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Original Research

CRITICAL CARE MEDICINE

Association of RBC Transfusion With Mortality in Patients With Acute Lung Injury*

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Background: **RBC transfusion has been associated with increased morbidity and mortality in a variety of clinical settings. We assessed the effect of RBC transfusion on in-hospital mortality in patients with acute lung injury (ALI).**

Methods: **Cohort study of 248 consecutive patients with ALI. RBC transfusion was evaluated as both dichotomous and continuous variables, with outcome being in-hospital mortality adjusted for clinical confounders and length of total hospital stay.**

Results: **Overall in-hospital mortality rate was 39.5%. Of these patients, 207 of 248 patients (83.5%) received ≥ 1 U of packed RBCs. The transfusion of any packed RBCs was associated with an increased risk of death (adjusted odds ratio [OR], 3.12; 95% confidence interval [CI], 1.28 to 7.58; $p < 0.001$). The overall OR per unit was 1.06 (95% CI, 1.04 to 1.09; $p < 0.001$) in the complete multivariable model. Transfusion after ALI onset was associated with an adjusted OR of 1.13 (95% CI, 1.07 to 1.20; $p < 0.001$), while transfusion before ALI onset was not associated with higher risk. The adjusted OR per unit of nonleukoreduced RBC transfused was 1.14 (95% CI, 1.07 to 1.21; $p < 0.001$), while the adjusted OR for leukoreduced cells per unit transfused was 1.06 (95% CI, 1.03 to 1.09; $p < 0.001$).**

Conclusions: **Transfusion of RBCs in patients with ALI was associated with increased in-hospital mortality. This risk occurred with RBC transfusion after the onset of ALI, and was greater for nonleukoreduced than for leukoreduced RBCs. Aggressive transfusion strategies in patients with established ALI should be questioned, pending further study.** ***(CHEST 2007; 132:1116–1123)***

Key words: blood component transfusion; blood transfusion; mortality; respiratory distress syndrome, adult

Abbreviations: ALI = acute lung injury; APACHE = acute physiology and chronic health evaluation; ARMA = Acute Respiratory Distress Syndrome Network Low Tidal Volume; CI = confidence interval; OR = odds ratio; TRALI = transfusion-related lung injury

Acute lung injury (ALI) and its more severe presentation, the ARDS, are common and devastating syndromes of acute hypoxemic respiratory failure. Although the incidence of ALI/ARDS was previously thought to be approximately 1.5 to 8.3 per 100,000, more recent literature[1–4] suggests that the incidence of ALI/ARDS is as high as 306 per 100,000 person-years in the oldest age group. Although the mortality rate has decreased in recent years, in part due to a protective lung ventilatory strategy, it remains high at 40%.[5] Thus, ALI may account for 74,500 deaths and 3.6 million hospital days in the United States alone.[4]

Blood transfusion has been implicated in worsening lung injury, and thus may lead to higher mortality. More than 20 years ago, blood transfusion was described as a potential risk factor for the

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development of ALI/ARDS.[6,7] Transfusion has also been associated with increased mortality after coronary artery bypass surgery, increased rate of ventilator-associated pneumonia and nosocomial infection, diminished organ function and increased mortality in

medical critically ill patients, and worsened outcome in burn injury and trauma.[8–23] More recent literature[24–26] shows the risk of ALI/ARDS is increased with transfusion in a medical-surgical population, as well as after trauma and cardiac surgery. In addition to increasing the risk for ALI/ARDS, transfusion may increase the risk of death from it.[27]

The use of liberal transfusion strategies remains widespread despite multiple studies showing that transfusion does not improve outcome in patients receiving ventilation and that outcomes are at least equivalent and may be improved in critically ill patients given fewer transfusions as part of a more conservative strategy.[28–30] In fact, the rate of transfusion and the clinical threshold for transfusion have not significantly changed in the past 10 years.[31]

We hypothesized that blood transfusion was associated with worsened outcome in patients with ALI/ARDS. The purpose of this cohort study was to evaluate the association between the transfusion of packed RBCs and mortality in patients with ALI/ARDS.

Materials and Methods

A single-center, prospective, cohort study was performed including 248 patients with ALI/ARDS admitted between 1999 and 2002 and followed up until death or hospital discharge. The data were collected as part of a prior National Institutes of Health, National Heart, Lung, and Blood Institute Specialized Centers of Research study in ALI/ARDS. Complete blood bank transfusion records were abstracted subsequently without knowledge of ALI/ARDS outcome. All patients >13 years old admitted to the medical or surgical ICUs of the Hospital of the University of Pennsylvania were screened for ALI/ARDS. Those who met American European Consensus Conference criteria[32] were enrolled into the study within 48 h of onset of ALI/ARDS. Patients were excluded if they had current or prior congestive heart failure, respiratory disease, or conditions that mimicked ALI/ARDS, including vasculitis with diffuse alveolar hemorrhage; were burned >30% of total body area; or were lung or bone marrow recipients. The institutional review board for the University of Pennsylvania reviewed and approved this study with waiver of informed consent.

The primary exposure variable, packed RBCs, was evaluated both as a dichotomous variable (any transfusion) and linear variable (total number of packed RBCs transfused). To correct for immortal time bias, the total number of packed RBCs was adjusted for length of stay in all analyses.[33,34] The primary outcome was in-hospital mortality because mortality as a dichotomous outcome is the standard outcome in studying critical illness.[35]

During the time period of the cohort study, several changes in practice occurred. Most notably, the blood bank at our institution had begun administering leukoreduced blood products, and the results of the National Institutes of Health, National Heart, Lung, and Blood Institute ARDS Clinical Trial Network study[36] of lower vs traditionally sized tidal volume ventilatory strategies was published (May 4, 2000). To address the effects of time, we tested our models for calendar date, using linear time adjustment, 365-day epochs, spline, marginal spline, functional cubic form for time, and quadratic time. Nearly all patients in this study who received transfusion of multiple units of packed RBCs received a combination of leukoreduced and nonleukoreduced RBCs. The percentage of leukoreduced products relative to nonleukoreduced also increased over time during the cohort. To assess the impact of leukoreduced and nonleukoreduced products, both were evaluated separately as risk factors, and both variables were included simultaneously in the same logistic regression model.

Furthermore, we sought to investigate whether transfusion of blood products occurring before ALI/ARDS onset had a different effect than transfusion occurring after ALI/ARDS onset. In comparing the association of mortality with RBCs transfused before and after the onset of ALI/ARDS, each was evaluated separately and included simultaneously in logistic regression models. Additionally, the effect of massive transfusion as an etiology of ALI/ARDS was evaluated as a potential confounder of this relationship.

Clinical confounding variables are presented in Table 1. We chose potential confounders based on review of relevant studies of ALI mortality,[37–39] as well as hypotheses regarding effects on transfusion requirement. The effect of these variables on the relationship of RBC transfusion took place in two stages. First, each variable was evaluated individually for effect on the association of RBC transfusion with mortality in logistic regression models. Second, those variables that altered the odds ratio (OR) of RBC transfusion by ≥15% were included in a final multivariable explanatory regression model.[40] All statistical analysis was conducted using statistical software (STATA v.9; StataCorp LP; College Station, TX).

Results

Between 1999 and 2002, 262 consecutive patients met eligibility criteria and were enrolled in the study.

Table 1—*Baseline Characteristics of the ALI Cohort**

Characteristics	Alive (n = 150)	Dead (n = 98)	p Value
Age, yr	45.2 ± 19.0	53.9 ± 17.1	<0.001
Male gender	92 (61)	64 (65)	0.527
Trauma	51 (34)	16 (16)	0.002
APACHE III score	59.5 ± 20.7	80.5 ± 28.0	<0.001
Total length of ICU stay, d	20.3 ± 17.3	12.6 ± 12.9	<0.001
Total length of stay, d	35.6 ± 25.8	17.2 ± 17.5	<0.001
Long-term alcohol use	17 (11)	25 (26)	0.004
Diabetes	16 (11)	21 (22)	0.020

*Data are presented as mean ± SD or No. (%).

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