The Impact of Erythrocyte Suspension Transfusion on Clinical Outcomes in Critical Care Settings

Yoğun Bakımda Eritrosit Transfüzyonunun Klinik Sonlanımlar Üzerine Etkisi

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Abstract

In this study, potential risks related to erythrocyte suspension (ES) transfusion in intensive care patients and the impacts on clinical results of the transfusion are aimed to be investigated. 259 patients who were hospitalized for more than 24 hours in intensive care unit (ICU) were included in the study. Demographic findings related to the patients, APACHE II scores, length of ICU stay, overall ICU mortality, culture results, causes of anemia in patients who are applied transfusion and levels of Hemoglobin (Hgb) and Hematocrit (Hct) with Hgb and Hct levels of post-transfusion and complications related to transfusion were recorded. Of the 259 cases included in the study, 78 (30.1%) were received transfusion and the mean Hgb threshold for transfusion was 7.35±1.00 gr/dL. In the transfusion group; chronic renal failure (p=0.007) and sepsis (p=0.001) were found significantly frequent and APACHE II score was higher (p=0.001). ICU length of stay (23.84±21.89 vs. 12.70±9.68) was also significantly longer in the transfusion group (p<0.001). Nosocomial pathogen-related infections were also significantly more frequent in the transfusion group (28.2%, p=0.043). Transfusion itself had a close relationship with mortality (37.2% vs. 22.7%, p=0.016). Mortality rates were found to be significantly higher in patients with transfusion-related complications (p=0.048), concomitant malignancy (p=0.020) and nasocomial pathogen-related infections (p=0.048). In addition to ES transfusion that is life saving, patients' needs should be carefully assessed considering its potential risks. Strategy of restrictive transfusion that has lower mortality rates is one of the most attention grabbing results.

Keywords: Erythrocyte Suspension, Hemoglobin, Intensive Care, Mortality, Transfusion

Öz

Bu araştırma ile yoğun bakım hastalarında eritrosit süspansiyonu (ES) transfüzyona ait potansiyel riskler ve transfüzyonun klinik sonuçlar üzerine etkilerinin araştırılması amaçlanmıştır. Yoğun Bakım Ünitesinde (YBÜ) 24 saatten uzun süre yatarak tedavi gören 259 hasta araştırmaya dâhil edilmiştir. Bu hastalara ait demografik veriler, APACHE II skorları, yoğun bakım yatış süreleri, mortalite, kültür üreme sonuçları, transfüzyon uygulanan hastaların anemi nedenleri ve Hemoglobin (Hgb) ve Hematokrit (Hct) düzeyleri ile transfüzyon sonrası Hgb ve Hct düzeyleri ve transfüzyona ait komplikasyonlar değerlendirildi. Araştırmaya dahil edilen 259 olgudan 78 (%30.1)'ne transfüzyon yapıldığı ve ortalama transfüzyon eşik hemoglobin değerinin 7.35±1.00 gr/dL olduğu saptandı. Transfüzyon grubunda kronik böbrek yetmezliği (p=0.007), sepsis (p=0.001) anlamlı oranda sık ve APACHE II skoru daha yüksek saptandı (p=0.001). YBÜ yatış süresi de transfüzyon grubunda (23.84±21.89 karşın 9.68±12.70 gün) anlamlı derecede uzundu (p<0.001). Nazokomiyal enfeksiyonlar transfüzyon grubunda %28.2 ile anlamlı derecede daha sıktı (p=0.043). Diğer yandan transfüzyonunun kendisi de mortalite (%37.2 karşın %22.7, p=0.016) ile yakın ilişkiye sahipti. Transfüzyon ile ilişkili komplikasyon izlenenlerde (p=0.048), eşlik eden malignite varlığında (p=0.020) ve nazokomiyal enfeksiyon gelişenlerde (p=0.048) mortalite oranı anlamlı düzeyde sık saptandı. ES transfüzyonunun hayat kurtarıcı olmasının yanı sıra potansiyel risklerin göz önünde bulundurularak hastaların ihtiyaçlarının titizlikle seçilmesi gerekmektedir. Kısıtlı transfüzyon stratejisinin daha düşük mortalite oranlarına sahip olması ise en dikkat çekici sonuçlarımızdan biridir.

Anahtar Kelimeler: Eritrosit Süspansiyonu, Hemoglobin, Mortalite, Transfüzyon, Yoğun Bakım

Introduction

According to the World Health Organization (WHO), anemia is defined as hemoglobin (Hgb) levels <13 g/dL in men over 15 years of age, <12 g/dL in non-pregnant women over 15 years of age and 11 g/dL in pregnant women (1,2). Although anemia is usually well tolerated by stable patients, it may have negative effects on prognosis in critically ill patients. It should be kept in mind that pathophysiologic conditions revealed by anemia may not be tolerated by geriatric age group, patients who have concomitant coronary, cerebrovascular, pulmonary diseases or cases struggling with respiratory failure. Critically ill patients who are mostly at the limit of tissue perfusion or oxygenation due to various reasons can tolerate anemia less than stable patients.

In the intensive care unit (ICU)s, the etiology of anemia has a wide range from acute or chronic blood loss to reduced production or hemolytic conditions (3). The incidence of anemia in critically ill patients has been reported in high frequency up to 95% in the first 3 days following the ICU admission (4,5). Although the causes vary, the main treatment option for rapidly increasing the hemoglobin concentration in critically ill patients with anemia is the erythrocyte suspension (ES) transfusion.

Although the ES transfusion incidence has been reduced in recent years due to the large number of studies that support the safety of restricted transfusion strategies in the critically ill patients, a significant amount of patients is still being transfused. The most known benefit of ES

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transfusion is the improvement of tissue perfusion by increasing oxygen delivery to the tissues (6). However; ES also contains a large number of immunomodulatory mediators that possibly may interact with immune cell function to produce immunosuppressive effects (7,8). To date, several randomized controlled trials have been reported as increased frequency of nosocomial infections with ES transfusion. In addition, ES transfusion also has some other potential risks such as transfusion-associated acute lung injury (TRALI) or transfusion-associated fluid overload (7). Uncertainty, the concerning risk/benefit profile of ES transfusion in critically ill patients maintains global controversies in this subject (9,10).

In this study, the data of the patients who were hospitalized in our ICU were analyzed retrospectively to investigate the incidence of anemia and transfusion, the effect of transfusion on ICU stay and mortality, the potential risks of transfusion and the outcomes of different transfusion thresholds.

Material and Method

The ethics committee approval (numbered 2018/36) was held from the ethics committee of the University of Health Sciences, Kanuni Education and Research Hospital. A total of 259 patients aged 18 years or more who were hospitalized for more than 24 hours in our 10-bed ICU of Traning and Research Hospital between April 4th, 2017 and April 4th, 2018 were included in the study. The study was performed in accordance with the Helsinki Declaration and approved by the local ethical committee. Patient's electronic records are reviewed retrospectively. Patients' demographics (age, gender), APACHE II scores on the day of ICU admission, ICU length of stay, ICU mortality, culture results, site of infection and comorbidities (malignancy, chronic renal failure, acute infection, sepsis and neurological diorders) were recorded. Basal levels of Hgb and hematocrit (Hct) were derived from the complete blood count (CBC) closest to the ES transfusion within 24 hours prior to the transfusion and the post-transfusion levels of Hgb and Hct derived from the CBC in the following 24 hours after transfusion were noted. In addition, causes of the anemia and transfusion-related complications were recorded in patients who underwent transfusion. Transfused patients were also divided into 3 groups according to pre-transfusion Hgb levels (Group 1 = Patients with Hgb levels $\leq$ 7 g/dL, Group 2 = Patients with Hgb levels > 7 g/dL and <8 g/dL, Group 3 = Patients with Hgb levels $\geq$ 8 g/dL). These groups were compared in terms of ICU mortality and length of ICU stay.

The statistical analysis was performed by using SPSS for macOS X version 20.0 (SPSS Inc. Chicago, IL, USA). APACHE-II scores, ICU length of stay, Hgb and Hct values and age of patients were summarized by mean±standard deviation. Comparisons of patient groups defined based on transfusion status and mortality status were assessed by independent t test. Mann-Whitney U-test was used in the analysis of continuous variables as ICU length of stay and age which didn't have a normal distribution. Furthermore, Kruskal-Wallis test was used to assess the difference of ICU length of stay between three groups of patients defined according to pre-transfusion Hgb levels. Rates of malignancy, CRF, Acute Infection, Sepsis, Neurologic disorders, Mortality rates, and Nosocomial infection were summarized using percentages. Chi-square test or Fisher's exact test were used to assess differences of rates between the groups. A p value less than 0.05 was considered statistically significant.

Results

Totally 259 patients were included in the study. There were seventy-eight patients in "transfusion group" who had received ES transfusion and one hundred and eighty-one patients in "no transfusion group" who had not received ES transfusions during the ICU stay.

a. Comparison of transfusion groups:

The mean age of the transfusion and no transfusion groups were similar (75.15±15.26 and 71.29±17.81 years, respectively). Gender was also similar between these groups. Patients who received a transfusion at any time during the ICU stay had higher APACHE II scores on the day of ICU admission than those who did not (p=0.001, t-test). Chronic renal failure and sepsis were significantly more frequent in the transfusion group (p=0.007 and p=0.001, respectively, chi-square test). Nosocomial pathogen-related infections were identified in 28.2% of the transfused patients and were significantly more frequent than those not transfused (p=0.043, chi-square test). The mean length of ICU stay was significantly longer in transfusion group than non-transfused group (23.84±21.89 vs 9.68±12.70 days, respectively) (p <0.001, mann-whitney u-test). The overall ICU mortality rates were also significantly higher among transfused patients (37.2% vs 22.7%) (p=0.016, chi-square test) (Table 1).

b. Data of transfusion group:

Pre-transfusion mean hemoglobin and hematocrit levels were 7.35±1.00 gr/dL and 22.26±3.10%, while post-transfusion ones were 9.30±0.90 gr/dL and 27.92±2.75% respectively. Transfusion-related complications were identified in 3.8% of them and all of reported complications were febrile non-hemolytic reactions (Table 2).

Table 1. Clinical characteristics and outcomes of the patients according to whether or not they had received ES transfusion during their ICU stay.

	Transfusion Group n=78 (30.1%)	**No Transfusion Group** n=181 (69.9%)	**p**
Demographics			
Age, year ±SD	75.15±15.26	71.29±17.81	.115
Female, n (%)	37 (47.4)	82 (45.3)	.752
APACHE-II score, mean±SD	26.44±7.76	22.81±8.50	**.001***
Comorbidities, n (%)			
Malignancy	16 (20.5)	29 (16)	.382
CRF	17 (21.8)	17 (9.4)	**.007***
Acute Infection	53 (67.9)	100 (55.2)	.057
Sepsis	32 (41)	38 (21)	**.001***
Neurologic disorders	20 (25.6)	56 (30.9)	.390
Nosocomial infections, n (%)	22 (28.2)	31 (17.1)	**.043***
Gram (-) pathogens	18 (23.07)	27 (14.91)	
Gram (+) pathogens	4 (5.12)	4 (2.20)	
ICU LOS, day±SD	23.84±21.89	9.68±12.70	< **.001***
Mortality rates, n (%)	29 (37.2)	41 (22.7)	**.016***

APACHE=Acute Physiology and Chronic Health Evaluation, CRF=Chronic Renal Failure, ICU=Intensive Care Unit, LOS=Length of stay, *= p<0.05

Table 2. Destrictive data of pre/post-transfusion Hgb, Hct levels and transfusion-related complications

Pre-transfusion Hgb, gr/dL±SD	7.35 ± 1.00
Pre-transfusion Hct, %±SD	22.26 ± 3.10
Post-transfusion Hgb, gr/dL±SD	9.30 ± 0.90
Post-transfusion Hct, %±SD	27.92 ± 2.75
Transfusion-related complication, n (%)	3 (3.8)*
Post-transfusion nosocomial infection, n (%)	22 (28.2)

Hgb=Hemoglobin, Hct=Hematocrit, *= febrile non-hemolytic reactions

c. Comparison of mortality and survival groups:

Of 259 ICU patients, 189 (72.9%) were discharged from the ICU and 70 (27.1%) had mortality. There was no significant difference between the survival and mortality groups in terms of demographic data. As expected, APACHE II scores on the day of ICU admission were significantly higher in the mortality group (p <0.001, t-test). Concomitant malignancy and sepsis were significantly more frequent in the the mortality group (p<0.001 and p=0.004, respectively, chi-square test). Nosocomial pathogen-related infections were also found significantly more frequent in the mortality group (p=0.021, chi-square test). However, there was no significant difference between the groups in terms of the length of ICU stay (Table 3).

d. Comparison of survival and mortality groups in patients who received ES transfusion:

There was no significant difference between the survival and mortality groups in terms of demographic features, and pre and post-transfusion Hbg and Hct levels in transfused patients. APACHE II scores on the day of ICU admission were significantly higher in the mortality group (p=0.031, t-test). The presence of malignancy in patients who had ES transfusion was significantly more frequent in patients resulted with mortality (p=0.019, chi-square test). Nosocomial pathogen-related infections (p=0.047, chi-square test) was also significantly more frequent in patients with mortality. All patients who had transfusion related complications (all 3 of them were febrile non-hemolytic reactions) died (Table 4).

e. Comparison of mortality and length of ICU stay in transfusion groups due to pre-transfusion hemoglobin levels:

The number of patients who received transfusion when their Hgb value was 7 g/dL or lower was 19 (24.3%). The number of patients with ICU mortality in this group was 5 (26.3%) and the mean length of ICU stay was 24.57±20.62 days. The number of patients received transfusion while the Hgb value was between 7 and 8 g/dL was 43 (55.1%). Mortality was seen in 17 (39.5%) of these patients and the mean length of ICU stay was 25.32±22.62 days.

Table 3. Comparison of mortality and survival groups

	Survivors n=189 (72.9%)	**Non-survivors** n=70 (27.1%)	**p**
Demographics			
Age, year±SD	71.51±17.65	75.00±15.52	.176
Female, n (%)	89 (47.1)	30 (42.9)	.544
APACHE-II score, mean.±SD	21.84±8.08	29.47±6.72	**<.001***
Comorbidities, n (%)			
Malignancy	23 (12.2)	22 (31.4)	**<.001***
CRF	25 (13.2)	9 (12.9)	.938
Acute infection	105 (55.6)	48 (68.6)	.059
Sepsis	42 (22.2)	28 (40)	**.004***
Neurologic disorders	59 (31.2)	17 (24.3)	.277
Noscomial infections., n (%)	32 (16.9)	21 (30)	**.021***
Gram (-) pathogen	29 (15.3)	16 (22.8)	
Gram (+) pathogen	3 (1.5)	5 (7.1)	
ICU LOS, day±SD	13.81±18.40	14.31±13.84	.964

APACHE=Acute Physiology and Chronic Health Evaluation, CRF=Chronic Renal Failure, ICU=Intensive Care Unit, LOS= Lenth of stay, *=p<0.05

Table 4. Comparison of survival and mortality groups in patients who received ES transfusion.

	Survivors n=49 (62.8%)	**Non-survivors** n=29 (37.2%)	**p**
Demographics			
Age, year±SD	73.61±16.53	77.75±12.69	.328
Female, n (%)	23 (46.9)	14 (48.3)	.909
APACHE-II score, mean±SD	25.12±8.51	28.68±5.73	**.031***
Comorbidities, n (%)			
Malignancy	6 (12.2)	10 (34.5)	**.019***
CRF	14 (28.6)	3 (10.3)	.060
Acute infection	31 (63.3)	22 (75.9)	.249
Sepsis	20 (40.8)	12 (41.4)	.961
Neurologic disorders	15 (30.6)	5 (17.2)	.191
Pre-transfusion Hgb, gr/dL±SD	7.24±1.18	7.53±0.54	.145
Pre-transfusion Hct, %±SD	21.96±3.60	22.77±1.95	.202
Post-transfusion Hgb, gr/dL±SD	9.18±0.86	9.49±0.96	.163
Post-transfusion Hct, %±SD	27.51±2.65	28.60±2.83	.101
Transfusion-related complications, n (%)	0 (0)	3 (10.3)	**.048***
Nosocomial infection, n (%)	10 (20.4)	12 (41.4)	**.047***
Gram (-) pathogen	10 (20.4)	8 (27.58)	
Gram (+) pathogen	0 (0)	4 (13.7)	
ICU LOS, day±SD	25.28±25.91	21.41±12.56	.623

APACHE=Acute Physiology and Chronic Health Evaluation, CRF=Chronic Renal Failure, ICU=Intensive Care Unit, LOS= Lenth of stay, *=p<0.05

The number of patients who received transfusion while the Hgb value was 8 g/dL or more was 16 (20.5%). The number of patients with mortality in this group was 7 (43.8%) and the mean length of ICU stay was 19.00±22.05 days. There was no significant difference between the 3 groups in terms of ICU mortality (p=0.507, chi-square test) and length of ICU stay (p= 0.259, kruskal wallis test) (Table 5).

Table 5. Comparison of mortality and length of ICU stay in transfusion groups for pre-transfusion hemoglobin levels.

	Mortality; rates, n (%)	**ICU LOS; day±SD**
Hgb ≤7 gr/dL n=19 (24.3%)	5 (26.3%)	24.57±20.62
7< Hgb <8 gr/dL n=43 (55.1%)	17 (39.5%)	25.32±22.62
Hgb ≥ 8 gr/dL n=16 (20.5%)	7 (43.8%)	19.00±22.05
p	.507	.259

Hgb=Hemoglobin, ICU=Intensive care unit, LOS=length of stay

According to our study results, presence of higher APACHE II scores on the day of ICU admission, chronic renal failure, sepsis or nosocomial pathogen-related infection have increased the rate of ES transfusions. Prolonged ICU stay also had a close relationship with ES transfusion. On the other hand, ES transfusion itself had a close relationship with ICU mortality. In univariate analysis; presence of malignancy, transfusion-related complications and nosocomial pathogen-related infections were identified as mortality risk factors in patients who received ES transfusion. On the other hand, in patients who received ES transfusion, different Hbg thresholds did not demonstrate significant difference on ICU mortality or ICU length of stay.

Discussion

We believe that this study presents an important information about transfusion practice in a 3rd level ICU in our country. In previous studies, the incidence of ES transfusion was reported between 26-44% in critically ill patients (5,9,11,12). In our study, the incidence of ES transfusion was 30.1% in parallel with the current literature. Transfusion Requirements in Critical Care (TRICC) study by Hebert et al. (13) has been a milestone for transfusion strategy in critically ill patients. They reported no significant difference between the restrictive (Hgb thresholds <7 g/dL for transfusion and Hgb level is maintained at 7-9 g/dL) and liberal transfusion strategy groups (Hgb thresholds <10 g/dL for transfusion and Hgb level is maintained at 10-12 g/dL) in terms of 30-day mortality. Similarly, there was no significant difference in terms of ICU mortality and length of ICU stay between Hgb threshold groups in our study. In the same study, they reported lower mortality rates in less severe ICU patients (patients with a lower APACHE II scores) with restrictive transfusion strategy (13). In line with this data, the overall ICU mortality was significantly higher in the transfusion group in our study (37.2% vs 22.7%). However, it was also indicated that the transfusion group had a significantly higher APACHE II scores on admission to the ICU. This result also interpreted as worse critically ill patients may have need for more transfusions. However, a study by Leal-Noval et al. (14) has revealed that mortality was higher in the transfusion group regardless of APACHE II score which carried out on groups with similar age, diagnosis, Hgb values, APACHE II and SOFA scores. The patients included in our study had a higher mean APACHE II scores (23.90±8.43), age (72.41±17.28 years) and also accompanying more comorbidities than included those studies. In 2004, Corwin et al. (12) reported an independent relationship between the amount of transfused ES and the ICU and hospital length of stay and mortality. Similarly, in our study, ICU length of stay was found to be significantly higher in the group who received ES transfusion.

In the previous studies, Corwin et al. (12) reported the Hgb threshold level for ES transfusion as 8.6 g/dL, while Vincent et al. (5) reported as 8.4 g/dL in the 2002 'European ABC study'. However, both of these studies were conducted at the beginning of 2000's and due to restricted transfusion efforts today, Hgb threshold levels for transfusion were started to be lowered. Therefore; one of latest transfusion studies which was performed by Vincent et al. (9), including a total of 9553 patients in 730 ICUs from 84 countries, revealed that the Hgb threshold level for transfusion was 7.6±2.1 g/dL on the day of ICU admission and 7.9±1.6 g/dL in other ICU days. Additionally, Surial et al. (15) reported the median Hgb trigger for transfusion as 7.3 g/dL in the medical patients. In accordance with these data, we found mean Hgb threshold for transfusion 7.35±1.00 g/dL in our study which mostly including medical ICU patients. Another noteworthy finding of our study is that mortality rate increases as the threshold Hgb level increases for ES transfusion. Although a remarkable increase in mortality rates was observed in these groups, no statistical significance was found. We believe that this is probably due to the limited number of patients in these groups.

Another important finding of this study was the significant increase in the frequency of nosocomial pathogen-related infections in the transfusion group. One of the most important reasons for this result which have been shown in many randomized controlled studies to date, is that the length of ICU stay of the patients receiving transfusion is longer than those without transfusion. Another possible reason is the potential immunomodulation risk of

transfusion. It is known that leucoreduced implementations for ES reduces the risk of nosocomial infections (16). However, mechanisms that mediate immunomodulation in allogeneic transfusion are still not fully elucidated and it is thought that immunomodulation may not be solely of leukocyte origin. In a previous study, which included 10 centers and 5158 cardiac surgery patients from the US and Canada, a 29% increase in the risk of major infection was reported with each unit ES transfusion (17). Similarly, in the TRACS study by Hajjar et al. (18) a 20% increase in the risk of infection with each unit of ES transfusion was reported in cardiac surgery patients. A meta-analysis by Rohde et al. (7), revealed that the restricted transfusion strategy was associated with a reduction in the risk of health care-associated infection in hospitalized patients compared to the liberal strategy. In a recent study by Dupuis et al. (19) which included septic patients, reported an increase in the rate of ICU-associated infection with ES transfusion. Our results, which are consistent with all these data, support the knowledge about the increased risk of nosocomial pathogen-related infections in transfused patients.

In this study, it has been pointed that the patients should be carefully selected for ES transfusion considering its effects on the prognosis and mortality or its potential risks of nosocomial infections as well as being life-saving in the patients with the proper indication. This study has the inherent limitation as a retrospective study as there may be other factors undocumented that may contribute to transfusion. We believe that the results will be improved by larger prospective studies.

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