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Classifying Transfusions Related to the Anemia of Critical Illness in Burn Patients

Joseph A. Posluszny Jr., MD, Peggie Conrad, BSN, Marcia Halerz, BSN, MBA, Ravi Shankar, PhD, and Richard L. Gamelli, MD, FACS

From the Department of Surgery (J.A.P., P.C., M.H., R.S., R.L.G.), Burn and Shock Trauma Institute, Loyola University Medical Center, Maywood, Illinois; and Department of Surgery (J.A.P.), Case Western Reserve University School of Medicine, Cleveland, Ohio.

Abstract

Background—Critically ill patients require transfusions because of acute blood loss and the anemia of critical illness. In critically ill burn patients, typically, no distinction is made between transfusions related to acute surgical blood loss and those related to the anemia of critical illness. We sought to identify the percentage of blood transfusions due to the anemia of critical illness and the clinical characteristics associated with these transfusions in severely burned patients.

Methods—Sixty adult patients with $\geq 20\%$ total body surface area (TBSA) burn who were transfused at least 1 unit of packed red blood cells during their hospitalization were studied. Clinical variables including age, %TBSA burn, Acute Physiology and Chronic Health Evaluation (APACHE) II score, number of ventilator days, inhalation injury, and number of operative events were correlated with the total number of packed red blood cell units and percentage of nonsurgical transfusions in these patients. Nonsurgical transfusions were defined as transfusions occurring after postoperative day 1 for each distinct operative event and were classified as being caused by the anemia of critical illness.

Results—Patients were transfused an average of $16.6 \text{ units} \pm 21.2 \text{ units}$. Nonsurgical transfusions accounted for 52% of these transfusions. APACHE II score, %TBSA burn, number of ventilator days, and number of operative events, all correlated with total transfusions. However, nonsurgical transfusions correlated with only APACHE II score ($p = 0.01$) and number of ventilator days ($p = 0.03$). There was no correlation between nonsurgical transfusions and other clinical variables.

Conclusion—The anemia of critical illness is responsible for $>50\%$ of all transfusions in severely burned patients. The initial severity of critical illness (APACHE II score) and duration of the critical illness (number of ventilator days) correlated with transfusions related to anemia of critical illness. Further investigation into the specific risk factors for these transfusions may help to develop strategies to further reduce transfusion rates.

Keywords

Anemia; Critical illness; Red blood cell transfusion; Burns

The anemia of critical illness afflicts medical and surgical intensive care patients both during their hospitalization¹ and for months later.² The anemia of critical illness is caused by a combination of persistent blood losses and decreased erythropoiesis.³ Blood losses occur

with dressing changes, minor procedures, and phlebotomy, while decreased erythropoiesis stems from decreased erythropoietin response and production, bone marrow dysfunction,⁴⁻⁶ and poor nutrition.⁷ Despite attempts to characterize the causes and burden of the anemia of critical illness,^{3,8,9} this anemia has not been quantified in a strictly surgical population.

Measuring transfusions related to the anemia of critical illness is a challenging task as the exact onset of this anemia is difficult to predict and define. Previous work has suggested that this anemia occurs after 7 days⁸ or 21 days⁹ in medical and surgical intensive care units. Of all the surgical critical care patients, the injury, operative, and prolonged recovery periods of burn patients make them ideal candidates to study the anemia of critical illness. Burn patients suffer possibly the greatest initial hemodynamic and metabolic stress of all critically ill patients, and the duration of their critical illness is often weeks to months. Severely burned patients undergo multiple operative events, at times, over several weeks. As a result, they suffer both the acute blood loss caused by the initial injury and subsequent operations and the anemia of critical illness from prolonged hemodynamic and metabolic derangements both of which require transfusions as a corrective measure.

Because multiple blood transfusions are associated with considerable risk including immune suppression and increased risk of nosocomial infections, measures to reduce transfusions will potentially benefit patient care. Since conditions that necessitate transfusions related to the anemia of critical illness in burn patients are not well defined, we sought to determine the percentage of blood transfused due to the anemia of critical illness in severely burned patients and to identify the clinical factors associated with the anemia of critical illness. This study design proposes a new model to categorize and to quantify transfusions in severely burned patients that will enable strategies to reduce anemia and transfusions and may be applicable to other patient populations.

PATIENTS AND METHODS

Data Collection and Patient Selection

This study is a retrospective review of a prospectively collected database. Secondary use of the Inflammation and Host Response to Injury database, a multicenter study which includes epidemiologic and clinical data from several burn centers, was performed. Burn patients from Loyola University Medical Center (LUMC) were selected from the larger database. Patients were only selected from LUMC to ensure a uniform transfusion threshold and to limit operative variability as previous work has shown considerable differences in transfusion triggers among burn centers.¹⁰ Consent for epidemiologic data retrieval was obtained during the initial prospective collection of these data. Patient data were queried from those with data collected between March 2003 and March 2008. This study was approved by the Institutional Review Board of LUMC.

Although exact hemoglobin concentrations at the time of transfusion are not supplied, our burn unit maintains a strict policy of transfusion for a hemoglobin concentration of 7 g/dL. In addition, no significant changes in our protocol for time to burn wound excision and grafting or operative technique were implemented during this time period. All burn wound excision and skin grafting were performed by one surgeon. The decision to transfuse packed red blood cells (pRBCs) in the operating room was made by the operating burn surgeon using the same thresholds. No transfusions were given immediately before excision and grafting in anticipation of surgical blood loss.

Clinical and epidemiologic data from 71 patients were collected of which 60 patients met the inclusion criteria (Fig. 1). Inclusion criteria included adults (aged >18 years), burn size ≥20% total body surface area (TBSA), survival of at least 10 days postburn, and at least

transfusion of one unit of pRBCs. Exclusion criteria included blunt or penetrating trauma and excessive blood loss from anticoagulant or platelet inhibitor use. Of these 71 patients, 2 were excluded from our analysis because of incomplete data. Eight patients were not transfused. Four of these patients died early in the hospital course (postburn days [PBDs] 5–8) and the remaining four, although requiring excision and grafting, were not transfused (TBSA, 20–24%). One transfused patient was excluded because of extensive blood loss from the wound bed secondary to clopidogrel use. There were no cases of significant gastrointestinal bleeding.

Classification of Time of Transfusion

Most studies on transfusion focus solely on total transfusions and do not differentiate between transfusions related to acute surgical blood loss and the anemia of critical illness. For this study, transfusions related to acute surgical blood loss anemia were defined as those transfusions given in the operating room, on the remainder of the operative day, and on postoperative day 1. This period is considered as the surgical window. The surgical window allows for ample time postoperatively for the correction of acute surgical blood loss. The surgical window is unique to this study and has not been previously validated. Transfusions given outside this surgical window are considered nonsurgical and are considered to be related to the anemia of critical illness. Transfusions given before the first operative event, although rare, were attributed to the acute blood loss anemia. In addition, the number of transfusions given after the last surgical window was collected to illustrate the length of time after the last surgical window for which transfusions are still necessary.

Collection of Clinical Variables

Clinical data collected included age, %TBSA burn, Acute Physiology and Chronic Health Evaluation (APACHE) II score within 24 hours of admission, number of ventilator days, presence or absence of inhalation injury, number of operative events, additional clinical factors that may contribute to blood loss, survival, cause of death, and PBD of death. Inhalation injury was diagnosed via bronchoscopy and was not graded for these purposes.

Statistical Analysis

Linear correlation through the Pearson correlation coefficient was used to compare clinical and transfusion variables. To gauge the range of values for which transfusion data may change, these clinical variables were divided into groups of approximately equal thirds. This classification scheme is listed in Table 1. Data are reported as mean $\pm$ standard deviation, and significance was attributed to $p < 0.05$. Statistical analysis was performed using SAS Software (SAS Institute, Cary, NC).

RESULTS

Patient Data, Clinical Variables, and Infection Profile

For the 60 patients included in this analysis, the average age was 45 ± 16 years. Twenty-two patients were women and 38 were men. Eighty-two percent (49 of 60) of the patients survived. The mean %TBSA burn was $39.8\% \pm 16.1\%$. The mean APACHE II score was 21.8 ± 9.4 . Forty-eight percent (29 of 60) of the patients had an inhalation injury diagnosed by bronchoscopy. Eighty percent (48 of 60) of patients were intubated at some point during their hospitalization. For patients who were intubated, the average number of ventilator days was $35.3 \text{ days} \pm 37.7 \text{ days}$. The average length of hospitalization was $55.8 \text{ days} \pm 46.7 \text{ days}$. Patients went to the operating room for excision and grafting 3.0 ± 3.0 times during their hospitalization.

Transfusion Profile

A total of 996 units of pRBCs were transfused to these 60 patients. The mean number of units of pRBCs transfused per patient was $16.6 \text{ units} \pm 21.2 \text{ units}$ with a range of 1 unit to 135 units. Forty-eight percent (478 of 996) of all units of pRBCs were transfused within the surgical window and 52% (518 of 996) outside the surgical window. Thirty-eight percent (383 of 996) of all units were transfused during the operative event. Approximately 10% of all transfusions occurred on postoperative day 1. By expanding the time attributed to surgical blood loss from the operating room time period to the surgical window ensures that these additional 10% of transfusions are assigned to the acute surgical blood loss anemia rather than the anemia of critical illness.

On average, the last transfusion was administered on PBD 44.0 ± 43.1 . Seventeen percent of all units were transfused after the last surgical window. The average number of days after the last surgical window that a patient was transfused was $18.5 \text{ days} \pm 9.6 \text{ days}$. Sixty-one percent (30 of 49) of patients who survived to discharge were transfused after the last surgical window. For those patients who survived to discharge, $15\% \pm 21.2\%$ of all blood was transfused after the last surgical window.

Clinical Variables

The relationship between the five parametric clinical variables examined (age, %TBSA burn, APACHE II score, number of ventilator days, and number of operative events) was measured using linear correlation (Table 2). As expected, the %TBSA burn correlated closely with number of operative events. Interestingly, the extent of the thermal injury (%TBSA burn) did not correlate with APACHE II score. The number of ventilator days correlated with %TBSA burn, APACHE II score, and number of operative events. Age did not correlate with any other variable.

Clinical Variables and Transfusions

All clinical variables (%TBSA burn, APACHE II score, number of ventilator days, and number of operative events) except age and inhalation injury were significantly correlated to total transfusions. However, the percentage of nonsurgical transfusions were only correlated to APACHE II score ($p = 0.01$) and number of ventilator days ($p = 0.03$; Table 3).

The relationship between transfusions and the different measures of these clinical variables are summarized in Figure 2, A and B. In general, these comparisons match the linear correlation data mentioned above. The total units transfused significantly increases with increasing %TBSA burn, number of ventilator days, and presence of an inhalation injury. For patients with mild APACHE II scores, the total transfusions were significantly less than for patients with moderate or severe scores. As expected, total transfusions also increased with number of operative events.

The percentage of nonsurgical transfusions was significantly increased with higher APACHE II scores and number of ventilator days. Although there was a trend, the percentage of nonsurgical transfusions did not significantly differ based on %TBSA burn, inhalation injury, or number of operative events.

DISCUSSION

In this study, the surgical window of operative day plus 1 postoperative day delineated transfusions related to the acute surgical blood loss anemia and the anemia of critical illness. By using this classification scheme, 52% of all transfusions are related to the anemia of critical illness, and these transfusions correlated with APACHE II score and number of

ventilator days. However, total transfusions are associated with %TBSA burn, APACHE II score, number of ventilator days, and number of operative events. Taken together, total transfusions are associated with the cutaneous injury and the critical illness, whereas transfusions specifically related to the anemia of critical illness are associated with the initial severity of injury (APACHE II score) and duration of the critical illness (number of ventilator days).

Our use of the surgical window of operative day plus one postoperative day as the basis for delineating transfusions attributable to acute surgical blood loss versus anemia of critical illness is subjective. Obviously, transfusions on the operative day are because of acute surgical blood loss. The addition of one postoperative day should allow enough time for equilibration of hemoglobin concentration from surgical blood loss and after the respective transfusions. In fact, the initial hemoglobin concentration increase after transfusion should persist for up to 24 hours if there is no additional blood loss.^{11,12} Some overlap between transfusions associated with each anemia surely exists, especially given the multiple operative events that these patients undergo. Despite this, our classification scheme brings to light the high percentage of total transfusions that are not temporally related to surgical blood loss. In fact, the correlation between clinical variables and type of transfusion supports this classification as transfusions related to the anemia of critical illness correlated with indicators of critical illness, whereas the remaining transfusions correlated with the degree of the cutaneous injury and subsequent surgical care.

Transfusion rates associated with acute surgical blood loss anemia have decreased with the incorporation of surgical techniques including tourniquet placement^{13,14} and subdermal tumescence with vasoconstricting agents.^{15,16} Overall transfusion rates have also declined with stricter transfusion thresholds.^{17,18} Still, in our population, 16.6 units of pRBCs were transfused per patient. Because 52% of these transfusions are related to the anemia of critical illness, further study into the causes and possible prevention of this anemia is essential to reduce overall transfusions.

The anemia of critical illness is a complex, multifactorial phenomenon.^{19,20} Some data suggest that erythropoiesis in the bone marrow is dampened after a burn injury, leading to a decrease in overall erythrocyte production.^{4,5} Studies in the critical care literature indicate that blood loss from phlebotomy may contribute as well.²¹⁻²³ For the burn population, blood is lost with dressing changes, although this has not yet been quantified. Taking into account these known contributors to the anemia of critical illness and those factors that still remain unknown easily demonstrates its multifactorial nature. In fact, the diverse mechanisms for the anemia of critical illness will probably make therapeutic interventions difficult and cumbersome. Our findings recognize the high rate of these transfusions providing an impetus for their study and provide a method of quantifying these transfusions allowing for measurement of interventions and prevention methods.

Our study is limited because of its retrospective nature, small sample size, and single-institution design. Given our findings, further prospective studies with a larger sample size that includes details of phlebotomy, fluid resuscitation volumes, blood loss because of dressing changes, and measures of erythropoiesis are needed to better delineate the causes of anemia of critical illness. Moreover, such studies are essential in our ability to find alternate methods to decrease the transfusion rate in these patients. As an advantage, one burn surgeon operating on all patients and dictating transfusion decisions ensured consistent clinical decision making, which would be otherwise eliminated with a larger, multicentered trial. In fact, despite modifications to transfusions thresholds over the past 20 years,^{17,24,25} resulting in the general acceptance of transfusing to maintain a hemoglobin of 7 g/dL, transfusion thresholds still differ between burn centers.¹⁰ Our strict thresholds and operative

strategies eliminate the profound and unforeseen confounding effects of differing transfusion thresholds and operative techniques.

In conclusion, more than half of all transfusions are administered because of the anemia of critical illness in severely burned patients when using a surgical window of operative day plus one postoperative day to distinguish between transfusions related to acute surgical blood loss anemia and the anemia of critical illness. Given the association between transfusion of pRBCs and immune suppression and increased nosocomial infection risk, further work delineating the causes of the anemia of critical illness may help to reduce overall transfusions and possibly improve patient outcome.

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Figure 1. Study design. Excluded and included patients and transfusion data of included patients are shown.

Figure 2.

Correlation between transfusion and clinical variables (A) Total transfusions administered to patients based on clinical variables. $p < 0.05$ for $a = \% \text{ TBSA}$ high v. low and high v. medium, $b = \text{APACHE II score}$ mild v. moderate, and mild v. severe, $c = \text{number of ventilator days}$ low v. medium, low v. high and medium v. high, $d = \text{inhalation injury}$ no v. yes, $e = \text{number of operative events}$ low v. high and medium v. high. (B) Percentage of non-surgical transfusions administered to patients based on clinical variables. $p < 0.05$ for $a = \text{APACHE II score}$ mild v. moderate; $b = \text{mild v. severe}$, $c = \text{moderate v. severe}$, $d = \text{number of ventilator days}$ low v. high, $e = \text{medium v. high}$.

TABLE 1

Classification of Clinical Variables Into Approximately Equal Thirds

Clinical Variable	Classification
%TBSA burn	Low: 20–29 Medium: 30–44 High: >45
APACHE II score	Mild: 5–17 Moderate: 18–27 Severe: 28–41
No. ventilator days	Low: 0–9 Medium: 10–39 High: >40
Inhalation injury	No: absent Yes: present
No. operative events	Low: 0–1 Medium: 2–3 High: >4

TABLE 2
Relationship Between Clinical Variables Using Linear Correlation With the Pearson Correlation Coefficient

	Age	%TBSA Burn	APACHE II	No. Ventilator Days
Age				
%TBSA burn	0.05; -0.26 (0.67)			
APACHE II	0.06; 0.25 (0.06)	0.25; 0.15 (0.02)		
No. ventilator days	0.83; 0.03 (0.001)	<0.001*; 0.59 (0.35)	0.0001*; 0.48 (0.23)	
No. OR events	0.77; 0.04 (0.001)	0.0009*; 0.42 (0.18)	0.06; 0.24 (0.06)	0.0009*; 0.42 (0.17)

Data are supplied as *p* value; Pearson correlation coefficients and (*r*²) values
* *p* < 0.05.

TABLE 3

Linear Correlation Between Total Transfusions and Percentage of Nonsurgical Transfusions and Clinical Variables

	Total Transfusions	Percentage of Nonsurgical Transfusions
Age	0.24; -0.15 (0.02)	0.08; 0.23 (0.05)
%TBSA burn	<0.0001 [*] ; 0.58 (0.33)	0.75; 0.04 (0.002)
APACHE II score	0.008 [*] ; 0.34 (0.12)	0.01 [*] ; 0.32 (0.10)
No. ventilator days	<0.0001 [*] ; 0.81 (0.65)	0.03 [*] ; 0.28 (0.08)
Inhalation injury	0.49; -0.13 (0.02)	0.36; -0.17 (0.03)
No. operative events	<0.0001 [*] ; 0.64 (0.41)	0.44; 0.10 (0.01)

Data are supplied as p value; Pearson correlation coefficients and (r^2) values.

^{*}
 $p < 0.05$.