

## Is There Transfusion-related Acute Renal Injury?

**E**RYTHROCYTE transfusion is the most common procedure in hospitalized patients; approximately 15 million erythrocyte units are transfused per year in the United States and 70 million units worldwide. Although the known risks of erythrocyte transfusion have substantially decreased as a result of improvements in testing and storage, serious adverse events associated with transfusion remain, and some new risks are emerging.

Adverse events are often categorized as infectious or non-infectious serious hazards of transfusion. Traditionally, non-infectious serious hazards of transfusion included transfusion-related acute lung injury, hemolytic transfusion reactions, and microbial contamination, which remain the leading causes of transfusion-related fatalities reported to the U.S. Food and Drug Administration.<sup>1</sup> New noninfectious serious hazards of transfusion, such as transfusion-associated morbidity and mortality, are increasingly recognized.<sup>2</sup> In this issue of ANESTHESIOLOGY, Engoren<sup>3</sup> performed a subset analysis of the ARDSNet05 Fluid and Catheter Treatment Trial to determine the effect of erythrocyte transfusion on renal injury.

The Fluid and Catheter Treatment Trial was a prospective, randomized, multicenter trial that evaluated the use of pulmonary artery catheter *versus* central venous catheter for the management of patients with acute lung injury or acute respiratory distress syndrome.<sup>4</sup> In addition, patients were randomized to receive liberal or conservative fluids guided by an explicit protocol. Fluid management prescribed by the protocol allowed choice of isotonic crystalloid, albumin, or blood products (although volumes were dictated) in patients who were not in shock but had oliguria or ineffective circulation with central venous pressure or pulmonary artery occlusion pressure below the target range. Study outcomes (death, ventilator-free days, intensive care unit-free days, and number of days without organ failure) did not differ among pulmonary artery *versus* central venous catheter cohorts. It is noteworthy that more patients in the pulmonary artery catheter group *versus* the central venous pressure group met shock criteria (37 *vs.* 32%,  $P = 0.06$ ) and were on vasopressors (36 *vs.* 30%,  $P = 0.05$ ) at enrollment. In addition, although the two groups had no significant differences in hemoglobin concentrations, mean arterial pressure, pulmonary artery occlusion pressure, or central venous pressure,

the pulmonary artery catheter group received more erythrocyte transfusion (38 *vs.* 30%,  $P = 0.008$ ). However, it is noteworthy that the results of the liberal *versus* conservative use of fluids were not included in Engoren's subset analysis,<sup>3</sup> even though all analyses were stratified by fluid-therapy assignment.

Engoren<sup>3</sup> matched erythrocyte-transfused and nontransfused patients based on propensity score, which included demographics, comorbidities, Acute Physiology and Chronic Health Evaluation III scores, etiology of acute respiratory distress syndrome, laboratory values, ventilator settings, and hemodynamic data. To determine the effect of transfusion on kidney injury, changes in creatinine concentrations between day of transfusion and day 7 were evaluated. The study concluded that there was no decrease or increase in kidney injury the next day, or by day 7, or by receiving dialysis on day 90 as a result of transfusion.

Concerns about study design include patient classification. For example, patients who received erythrocyte transfusion after acute kidney injury occurred were deemed "non-transfused." In addition, the model only considered the first transfusion day and not subsequent transfusion days. Thus, the additive effect of transfusion on renal function in patients with kidney injury and the additive effect of subsequent transfusions were not considered. Furthermore, the number of transfusions, duration of blood product storage, other blood product administration (*i.e.*, plasma, platelets, or cryoprecipitate), and component modification (*e.g.*, leukoreduction) were not considered. Finally, other organ dysfunctions, particularly lung injury, were not assessed. Thus, the paper gives an initial finding that erythrocyte transfusion is not associated with kidney injury, but the study design and lack of important data require that the question be more fully addressed by future research designed primarily to look at the adverse effects of erythrocyte transfusion.

Also of note is the fact that the erythrocyte transfusion and nontransfusion groups had similar hemoglobin concentrations and blood pressure measurements. Indeed, in this study, the mean hemoglobin concentration of 93 g/l is above the typical threshold of 70 g/l, which has outcomes equivalent to a threshold of 90–100 g/l.<sup>5</sup> Therefore, the study results may be confounded by the fact that patients were

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transfused at hemoglobin concentrations above which outcomes may be effected.

Multiple studies have investigated the association of erythrocyte transfusion and mortality, hospital length of stay, infection, multiorgan failure, and acute respiratory distress syndrome, but renal injury has not been extensively investigated.<sup>5</sup> A study querying a large U.S. database on the effects of transfusion in 8,799 patients undergoing lower-extremity revascularization procedures demonstrated that intraoperative transfusion was associated with renal failure as well as mortality, morbidity, sepsis, and pulmonary occurrence after propensity and risk adjustment.<sup>6</sup> Another retrospective study of cerebral trauma patients investigating risk factors for acute kidney injury demonstrated that an accumulative dose of mannitol, but not erythrocyte transfusion volume, was associated with kidney injury.<sup>7</sup>

Erythrocyte component factors, including product modification or storage duration, may increase or decrease the risk of renal injury. One study investigated the effects of leukoreduction in 1,034 cardiac surgery patients and demonstrated that patients who received leukoreduced *versus* nonleukoreduced erythrocyte transfusion had lower risk of acute kidney injury and in-hospital mortality.<sup>8</sup> In a retrospective study of moderately injured trauma patients, old (14 days or more), but not young (fewer than 14 days), erythrocytes were associated with increased mortality, renal dysfunction, and pneumonia.<sup>9</sup>

Thus, the effects of erythrocyte transfusion on the kidneys are currently unknown. Theoretically, erythrocyte transfusion increases erythrocyte mass, which should result in improved tissue oxygen delivery. Tissue oxygen delivery is dependent on additional factors, however, such as cardiac output and oxygen saturation. In addition, oxygen delivery depends on adequate blood flow, which is regulated by hypoxic vasodilation. Therefore, erythrocyte transfusion should improve tissue oxygenation and renal blood flow in addition to protecting against renal injury. Yet, stored erythrocyte blood products may have impaired ability to deliver oxygen—potentially associating transfusion with kidney injury.

In contrast to the kidney, transfusion is associated with lung injury, secondary to transfusion-related acute lung injury and transfusion-associated circulatory overload. In particular, transfusion-related acute lung injury is the result of neutrophil activation within the pulmonary capillaries, which leads to endothelial apoptosis and pulmonary edema. Neutrophil activation results from leukocyte antibodies or other blood product contaminants; the neutrophils are generally previously primed through pulmonary endothelial activation, infection, or another event. The lung has a high concentration of neutrophils, which may be the reason transfusion-related acute lung injury occurs in the lung *versus* other organs. Transfusion-associated circulatory overload results from an increase in intravascular volume leading to

pulmonary edema. Hence, transfusion-related acute lung injury and circulatory overload-like events should not occur in the kidney.

Engoren's article in this month's ANESTHESIOLOGY<sup>3</sup> proposes an important question: *Does erythrocyte transfusion cause acute kidney injury?* This question should be taken into consideration when designing future studies on the effects of transfusion, including the effects of storage duration and other product modifications. Hopefully, as more is learned about the effects of transfusion, appropriate management or changes in blood products will occur to optimize patient care.

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