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TRANSFUSION-RELATED RISK OF SECONDARY BACTERIAL INFECTIONS IN SEPSIS PATIENTS: A RETROSPECTIVE COHORT STUDY

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ABSTRACT—There is a need for insight into factors that contribute to late mortality of sepsis patients. Immunomodulatory effects have been ascribed to blood transfusion. This retrospective cohort study investigates the association between the development of nosocomial bacterial infection and transfusion of leukodepleted red blood cells (RBCs) or platelets (PLTs) in survivors of the initial phase of sepsis. Patients diagnosed with sepsis after admission to the intensive care unit of a tertiary referral hospital were included. Of 134 patients with sepsis, 67 received a blood transfusion (50%). A secondary infection developed in 19 patients (14%). A multiple logistic regression model revealed that the use of immunosuppressive medication with an odds ratio (OR) of 1.17 (95% confidence interval [CI], 1.04–1.31), but not Acute Physiology and Chronic Health Evaluation II score, malignancy, HIV infection, alcohol abuse, or diabetes mellitus, was a risk factor for nosocomial infection. In an adjusted model, the amount of transfused RBCs was associated with secondary infection with an OR of 1.18 (95% CI, 1.01–1.37). Storage time of RBCs was a relevant confounder of the effect of the amount of RBCs on infection, with an adjusted OR of 1.25 (95% CI, 1.04–1.51), $P = 0.02$. Also, the amount of transfused PLTs was associated with secondary infection, with an OR of 1.36 (95% CI, 1.05–1.78). In conclusion, transfusion of RBCs and PLTs is associated with the onset of secondary bacterial infection in sepsis patients. Storage time of RBCs influences this increased risk. These findings suggest that immunomodulatory effects of blood transfusion contribute to adverse outcome in the convalescent phase of sepsis.

KEYWORDS—Red blood cells, platelets, immunomodulation, nosocomial infection, sepsis, critically ill

INTRODUCTION

Provision of evidence-based improvements in the management of sepsis, such as early goal-directed therapy, low-dose steroids, glucose control, and selective use of activated protein C, have had only a modest effect in decreasing mortality (1, 2). An explanation may be that death from septic shock does not solely result from the initial overwhelming proinflammatory immune response, but also from immune dysfunctions occurring in patients who survive the hyperinflammatory phase (3). This state of immune depression may predispose to the development of secondary infections. Blood transfusion, although lifesaving at times, has clinically significant immunomodulatory effects, including the onset of nosocomial infection. Proposed mechanisms include downregulation of the recipient's immune function by leukocytes (4) and release of soluble mediators during storage of blood products into the supernatant of red blood cells (RBCs) and platelets (PLTs) (5, 6).

A number of studies in trauma and surgical patients have indicated a possible relation between storage time of RBCs and risk of infection (7–9). In sepsis patients, data are limited to a study performed over 10 years ago, in which aged RBCs were found to be associated with mortality (10). However, this study was performed in patients receiving packed RBCs. To counteract presumed immunomodulatory effects of leukocytes in RBC and PLT products, leukoreduction has been implemented in most hospitals since the late 1990s.

Also, although PLTs have distinct immunomodulatory properties (11–13), studies that have evaluated the impact of PLT transfusion on infection are scarce and limited to surgical patients (13–15). In this patient population, no consistent effect of leukodepletion was found. The effect of storage time of PLTs on the risk of infection is unknown.

Blood transfusion has a clear relation with adverse outcome in the critically ill (16). Given the immune dysfunction in the convalescent phase, it can be hypothesized that sepsis patients may be susceptible to transfusion-related risk of infection, thereby contributing to late mortality. Insight in the immunomodulating effects of blood transfusion in sepsis patients may help in understanding the causes and mechanisms of late mortality in sepsis patients and may identify possible interventional strategies. The aim of this study was to investigate whether the onset of secondary bacterial infection in critically ill sepsis patients is associated with transfusion of (leukodepleted) RBCs and PLTs.

MATERIALS AND METHODS

This retrospective cohort study was performed in a 30-bed mixed medical-surgical intensive care unit (ICU) of a university hospital in the Netherlands. The study was approved by the ethical committee of our hospital. Sepsis patients with a first admission to the ICU between the period of January 1, 2004, and November 30, 2007, were included. Patients with sepsis were retrieved from the National Intensive Care Evaluation (NICE) minimal data set (17, 18), in which the diagnosis is scored within 24 h after admission according to the judgment of the treating ICU physician. Patients developing sepsis during or after ICU admission were not included.

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In patients developing a secondary infection, the causative agent resulting in sepsis was not taken into account. Only bacterial infections were studied, as they are most common and most clinically relevant in the ICU (19). Infections were diagnosed based on a positive culture of samples of blood, sputum, bronchoalveolar lavage fluid, pleural fluid, ascites, or urine, which were taken when infection was considered by the treating physician. Recrudescent infection was not considered as a secondary infection. When contamination with skin flora was considered, the pathogen needed to be cultured from two samples before the culture was scored as positive. Results from surveillance cultures were considered when there was a concomitant suspicion of infection by the treating physician. Controls originated from the source population of sepsis patients.

Data on sex, age, alcohol abuse (as determined from the medical record), diabetes mellitus, HIV infection, hematologic or solid malignancy, and the use of immunosuppressive medication were retrieved from the patient digital medical system. Immunosuppressive medication included the use of azathioprine, methotrexate, mycophenolate, or steroids more than 300 mg of hydrocortisone or an equivalent of other steroids per day.

Administration of selective digestive tract decontamination (SDD) status was scored. Selective digestive tract decontamination is part of standard patient care for long-stay ICU patients, including systemic administration of cefotaxime during 4 days. Acute Physiology and Chronic Health Evaluation II (APACHE II) score was retrieved from the NICE data set.

Transfusion data were extracted from the hospital blood transfusion service computer system, including date, number of units, and storage time of the blood product. Blood products were leukoreduced by removal of the buffy coat followed by filtration. Red blood cells were categorized as being less than or equal to 14 days old or more than 14 days old. This cutoff point is based on a large observational study on the relation between storage of RBCs and outcome (7). Platelets were categorized as being less than or equal to 4 days old or more than 4 days old. A clear cutoff point based on changes of PLTs that occur during storage is not available as yet. The cutoff point of 4 days was chosen to ensure groups large enough for a meaningful comparison. Blood products are allocated from the blood bank following the "longest shelf life, first out" principle for all indications. Only RBC and PLT transfusions given in a 2-week time frame before the onset of the infection were included for analysis. According to our institutional transfusion protocol, hemoglobin concentrations are targeted between 7 and 9 g/dL, unless the attending physician decides to target hemoglobin concentrations greater than 9 g/dL in the presence of ischemic heart disease or cardiogenic shock, by administration of 1 unit at a time. Platelet levels are targeted greater than 10×10^9/L or greater than 50×10^9/L in case of use of aspirin, by administration of 1 unit of five pooled donors at a time.

Continuous data were expressed as mean and SD or as medians and interquartile ranges according to their distribution. Categorical variables were expressed as n (%). For comparisons between patients developing infections versus patients not developing an infection, a Student *t* test was done or a Mann-Whitney *U* test, according to distribution of the variable. To examine the effect of variables on the occurrence of secondary infections, a logistic regression model was built. First, the influence of the sum of RBC and PLT transfusion on the risk of infection was determined. Then, the risk of infection was analyzed separately for RBCs and PLTs. In the separate analysis, the influence of storage time of blood products in relation to the central determinant, i.e., the amount each product transfused, was determined. In both models, the influence of confounding and effect modification from preselected covariates was investigated. The criterion for confounding was a change of 10% or greater in the transfusion coefficient as a consequence of adding a covariate. The criterion for effect modification was a significant *P* value for the interaction term added to the model. Covariates without a confounding effect or effect modification were excluded from the models. $P \leq 0.05$ was considered significant. Statistical analyses were conducted with the use of SPSS 16 (SPSS Inc, Chicago, Ill).

TABLE 1. **Characteristics of sepsis patients with and without a secondary infection**

	Infection		
	No (n = 115)	Yes (n = 19)	*P*
Age, mean (SD), y	56 (18)	52 (16)	0.4
Male sex, n (%)	64 (56)	11 (58)	0.9
APACHE II, median (95% CI)	22 (14–55)	26 (14–47)	0.2
Alcohol abuse, n (%)	9 (8)	1 (5)	0.6
Diabetes, n (%)	28 (24)	5 (26)	0.5
Malignancy, n (%)	15 (13)	6 (31)	0.08
Immune suppressive medication, n (%)	46 (40)	15 (79)	0.002
HIV infection, n (%)	3 (3)	4 (21)	0.008
Receiving SDD, n (%)	75 (65)	18 (95)	0.006

TABLE 2. **Characteristics of sepsis patients who did and did not receive a blood transfusion**

	Transfused		
	No (n = 67)	Yes (n = 67)	*P*
Nosocomial infection, n (%)	3 (4)	16 (26)	0.001
Age, mean (SD), y	58 (17)	54 (18)	0.4
Male sex, n (%)	39 (58)	36 (54)	0.8
APACHE II, median (95% CI)	19 (14–38)	24 (14–42)	0.08
Alcohol abuse, n (%)	8 (12)	2 (3)	0.7
Diabetes, n (%)	16 (24)	17 (25)	0.9
Malignancy, n (%)	2 (3)	19 (28)	0.1
Immune suppressive medication, n (%)	5 (7)	20 (60)	0.001
HIV infection, n (%)	0	7 (10)	0.07
Receiving SDD, n (%)	34 (51)	59 (88)	0.01

RESULTS

During the study period, 134 patients with sepsis diagnosed in the first 24 h of their admission were included. Of these, 19 (14%) developed a secondary bacterial infection. Patient characteristics are shown in Table 1. Nosocomial infections included pneumonia (52%), bacteremia (32%), urinary tract infection (11%), and wound infection (5%). Patients developing an infection more often received immunosuppressive medication and more often had HIV or a malignancy. Of note, the use of SDD was higher in the group developing a nosocomial infection.

Concerning transfusion, 67 (50%) of 134 sepsis patients received a transfusion with 373 cell-containing units, including 271 units of RBCs and 102 units of PLTs. Blood products were given to correct anemia or thrombopenia. Massive hemorrhage did not occur in this population. Transfused patients more often developed a nosocomial infection compared with nontransfused patients (Table 2). Also, transfused patients more

TABLE 3. **Transfusion variables of sepsis patients with and without a secondary infection**

	Infection*		
	No (n = 51)	Yes (n = 16)	*P*
Total units transfused	3 (2–5)	7.5 (2–14)	<0.001
RBC units	2 (2–5)	5.5 (2–7)	0.001
PLT units	0 (0–1)	1.5 (0–4.8)	<0.001
RBC storage time, d	23 (18–25)	21 (14–24)	0.5
RBC storage time >14 d, units	2 (2–4)	2 (1–7)	0.8
PLT storage time, d	3 (2–4)	4 (2–5)	0.5
PLT storage time >4 d, units	1 (1–2)	2 (1–4)	0.2

*All values are expressed as median (IQR).

often received immunosuppressive medication and tended to have a higher APACHE II score compared with nontransfused patients. Of note, SDD was more often administered to transfused patients compared with nontransfused patients. Transfused sepsis patients developing a secondary infection had received a higher amount of total RBCs and PLTs compared with noninfectious transfused controls (Table 3). For both RBCs and PLTs, the median storage time of blood products did not differ between infectious and noninfectious patients. Also, groups did not differ in the amount of transfused RBCs stored more than 14 days or in the amount of transfused PLT units stored for more than 4 days. For those who exclusively received RBCs stored for less than 14 days, the mean number of units did not differ from those who received exclusively RBCs stored for more than 14 days or from those who received mixed units (3.2 [2.6], 3.6 [4.1], and 3.8 [2.4] respectively; $P = 0.93$).

Multivariate logistic regression analyses of the sepsis cohort are shown in Table 4. First, the association between total amount of blood transfusion (transfused RBCs and PLTs taken together) and risk of infection was assessed. Patient-related factors influencing the risk of infection were the use of immunosuppressive medication and SSD, but not the presence of HIV infection or a malignancy. When the model was adjusted for these covariates, we found that the total amount of blood products increased the risk for nosocomial infection with an odds ratio (OR) of 1.15 (95% confidence interval [CI], 1.02–1.28). Then, the effects of transfusion of RBCs and PLTs were analyzed separately (Table 4). The amount of RBCs was a risk factor for the onset of nosocomial infection. Storage time was a confounder for the association of RBCs with infection. When the model was adjusted for storage time, the OR for the onset of infection increased. From the adjusted model, it can be calculated that in patients receiving 4 units of RBCs, the OR for acquiring an infection is 2.46 (95% CI, 1.66–2.60).

TABLE 4. **Multiple logistic regression model for the risk of sepsis patients of acquiring a nosocomial infection after blood transfusion**

Model (Adjusted for)	OR (95% CI)	*P*
Total transfusion		
Total transfusion	1.214 (1.09–1.35)	0.02
Total transfusion (immunosuppression)	1.17 (1.04–1.31)	0.008
Total transfusion (immunosuppression and SDD)	1.15 (1.02–1.28)	0.02
Total RBCs		
Total RBCs transfused	1.26 (1.09–1.45)	0.001
Total RBCs transfused (immunosuppression)	1.18 (1.01–1.37)	0.03
Total RBCs transfused (immunosuppression, SDD, and median storage time RBC)	1.25 (1.04–1.51)	0.02
Total PLTs		
Total PLTs transfused	1.5 (1.15–1.95)	0.003
Total PLTs transfused (immunosuppression)	1.4 (1.08–1.84)	0.01
Total PLTs transfused (immunosuppression and SDD)	1.36 (1.05–1.78)	0.02

The amount of PLTs was also associated with the onset of secondary infection in the adjusted model (Table 4). In patients receiving 4 units of PLT transfusion, the OR for infection is 3.46 (95% CI, 1.23–9.72). Storage time of PLTs was not a confounder for the association between PLT transfusion and the occurrence of infections.

DISCUSSION

This retrospective cohort study identifies an association between the amount of RBCs as well as of PLTs transfused and onset of secondary infection in sepsis patients. Storage time of RBCs appeared to be an important confounding factor in estimating the effect of the amount of RBCs on the risk of infection. These findings suggest that immunomodulatory effects of blood transfusion contribute to adverse outcome in the convalescent phase of sepsis.

To our knowledge, this is the first report describing an association between RBC transfusion and secondary infection in a cohort of sepsis patients. These data are in line with the relation that seems to exist between RBC transfusion and adverse outcome in the critically ill, reviewed in Marik and Corwin (16), although not all reports support this association (20). The presumed mechanisms of the immunosuppressive effect of RBCs are ill-understood. We found that leukoreduced RBCs, which are now widely used in Europe and the United States, are associated with increased risk of secondary infection in sepsis. In accordance, of the 17 randomized controlled trials on the association of nonleukoreduced blood with mortality, a benefit of leukoreduction was found only in cardiac surgery patients (21). This suggests that the immunosuppressive effect is not due to leukocytes in the blood product, but rather to soluble factors or to the aged erythrocyte itself, which undergoes morphological and functional changes during storage. Our findings are in line with a study in trauma patients, reporting a persistent association between RBC transfusion and infection after implementation of leukoreduction (22).

Of interest, storage time of RBCs was a confounder for the risk of infection in this study, suggestive of an increased risk of infection after transfusion of stored RBCs. A number of articles have described an association between storage time of RBCs and adverse outcome, but these reports largely pertain to surgical and trauma patients (7–9, 23–25). In a limited case series of sepsis patients, transfusion of aged packed RBCs was related to increased mortality (10).

This study also identifies an association between the amount of PLTs and increased risk of bacterial infection in sepsis patients. Observational studies that have specifically examined immunomodulatory effects of transfusion of PLTs are limited to cardiothoracic surgery patients and show conflicting results (13–15, 26). Our findings are in accord with Spiess et al. (13), who found that the amount of transfused PLTs was associated with infection, but not with most reports that did not confirm this association (14, 15, 26). Obviously, contrasting results may be related to different patient populations. In sepsis patients, inflammation may have activated the endothelium,

facilitating an interaction with PLTs. Platelets can adhere to inflamed endothelium and capture leukocytes from the circulation. Also, PLTs can directly facilitate adhesion of leukocytes to endothelium (27). Notably, these platelet-leukocyte interactions have been demonstrated out of the context of a platelet transfusion. The mechanisms by which transfused PLTs increase risk of infection remain speculative. Interestingly, platelet-mediated neutrophil recruitment during sepsis (28, 29) is mediated via CD40L derived from PLTs (29). Soluble CD40L, which accumulates during storage of PLT concentrates, has the capacity to activate adherent neutrophils after transfusion (30). Whether this mechanism underlies the association between PLT transfusion and infection remains to be determined. As none of the PLT products were positive on the BacT/Alert monitoring system, we do not think that bacterial contamination of the PLTs contributed to the observed effect.

No association was found between storage time of PLTs and the onset of secondary infection in survivors of sepsis. This finding is in line with previous experiments showing that transfusion of fresh PLTs induced immunomodulating effects, including the production of antibodies, whereas aged PLTs were unable to stimulate antibody production (11).

Concerning patient-related risk factors, the use of immunosuppressive medication was a risk factor for the onset of secondary bacterial infection in survivors of sepsis. Vigilant observation of signs of secondary infections in these patients remains appropriate. Of importance, SDD did not protect against the association between transfusion and nosocomial infection in our sepsis cohort. An explanation may be that secondary infections included all kinds of infections, not only pulmonary infections. Alternatively, use of SDD may indicate prolonged length of ICU stay with concomitant risk of infection, as SDD is administered only to patients expected to be mechanically ventilated for longer than 72 h (31). However, after adjustment of the model for SDD use, the association between transfusion and infection remained. Of note, not all patient-related risk factors for onset of infection were taken into account, including presence of a central venous catheter or use of total parenteral nutrition. Although groups were derived from the same cohort, rendering an even distribution of variables likely, the presence of unadjusted confounding variables cannot be excluded.

This study has limitations. Receipt of larger volumes of blood likely reflects more serious illness and therefore a greater likelihood of any adverse association. Although APACHE score did not differ between the groups with secondary infection compared with noninfectious patients, transfused patients tended to have a higher APACHE II score compared with nontransfused patients, as found before (16). Also, the amount and storage time of transfused blood products are inherently interdependent variables. Observations of associations between transfusion of relatively older blood and morbidity may reflect the effect of transfusion volume rather than blood age. We have tried to capture this interrelation in our logistic model, but study results must be considered in the context of a retrospective design. Also, to be sure of the bacterial infection, we considered only culture-positive infections. The real number of (secondary) infections is possibly higher. Lastly, the sepsis population had a relatively small size of 134 patients. Inclusion of sepsis patients was done using the NICE minimal data set, in which diagnosis is scored 24 h after admission according to the treating physician. Therefore, we may have missed patients. Also, we did not include patients who developed sepsis during their ICU stay. However, to date, this study is the largest sepsis cohort in which transfusion-related risk factors for infection have been studied. Results underline the hypothesis that transfusion of RBCs and PLTs can modulate host response and contribute to adverse outcome in sepsis. In an effort to reduce late mortality from sepsis, this issue needs to be further addressed in experimental settings or in prospective studies.

CONCLUSIONS

Red blood cell and PLT transfusions are independently associated with the onset of secondary bacterial infections in sepsis patients. Red blood cell storage time of more than 14 days influences the risk of infection. Results suggest that immunomodulating effects of blood transfusion result in adverse outcome in critically ill sepsis patients.

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