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Use of Leukoreduced Blood Does Not Reduce Infection, Organ Failure, or Mortality Following Trauma

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Abstract
Background Leukoreduced (LR) blood has been demonstrated to reduce morbidity and mortality in high-risk surgical patients, but not in trauma patients. The objective of the present study was to determine the effect of LR blood on morbidity and mortality. We hypothesized that the use of LR blood does not improve outcome in trauma patients.
Methods This study was a retrospective cohort analysis of trauma patients transfused at a level 1 Trauma Center from 2001 to 2004. Between 2002 and 2003, LR blood was transfused. Prior to that time and subsequent to it, non-leukoreduced (NLR) blood was transfused. This created two historical comparison groups. Data collected included patient demographics, units of blood transfused, intensive care unit (ICU) and hospital days, ventilator days, injury severity score (ISS), mortality, presence of acute respiratory distress syndrome (ARDS), and infectious complications. A multiple organ dysfunction syndrome (MODS) score was calculated.
Results The distribution of patients was as follows: 284 patients received only NLR blood, 153 received only LR blood, and 58 received at least one unit of each. The mean ISS was similar (NLR: 26, LR: 24; $P > 0.1$). No differences were seen between groups in units transfused (6.2 vs. 5.5), number of ICU days (8.2 vs. 9.0), number of hospital days (16.9 vs. 18.6), number of ventilator days (6.1 vs. 5.7), incidence of ARDS (8.3% vs. 8.5%), MODS score (5.5 vs. 5.9), mortality rate (15.1% vs. 15.7%), or infection rate (36% vs. 30%) ($P > 0.1$).
Conclusions This study represents the largest series comparing trauma patients who received either LR or standard blood transfusions. The use of LR blood does not improve outcome in trauma patients.

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Introduction

Critically ill trauma patients are frequently transfused with packed red blood cells (PRBCs), either as an initial resuscitative measure or in response to anemia in the post-injury period [1, 2]. Blood transfusion in trauma patients has been demonstrated to be an independent predictor of mortality, intensive care unit (ICU) admission, length of hospital stay, and infection regardless of degree of shock [3, 4]. Allogeneic blood transfusion also is associated with numerous additional side-effects to include febrile nonhemolytic transfusion reactions, transfusion-related acute lung injury (TRALI), viral transmission (cytomegalovirus [CMV], human immunodeficiency virus [HIV], hepatitis), and transfusion-related immunomodulation [5–12]. Donor leukocytes present in the allogeneic blood have been implicated as a potential cause of these complications. Proposed mechanisms include induction of T-cell anergy in the recipient, decreased natural killer cell function, altered ratio of T helper to T suppressor cells, and soluble pro-inflammatory cytokines produced by leukocytes during

storage [13–15]. Together, these effects can suppress the recipient immune system and promote a worse pro-inflammatory state leading to increased infection and complications [16]. This has led many investigators to suggest that the use of pre-storage leukoreduced (LR) blood may mitigate some of the immunomodulatory effects of allogeneic blood transfusion and reduce associated morbidity and mortality [6, 17–21].

Numerous randomized controlled trials and several observational studies in medical and surgical patients have compared rates of infection, organ failure, and mortality in patients receiving either LR or standard, non-leukoreduced (NLR) blood [22–26]. The results of these trials have demonstrated a modest reduction in length of hospital stay by some, or a reduced infection rate, or no difference at all between groups. This led to the publication of two meta-analyses, both of which concluded that the use of LR blood might reduce postoperative infection and that mortality is reduced, but only in cardiac surgery patients [27, 28]. Interpretation of these studies has been hampered by the heterogeneous nature of the study populations, the methods of leukoreduction employed, and differences in transfusion practices [29].

To date only one randomized trial has compared outcomes in trauma patients receiving either LR or NLR blood, demonstrating no difference in infectious complications, mortality, or incidence of organ dysfunction [26]. This study has been criticized for a small study population. Given the heterogeneous results seen among various patient populations and the limited data available concerning trauma patients, we examined the effects of preferential transfusion of LR blood over NLR blood on infection, organ failure, length of stay, and mortality in trauma patients. We hypothesized that the use of LR blood would not reduce the incidence of morbidity or mortality following trauma.

Materials and Methods

We conducted a retrospective cohort analysis of all trauma patients admitted to our level I trauma center from May 2001 through May 2004. Between August 2002 and August 2003, the Red Cross supplied our hospital with only LR blood. Prior to that time, our hospital was supplied almost exclusively NLR blood. After August 2003 both LR and NLR blood were available for transfusion. This naturally created three distinct groups of patients: those who received only LR blood, those who received only NLR blood, and those who received at least one unit of each (mixed group). The American Red Cross performed pre-storage leukoreduction of whole blood or PRBCs via a filtration process to achieve $<5 \times 10^6$ leukocytes/unit or less. This level has been suggested to be sufficient to prevent alloimmunization [30].

All charts of patients admitted during the study period were reviewed. Patients were included in the study if they received at least one unit of PRBC transfusion during their hospital stay. We analyzed data from the trauma registry, blood bank, and the patient's chart. Analyzed variables include patient demographics, injury severity score (ISS), type and number of units of blood and blood products transfused, length of ICU and hospital stay, number of ventilator days, in-hospital mortality, use of vasopressors at any time during a patient's hospitalization, presence of acute respiratory distress syndrome (ARDS), and infectious complications. A maximum multiple organ dysfunction syndrome (MODS) score was calculated for each ICU day for each patient according to the Marshall scoring system [31]. The primary outcomes were infection and incidence of ARDS.

Infectious complications analyzed included pneumonia, bacteremia, urinary tract infection (UTI), central line infection, and skin infection. Pneumonia was defined according to the CDC criteria requiring the presence of three of the following features: fever, infiltrate on chest X-ray film, elevated white blood cell count, positive sputum culture. Blood cultures were considered positive if the same organism was demonstrated in two or more cultures from different sites. Central lines were considered infected if peripheral blood cultures and catheter tip cultures were positive for the same organism. Urinary tract infection was defined as urine cultures growing greater than 100,000 colonies/ml of bacteria. Skin infections was considered positive if patients were febrile with an identified organism on wound culture. The presence of ARDS was defined according to the American and European Consensus Conference Criteria as a P/F (PaO_2/FiO_2) ratio <200, presence of bilateral infiltrates, and absence of elevated venous pressures or right-sided heart failure. Each chest radiograph for each ICU patient was evaluated by the first author to ensure a consistent evaluation of infiltrates or abnormalities.

Massive transfusion was defined as receiving greater than 10 units of PRBCs within a 24 h period. Transfusion reactions were defined as significant reactions to include TRALI, hemolytic reactions, hypotension during transfusion, development of a rash or cellulitis during or immediately after blood transfusion. Febrile nonhemolytic transfusion reactions were not included given the difficulties in discerning this information from the patient charts in a retrospective fashion.

This study protocol was approved by the Institutional Review Board at Oregon Health & Science University. Informed consent was waived as this was a retrospective analysis. An independent samples *t*-test was used to

compare the means of continuous variables between the two groups. Values within a group and comparisons between groups were performed using a post hoc analysis of variance (ANOVA). Any data that did not follow a normal distribution were analyzed with a nonparametric analysis (Mann–Whitney *U*-test). Categorical variables were analyzed with a chi-squared test, except when the *n* for a given data set was less than 5, and then Fisher's exact test was used. Statistical significance was defined as a *P* value <0.05. These values were calculated using SPSS version 13.0 software (SPSS Inc., Chicago, IL). Graphs were produced with Microsoft Excel 2003 (Microsoft Inc., Redmond, WA).

Results

During the study period 6,189 patients were admitted to our hospital. Of those, 504 received at least one unit of blood during the hospital stay. Charts for nine of the patients were missing significant portions of data that prohibited any meaningful conclusions and were thus excluded. Of the remaining patients, 284 received at least one unit of NLR PRBCs, 153 received at least one unit of LR blood, and 58 received at least one unit of each (mixed group). Baseline demographic data are presented in Table 1. The LR and NLR patients were equally matched with respect to ISS, number of ICU and hospital days, in-hospital mortality, number of days on the ventilator, incidence of ARDS, worst MODS score, and overall incidence of infection ($P > 0.1$). Patients in the mixed group had a significantly longer ICU stay, days on the ventilator, and a worse MODS score than both the LR and NLR groups ($P < 0.05$). Mixed group patients had a similar ISS score and a similar incidence of ARDS, infectious complications, and mortality.

Data on the quantity and type of blood product transfused are presented in Table 1 and Fig. 1. Patients in the

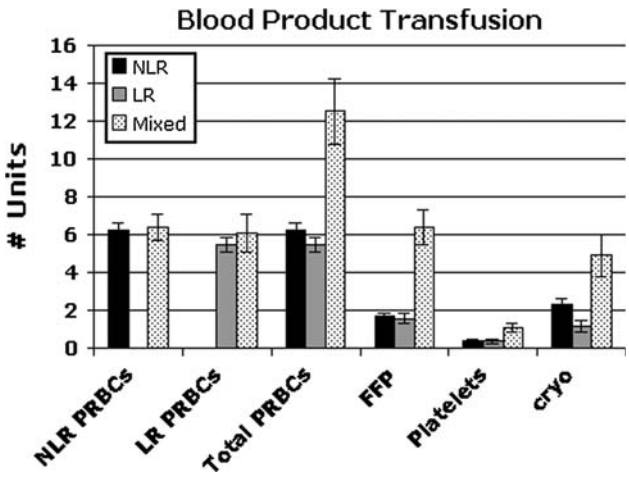

Fig. 1 Blood product requirements. Data are presented as means ± standard error of the mean. * $P < 0.05$

Table 1 Baseline characteristics, blood product requirements, and outcomes for all patients[a]

	NLR ($n = 284$)	LR ($n = 153$)	Mixed ($n = 58$)	*P* value		
				NLR vs. LR	NLR vs. mixed	LR vs. mixed
Age	45.1 ± 1.3	45.1 ± 1.7	50.0 ± 2.8	1.0	0.318	0.404
Gender (% male)	65.8	71.9	76.2	>0.1	>0.1	>0.1
Mean units NLR PRBCs	6.2 ± 0.4	0	6.4 ± 0.7	<0.001	1.0	<0.001
Mean units LR PRBCs	0	5.5 ± 0.4	6.1 ± 1.0	<0.001	<0.001	0.853
Mean units total PRBCs	6.2 ± 0.4	5.5 ± 0.4	12.5 ± 1.7	0.224	<0.001	<0.001
% transfusion reaction	1.1	2.0	0	0.356	0.570	0.379
% requiring massive transfusion	19.4	15.0	51.7	0.159	<0.001	<0.001
ISS	25.7 ± 0.8	24.3 ± 0.9	28.4 ± 2.0	0.914	0.470	0.140
ICU days	8.2 ± 0.7	9.0 ± 0.8	14.3 ± 2.0	1.0	0.001	0.007
Hospital days	16.9 ± 1.0	18.6 ± 1.5	25.0 ± 2.9	1.0	0.006	0.067
In-hospital mortality (%)	15.1	15.7	22.4	0.491	0.123	0.172
Ventilator days	6.1 ± 0.6	5.7 ± 0.7	12.2 ± 2.3	1.0	<0.001	0.001
% ARDS	8.3	8.5	15.5	0.544	0.081	0.110
Worst MODS score	5.5 ± 0.3	5.9 ± 0.3	7.5 ± 0.6	1.0	0.003	0.040
% infection	37.5	31.7	45.5	0.146	0.169	0.051
% required pressors	25.2	20.9	46.6	0.346	0.002	<0.001

[a] Data are presented as mean ± standard error of the mean

LR leukoreduced blood, *NLR* non-leukoreduced blood, *PRBC* packed red blood cells, *ISS* injury severity score, *ICU* intensive care unit, *ARDS* acute respiratory distress syndromes, *MODS* multiple organ dysfunction disorder

NLR and LR groups received a mean of 6.2 and 5.5 units of PRBCs, respectively ($P > 0.1$), compared to the significantly higher 12.5 units for the mixed group patients ($P < 0.05$). Mixed group patients also received a significantly greater amount of fresh-frozen plasma (FFP), platelets, and cryoprecipitate, and were also much more likely to have received a massive transfusion ($P < 0.05$). All three groups had a similar incidence of transfusion reactions. Similar analyses on patients who received a massive transfusion are presented in Table 2. These patients had a greater ISS, total number of units of blood transfused, ICU days, hospital days, ventilator days, incidence of ARDS, overall infection rate, vasopressor requirement, a worse MODS score, and a greater in-hospital mortality when compared with patients who did not receive a massive transfusion ($P < 0.05$). All transfusion reactions seen in this study were among massively transfused patients. There were no differences observed between groups among massively transfused patients in any of these categories ($P > 0.05$).

Infectious complications for all three groups are presented in Fig. 2. Mixed group patients had a significantly higher incidence of pneumonia than the LR or NLR groups ($P < 0.05$) but a similar incidence of UTI, bacteremia, central line infection, and skin infection ($P > 0.1$). The overall incidence of a patient having any infection was not different between the three groups, but it approached significance for LR vs. mixed patients ($P = 0.051$).

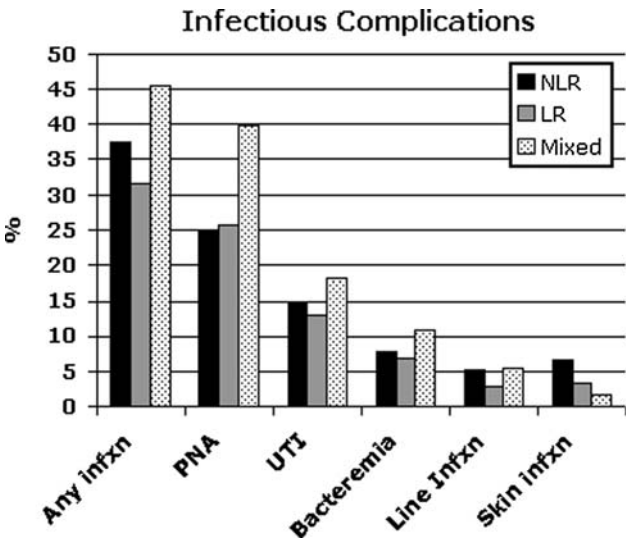

Fig. 2 Infectious complications. * $P < 0.05$. *PNA* pneumonia, *UTI* urinary tract infection

Discussion

Numerous European countries, including the United Kingdom, have already adopted universal leukodepletion as a precautionary measure to help reduce the incidence of transmission of infectious agents, namely Creutzfeldt-Jakob disease. The U.S. Food and Drug Administration has previously issued a recommendation for universal leukoreduction, but it has yet to become a national standard [32,

Table 2 Baseline characteristics and outcomes among massively transfusion patients[a]

	NLR ($n = 55$)	LR ($n = 23$)	Mixed ($n = 30$)	*P* value		
				NLR vs. LR	NLR vs. mixed	LR vs. mixed
Age	45.2 ± 2.8	51.5 ± 3.9	51.3 ± 4.4	0.698	0.623	1.0
Gender (% male)	78.2	78.3	76.7	>0.1	>0.1	>0.1
Mean units NLR PRBCs	17.0 ± 0.9	0	9.8 ± 1.0	<0.001	<0.001	<0.001
Mean units LR PRBCs	0	14.6 ± 1.4	9.5 ± 1.6	<0.001	<0.001	0.005
Mean units total PRBCs	17.0 ± 0.9	14.6 ± 1.4	19.3 ± 1.5	0.539	0.442	0.054
% transfusion reaction	1.1	2.0	0	0.356	0.570	0.379
ISS	33.0 ± 1.8	31.6 ± 2.6	31.4 ± 3.0	1.0	1.0	1.0
ICU days	14.6 ± 2.3	14.2 ± 2.3	19.2 ± 3.3	1.0	0.657	0.820
Hospital days	24.4 ± 3.3	24.9 ± 4.4	32.3 ± 5.0	1.0	0.484	0.848
In-hospital mortality (%)	30.9	26.1	30.0	1.0	1.0	1.0
Ventilator days	11.8 ± 2.3	11.5 ± 1.9	17.9 ± 3.9	1.0	0.362	0.553
% ARDS	21.6	17.4	20.0	1.0	1.0	1.0
Worst MODS score	10.1 ± 0.4	10.9 ± 0.4	9.7 ± 0.8	0.95	1.0	0.535
% infection	55.6	50.0	55.6	1.0	1.0	1.0
% required pressors	37.0	39.1	53.3	1.0	0.455	0.910

All data points, except age, are significantly greater for massive transfusion patients than for those who did not require a massive transfusion

[a] Data are presented as mean ± standard error of the mean

33]. The rationale for such a mandate is based on reduced transmission of infectious agents, transfusion-related immunomodulation, transfusion reactions, and a potential increase in cancer recurrence rates. Although these basic science studies of blood transfusion have helped to develop an understanding of the presumed benefits of leukoreduction, clinical studies comparing transfusion of LR blood vs. standard PRBCs have produced variable results. A large Canadian study carried out after institution of a universal leukoreduction program demonstrated a significant reduction in mortality from 7 to 6% but no effect on infection [25]. Studies among cardiac surgery patients have demonstrated a minimal but significant decrease in hospital length of stay without differences in infection or mortality [22, 23]. Perhaps the greatest benefit of LR blood was seen in patients undergoing elective colorectal surgery, with a tenfold reduction in rates of infection [34]. In an effort to clarify these seemingly conflicting results, two meta-analyses have been conducted. Unfortunately, because of the heterogeneous nature of the study populations, difference in transfusion practices, and varied methods of leukoreduction, neither of these studies could draw meaningful conclusions [27–29]. The only study comparing outcomes in trauma patients failed to demonstrate any clinical benefit in incidence of infection, organ failure, or mortality [26].

This retrospective cohort study of LR vs. NLR PRBCs in trauma patients demonstrated no significant differences in rates of infection, ARDS, MODS, length of ICU and hospital stay, or mortality. The mean ISS for all patients in the study was over 25, indicating severe injury. To date this is the largest series in the literature comparing LR and NLR blood in severely injured trauma patients. The use of LR blood in trauma patients may not confer additional benefit over standard PRBCs.

Patients who received at least one unit of each type of blood had longer ICU and hospital stays, more days on the ventilator, and a worse MODS score, but no difference in infection or mortality. Patients in the mixed group received more blood overall and were more likely to require a massive transfusion despite having ISS similar to patients in the other groups. Greater than 50% of the mixed group received massive transfusions compared to less than 20% in the other groups. In most cases, it is likely that the patients in the mixed group received both LR and NLR blood because their transfusion needs exceeded the blood bank supply of either type of blood. It is because they received both types of blood that the mixed group had more ICU days, more hospital days, more ventilator days, and higher MODS scores. Massively transfused patients had similar baseline characteristics and outcomes between all three groups. Based on these findings, we conclude that patients received both LR and NLR blood because the blood bank was acutely overwhelmed and did not have enough of either type of blood to meet the patients' requirements with one type alone. This introduces an obvious bias in that while the ISS was similar, the need for a massive transfusion predicts a more severely injured patient. The increased lengths of stay and morbidity seen in the mixed group are probably reflective of the fact that patients in this group were more likely to be massively transfused.

There are numerous limitations to this study. As a retrospective analysis, this study is subject to the inherent biases of inadequate documentation, misinterpretation of clinical situations that occurred in the remote past, and subjective analysis by the research team. Research personnel involved in data collection evaluated every chart for a specific outcome measure to limit the subjectiveness and misinterpretation of clinical data. To limit heterogeneous data interpretation, research individuals were assigned a given outcome measure to evaluate rather than a series of patients and charts. The unique opportunity provided by the American Red Cross provision of only LR blood for one year provided the study a unique "before and after" analysis. This allows for somewhat of a natural randomization of patients, strengthening the analysis. Certainly, within the study period there could have been institutional and national changes in transfusion practices, critical care management, individual surgeon performance, and initiation of standardized protocols that potentially confound some of the results.

Perhaps the largest limitation is that the age of the blood transfused in this study is unknown. The American Red Cross does not keep records of the age of the blood at the time of transfusion, and unfortunately we were unable to determine this information retrospectively. The age of the blood at the time of transfusion has been found to be a significant factor in assessing outcomes following transfusion [1, 35]. Additionally, febrile nonhemolytic transfusion reactions were not included in the analysis, in part because of the significant difficulty in assessing this outcome retrospectively. Ensuring that a febrile episode could be attributed to a blood transfusion rather than a source of infection retrospectively is problematic. This may have dramatically lowered the incidence of overall transfusion reactions and potentially affected the analysis between groups.

The mixed group is a heterogeneous patient population, which makes statistical interpretation difficult. Some patients received only one unit of LR and NLR blood, whereas some received numerous units of either LR or NLR PRBCs and only one of the other, and every combination in between. Interpretation of these data must therefore be met with caution. These patients had to have received at least two units of PRBCs, whereas patients in the LR and NLR groups could have received only one unit.

Also, for the mixed group, the overall number of units was over twice that of the other two groups. In theory this could dramatically alter the statistical evaluation. However, when patients in the LR and NLR groups who received only a single unit of blood were removed from the analysis, that did not dramatically alter the statistical results of any outcome measure (data not shown).

This study represents the largest series in the literature to date concerning outcomes following transfusion of LR over standard PRBCs. Preferential transfusion of LR blood did not significantly affect the incidence of infection, organ failure, transfusion reaction, ICU or hospital length of stay, ventilator days, or mortality. The universal use of LR blood may not be beneficial in the trauma population and may add unnecessary costs to the patient and the blood bank. Patients who received at least one unit of LR and NLR blood were more likely to have received a massive transfusion and had longer ICU and hospital days, ventilator days, and worse MODS scores. There was no effect on infection or mortality. Massive transfusion predicts a worse outcome following trauma.

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