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PRESTORAGE LEUKOREDUCTION AMELIORATES THE EFFECTS OF AGING ON BANKED BLOOD

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Abstract

Background—Prior studies have demonstrated that the transfusion of older blood is independently associated with higher rates of infectious complications, multiorgan failure, and mortality. Putative mechanisms implicate leukocytes in stored blood which generate immunomodulatory mediators as the stored blood ages. The purpose of this retrospective cohort study was to describe the effect of prestorage-leukoreduction (PS-LR) on the detrimental clinical effects of increasing age on blood products utilized in trauma patients.

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Methods—All patients receiving ≥ 6 units of packed red cells and surviving ≥ 48 hours since May, 1999 when institutional universal PS-LR was begun were identified. Transfusion requirements, demographic data, and causes of death were collected. Blood bank records were reviewed to determine the age of each unit of blood transfused. Multivariate logistic regression was used to determine the relationship between the age of PS-LR blood transfused and mortality after adjusting for total transfusion requirement, patient age, ISS, Head AIS, mechanism of injury, and gender. A subgroup analysis was performed excluding those patients in whom care was withdrawn at 48–72 hours post-injury for brain death or neurologic devastation.

Results—A total of 399 patients, receiving 6,603 units of blood, met inclusion criteria. Mortality analysis showed that increasing ISS, patient age, head AIS, and number of units of packed red cells transfused were all independently associated with an increased risk of death. When mean age of blood was analyzed as a continuous variable, a significant reduction in the risk of death with increasing mean age of transfused PS-LR blood was noted (OR 0.959; 95% CI 0.924–0.996). Both of these findings persisted when the mean age of blood was dichotomized at 14 days (OR 0.426; 95% CI 0.182–0.998) and 21 days (OR 0.439; 95% CI 0.225–0.857). The area under the curve for the receiver operating characteristics of our mortality model was 0.90. After excluding 13 patients in whom care was withdrawn 48–72 hours post-injury for brain death or neurologic devastation, the mortality analysis still showed that increasing injury severity, number of units of packed red cells transfused, and age were all independently associated with an increased risk of death. The protective effect of receiving older blood seen in the all-cause mortality analysis disappeared as no association was found between odds of dying and increasing age of PRBC units transfused. This was true whether the mean age of blood transfused was dichotomized at 14 days (OR: 0.93; CI: 0.30–2.83) or at 21 days (OR: 0.54; CI: 0.25–1.16).

Conclusion—Our data suggest that the deleterious effects of aging on banked blood are ameliorated by PS-LR. We are currently conducting a prospective observational study in an effort to duplicate the findings of this retrospective investigation.

Keywords

leukoreduction; trauma; mortality; transfusion

Introduction

Although frequently life-saving, blood transfusions are associated with potential morbidity and mortality. The immunomodulatory effects of red cell transfusions are well documented^{1–8}, and red cell transfusion has been shown to be an independent risk factor for multiple organ failure after injury⁹. The length of time that a given unit of blood sits in storage after donation is one potential cause of these immunomodulatory properties. Previous studies have shown that receiving older blood results in higher rates of mortality¹⁰, multiorgan failure¹¹, and infectious complications¹². One hypothesis for the mechanism of this age effect on transfused blood centers on the role of leukocytes in the donor units. These leukocytes are known to exert a variety of immunomodulatory effects on the recipient, and the magnitude of this effect is proportional to the length of time the donor unit is stored^{13–16}.

The process of prestorage leukoreduction (PS-LR) removes 99.9% of donor white blood cells, and would presumably abrogate any immunomodulatory effect resulting from donor leukocyte storage and transfusion. Our group as well as others have failed to show an effect of PS-LR on mortality in transfused trauma patients^{17,18}, but we have found evidence that it does reduce infections in trauma patients in a manner proportional to the quantity of blood transfused¹⁹. However, none of these investigations controlled for the age of transfused units. In a recent investigation examining the impact of PS-LR on the detrimental age effect on mortality in transfused trauma patients, PS-LR did not seem to have an effect²⁰.

However, that study chose to examine the transfusion burden on a unit-by-unit basis rather than the mean age of blood transfused. The purpose of this study was to examine whether the process of PS-LR ameliorated the detrimental effects of increasing packed red cell age on mortality in transfused trauma patients when considering the mean age of all blood transfused.

Materials and Methods

This study was a retrospective cohort analysis of patients treated at the University of South Alabama Medical Center (an urban state-designated Level I trauma center) from May, 1999 through November, 2006. Beginning in May of 1999 the institution initiated a policy of universal PS-LR. The trauma registry was queried for all patients admitted to the trauma service during the study period meeting the following inclusion criteria: age ≥ 18 years, transfusion of ≥ 6 units of packed red blood cells (PRBC) over their entire hospital course, and survival of ≥ 48 hours after admission. Demographic data collection included patient age, gender, mechanism of injury, head Abbreviated Injury Score (AIS), Injury Severity Score (ISS), and intensive care unit (ICU) length of stay (LOS). Information on the total number and age of PRBC transfused per patient was extracted from the blood bank record, and information on cause of death and presence of multiple organ dysfunction were extracted from the medical record. The modified Multiple Organ Dysfunction Score²¹ was used to define organ dysfunction. Initial scores were calculated at 48 hours post-injury with the neurologic component (Glasgow Coma Score) omitted. A daily score was calculated by utilizing the highest value for each component within a 24 hour period. Daily scores were calculated for the entire length of stay in the intensive care unit. Patients were considered to have met criteria for multiple organ dysfunction if their MODS score was ≥ 6 at any point during their ICU course. This study was approved by the Institutional Review Board.

Multivariate logistic regression analysis was used to determine the relationship between the age of PS-LR red cell products and the risk of death while adjusting for total transfusion requirement, age, gender, mechanism of injury, ISS, head AIS, and hospital and ICU LOS for the entire sample. First, the effect of the mean age of blood was entered into the model as a continuous variable. Further regression analyses were performed in which the mean age of PS-LR blood was dichotomized at 14 days as well as 21 days. A p value of ≤ 0.05 was considered to be significant for all analyses. Area under the receiver operating characteristic curve (AUC) was calculated to assess the strength of the model. Data storage and management was performed with Microsoft Excel (Redmond, WA) software package. All statistical analyses were performed for this portion of the analysis using SPSS 14.0 statistical software (Chicago, IL).

An additional subgroup analysis was conducted in which those patients who had care withdrawn for neurologic devastation or brain death for the discrete time period of 48 to 72 hours post-injury were excluded. Multivariate logistic regressions controlling for the same variables were conducted in which the mean age of blood was dichotomized at 14 and 21 days. This analysis was conducted using SAS version 9.2 (SAS Institute Inc., Cary, NC).

Results

Three hundred and ninety-nine patients receiving a total of 6,603 units of PS-LR packed red cells met entry criteria and comprised the study group. The median age of blood transfused was 24.7 ± 7.0 days. Demographic characteristics for this group can be found in Table 1. The overall mortality for the group was 19.5%, and causes of death are classified in Table 2. Eight charts had their blood bank data tabulated, but were unable to be located by medical records while awaiting an evaluation of their causes of death. Unsurprisingly given the high

ISS of the sample, 60.7% of deaths whose causes were known were due to multiple organ dysfunction syndrome (MODS).

Mortality analysis showed that increasing ISS, patient age, head AIS, and number of units of packed red cells transfused were all independently associated with an increased risk of death (Figure 1a). When the multivariate logistic regression model was used to analyze the mean age of blood as a continuous variable, a significant reduction in the risk of death with increasing mean age of the transfused PS-LR blood was noted (OR 0.959; 95% CI 0.924–0.996). Both of these findings persisted when the mean age of blood was dichotomized at 14 days (OR 0.426; 95% CI 0.182–0.998) and 21 days (OR 0.439; 95% CI 0.225–0.857) (Figures 1b and 1c). The area under the curve for the receiver operating characteristics of our mortality model was 0.90.

When a subgroup analysis was performed on those patients who had care withdrawn between 48 and 72 hours for brain death or neurologic devastation was performed, the mortality analysis still showed that increasing injury severity, number of units of packed red cells transfused, and age were all independently associated with an increased risk of death (Figures 2a and 2b). In this subgroup of patients, however, the protective effect of receiving older blood seen in the all-cause mortality analysis disappeared as no association was found between odds of dying and increasing age of PRBC units transfused. This was true whether the mean age of blood transfused was dichotomized at 14 days (OR: 0.93; CI: 0.30–2.83) or at 21 days (OR: 0.54; CI: 0.25–1.16). Unsurprisingly given that those patients with severe neurotrauma were excluded from this subgroup analysis, the association found between increasing severity of head injury and death in the all-cause mortality analysis did not reach significance at either the 14 or 21 day dichotomy analysis in the subgroup analysis.

Discussion

This retrospective cohort analysis found that the use of older PS-LR blood products are not associated with an increased risk of death when the mean age of blood transfused to a given trauma patient is used as the basis for analysis. It remains unclear whether the effect on mortality is neutral or actually protective.

The first clinical evidence that allogeneic blood transfusion exerts an immunomodulatory effect was provided by Opelz who found that renal transplant patients who received transfusions had a higher rate of allograft survival^{1,2}. Subsequent studies suggesting that allogeneic blood transfusion was a risk factor for cancer recurrence and multiorgan failure strengthened this association^{3–9}. This clinical syndrome came to be known in the transfusion literature as transfusion associated immunomodulation (TRIM), and considerable work has gone into delineating the mechanism of this effect. Evidence exists implicating the red cells themselves, the leukocytes that accompany allogeneic blood transfusion, and the length of time that a unit of packed cells sits waiting to be transfused.

Red blood cells and their storage media undergo characteristic morphologic and biochemical changes with *ex vivo* banking. These changes are collectively referred to as the “red cell storage lesion”²², and include lipid peroxidation of the red cell membranes²³, loss of deformability²⁴, loss of 2,3 diphosphoglycerate (and thus an increased oxygen affinity)²⁵, and depletion of ATP which results in crenation, spicule formation, and cell swelling²⁶. Other investigators have shown that donor leukocytes secrete cytokines in a time-dependent manner after donor unit storage^{13,15}. Additionally, lipid mediators capable of priming neutrophils accumulate in donor unit plasma. These increased lipid mediators may be a function of leukocyte activity on red cell membranes during storage^{16,27–30}. Collectively, these changes result in decreased red cell viability, oxygen delivery, and the elaboration of

bioactive substances with immunomodulatory properties. Importantly, they also all appear to be time-dependent in that these effects are magnified with prolonged storage times. Indeed, this age effect has been clinically shown to result in higher mortality rates¹⁰, multiorgan failure rates¹¹, and infection rates¹² in critically ill patients. Taken together, it is easy to see why the search for modifiable factors associated with these deleterious effects of blood transfusion have centered on the passenger leukocytes as well as the age of the blood transfused.

By removing donor white blood cells, PS-LR would presumably attenuate any immunomodulatory effect resulting from their storage and transfusion. Both bench³¹ and clinical^{32–40} studies have yielded mixed results on the effect of PS-LR.

The largest clinical trial demonstrating a positive effect of LR on outcomes was a retrospective before-and-after cohort study performed in Canada after the institution of a nationwide policy of PS-LR. This study examined 14,786 postoperative patients, and found a significant decrease in mortality rates from 7.03% in those patients transfused prior to universal PS-LR to 6.19% after institution of universal LR³³. Interestingly, this improvement in mortality rates occurred without a commensurate decrease in serious nosocomial infections. Trauma patients constituted a small minority of the study population, and no subset analysis of trauma patients was performed. These results stand in contrast to our group's earlier efforts which found no mortality benefit to PS-LR in trauma patients¹⁷, but did see a decrease in infectious complications¹⁹. Further, a recent randomized controlled trial showed no effect of PS-LR on either mortality or infectious complications after injury¹⁸. However, none of these trials accounted for the possible effects of aging on stored LR blood.

Clinically, PS-LR has been shown to blunt the detrimental effects of age on the uptake of oxygen delivered by older transfused red cells in critically ill patients^{41,42}. Murrell and colleagues retrospectively showed that after having 95% of transfused units at their institution undergo PS-LR, age of blood was not independently associated with the risk of death. However, rates of infectious complications and MODS were not measured in their study⁴³. Most prior studies documenting the deleterious clinical effects of age of blood transfusions^{10–12} were performed in populations receiving blood that had not undergone PS-LR. Interestingly, a recent investigation has suggested that PS-LR does nothing to impact the age effect of blood²⁰ in transfused trauma patients. That study chose to examine the question by examining the actual number of "young" or "old" units transfused rather than the mean age of blood transfused. This method arises from a fundamentally different set of suppositions than the present investigation. That manner of investigation proceeds from the assumption that there is no "net effect" of age of blood transfusion, and that the units of blood can be considered in isolation from each other. Since this is clearly not what happens in clinical practice, we elected to examine the issue in terms of mean age of blood. This debate will not be settled until a study is performed in which two groups receiving exclusively old or young blood are compared. In this investigation, the numbers of patients who received exclusively young or old blood were too small for a meaningful comparison.

Our results suggest that the process of PS-LR mitigates the harmful effects of age of blood on rates of mortality in transfused trauma patients. While we had hypothesized that the act of PS-LR would take the age of transfused blood from being a detrimental factor to a non-issue for mortality, it was startling to find that our analysis indicated that the transfusion of older blood was actually associated with a lower mortality rate which reached significance in our population. This protective effect seems counterintuitive and is difficult to explain mechanistically. Given that, a post-hoc analysis was conducted excluding the 13 patients who had care withdrawn between 48 and 72 hours post-injury for brain death or neurologic

devastation. These patients had survived their resuscitations, were hemodynamically normal, and had no manifestations of multiple organ dysfunction. Since these patients were doing well physiologically but had care withdrawn at the wishes of family, it was felt that this might be a confounding influence which could account for these results which were so at odds with previous work. Indeed, when these patients were excluded the protective effect of older blood disappeared, and the age of transfused blood which had undergone PS-LR was not found to be independently associated with risk of death. While the issue of whether or not the true effect of PS-LR on mean blood age is to be protective or a non-issue is not settled by these analyses, this data would suggest at a minimum that the process of PS-LR abrogates the previously-described detrimental effects of age on banked blood. In other words, our results suggest that while it is unclear whether patients receiving older PS-LR blood do better or the same as those receiving younger PS-LR blood, at a minimum we can say that our data suggests that they do not do worse.

The findings of our study must be interpreted within the context of its limitations. First, we elected to only examine those patients who received at least 6 units of blood based on the finding that transfusions of this magnitude are a predictor of multiple organ failure after injury⁴⁴. Next, in an effort to weed out those patients who died of exsanguination or irreversible shock in a failed resuscitation, we only examined those patients who survived at least 48 hours after injury. This practice may have introduced survivor bias. Additionally, this study was conducted over a seven year period. Critical care protocols have changed significantly over this time period. Specific critical care practices that may have impacted mortality and MODS during the study period include a lower transfusion trigger (hemoglobin 7.0 mg/dL), ventilator weaning practices, and aggressive blood sugar control. Unfortunately, the retrospective design of this study does not allow us to control for the effects of these practices. Further, since all units transfused over the entire inpatient stay were used for the analysis, we were not able to analyze any cause and effect regarding MOF or infectious complications as we did not capture whether certain units were given before or after the infectious insult or an incident of MOF occurred.

Lastly, given that the effect of aging is known to be multifactorial, it is possible that a confounding effect was present for which we did not control in the multivariate model. Indeed, evidence for other non-white cell-associated immunomodulators has been put forth by Biffi and associates who found that PS-LR did not mitigate the proinflammatory effects of aging on blood as marked by delayed apoptosis and priming of polymorphonuclear (PMN) cells³¹. This effect was attenuated by poststorage washing of the cells, however. Other possible confounders that were not addressed in our model include the use of other blood products such as fresh frozen plasma, platelets, and cryoprecipitate which may possess immunomodulatory properties.

While many of these limitations are problematic, we are addressing them with a follow up prospective observational study on the effects of age of PS-LR blood in trauma patients which has accrued over 140 patients to date. The protocol was constructed in a manner designed to address the weaknesses of this preliminary retrospective study. Infectious complications and MOF rates are being measured, and no major critical care protocol changes have gone into effect since the study's inception. The present study has served as preliminary data for this prospective evaluation, and despite its limitations serves as a good starting point.

In summary, the process of PS-LR appears to mitigate the detrimental effects of aging on banked blood prior to transfusion when the mean age of blood transfused to a given patient is used as the basis for comparison. These retrospective findings have served as the foundation for an ongoing prospective study.

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1a

1c

Figure 1.

Figure 1a. All-cause mortality

PRBCs = Packed Red Blood Cells

ISS = Injury Severity Score

AIS = Abbreviated Injury Score

Figure 1b. All-cause mortality

PRBCs = Packed Red Blood Cells

ISS = Injury Severity Score

AIS = Abbreviated Injury Score

Figure 1c. All-cause mortality

PRBCs = Packed Red Blood Cells

ISS = Injury Severity Score

AIS = Abbreviated Injury Score

2b

Figure 2.

Figure 2a. Mortality excluding patients with care withdrawn at 48 to 72 hours post-injury for brain death or neurologic devastation

PRBCs = Packed Red Blood Cells

ISS = Injury Severity Score

AIS = Abbreviated Injury Score

Figure 2b. Mortality excluding patients with care withdrawn at 48 to 72 hours post-injury for brain death or neurologic devastation

PRBCs = Packed Red Blood Cells

ISS = Injury Severity Score

AIS = Abbreviated Injury Score

Table 1

Overall cohort demographics.

	Overall
Patients (n)	399
Total PRBC's transfused (n)	6,603
Mean PRBC units/patient (n)	16.5 ± 16.3
Mean Age of PRBCs (days)	24.7 ± 7.0
Median ISS [IQR]	29.0 [22.0,39.5]
Median Head AIS [IQR]	0 [0,4]
Mean Patient Age (yrs)	41.6 ± 17.7
Male (%)	78.2
Blunt (%)	76.4
Mean ICU LOS (days)	17.4 ± 21.2
MODS (%)	49.9
Mortality (%)	19.5

Table 2

MODS = Multiple Organ Dysfunction Syndrome, ARDS = Acute Respiratory Distress Syndrome, TBI = Traumatic Brain Injury.

Causes of death	n
MODS	34
Withdrawal for brain death/neurologic devastation at 48–72 hours post-injury	13
Withdrawal for severe TBI and worsening clinical picture >72 hours post-injury	12
Unknown (chart missing)	8
Myocardial Infarction	2
Cardiac arrest, etiology unknown	2
ARDS	2
Overwhelming sepsis without MODS	2
Liver failure	1
Remote exsanguination	1