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The Effects of Red Cell Transfusion Donor Age on Nosocomial Infection among Trauma Patients

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Abstract

Background—We hypothesized that packed red blood cell (PRBC) transfusions from older donors would be associated with fewer nosocomial infections among trauma patients.

Methods—We performed a four-year retrospective analysis of 264 consecutive adult trauma patients who received ≥1 PRBC transfusion during admission. The capacity of donor age to predict nosocomial infection was assessed by logistic regression.

Results—Thirty-three percent of all patients developed a nosocomial infection. Donor age was significantly higher among patients with nosocomial infection (40.3 vs. 37.6 years, $p = 0.035$), and the incidence of infection was directly proportional to donor age. The association between donor age and infection was strongest among recipients age ≥60 years, and was significant on multivariate regression for this cohort (OR 1.07 (95% CI 1.01–1.13), $p = 0.024$).

Conclusions—Among trauma patients receiving PRBC transfusions, blood from older donors may be associated with increased risk for nosocomial infection.

Keywords

Trauma; transfusion; donor; recipient; age; nosocomial infection

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Introduction

Blood loss and anemia are common among patients with traumatic injuries. Severely anemic trauma patients often receive packed red blood cell (PRBC) transfusions to restore hemoglobin levels and oxygen delivery capacity. Unfortunately, PRBC transfusion is also associated with immunomodulation and infectious complications.[1–6] Previous studies have investigated the impact of PRBC storage duration and pre-storage leukoreduction on transfusion-related immunomodulation and post-transfusion morbidity and mortality, leading to the adoption of blood bank policies favoring short PRBC storage duration and universal pre-storage leukoreduction.[1, 7, 8] However, the effects of blood donor age on post-transfusion morbidity and mortality remain unclear. Multicenter studies investigating relationships between donor age and mortality for diffuse patient populations have reported conflicting results,[9, 10] and the effects of blood donor age on nosocomial infection have not been previously reported.

Several pre-clinical studies suggest that the age of a blood donor may affect the immunomodulatory effects of transfused blood. Animal studies have demonstrated that transfusion of aged mice with blood from young mouse donors has significant vascular, muscular, and neurologic effects.[11–13] With advanced age, hematopoietic stem cells lose their full proliferative capacity, and their microenvironment is gradually replaced by fat.[14] Total myeloid cell output is maintained throughout the aging process, whereas lymphocyte production decreases over time.[15, 16] These phenomena may be inconsequential for donated blood that is subjected to pre-storage leukoreduction, which removes nearly all white blood cells, minimizing their physiologic impact and immunosuppressive potential. However, allogenic red blood cells themselves may suppress T-cell receptor expression by an arginase-dependent mechanism, and aging has been associated with decreased erythrocyte arginase production.[17–20] Therefore, it is plausible that PRBCs donated from older subjects may be less immunosuppressive than blood from young donors, leading to fewer infections.

The purpose of this study was to assess the effects of PRBC donor age on nosocomial infections among trauma patients, and therefore whether blood donor age should be considered in blood bank policies regarding allocation of PRBC products. We hypothesized that blood from elderly donors would be associated with fewer infectious complications.

Methods

We performed a retrospective analysis of 264 consecutive adult trauma patients who received one or more PRBC transfusions at our level one trauma center from 6/1/2011 – 10/1/2015. Subjects were identified by searching our institutional research database for adult patients (age ≥ 18 years) who received at least one PRBC transfusion. Patients were excluded if they had burn injuries, were transferred from an outside facility, underwent massive transfusion (≥ 10U PRBC within 24 hours), had unmeasured blood loss unrelated to their injury (e.g. postoperative or gastrointestinal bleeding), or death within 48 hours.

Universal pre-storage leukoreduction was performed at our institution for the duration of the study period. Storage duration and donor age were determined for each PRBC unit

transfused to each patient in the study population. These variables were collected in cooperation with LifeSouth Community Blood Centers, the private institution that supplied our blood products during the study period. All other data was collected from our institutional research database and by retrospective review of the electronic medical record. Hemorrhagic shock was defined as systolic blood pressure < 90 mmHg or lactic acid ≥ 4 mmol/L on admission. Nosocomial infections were assessed from 48 hours after admission to 30 days after discharge. Six percent of all patients had no post-discharge follow-up, and another six percent had follow-up within 30 days but not beyond 30 days. Urinary tract infection (UTI) was defined as a urine culture with $\geq 10^5$ pathogenic colony forming units/mL. Pneumonia was defined as a quantitative bronchoalveolar lavage culture with $\geq 10^4$ pathogenic colony forming units/mL or a clinical diagnosis of pneumonia for a non-intubated patient. Bloodstream infection was defined as ≥ 2/4 bottles positive for likely contaminants (*Staphylococcus epidermidis, Propionibacterium acnes, Bacillus* species, and *Corynebacterium* species) or ≥ 1/4 bottles positive for all other organisms. Deep and organ/space surgical site infection (SSI) was defined according to CDC criteria.[21] Superficial SSIs were not considered due to variability in culture availability and reporting practices.

Statistical analysis was performed with SPSS v23 (IBM, Armonk, NY). Characteristics of the study population were reported as mean (95% confidence interval) or n (%). The difference in blood donor age between patients with and without nosocomial infection was assessed by one-way analysis of variance. Correlations were assessed by Pearson's r. The effects of donor age on nosocomial infection were analyzed by Fisher's Exact test and illustrated in a figure created in GraphPad Prism (v6.05, GraphPad Software, La Jolla, CA). Predictors of nosocomial infection were identified on univariate and multivariate logistic regression. Factors were selected for inclusion in the multivariate model if they were predictive of nosocomial infection on univariate analysis and were not collinear to other variables in the model ($|r| < 0.20$ and $p > 0.05$). Confidence intervals were set at 95% and significance was set at $\alpha = 0.05$.

Results

Patient characteristics, management, and outcome parameters are listed in Table 1. The predominant phenotype was a middle aged patient who sustained moderate-severe blunt injury (age 48 years, 89% blunt trauma, Injury Severity Score 25). On average, patients underwent three operations and received five units of PRBCs. The average PRBC storage duration was 21 days; average PRBC donor age was 38 years. One in three patients developed a nosocomial infection, and 9% had multiple infections. Patients with a nosocomial infection had significantly longer ICU length of stay (15.0 (12.7–17.7) vs. 7.4 (6.3–8.6) days, $p < 0.001$). Inpatient and 180-day mortality were 8% and 11%, respectively. One in ten patients had an unplanned readmission within 30 days, and approximately half of these were related to infectious complications.

Univariate and multivariate predictors of nosocomial infection are listed in Table 2. Mean and maximum blood donor age were each associated with nosocomial infection. Maximum blood donor age was collinear with the total number of PRBCs transfused ($r = 0.55$, $p < 0.001$), whereas mean donor age was not ($r = 0.10$, $p = 0.105$); mean donor age was selected

for further analysis. The incidence of nosocomial infection increased proportional to blood donor age (Figure 1). Mean donor age was significantly higher among patients who developed a nosocomial infection compared to those that did not (40.3 (38.4–42.2) years vs. 37.6 (36.1–39.1) years, $p = 0.035$). This association was strongest among older transfusion recipients (Figure 2).

Mean PRBC donor age was entered into a multivariate logistic regression model with three other factors that were associated with nosocomial infection on univariate analysis: hemorrhagic shock, total number of PRBC units transfused > 24 hours after admission, and Injury Severity Score (Table 2). When controlling for these factors and assessing the entire study population, mean donor age was no longer statistically significant ($p = 0.074$).

Associations between blood donor age and nosocomial infection were stratified by age of the transfusion recipients (Table 3). With increasing age of the transfusion recipient, the correlation between blood donor age and nosocomial infection grew incrementally stronger. The same trend was observed on univariate logistic regression and on multivariate analysis while controlling for hemorrhagic shock, Injury Severity Score, and the number of red cell transfusions administered after 24 hours. Pearson's correlation, univariate odds ratio, and multivariate odds ratio each became statistically significant at recipient age ≥ 50 and were strongest at age ≥ 60.

Discussion

Our data indicate that PRBC transfusions from older donors may be associated with increased risk for nosocomial infections, especially among elderly transfusion recipients. Although the relationship between PRBC donor age and infection became non-significant when controlling for injury severity and transfusion burden, the effect was significant among trauma patients age ≥ 50 years. Although donor age may make a small contribution to transfusion-related morbidity and mortality, this contribution may be clinically significant on a larger scale when applied to blood bank allocation policies. Therefore, this phenomenon warrants further investigation, particularly among elderly transfusion recipients. The observed effect of blood donor age was directly opposed to our hypothesis. Therefore, the mechanisms implicated in generating our hypothesis (fewer immunosuppressive leukocyte products and lower arginase levels in blood from older donors) may have been interpreted and applied erroneously. Delineating the mechanism may be arduous; there are over 250 candidate RBC antigens that may be responsible for the immunosuppressive effects of erythrocytes.[22, 23] Bernard et al.[24] have demonstrated that leukoreduced RBC suppress T-cell proliferation independent of arginine depletion, and proposed direct cell-cell contact as a component of this poorly understood pathway.

PRBC storage duration was not associated with infectious complications. This may be attributable to universal performance of pre-storage leukoreduction during the study period. Previous work has shown that transfusion of PRBCs stored for more than 14 days increases infectious complications following severe injury.[1] However, leukoreduction may abrogate these effects by removing nearly all white blood cells from the donated blood.[7, 8] A randomized control trial has shown a non-significant trend toward decreased infectious

complications for trauma patients receiving leukoreduced blood within 24 hours of injury.[25] The storage duration of transfused PRBCs was similar between groups, and this study may have been underpowered to detect a clinically significant difference in infection rates.[25] Widespread adoption of pre-storage leukoreduction and apparent lack of clinical equipoise based upon several additional advantages of leukoreduction (decreased febrile transfusion reactions, HLA alloimmunization among blood cancer patients, and transmission of leukocyte-borne viruses) undermine the feasibility of a large multicenter prospective trial.[26–28] However, more recent retrospective and prospective observational data from trauma populations support the conclusion that pre-storage leukoreduction attenuates the effects of prolonged PRBC storage.[29, 30]

This study was limited by its retrospective design, proclivity to generate false positive results by making multiple comparisons, and small sample size (n = 264). The false-positive rate was limited as much as possible by making comparisons driven by our hypothesis and by controlling potential confounders on multivariate analysis. This study was performed at a single institution, limiting the generalizability of these findings. Our study population was severely ill, and morbidity and mortality were high. One likely explanation is that we selected a high-risk population by including patients who received a transfusion, therefore excluding most patients who had relatively little injury-related blood loss and ICU-related phlebotomy blood loss, and including patients who were at increased risk for transfusion-related morbidity and mortality. In addition, the presence of invasive catheters and intraoperative hypothermia are associated with increased risk for nosocomial infection, but were not described in this study. Future studies should investigate the relationship between PRBC donor age and nosocomial infection in a larger population, focusing on older transfusion recipients.

Conclusions

Among trauma patients receiving PRBC transfusions, blood from older donors may be associated with increased risk for nosocomial infection, especially among older transfusion recipients. The impact of PRBC donor age on immune function and infectious complications warrants further investigation in experimental and clinical settings. Better understanding of the relationships among blood donor age, transfusion-related immunomodulation, and post-transfusion morbidity and mortality may allow for the formation of more effective blood bank procurement and allocation policies.

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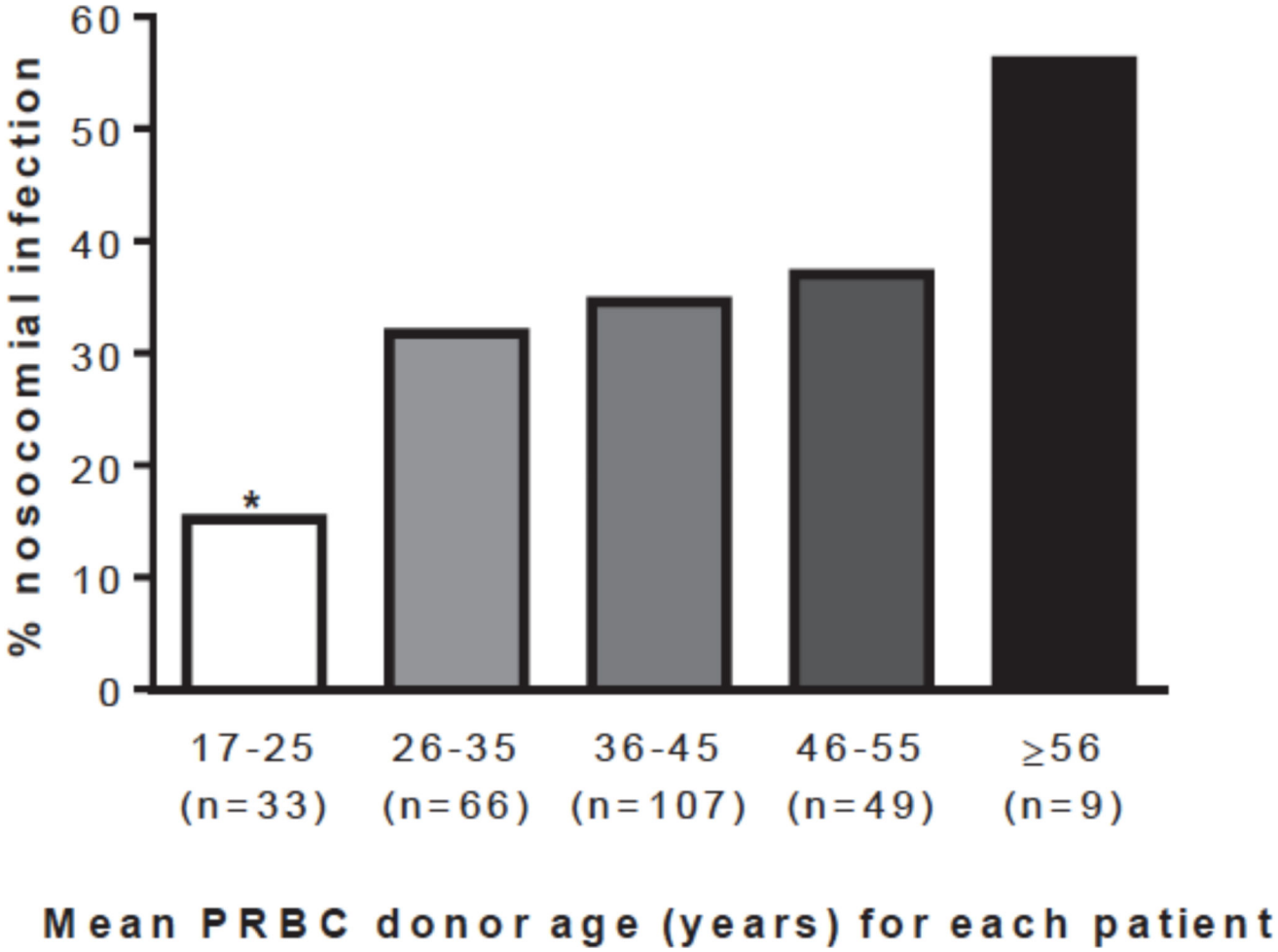

Figure 1.

The incidence of nosocomial infection increased in proportion to blood donor age (PRBC: packed red blood cell, $*p = 0.028$ vs. all other groups combined).

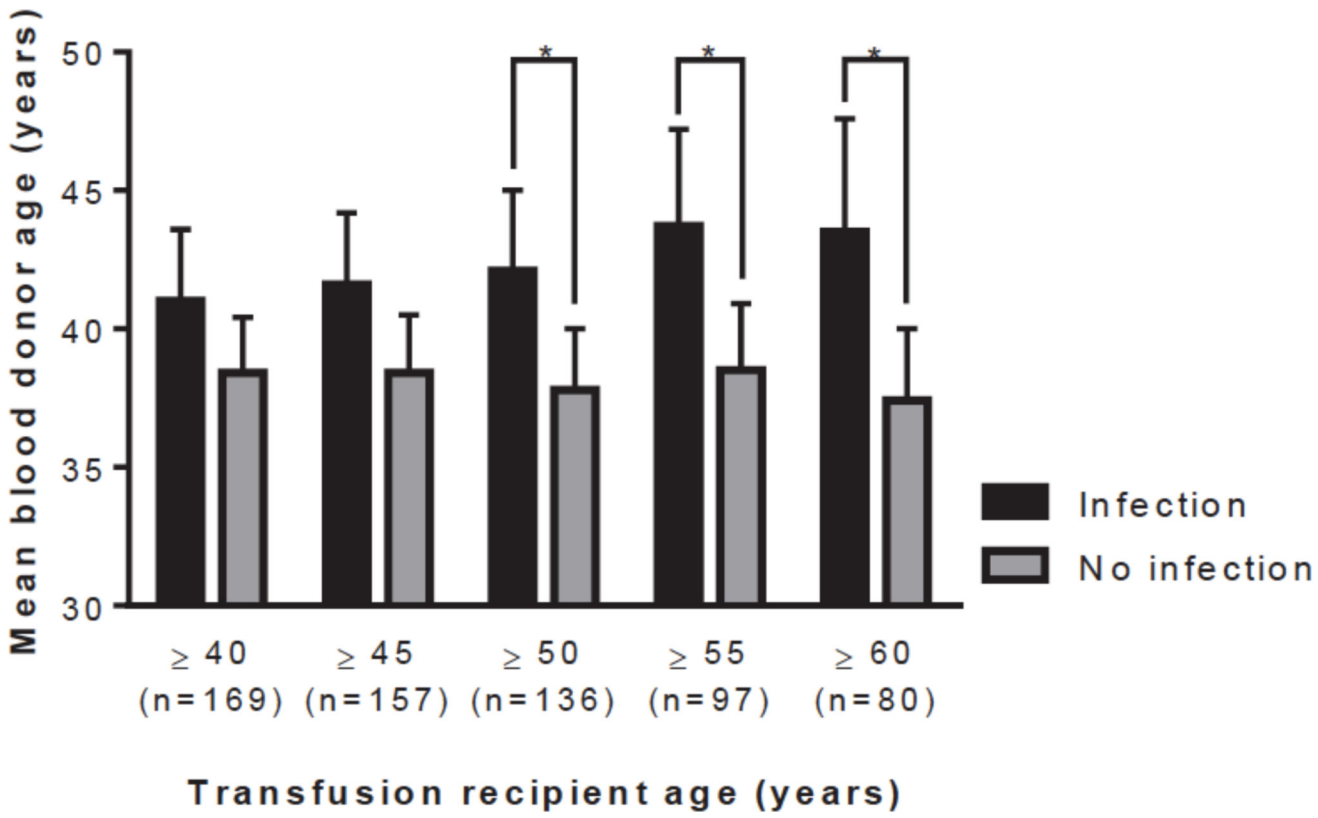

Figure 2.

The difference in blood donor age between recipients with infection versus no infection was greatest among older recipients (PRBC: packed red blood cell, $*p < 0.022$).

Table 1

Patient characteristics, management, and outcomes.

Characteristics, management, and outcomes	n = 264
Age (years)	48 (46–51)
Male	169 (64%)
Charlson comorbidity index	0.6 (0.5–0.8)
Penetrating trauma	29 (11%)
Injury Severity Score	25 (23–26)
On admission	
Heart rate	100 (98–103)
Systolic blood pressure (mmHg)	124 (120–128)
pH	7.29 (7.27–7.30)
Lactic acid (mmol/L)	2.9 (2.7–3.2)
Hemoglobin (g/dL)	11.2 (10.9–11.4)
Hemorrhagic shock[#]	59 (22%)
Number of operations during admission	3.1 (2.8–3.4)
Total PRBC transfusions during admission	5.3 (4.9–5.8)
Received a PRBC transfusion within 24h	154 (58%)
PRBC transfusions within 24h	2.4 (2.1–2.7)
Received a PRBC transfusion after 24h	217 (82%)
PRBC transfusions after 24h	3.0 (2.7–3.3)
PRBC storage duration (days)	21 (20–22)
PRBC donor age (years)	38 (37–40)
Patients who had a nosocomial infection	86 (33%)
Urinary tract infection	41 (16%)
Pneumonia	47 (18%)
Bloodstream infection	16 (6%)
Deep or organ/space SSI	10 (4%)
Hospital length of stay (days)	18 (17–20)
Intensive care unit length of stay (days)	10 (9–12)
Inpatient mortality	20 (8%)
Unplanned readmission within 30 days	26 (10%)
Readmission with infection	12 (5%)
Mortality within 180 days	28 (11%)

PRBC: packed red blood cell,

[#]systolic blood pressure < 90 mmHg or lactic acid ≥ 4 mmol/L.

Data are presented as mean (95% confidence interval) or n (%).

Table 2

Univariate and multivariate predictors of nosocomial infection.

Factor	Univariate OR (95% CI)	*p*	Multivariate OR (95 CI)	*p*
Mean PRBC donor age	1.03 (1.00–1.05)	*0.047	1.03 (1.00–1.05)	0.074
Minimum PRBC donor age	1.01 (0.99–1.04)	0.267		
Maximum PRBC donor age	1.02 (1.00–1.03)	*0.035	*collinear to total transfusions*	
Mean PRBC storage duration	0.99 (0.96–1.03)	0.693		
Minimum PRBC storage duration	0.99 (0.96–1.01)	0.317		
Maximum PRBC storage duration	1.02 (0.99–1.04)	0.171		
Total PRBCs transfused	1.12 (1.04–1.19)	*0.001	*collinear to hemorrhagic shock*	
within 24 hours	1.06 (0.97–1.17)	0.202		
after 24 hours	1.18 (1.07–1.30)	*0.001	1.17 (1.06–1.29)	*0.003
Injury Severity Score	1.03 (1.01–1.06)	*0.004	1.03 (1.01–1.06)	*0.013
Hemorrhagic shock[#]	1.80 (1.09–3.13)	*0.023	2.12 (1.13–4.00)	*0.020

OR: odds ratio, CI: confidence interval, PRBC: packed red blood cell,

[#]systolic blood pressure < 90 mmHg or lactic acid ≥ 4 mmol/L on admission

Table 3

The relationship between blood transfusion donor age and nosocomial infection became stronger with increasing age of the patient who received the transfusion. Multivariate odds ratios (OR) were calculated while controlling for three variables associated with nosocomial infection: hemorrhagic shock, Injury Severity Score, and the number of red cell transfusions administered after 24 hours (CI: confidence interval).

Recipient age (years)	n	Pearson's r	*p*	Univariate OR (95% CI)	*p*	Multivariate OR (95% CI)	*p*
≥ 40	169	0.113	0.145	1.02 (0.99–1.06)	0.146	1.02 (0.98–1.05)	0.342
≥ 45	157	0.147	0.067	1.03 (0.99–1.07)	0.069	1.03 (0.99–1.07)	0.107
≥ 50	136	0.190	0.027	1.04 (1.00–1.08)	0.030	1.04 (1.00–1.08)	0.049
≥ 55	97	0.238	0.019	1.06 (1.01–1.11)	0.023	1.06 (1.01–1.11)	0.027
≥ 60	80	0.278	0.012	1.07 (1.01–1.13)	0.016	1.07 (1.01–1.13)	0.024