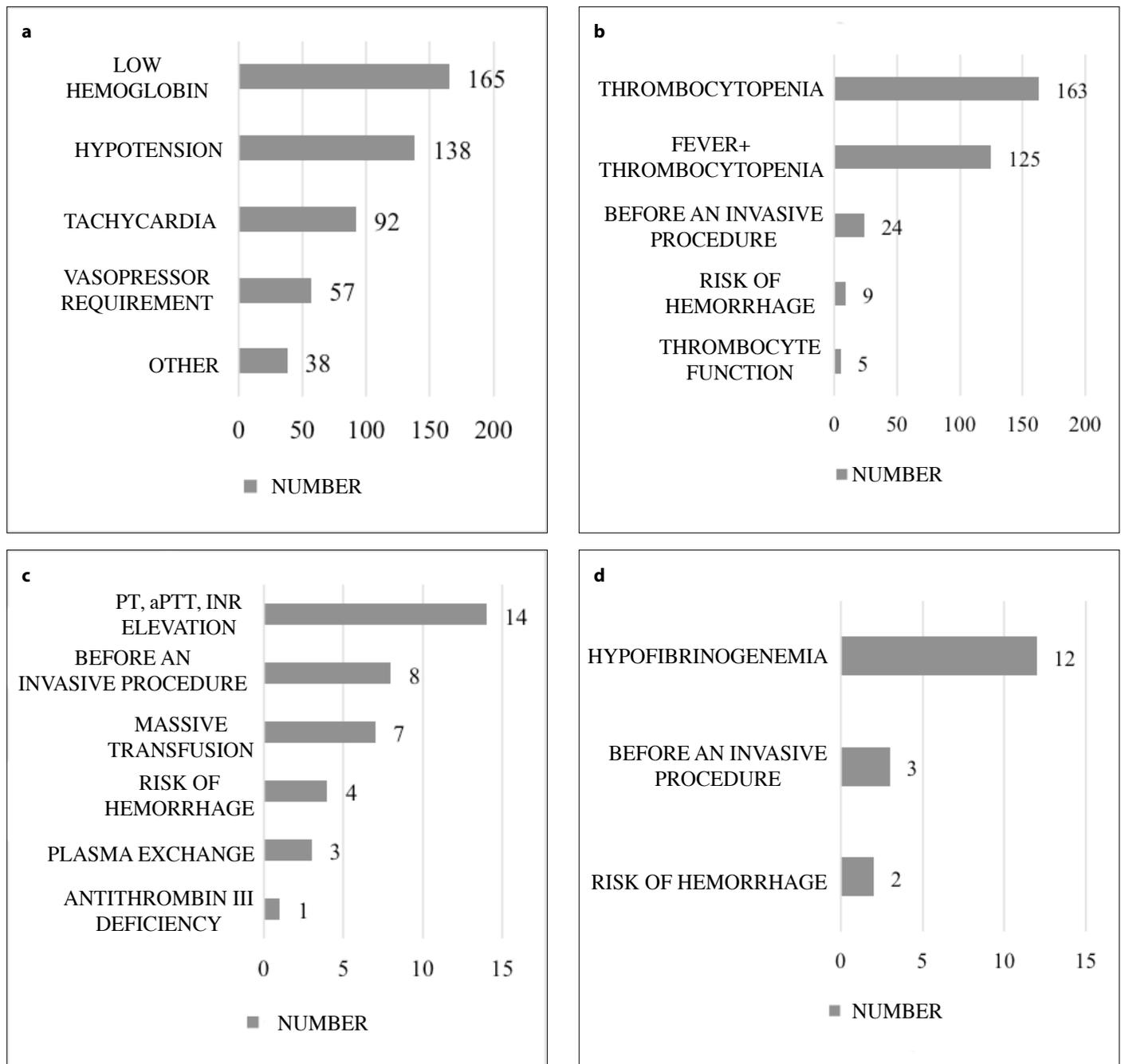


Figure 1. a-d. Indications and numbers of transfusions 1a: Erythrocyte 1b: Platelet 1c: Freshly frozen plasma 1d: Cryoprecipitate

Cryoprecipitate was given to 2% (2) of the patients. Cryoprecipitate transfusion was given to the patients most frequently due to hypofibrinogenemia (12 times). Cryoprecipitate transfusion was given three times to the patients before an invasive procedure. A total of 17 units of cryoprecipitate transfusion were given. All of the patients who received cryoprecipitate transfusion lost their lives.

The indications for transfusion are presented in transfusions (Figure 1).

Invasive mechanical ventilation (MV) was applied to 77% (79) of the patients included in the study, and these patients were followed up for median 3 (range: 0-38) days in MV. The median duration of ICU stay of the patients was 6 (range: 3-39) days, and the duration of hospital stay was 15 (3-98) days.

While 94% (63) of the patients who received blood and blood product transfusion lost their lives, 6% (4) were discharged from the ICU. Seventy two percent (26) of the patients who did not receive blood product lost their lives. Mortality was found to be higher in patients who received blood and blood product transfusion (p=0.002).

Discussion

As a result of this study, it was determined that a blood and blood product transfusion was given to 65% of the patients. The most commonly given blood product was ES (167 units).

ES transfusion is common in the ICU, and approximately half of critically ill patients receive at least one transfusion in the ICU (7). Rosland et al.

investigated ES transfusion in 213 septic shock patients treated in 7 general ICUs in their prospective study, and ES was given to 45% (95) of the patients. A total of 398 units, median 3 (range: 2-5) units of ES were given. The pre-transfusion Hg level was found to be 8.1 (7.4-8.9) g/dL. Patients with cardiovascular disease were given transfusion at higher Hg levels (2). Rivers et al. found out in their studies on Early Directed Goal Therapy (EDGT) showing the effects of the early target resuscitation protocol in patients with sepsis and septic shock, including ES transfusion in the case of permanent hypoperfusion, that ES transfusion was given to 63% (148) of the patients (5). In the study of Mazza et al. carried out with 46 septic shock patients and investigating the effect of ES transfusion on the change in lactate and central venous oxygen, a total of 74 units of ES were given to the patients (8). In the Transfusion Requirements In Septic Shock (TRISS) study, in which 998 patients with septic shock were evaluated, two groups, of which threshold Hg values in ES transfusion were 7 and 9 g/dL, were compared. To the group with the low threshold Hg value, median one unit (range: 0-3), a total of 1545 units of ES were given. Median four units (range: 2-7), a total of 3088 units of ES were given to the group with the high threshold Hg value. Less transfusion was given to the low threshold value group (9). Ninety days after randomization, 216 patients (43.0%) in the low threshold value group and 223 patients (45.0%) in the high threshold value group died (relative risk, 0.94; 95% confidence interval, 0.78-1.09; $p=0.44$). According to the SCC 2016, in adults without causes such as myocardial ischemia, severe hypoxemia, and acute hemorrhage, ES transfusion is recommended only when the Hg level is below 7.0 g/dL (6). In our study, median 2 (range: 1-14) units, a total of 167 units of ES were given to 56% (58) of the patients. The average pre-transfusion Hg values of the patients who received ES transfusion were found to be 8.6 ± 1.5 . The average Hg values of the patients who did not receive a transfusion were 11.8 ± 2.0 g/dL.

In a study that examined erythrocyte transfusion prospectively in 213 septic shock patients, 60% (57) of the patients were male (2). In the study conducted by Mazza et al., 54.3% (25) of the patients who received blood transfusion were male (8). In our study, 53% (31) of the patients receiving ES were male, similarly to the studies mentioned above.

In sepsis and septic shock, many indications for ES transfusion have been described. Rosland et al. (2) found out that the Hg level was the most important factor in the ES transfusion indication in their prospective study examining ES transfusion in 213 septic shock patients. In their study examining adult trauma and ES in critical patients, Napolitano et al. (10) attributed the ES transfusion decision in patients without hemorrhage to low Hg levels and deterioration in tissue oxygenation (10). In our study, the most common cause of ES transfusion was low Hg level (165 times). The second most common cause of ES transfusion to patients was hypotension (138 times).

Blood transfusion was found to be associated with increased mortality in the subgroups of critically ill patients, both in cohort and randomized studies (11-14); however, there are also cohort studies in which transfusion improves survival, including patients with sepsis (15). In the study in which Rosland et al. (2) evaluated ES transfusion prospectively in 213 patients with septic shock in the ICU, 70% of the patients were transfused, and 30% died (2). In another study examining ES transfusion in patients with acute lung injury, sepsis, and septic shock, no significant correlation was found between mortality and blood transfusion (16). In our study, 94.8% of the patients who received ES transfusion lost their lives, and mortality was significantly higher in the ES transfusion group ($p=0.005$). The reason for the high mortality was considered as the high

comorbidity of the patients receiving ES and the high SOFA score. Furthermore, leukocyte-poor ESs are thought to affect the result.

Thrombocytopenia in sepsis depends on both deterioration in platelet production and an increase in platelet destruction. Current recommendations and guidelines for PS transfusion are made in the light of clinical studies of prophylactic PS transfusion in treatment-related (leukemia and stem cell transplant) patients (193-200) (17-23). For patients with severe sepsis and septic shock, the SSC 2016 Guidelines recommend the prophylactic PS transfusion at platelet count less than $10.000/mm^3$ if there is no significant hemorrhage, and at platelet count less than $20.000/mm^3$ if there is a risk of hemorrhage in the patient. For patients with active hemorrhage and patients to whom surgical or invasive procedures will be applied, PS transfusion up to $50.000/mm^3$ of platelets is recommended (6). In their study, Stanwort et al. (21) evaluated 600 patients with hematological malignancies as the patients receiving prophylactic PS transfusion and not receiving a transfusion. In this study, while an average of 1.7 ± 2.6 units and a total of 580 units of PS transfusion were given to 59% of the group not receiving prophylactic PS transfusion, an average of 3.0 ± 3.2 units and a total of 964 units of PS transfusion were given to 89% of the group receiving prophylactic transfusion (21). In our study, 30% (31) of the patients received median 3 (range: 1-28) units and a total of 163 units of PS transfusion. The platelet values of the patients before transfusion were median $23000/10^3/\mu L$ (range: $6000-191000/10^3/\mu L$) and the most common reason for transfusion was thrombocytopenia (163 times). The second most common indication for giving PS transfusion was thrombocytopenia accompanied by fever (125 times). All patients who received platelet transfusion lost their lives.

Coagulation disorder (increased prothrombin time, increased INR, increased aPTT), the presence of active hemorrhage, giving a transfusion before an invasive procedure or surgery are current recommendations based on expert opinions (24). In patients without hemorrhage and with a mild abnormality, FFP transfusion is ineffective in PT correction. There are not enough studies demonstrating that the correction of more severe coagulation abnormalities in patients without hemorrhage may be beneficial to the patient (6). According to the SSC, if there is no hemorrhage or invasive procedure plan, it is recommended not to use FFP to correct coagulation abnormalities. In the study in which Moylan et al. (25) examined the compatibility of FFP transfusion in 1923 patients in the ICU with the guidelines, 12.7% of the patients received FFP. The most common indication for giving FFP was hemorrhage, and the second was prophylaxis before surgery. Pre-transfusion INR was found to be <2.5 (25). In our study, a total of 37 units of FFP, median 2 (range: 1-8) units were given to 15% (15) of the patients. Before the transfusion, the average PT was 21.2 ± 7.4 sec, aPTT was 40 ± 14.2 sec, and INR was 1.7 ± 0.5 . While FFP transfusion was given to the patients mainly due to PT, aPTT, INR elevation, a transfusion was given before an invasive procedure at the second place. In accordance with the literature, there is no clear indication for a significant part of FFP transfusion.

Conclusion

As a result of this study, it was determined that blood and blood products were given at a high rate to sepsis and septic shock patients followed up in the intensive care unit. The most common ones of these products were found to be ES and PS. Mortality was found to be higher in patients who were given blood and blood products. The SOFA score was higher in the group with high mortality.

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