Role of Leukoreduction of Packed Red Blood Cell Units in Trauma Patients: A Review

Young Kim, Brent T Xia, Alex L Chang, Timothy A Pritts

Hemorrhagic shock is a leading cause of mortality within the trauma population, and blood transfusion is the standard of care. Leukoreduction filters remove donor leukocytes prior to transfusion of blood products. While the benefits of leukocyte depletion are well documented in scientific literature, these benefits do not translate directly to the clinical setting. This review summarizes current research regarding leukoreduction in the clinical arena, as well as studies performed exclusively in the trauma population.

Key words: Leukocyte reduction; Blood transfusion; Erythrocyte transfusion; Trauma; Review

© 2016 The Authors. Published by ACT Publishing Group Ltd.
was no significant difference in mortality, presumably because non-hemorrhagic causes of death outweighed hemorrhagic causes\cite{16}.

Another multicenter prospective trial, the Pragmatic Randomized Optimal Platelet and Plasma Ratios (PROPR) study, investigated the ideal ratio of blood components for the hemorrhagic patient. Among 680 patients across 12 level I trauma centers, transfusion of 1: 1 vs 1: 1: 2 ratio of plasma to platelets to RBCs was compared, with primary endpoints of 24-hour and 30-day all-cause mortality. While there were no significant differences in mortality at either time point, significantly higher rates of hemostasis and fewer deaths due to exsanguination were observed in the 1: 1: 1 group\cite{10-12}. Both the PROMMTT and PROPR studies suggest a critical role of transfusion of plasma and platelets along with packed RBCs in the acutely hemorrhaging trauma patient.

Unfortunately, transfusion of large volumes of blood may be associated with significant complications. Common transfusion-associated reactions include hemolytic reactions, febrile non-hemolytic transfusion reactions (FNHTR), allergic transfusion reactions (ATR), transfusion-related acute lung injury (TRALI), transfusion-associated circulatory overload (TACO), nosocomial infections likely secondary to immunosuppression, and reperfusion injury\cite{10-12}. These complications are attributed to the transfused blood itself. Several factors have been implicated as the injurious element, including the RBC storage lesion, RBC-derived microparticles, stored cytokines, donor antigens, and donor leukocytes\cite{13}. RBC-derived microparticles, for example, activate lung endothelial cells and provoke lung injury in animal models\cite{14-16}.

Leukoreduction

Leukoreduction (LR) aims to attenuate transfusion-associated reactions by filtering donor leukocytes from packed RBC units. In order to achieve leukoreduction, freshly collected RBC units are passed through a filter (Figure 1) that operates by two mechanisms: barrier filtration and centrifugal force. Each approach has its advantages and disadvantages. Leukoreduction in the Trauma Population

Filtering PRBC units does more than removing donor leukocytes. LR also filters pro-inflammatory mediators, prevents transmission of
blood-borne infectious agents, and reduces human leukocyte antigen (HLA) antibody production in sensitized transfusion recipients.[20]

Stored RBC units carry inflammatory cytokines that accrue throughout the storage period, such as tumor necrosis factor (TNF-α), interleukin-1 (IL-1), and IL-8[21]. In addition, stored RBC units can prime unstimulated neutrophils in vitro[22]. LR reduces the amount of inflammatory cytokine accumulated during storage and abrogates this inflammatory response[23,24]. Prestorage LR is more effective in reducing cytokines than poststorage LR, suggesting that these cytokines may be generated from donor leukocytes themselves[24]. LR also removes human neutrophil peptides, the major antimicrobial peptides of neutrophils[25].

LR filters may restrict the transmission of infectious agents stored in the blood. Viral agents commonly transmitted via leukocytes include Epstein-Barr virus (EBV), cytomegalovirus (CMV), and human T-cell lymphocytic virus (HTLV)-I. LR is an effective alternative to CMV-seronegative blood products in preventing transfusion-associated CMV infection in bone marrow recipients[26,27]. EBV tilters are also significantly reduced by RBC filtration, rendering most filtered units EBV-negative[28]. HTLV-I tilters decline as well after LR, though not completely[29]. Other blood-borne infectious diseases curbed by RBC filtration include malaria, leishmaniasis, human granulocytic anaplasmosis, and Yersinia enterocolitis[30,31].

Despite these benefits, leukocyte depletion is not without its drawbacks. Up to 10% of RBCs may be inadvertently removed during the filtering process[32]. Considering 12-14 million units of blood are donated each year, that amounts to a considerable fraction of discarded cells[33]. RBCs have also been shown to hemolyze during processing, further reducing their oxygen-delivering capacity[34]. The acceptable level of hemolysis is currently set at 1% in the United States[35]. In response to this concern, Gandhi et al reported in 2006 that leukoreduced RBCs did not demonstrate a significant difference in hemolyzed cells when compared to nonleukoreduced RBCs[36]. Altogether, the advantages of LR far outweigh the technical difficulties, at least on a scientific level.

Should all pRBC units be leukoreduced?

While the advantages of LR are well documented, the cost-to-benefit ratio of universal leukoreduction (ULR) remains a topic of controversy[37,38]. Approximately 3-4 million patients receive blood transfusions each year, and the cost of LR amounts to approximately $30 per unit[39]. This calculates to an annual expenditure of over $500 million[40]. Critics argue that this cost may not be worth the clinical benefits, and that LR should be considered on a case-by-case basis. Proponents nevertheless insist that the United States is lagging behind Europe and Canada, who have already instituted ULR into their blood-banking industries.

One such proponent, the Advisory Committee on Blood Safety and Availability from the Department of Health and Human Services (DHHS), issued a formal statement in 2001 recommending ULR to the FDA. Today, nearly fifteen years later, ULR has yet to be adopted. Nevertheless, approximately 80% of all RBC units transfused in the United States are leukoreduced. The Red Cross, who supplies nearly half of the blood transfused, has incorporated ULR into its practices. United Blood Services, which provides 10% of transfused blood in the United States, follows ULR standards. Among the independent services, which account for the remainder of the blood banking industry, almost half abide by ULR standards.

Indications for leukoreduction

In response to the debate over ULR, the University HealthSystem Consortium (UHC) convened an Expert Panel to establish consensus recommendations for the use of leukoreduced blood products. Their evidence-based indications for LR are as follows[41]:

1. Patients that require long-term platelet support in order to decrease refractory platelet transfusion due to HLA alloimmunization;
2. CMV-seronegative patients who require reduced risk of CMV transmission.
3. Patients with documented FNHTR, in order to prevent future episodes.
4. Solid organ transplant candidates (nonhepatic), in order to decrease the incidence of HLA alloimmunization.

The UHC Expert Panel also established nonindications for LR based on clinical data available in 2001[42]:

1. Prevention of viral reactivation in CMV or HIV-positive patients.
2. Prevention of general immunomodulatory effects, including cancer recurrence, postoperative infection, and postoperative mortality.

Key: †leukoreduced arm, ‡nonleukoreduced arm, *significant result.

![Leukoreduction filter. Standard leukoreduction filter. Pink filter is used to filter red blood cells, and white filter is used to filter platelets. Image courtesy of Robert Giuletto at Hoxworth blood center.](Image)
3. Reduction of hospital length of stay (LOS).
4. Prevention of transfusion-associated graft-versus-host disease (GVHD) or TRALI.
5. Prevention of bacterial sepsis.
6. Prevention of transfusion-related infections including HTLV-I, EBV, human herpesvirus-8 (HHV-8), and other blood borne infections.
7. Prevention of acquired prion diseases such as variable Creactive protein disease (vCJD).

Their unanimous conclusion was that the cost-to-benefit ratio for ULR was not justified, and that the FDA should not mandate ULR based on their evidence-based review.

**Leukoreduction in the clinical setting**

Since the establishment of the UHC Expert Panel guidelines in 2001, many clinical trials and retrospective analyses have been performed comparing filtered versus unfiltered blood products. Various endpoints have been scrutinized in determining whether the scientific advantages of leukocyte filtration translate to the clinical setting. These endpoints include transfusion reactions, infection rates, and hospital-related parameters. Clinical studies are summarized in Table 1.

FNHTR is the most common acute transfusion reaction, and the most common endpoint analyzed across all studies. It is defined as a ≥1°C temperature increase above baseline within three hours of transfusion, which is not attributed to separate causes. Because FNHTR is associated with the presence of donor leukocytes and platelets, many have postulated that LR prevents FNHTR through the removal of released cytokines. In concordance with these scientific findings, five large studies have found significantly decreased rates of FNHTR associated with leukoreduced blood (n = 2780, 36 162, 143 345, 778 559). A similar study conducted a single-center, double-blinded randomized control trial comparing transfusion of leukocyte depleted versus non-depleted blood products (n = 268). He noted no significant difference in 28-day rate of infection (primary endpoint), febrile episodes, organ dysfunction scores, or overall mortality rates. A similar study was carried out by Phelan et al., observing no significant difference in hospital LOS or overall mortality rates (n = 679).

In 2006, Utter et al performed a study on the development of transfusion-associated microchimerism (TAMC) within the trauma population. TAMC is defined as the long-term survival of donor leukocytes in the recipient’s blood, and is thought to play a role in the development of autoimmune diseases such as graft-versus-host disease (GVHD). Given that LR removes donor leukocytes prior to blood transfusion, Utter postulated that LR may attenuate the development of TAMC and GVHD. At least one month following hospital discharge, trauma patients were evaluated using blood tests and a survey for GVHD symptoms. Neither endpoint was found to be significantly different between the leukoreduced versus non-reduced arms (n = 67).

In 2008, a single-center, double-blinded randomized control trial was performed evaluating whether LR affected the incidence of acute respiratory distress syndrome (ARDS) or acute lung injury (ALI, now classified as mild ARDS). Watkins et al found that LR did not significantly affect the incidence of early (< 72 hours) or late ALI/ARDS (≥ 72 hours). In addition, secondary endpoints such as ventilator parameters and ventilator-free days were not significantly different among the two groups (n = 268).

**CONCLUSION**

As long as traumatic injury exists, hemorrhagic shock will remain a leading cause of death, and patients will continue to require blood transfusion. The benefits of filtering these blood products far outweigh its disadvantages from a scientific perspective. As evidenced by many clinical trials, these benefits do not always clearly translate to the clinical setting. Thus, the cost-effectiveness of LR remains a topic for debate.

Among the trauma population, none of the studies performed to date have noted any significant effect of LR on the various endpoints. These studies have mostly been limited to smaller patient populations, however, in comparison to other clinical studies. One reason for this is the implementation of leukoreduction across various institutions. Larger non-trauma clinical studies have been able to retrospectively analyze their endpoints between pre-ULR and post-ULR periods, while the smaller trauma-related trials are limited to prospective investigation.

Another reason for the lack of significant results in the trauma population may be due to the heterogeneity of the trauma population itself. Trauma patients may have a wide range of underlying conditions and comorbidities, which can affect the outcomes of transfusion. Furthermore, the timing and volume of transfusions may also play a role in the development of transfusion-related complications.

In conclusion, while leukoreduction may offer some potential benefits in the trauma population, more research is needed to fully understand its impact on clinical outcomes. Future studies should focus on identifying subgroups of trauma patients who may benefit most from LR, as well as exploring the role of alternative strategies for managing transfusion-related complications.
studies may be the patient demographic. The average trauma patient is younger and healthier compared to the general hospital population, and may be better equipped to handle minor inflammatory insults. A third reason may be that the smaller effects of unfiltered erythrocytes are outweighed by the huge physiological stress inherent to traumatic injury. The hypermetabolic and endocrine responses to trauma are well known to caregivers of this patient population.

In conclusion, further and better-powered studies are necessary to evaluate the benefits, if any, of leukocyte depletion in the trauma population.

CONFLICT OF INTEREST

There are no conflicts of interest.

ACKNOWLEDGMENTS

TAP was supported in part by grant R01 GM107626 from the National Institute of General Medical Sciences of the US National Institutes of Health. YK was supported by National Institutes of Health grant T32 GM008478-23. The funders had no direct role in preparation of, or the decision to publish this manuscript.

REFERENCES

15. Kim Y, Chang AL, Seitz AP, Schuster MS, Pritts TA. Microparticles from stored red blood cells activate lung endothelial cells. ACS Ohio Committee on Trauma, Cleveland OH, 2015.
An association between decreased cardiopulmonary complications (transfusion-related acute lung injury and transfusion-associated circulatory overload) and implementation of universal leukoreduction of blood transfusions. Transfusion 2010; 50: 1738-44.


