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Trauma and Acute Respiratory Distress Syndrome: Weighing the Risks and Benefits of Blood Transfusions

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Traumatic injuries are responsible for one in ten deaths worldwide.[1] Though potentially reversible, hemorrhagic shock remains one of the leading causes of early death in these patients. During the initial resuscitation, physicians are charged with the difficult task of balancing the benefits and risks of blood product transfusions. Some of the potential benefits of transfusions include replacement of intravascular volume, correction of coagulopathy, and improved oxygen delivery. Some of the harmful effects of transfusions including allergic reaction, infectious transmission and mismatched blood have become less common. However, there is a growing list of dangerous and increasingly recognized risks of blood transfusions including nosocomial infections and the development of the acute respiratory distress syndrome (ARDS). In this issue of *Anesthesiology*, Chaiwat et al. add to this growing body of literature by reporting that early transfusion (≤ 24 hours from hospital admission) of both packed red blood cells (PRBCs) and fresh frozen plasma (FFP) are independent risk factors for ARDS.[2]

The various acronyms use to describe pulmonary infiltrates that develop after transfusions likely identify overlapping syndromes. The diagnostic criteria for most of these syndromes are based on the American-European Consensus Conference definition for ARDS: bilateral infiltrates on chest radiograph, a PaO_2/FiO_2 ratio < 200, and a pulmonary artery occlusion pressure of < 18 mm Hg or no clinical evidence of left atrial hypertension.[3] Acute lung injury (ALI) is a less severe form of ARDS defined by PaO_2/FiO_2 ratio < 300 mm Hg. The most recent consensus guidelines for transfusion associated lung injury (TRALI) require the diagnosis of ALI to be temporally (within 6 hours) and mechanistically related to the transfusion of blood or blood components, without the presence of any preexisting ALI risk factors. If TRALI criteria are met in the presence of an ALI risk factor, the syndrome is called "possible TRALI." Transfusions may also be associated with a delayed form of ALI (6–72 hours after transfusion) that often occurs in patients with other ALI risk factors. This syndrome has been termed the "delayed TRALI syndrome".[4] Finally, ALI may be difficult to differentiate from hydrostatic edema in trauma patients because patients frequently receive aggressive resuscitation with crystalloid and blood products. This hydrostatic form of pulmonary edema associated with blood products is called transfusion associated circulatory overload. Clearly we need to determine the clinical overlap between these related syndromes to further unravel their complex pathophysiologic relationships.

In this study, Chaiwat et al. demonstrated that early transfusion of PRBCs to trauma patients increases both their incidence of ARDS and hospital mortality.[2] This association has been described previously in small single center studies, but this larger multicenter study with multiple controls for severity of injury and coexisting risk factors demonstrates generalizability of these results. Previous studies have suggested that a safe threshold for the number of

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transfused units of blood may exist. In this study, a dose dependent association between the number of transfused units and the development of ARDS was exhibited, though receipt of > 5 units was needed to obtain statistical significance. Similarly, in a mixed intensive care unit population, ARDS incidence increased with each unit of PRBCs administered in patients with preexisting ARDS risk factors.[5] It is likely that with each biologically active unit of blood product, there is a unique interaction with the host that determines the probability of causing lung injury. Therefore, a host with "primed neutrophils" from preexisting ALI risk factors may be highly vulnerable to each transfused unit.[6] Given these risks, should we adopt a more restrictive transfusion strategy in those critically ill patients with preexisting risk factors such as major trauma?

The study by Chaiwat et al. is also the first to report an independent association between transfusion of FFP and the development of ARDS in trauma victims.[2] Earlier retrospective trauma studies that consistently linked massive transfusion to ARDS failed to control for FFP administration. In a medical intensive care unit population, FFP has recently been shown to be independently associated with the development of ARDS. [7] In this study, after controlling for the administration of FFP and platelets, the association between transfusion of PRBCs and the development of ARDS became insignificant.[7] Therefore, FFP appears to be an emerging and possibly predominant risk factor for the development of transfusion related ARDS.

While a restrictive strategy of PRBC transfusion may only decrease exposure by a few units, a restrictive strategy in the use of FFP has the potential to prevent large exposure to blood products. Approximately 33–50% of the FFP used in critically ill patients is inconsistent with guideline indications.[8] Correction of coagulation abnormalities occurs commonly and is of unproven benefit in non-bleeding critically ill patients. Furthermore, the optimal PRBC:FFP ratio employed during massive transfusion in trauma patients remains unclear.[9] Prothrombin time and the international normalized ratio are poor determinants of decreased clotting factor levels and poor predictors of bleeding in critically ill patients.[8] They are especially misleading in patients bleeding from traumatic injury or complications of liver disease where the *in vivo* hemostatic mechanisms are dynamic, complex and poorly reflected by traditional clotting assays.

The main limitation of this study is the diagnostic criteria used to define ARDS. In trauma patients, the assessment of "no clinical evidence of left atrial hypertension" that was used to diagnose 43% of ARDS is subject to interpretation error. The authors were also unable to demonstrate a clear temporal relationship between transfusion and ARDS. Patients who developed ARDS prior to initial transfusion would ideally have been excluded from this study. Given the size of this data set, information regarding the timing of ARDS and relationship to amount of fluid resuscitation may help to differentiate the various transfusion related syndromes (TRALI *vs.* "delayed TRALI syndrome" *vs.* transfusion associated circulatory overload). The authors were also unable to account for leukoreduction or age of blood. Older blood and the presence of leukocytes in stored blood have both been associated with adverse outcomes in critically ill patients. However in a recent randomized controlled trial in trauma patients, the use of leukoreduced blood was not associated with a decrease in the incidence of ARDS.[10] Age of blood remains associated with severe infection, hospital length of stay, multi-organ failure and mortality in trauma victims.[11]

This study strengthens the existing literature regarding transfusion risks in trauma patients. In light of inconsistent improvement in tissue oxygenation demonstrated with transfused PRBCs and the unproven benefit of using FFP to correct coagulation tests, all critical care clinicians should have a compelling physiologic reason to transfuse each individual unit of PRBCs or FFP to critically ill patients, especially if ARDS risk factors are present. Evidence exists for restrictive transfusion in resuscitated trauma patients[12] and non-bleeding medical intensive

care unit patients[13], but multifaceted transfusion strategies are likely needed in bleeding patients to decrease exposure to blood product. Future randomized clinical trials will be necessary to confirm the important results of Chaiwat et al.[2] that the use of less blood products during the initial resuscitation of trauma victims actually decreases the risk of developing ARDS. Less may actually be more.

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