PAPER

Increased Rate of Infection Associated With Transfusion of Old Blood After Severe Injury

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Hypothesis: Blood components undergo changes during storage that may affect the recipient, including the release of bioactive agents, with significant immune consequences. We hypothesized that transfusion of old blood increases infection risk in severely injured patients.

Design: Prospective cohort study.

Setting: Urban level I regional trauma center.

Patients: Sixty-one trauma patients with an Injury Severity Score greater than 15, age older than 15 years, and survival longer than 48 hours who were transfused with 6 to 20 U of red blood cells in the first 12 hours after injury were studied. By means of blood bank records, the age of each unit of blood was determined.

Intervention: Transfusion of allogeneic red blood cells.

Main Outcome Measurements: Major infectious complications.

Results: The early (<12 hours) transfusion requirement was 12±0.6 U, with a mean age 27±1 days. Major infections developed in 32 patients (52%). Age and Injury Severity Score were not significantly different between patients who developed infections and those who did not (age, 39±4 vs 36±3 years; Injury Severity Score, 33±1.5 vs 29±1.5). Transfusion of older blood was associated with subsequent infection; patients who developed infections received 11.7±1.0 and 9.9±1.0 U of red blood cells older than 14 and 21 days, respectively, compared with 8.7±0.8 and 6.7±0.08 in patients who did not develop infections (both $P<.05$, *t* test). Multivariate analysis confirmed age of blood as an independent risk factor for major infections.

Conclusions: Transfusion of old blood is associated with increased infection after major injury. Other options, such as leukocyte-depleted blood or blood substitutes, may be more appropriate in the early resuscitation of trauma patients requiring transfusion.

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SINCE 1973, when Opelz et al[1] first described improved renal allograft survival in patients who received stored blood, allogeneic blood transfusion has been recognized as having clinically significant immunomodulatory effects. Increased risk of cancer recurrence after surgical resection and postoperative infections are 2 adverse effects frequently associated with blood transfusion.[2-4] The mechanisms responsible for transfusion-related immune alterations have not been completely elucidated. Various bioactive substances accumulate during storage of red blood cells (RBCs), including cytokines, histamine, and proinflammatory lipids.[5-7]

Our Trauma Research Center has investigated the relationship between allogeneic blood transfusion and circulating neutrophils. In trauma patients receiving early blood transfusions, neutrophils are primed for superoxide and elastase release within 12 hours of injury.[8] After 24 hours, neutrophil function is depressed for several days, potentially placing patients at risk for infectious complications. These neutrophil derangements are attenuated by using a blood substitute, devoid of any immune modulating properties, in lieu of stored blood.[9] Silliman et al[10] demonstrated that routine storage of whole blood and packed RBCs resulted in accumulation of agents within the plasma fraction that significantly primed the neutrophil nicotinamide adenine dinucleotide phosphate oxidase system. The authors subsequently identified the responsible mediators to be proinflammatory lipids, in particular lysophosphatidylcholines.[11] Moreover, the ability of stored RBC plasma to prime neutrophils is related to the duration of storage. The effect is not significant until after

PATIENTS AND METHODS

PATIENT POPULATION

Since 1992, we have maintained a prospective database (MOF database) of injured patients admitted to the trauma intensive care unit of our level I trauma center who are at high risk of developing MOF. Inclusion criteria include an Injury Severity Score (ISS) greater than 15, age older than 15 years, and survival longer than 48 hours. Patients transferred from another facility are excluded if the transfer occurs more than 24 hours after injury. The care of these patients is directed by existing protocols and supervised by 5 general surgeons with expertise in trauma and critical care. All patients are prospectively identified and followed up until death or discharge.

Sixty-one patients were identified who were transfused with between 6 and 20 U of allogeneic packed RBCs within the first 12 hours after injury. By means of blood bank records, the duration of storage before transfusion (age, in days) of each unit was determined.

PRIMARY OUTCOME

Patients were monitored for the development of infectious complications, which were categorized as either major or minor. Major infections included pneumonia, empyema, lung abscess, abdominal or pelvic abscess, extensive wound infection, meningitis, and other major infections.

Pneumonia was diagnosed on the basis of the following criteria: (1) infiltrate on plain radiograph persistent for more than 48 hours; (2) temperature higher than 38°C; (3) sputum gram stain showing many polymorphonuclear leukocytes; (4) leukocytosis (white blood cell count >12 000/μL) or leukopenia (white blood cell count <4000/μL); (5) blood culture positive for the same pathogen noted on sputum culture; (6) bronchoalveolar lavage quantitative culture with pathogen growth greater than 10^3 colony-forming units/mL; and (7) histopathologic diagnosis (autopsy or open lung biopsy). Pneumonia was defined as one of the following combinations of these criteria: criterion 1 plus criterion 5; criterion 1 plus at least 2 of criteria 2, 3, and 4; or criterion 1 plus criterion 6 plus at least 1 of criteria 2, 3, 4, and 7. Pneumonia was excluded if there was clinical resolution without antimicrobial therapy or when an alternative diagnosis was established (clinically or at autopsy).

Lung abscess was diagnosed on the basis of clinical and radiographic evidence. Empyema and abdominal abscesses were defined as purulent fluid collections requiring drainage. Major wound infections were those that required operative debridement. Meningitis was diagnosed by Centers for Disease Control and Prevention criteria.[16] Other infections were classified as major if they were associated with septic shock (for example, urosepsis).

STATISTICAL ANALYSIS

The MOF database is maintained on an IBM personal computer (IBM, White Plains, NY) with the use of Microsoft Access 97 software (Microsoft Corp, Redmond, Wash). Data were analyzed with SPSS 10.1 for Windows (SPSS Inc, Chicago, Ill). Univariate analysis was performed with the χ^2 test or Fisher exact test for categorical data and *t* test for normally distributed continuous variables. The Mann-Whitney test was used for nonnormally distributed continuous variables.

Multiple logistic regression analysis was performed to assess age of transfused blood as an independent risk factor for postinjury infections after controlling for other risk factors such as patient age, mechanism of injury, and ISS. $P<.05$ was considered significant. Continuous data are shown as mean±SEM.

2 weeks of storage and is maximal at out date of each component (42 days).[7,10] Furthermore, plasma from 42-day-old RBCs induced tissue damage in an isolated, perfused rat lung model, whereas fresh RBC plasma did not.[12]

The clinical significance of the length of storage of blood before transfusion has not been well studied. Vamvakas and Carven[13] reported an association between the storage length of transfused allogeneic blood and the development of pneumonia after coronary artery bypass surgery. Purdy and colleagues[14] observed that critically ill septic patients who died were transfused with older blood than patients who survived. Recently, our group confirmed that transfusion of aged stored RBCs after severe injury was associated with the development of multiple organ failure (MOF).[15]

The purpose of the present study was to investigate the relationship between storage time of transfused blood and infection after severe injury. We hypothesized that early transfusion of old blood after severe injury increases the risk of subsequent major infections.

RESULTS

Sixty-one patients were given a total of 732 U of packed RBCs within the first 12 hours after injury, for a mean early transfusion requirement of 12±0.6 U. Mean age and ISS were 37±2 years and 31±1, respectively; 49 (80%) of patients were male and 38 (62%) suffered blunt injury. The mean age of each unit of RBCs transfused was 27±1 days.

Thirty-two patients (52%) developed 44 major infections. Pulmonary infections were most common, occurring in 27 patients (pneumonia in 26 and empyema in 1). Intra-abdominal abscesses developed in 5 patients, complicated skin structure infections in 3, and other infections in 9. Eleven patients experienced more than 1 major infection during their course in the intensive care unit. The initial infection occurred a mean of 6±1 days after injury.

There was no difference in patient age, sex, or injury severity between patients who did and did not develop major infections (**Table 1**). Similarly, mechanism of injury, worst base deficit, and worst serum lactate level within the first 12 hours of injury were not different between patients with and without subsequent infections. Total transfusion requirement in the first 12 hours, however, was higher in patients who developed infections (12.8±0.9 U vs 10.4±0.8 U; $P=.04$, Mann-Whitney test).

Patients who developed major infections received a significantly greater amount of old packed RBCs

Table 1. Selected Patient Data Stratified by Presence or Absence of Infection*

	Major Infection	No Infection	*P* Value
Patient age, y	39 ± 4	36 ± 3	.48†
Sex, No. M/F	25/7	24/5	.75‡
Injury Severity Score	33 ± 2	29 ± 2	.12§
Mechanism of injury, No. blunt/penetrating	22/10	16/13	.30‡
Base deficit, mEq/L	10.3 ± 1	10.1 ± 1	.89§
Serum lactate, mmol/L‖	5.3 ± 0.5	4.3 ± 0.4	.15§
PRBCs transfused in the first 12 h	12.8 ± 0.9	10.4 ± 0.8	.04†

*Values are mean ± SEM unless otherwise specified. PRBCs indicates packed red blood cells
†Mann-Whitney test.
‡χ^2 Test.
§*t* Test.
‖To convert to milligrams per deciliter, divide by 0.111.

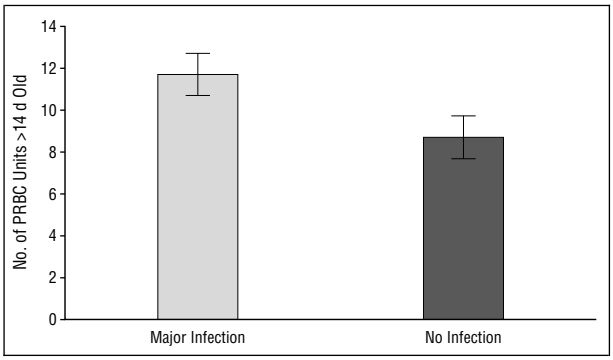

Figure 1. Number of packed red blood cells (PRBCs) more than 14 days old in patients who developed major infections after injury vs those who did not. Patients who did develop major infections received significantly more units (*P*=.02, *t* test).

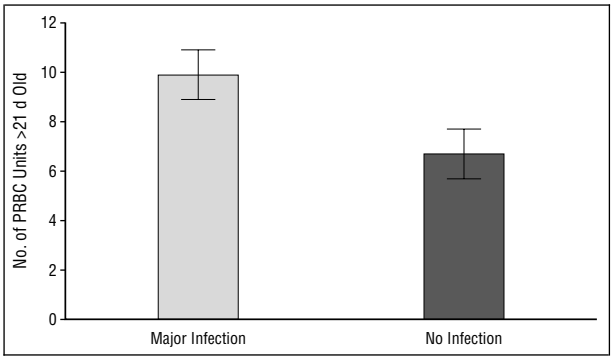

Figure 2. Number of packed red blood cells (PRBCs) more than 21 days old in patients who developed major infections after injury vs those who did not. Patients who did develop major infections received significantly more units (*P*=.02, *t* test).

(**Figure 1** and **Figure 2**). Multivariate analysis confirmed that the number of units transfused that were older than 14 days and older than 21 days were independent risk factors for major infections after controlling for patient age, ISS, sex, and mechanism of injury (**Table 2**). For each transfused unit of RBCs more than 14 days old, the risk of a major infection increased 13%.

These logistic regression models did not adjust for total RBC transfusions because of significant collinearity between the total number of RBC units transfused and the number of units greater than 14 and 21 days old. Regression models incorporating variables with near collinearity may yield unreliable or impossible results. Analysis after stratification by total transfusion requirement avoids this problem (**Table 3**). In the subgroup receiving 6 to 10 U of packed RBCs, patients developing major infections received more RBCs greater than 14 days old. Similarly, patients receiving 16 to 20 U and developing a major infection received significantly more RBCs greater than 21 days old. No differences were seen in patients receiving 11 to 15 U; however, the groups were small, limiting the power of detecting any differences between them.

Table 2. Multivariate Analysis Results*

Variable	Odds Ratio (95% Confidence Interval)	*P* Value
Model 1		
Patient age, y	1.01 (0.98-1.04)	.54
Sex	0.805 (0.19-3.42)	.77
Mechanism	0.628 (0.18-2.24)	.47
Injury Severity Score	1.044 (0.97-1.12)	.24
No. of Units >14 d Old	**1.127 (1.01-1.26)**	**.03**
Model 2		
Patient age, y	1.007 (0.98-1.04)	.67
Sex	0.95 (0.22-4.05)	.94
Mechanism	0.565 (0.16-2.03)	.38
Injury Severity Score	1.037 (0.96-1.11)	.32
No. of Units >21 d Old	**1.13 (1.00-1.27)**	**.04**

*Boldface type indicates statistical significance.

Table 3. Results Stratified by Total RBC Transfusion Requirement*

	Infection	No Infection	*P* Value
Total RBCs: 6-10 U (n = 34)			
Total RBCs	8.5 ± 0.40	7.7 ± 0.34	.12
RBCs >14 d old	7.8 ± 0.60	5.9 ± 0.60	.04
RBCs >21 d old	6.6 ± 0.72	4.8 ± 0.81	.11
Total RBCs: 11-15 U (n = 12)			
Total RBCs	13.5 ± 0.5	13.1 ± 0.5	.67
RBCs >14 d old	10.5 ± 3.5	12.5 ± 0.6	.44
RBCs >21 d old	8 ± 3	11.4 ± 0.8	.19
Total RBCs: 16-20 U (n = 15)			
Total RBCs	18.3 ± 0.6	19.3 ± 1.2	.46
RBCs >14 d old	17.4 ± 1	15 ± 2.9	.33
RBCs >21 d old	15 ± 1.4	7.3 ± 1.3	.02

*Values are mean ± SEM. RBC indicates red blood cell.

COMMENT

The use of blood transfusion dates back to the mid-17th century.[17] By the early 1900s, blood transfusion emerged as a standard of clinical practice that was perceived as relatively free of risk. The value of blood transfusion was largely unchallenged until the early 1980s, when transfusion-related transmission of diseases, particularly human immunodeficiency virus infection, became a huge

Table 4. Selected Changes Characteristic of the "Storage Lesion" and Their Consequences*

Storage Effects	Consequences
Decreased 2,3-diphosphoglycerate	Increased oxygen affinity and decreased oxygen unloading by hemoglobin
ATP depletion	Erythrocyte shape changes Increased osmotic fragility Decreased deformability
Microvesiculation and loss of lipid membrane	Decreased erythrocyte viability
Lipid peroxidation	Cellular injury and death
Bioactive substance generation	
Neutrophil/platelet enzymes	Febrile transfusion reactions
Histamine	Neutrophil priming/endothelial activation
Cytokines	Cellular injury/monocyte priming
Arginase	Transfusion-related acute lung injury
Lipids	Possible multiple organ failure

*ATP indicates adenosine triphosphate.

public health concern.[18-20] Intense scrutiny and evaluation of transfusion practice and its risk-benefit balance followed. Clearly, the view of blood transfusion as risk free is no longer valid. Adverse consequences of RBC transfusion include hemolytic and nonhemolytic transfusion reactions, transmission of infectious agents, transfusion of contaminated RBCs, and transfusion-mediated immunomodulation.

The first indication that immunomodulation secondary to allogeneic blood transfusion existed in humans was reported more than 25 years ago, when Opelz et al[1] observed improved renal allograft survival with pretransplant allogeneic RBC transfusions. Recently, Opelz et al[21] reaffirmed a clear improvement in renal allograft survival with allogeneic blood transfusion in the modern era of immunosuppressive therapy. Moreover, allogeneic blood transfusion–associated immunosuppression has been associated with a decreased recurrence rate of spontaneous abortion in affected women[22] and a reduced clinical relapse rate in patients with chronic inflammatory bowel disease.[23,24] It has also been argued that immunosuppressive effects of allogeneic blood transfusion might adversely affect the outcome of patients undergoing curative operation for malignancy.[24] In addition, several clinical studies demonstrated that allogeneic transfusion is an independent risk factor for postoperative bacterial infections.[25,26] In many of these studies, transfusion is the most significant factor predicting postoperative infection. The reported prevalence of bacterial infection in patients receiving allogeneic transfusion ranges from 20% to 30%, compared with 2% to 10% in those not transfused or receiving autologous blood.[25-27]

The mechanisms responsible for the observed immunologic effects of allogeneic blood transfusion remain unclear. It is generally accepted that "passenger leukocytes" present in RBCs are critical elements involved in transfusion-related immunomodulation.[28] In a prospective randomized trial, Jensen et al[26] demonstrated that transfusion with leukocyte-depleted allogeneic RBCs significantly reduced the occurrence of bacterial infection after operation for colorectal carcinoma.

The advancement of transfusion medicine as a specialty has paralleled our ability to store blood ex vivo in its liquid state. As storage techniques have improved and extended the storage period up to 42 days, there has been a shift from focusing on maintaining RBC viability to including the quality of transfused RBCs as well. Recently, the effects of blood storage have come under renewed scrutiny.[29,30]

The *storage lesion* has been defined as the constellation of changes, including metabolic, biochemical, and molecular changes, occurring to the RBC during storage, which eventually results in irreversible damage and ultimately limits the storage duration.[29] Although the term has traditionally been restricted to corpuscular damage, recent evidence shows that a number of bioreactive substances accumulate in the medium during storage.[6,10,31] Selected changes characteristic of the storage lesion and their potential consequences are listed in **Table 4**.

Our group has been particularly interested in the relationship between blood transfusion and systemic neutrophil priming. Silliman et al[7,10] demonstrated that, during routine storage of whole blood and packed RBCs, agents were generated that significantly primed the nicotinamide adenine dinucleotide phosphate oxidase system. This effect was not significant until after 2 weeks of storage and was maximal by out date of each component. The authors subsequently showed that this effect was largely due to accumulation of proinflammatory lipids, in particular lysophosphatidylcholines.[11]

Despite the relative wealth of data regarding the changes related to storage of blood products, evidence of clinical significance has been sparse. As noted earlier, multiple studies now document adverse effects of allogeneic blood transfusion. The relationship between these adverse effects and the age of transfused blood, however, has not been adequately studied.

Red blood cell transfusions are frequently advocated to increase oxygen delivery in critically ill patients.[32-34] The immediate effectiveness of this therapy to increase systemic oxygen uptake is questionable, since storage depresses the ability of RBCs to deform as well as unload oxygen peripherally.[35,36] Since 2,3-diphosphoglyceric acid and deformability recover in vivo after transfusion, one would expect to see a delayed increase in systemic oxygen consumption after RBC transfusion. Marik and Sibbald,[37] however, noted no improvement in systemic oxygen consumption for up to 6 hours after transfusion. Moreover, these authors noted an unexpected decrease in gastric intramucosal pH (measured by gastric tonometry) after transfusion with blood stored for longer than 15 days. They suggest that transfusion of old, poorly deformable RBCs leads to microcapillary sludging and obstruction resulting in gut ischemia.

In light of the potential for transfusion of stored RBCs to adversely affect oxygen delivery and uptake, Purdy and colleagues[14] studied the relationship between age of transfused blood and survival in critically ill septic patients. The authors retrospectively studied 31 patients admitted to their intensive care unit with severe sepsis. The

number of units of packed RBCs transfused and the age of each unit was determined by means of blood bank records. There was no difference between survivors (n=12) and nonsurvivors (n=19) in age, sex, length of intensive care unit stay, incidence of septic shock, Acute Physiology and Chronic Health Evaluation II score, or total number of packed RBCs transfused. Nonsurvivors, however, were given significantly older RBCs (median, 24 days vs 21 days in survivors). Moreover, survivors were given a greater proportion of RBCs less than 10 days old (85%), while nonsurvivors received a greater proportion of RBCs greater than 20 days old (76%).

Our results are consistent with the findings of Vamvakas and Carven,[13] who investigated the association between the length of storage of transfused RBCs and postoperative infection after coronary artery bypass graft surgery. The authors observed that the mean length of storage of all transfused RBCs was a significant predictor of postoperative pneumonia and wound infection. The risk of pneumonia increased by 1% per day of mean RBC storage time. Moreover, age of transfused RBCs remained a significant predictor of postoperative infection after controlling for other known risk factors.

In our epidemiologic studies, blood transfusion consistently emerged as a major risk factor for postinjury MOF.[38,39] Initially, transfusion requirement was thought to be a surrogate for injury severity, but subsequent investigation convinced us that the blood transfusion itself was an independent risk factor for postinjury MOF.[40] To further investigate the relevance of these clinical and laboratory findings, our group performed a multivariate analysis of trauma patients receiving transfusions to examine the effects of the age of stored blood on the development of postinjury MOF.[15] We observed that patients who developed MOF received significantly older packed RBC units and, furthermore, that the age of the blood was an independent predictor of MOF. The current study extends these findings and confirms that the age of stored blood is a significant risk factor for major infections after severe trauma.

In summary, current evidence shows that metabolic, biomechanical, and molecular changes occur during the storage of blood products. Moreover, data are accumulating that these changes may lead to harmful consequences in the recipient. In particular, transfusion of RBCs stored for more than 14 days is associated with increased major infections after severe trauma. Further studies are necessary, however, to clarify this relationship. Changes in blood banking practice (ie, leukocyte reduction), clinical practice (ie, lower transfusion "trigger," recombinant erythropoietin), and continued development of blood substitutes may help avoid the adverse effects of allogeneic blood transfusion.

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DISCUSSION

David R. Antonenko, MD, PhD, Grand Forks, ND: I anticipated this paper very much because I had hoped that it would also confirm a prejudice of mine regarding not only the use of blood in some of these patients but the use of old blood.

As Dr Offner has pointed out, blood transfusions have been an integral part of trauma resuscitation for decades. In the last 25 years we have begun to realize that immunomodulation associated with transfusions is a significant cause of both morbidity and, as more recent studies have shown, mortality. The studies that have identified this include areas of colorectal surgery, oncology, cardiovascular surgery, orthopedics, and critical care medicine. The Denver group has been at the forefront in the last decade in trying to elucidate the causes of the immunomodulation that has occurred, and I have been following the literature from them with interest. They and others are defining the molecular and cellular basis of this immunomodulation.

The role of neutrophil activation, as Dr Offner pointed out, and its relationship to the duration of blood storage is pertinent to this and to other studies. They and others have shown that more than 14-day-old blood is associated with much of this immunomodulation. The problem with this study, however, is its size and its selection of patients. This is a retrospective level 3 study examining the infection rates in a very small group of 61 injured patients receiving older than 14-day-old blood. They unfortunately did not include in the paper nor in the presentation a similar cohort receiving large volumes of blood that may have been fresh, ie, less than 14 days old, and I don't know based on their database whether or not they have this information, but if they do, it would be interesting to compare the 2 groups.

Is it in fact the old blood that is producing the problem in those who are receiving 12 U of blood, or is it the severity of injury that is associated with the increased infection rate? If we had that additional cohort, then we might be able to define this a little bit better.

The study group is curiously small based on the very large database that this group has presented in previous papers. I would like to clarify why they selected just this small group of patients because they do have a wealth of data. From 1992 until now with only 61 patients identified, this is fewer than 7 patients per year, and this would bring up questions of differences in operative technique, differences in the transfusion trigger that may be used from the early to later patients, which may also influence the outcomes of these patients. Would Dr Offner clarify his inclusion or selection criteria?

The study is also a mix of both blunt and penetrating injury and, as other studies have shown, a blunt injury is frequently associated with a different type of complication than a penetrating injury that may include colon injuries and septic peritonitis. Because of the small numbers in each, I feel that the generalizability of this study to other trauma and surgery is very limited. Could they clarify if they have information as to whether or not there is a true difference between the groups on pure penetrating and pure blunt injury?

Would the authors also describe the types of injuries that these individuals had and whether in their study as in others there may be a gender difference in the results?

In their study and in the paper they describe only major infections, and that is acceptable, but what would the results be if you included all infections, not only minor urinary tract infections but also minor wound infections?

With respect to the total numbers of blood transfusions given to these patients, there may be a statistical difference between 12.8 and 10.4 units of blood, but I am not sure that there is a clinical significance. The volume of blood used was high in both groups, implying a relatively liberal transfusion protocol. What was your transfusion trigger, as I asked earlier?

In view of the status in other specialties demonstrating the advantage of selective transfusion protocols, are you planning to evaluate a more selective protocol and its effects or infection rates?

I agree with your conclusion that the translation of your and other molecular and cellular data to prospective randomized studies is a requirement. I strongly suggest at the present time that the liberal transfusion protocol that is currently being used and presented at this and other organizations is no longer tenable based on our current understanding and needs to be reevaluated.

James G. Tyburski, MD, Detroit, Mich: I want to congratulate the authors also and bring up one of my biases on the use of old blood. I have several questions for the authors. Could they define in the patient population some more confounding infections factors, and I think Dr Antonenko touched on some of these, such as colonic injuries? In particular, we found hypothermia to be a problem for infectious complications. Can they comment if they have any temperature data?

Also, maybe I missed this, but what types of transfusions were given? Did they receive equal amounts of fully typed and cross blood? Was some of the blood type-specific? Was some of it O-negative blood? Did they get fresh frozen plasma in these massive transfusions?

Also, although it may not make a clinical difference, you did point out there was a statistical difference between the amount of blood given in the first 12 hours. Why was that? Did these patients go back to the operating room more often?

Christine S. Cocanour, MD, Houston, Tex: There was not much difference, although it was statistically significant, between those with infections and those without. Do you think there is a specific amount of blood, and I know you said it was an increase of 13% with each unit, but are we going to throw out all of the units of blood that are over 14 days? Is there a specific amount that we shouldn't be giving more than of old blood, especially to trauma patients or any patient who requires a large volume of transfusion?

Richard C. Thirlby, MD, Seattle, Wash: The patients in the infected group received more transfusions than the noninfected group. You could assume, therefore, that the patients in the infected group would get more blood over the 21 days than the noninfected group. Do you have any data on the percentage of patients in the infected and noninfected groups that got blood

less than 21 days old? I suspect that these numbers would result in conclusions exactly opposite of those presented today.

Claude H. Organ, Jr, MD, Oakland, Calif: Would you also just define once again what you mean by old blood so it will be clear to the audience?

Dr Offner: I will try to answer all of [the questions], and I will start with Dr Thirlby's because I have found that age makes a difference in other areas as well and I will forget it.

Yes, age does matter. We defined old blood for the purpose of this study as age greater than 14 days, and we based that on Chris Silliman's neutrophil priming studies. We also know from other studies, however, that there is continued accumulation of bioactive substances during the entire storage period, some to a greater extent than others. For instance, the accumulation of cytokines is less than the lipid mediators, mainly because cytokine release is inhibited by storage at 4°C.

Seriously, Dr Thirlby, what was your question again? [Dr Thirlby: The fact that infected patients get so much more blood than the noninfected patients. Your statistical methods are a little flawed. I suspect that if you showed a table showing number of units less than 14 days old, the infected groups would also be higher in that group. In other words, implying that . . . .]

You are partly right. Over the course of the entire hospital stay, it may be that the infected patients also received more blood, but remember that we were specifically looking at early transfusion requirements. That is to say, in the first 12 hours of their injury, and this is the answer to several of the questions. The reason we chose this early time window is because transfusion triggers are less of an issue in severely injured patients in the first 12 hours. It is difficult to define a clear transfusion trigger in a hemodynamically unstable patient, whether he is in the intensive care unit or in the operating room. With these patients, we tend to have a more liberal transfusion threshold. We don't have the luxury of waiting in a patient who is actively bleeding or in whom we are unsure of whether or not the bleeding is controlled. Rather, we don't want to get behind the eight-ball in these patients and transfuse presumptively. I don't think that this is going to change in the trauma scenario anytime soon, although the availability of blood substitutes may help in this regard.

In the elective scenario, it behooves us to be more thoughtful in terms of our transfusion practice and in terms of our own personal transfusion trigger. We should base our threshold more on the patient's physiology rather than a specific hemoglobin level.

Dr Antonenko correctly pointed out some of the limitations of our study, in particular, the small size of the study and its retrospective nature. Clearly, this study will suffer from all of the problems that are inherent to retrospective studies. Why we chose such a small group of patients when we have a large database is a good question that I can answer pretty simply. The determination of the age of the blood was fairly labor-intensive, so, although we have close to 1000 patients in our database, we decided to select a smaller subpopulation, essentially a convenience sample. So there is the possibility of some unrecognized selection bias in selecting these 61 patients from the database.

Moreover, we deliberately selected patients who received between 6 and 20 U of transfusion within 12 hours of injury. Our rationale was that patients who received less than 6 U may not reach a threshold of transfusion that was significant enough to show us a difference between patients and that patients who received more than 20 U were so severely injured and critically ill as to overshadow any transfusion effect. We selected our patients to maximize the power of finding a difference between the 2 groups. I guess you could argue that we were answering the question before we started, but that really wasn't the intent. When we selected these patients, we didn't know their infection status.

The possibility of differences due to blunt or penetrating mechanism was also raised. This is a relevant issue. When we looked at mechanism, there wasn't a difference in blunt and penetrating injury between the 2 groups. We did not look at differences in specific injuries, ie, colon injuries or pulmonary contusions, between the 2 groups. This would be a good thing to do but the small numbers may make it difficult.

The question of old blood being the reason for this effect or the severity of injury is also a good one, and, again, my answer is going to have to be relatively simplistic. The average ISS between patients who did and did not develop an infection was no different. Moreover, because of this concern, we still included ISS in our multivariate models and age of the blood remained an independent predictor of infection.

IN OTHER AMA JOURNALS

ARCHIVES OF INTERNAL MEDICINE

Hereditary Angioedema: A Broad Review for Clinicians

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Hereditary angioedema (HAE) is an autosomal dominant disease that afflicts 1 in 10000 to 1 in 150000 persons; HAE has been reported in all races, and no sex predominance has been found. It manifests as recurrent attacks of intense, massive, localized edema without concomitant pruritus, often resulting from one of several known triggers. However, attacks can occur in the absence of any identifiable initiating event. Historically, 2 types of HAE have been described. However, a variant, possibly X-linked, inherited angioedema has recently been described, and tentatively it has been named "type 3" HAE. Signs and symptoms are identical in all types of HAE. Skin and visceral organs may be involved by the typically massive local edema. The most commonly involved viscera are the respiratory and gastrointestinal systems. Involvement of the upper airways can result in severe life-threatening symptoms, including the risk of asphyxiation, unless appropriate interventions are taken. Quantitative and functional analyses of C1 esterase inhibitor and complement components C4 and C1q should be performed when HAE is suspected. Acute exacerbations of the disease should be treated with intravenous purified C1 esterase inhibitor concentrate, where available. Intravenous administration of fresh frozen plasma is also useful in acute HAE; however, it occasionally exacerbates symptoms. Corticosteroids, antihistamines, and epinephrine can be useful adjuncts but typically are not efficacious in aborting acute attacks. Prophylactic management involves long-term use of attenuated androgens or antifibrinolytic agents. Clinicians should keep this disorder in their differential diagnosis of unexplained, episodic cutaneous angioedema or abdominal pain. (*2001;161:2417-2429*)

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