

Should Patients in Intensive Care Units Receive Erythropoietin?

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REDUCING THE FREQUENCY OF RED BLOOD CELL TRANSFUSION is a goal of modern blood management. The primary driving force during the past 15 years has been safety. In the mid 1980s the HIV (human immunodeficiency virus) epidemic and frequent transmission of hepatitis C led to careful examination of transfusion practices.¹ A review of the data available then showed no evidence for maintaining hemoglobin concentrations at 10 g/dL or hematocrit at 30%,¹ the so-called 10/30 rule. Subsequent new guidelines urged a lower threshold and consideration of symptoms and other clinical parameters,² although clinical judgment was the cornerstone of many of the recommendations.

Blood transfusion has many known adverse effects aside from the potential transmission of infectious disease, including allergic reaction; febrile, nonhemolytic transfusion reactions; red blood cell alloimmunization; and leukocyte/platelet alloimmunization.³ In most patients these events have few clinical consequences. Less common but more serious adverse effects include acute hemolytic reactions, delayed hemolytic reactions, and transfusion-related acute lung injury. Most acute hemolytic reactions from ABO incompatibility are caused by human error, resulting from a patient receiving an incorrect unit of blood.³ Allogeneic transfusion has been suggested to have an immunomodulating effect that increases the risk of cancer recurrence and bacterial infections, but evidence from a randomized trial comparing autologous with allogeneic transfusions in patients with colon cancer showed no association of allogeneic transfusions with cancer.⁴ Trials have yielded inconsistent results regarding the risk of bacterial infections.⁴⁻⁸ It is not known whether leukodepletion will reduce the immunomodulating effect of allogeneic transfusion.

During the past decade the safety of the blood supply with regard to infectious disease transmission has greatly improved. Very sensitive assays have been developed that detect disease at lower concentrations and shorten the window between the onset of disease and detection by screening tests.⁹ More recently, an even more sensitive technique, nucleic acid amplification testing, has been implemented in

the United States.^{10,11} A recent study evaluated the rates of viral markers in about half of the US blood supply for a 3-year period and estimated the residual likelihood of a given unit having detectable levels of hepatitis B, hepatitis C, HIV, or human T-lymphotrophic virus. After screening the blood supply with the new nucleic acid amplification tests, the estimates of residual units of infected blood donated by repeat donors were 1 per 1.935 million for hepatitis C and 1 per 2.135 million for HIV.¹² The rates for first-time donors were about twice the rates for repeat donors. This improvement in detection of infected donated blood is a remarkable achievement of investigators, the blood banking community, and regulators.

But even these low rates are not good enough.¹³ While the goal is achieving a “zero”-risk blood supply,¹³ what price is the United States willing to pay to achieve this? For example, one of the latest US policies excludes donors who lived in the United Kingdom and parts of Europe. As a result, about 2% to 5% of the donor pool can no longer donate blood,^{14,15} reducing the donor pool and increasing the likelihood of blood shortages. This is good policy if it results in improved safety. However, while blood transfusion can transmit bovine spongiform encephalopathy, the infectious agent that causes variant Creutzfeldt-Jakob disease, in sheep,^{16,17} the risk in humans is uncertain. Thus, the current policy is designed to reduce the risk of a possible (unknown) dangerous infection at the cost of increasing the possibility of blood shortages.

Erythropoietin, which stimulates red blood cell production and thereby reduces the need for transfusion, has been proposed as a possible alternative to blood transfusion for some patients.¹⁶ A previous study¹⁸ found that when 160 critically ill patients were randomized on intensive care unit (ICU) day 3 to erythropoietin, 300 U/kg, or placebo daily for 5 days followed by every-other-day administration, eryth-

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ropoietin reduced red blood cell transfusions by almost 50%. Recombinant human erythropoietin (rHuEPO) has been used to treat patients with cancer¹⁹ and reduces allogeneic blood use in patients undergoing joint replacement.²⁰ In addition, erythropoietin use could avoid the adverse effects of stored allogeneic blood, which has lower levels of 2,3-diphosphoglyceric acid^{21,22} and decreased red blood cell membrane deformability.²³ Age of blood has been associated with decline in gastric pH,²⁴ pneumonia,²⁵ and mortality.²⁶

In this issue of *THE JOURNAL*, Corwin and colleagues²⁷ provide evidence to support the use of rHuEPO to reduce allogeneic blood transfusion in critically ill patients. In their randomized controlled trial of patients admitted to the ICU for longer than 3 days, patients were randomly assigned to receive weekly injections of 40 000 units of erythropoietin (n=650) or placebo (n=652); all patients received iron. The primary outcome was transfusion avoidance within 28 days. The study has a number of important features of a well-designed trial, including concealed randomization, multicenter implementation, and stratified allocation. However, only 19% of eligible patients were approached for consent. The final sample was only 13% of those eligible, raising questions about the generalizability of the study.

The study showed that weekly injection of rHuEPO reduced exposure to any allogeneic blood by about 10% (the rate of receiving any transfusion was 60.4% with placebo vs 50.5% with rHuEPO). Among enrolled patients, who had to be in the ICU for 3 days or longer, 10 patients had to be treated with rHuEPO to prevent 1 patient from receiving a transfusion during the 28-day study. In addition, patients receiving rHuEPO had a median reduction of 1 unit of blood transfusion and a 0.38-g/dL greater increase in hemoglobin concentration compared with placebo. On the other hand, the clinical outcomes (which the authors acknowledge the study was underpowered to detect), including mortality, morbidity, length of stay, number of days receiving mechanical ventilation, or readmission to the ICU, were not significantly different. A total of 111 patients in the rHuEPO group died compared with 120 in the placebo group, making it unlikely that even a much larger study would find a significant difference in mortality. No substantive differences across subgroups were seen in transfusion reduction or mortality.

Several aspects of this trial require examination. First, is transfusion sufficiently harmful that simply preventing transfusion is the appropriate outcome? Given the current safety of the blood supply, perhaps this is no longer an adequate outcome on which to base treatment decisions and regulatory approval. However, since US policy seems to adhere to the belief that the blood supply can never be safe enough, perhaps this outcome could be appropriate. Regardless, improvement in mortality or morbidity would be a more convincing outcome for clinical decision making.

Second, the transfusion trigger in the study by Corwin et al²⁷ was a hemoglobin level of about 8.5 g/dL. This trigger level is disappointing given the Transfusion Require-

ment in Critical Care (TRICC) trial, which found that ICU patients experienced no advantage from a transfusion threshold to keep their hemoglobin concentrations above 10 g/dL compared with a threshold to keep hemoglobin concentrations above 7 g/dL.²⁸ In another recent study²⁹ evaluating transfusion practices in European ICU patients in 1999, 2 years after the TRICC study was published, the mean (SD) hemoglobin level before transfusion among patients who were not actively bleeding was 8.5 (1.1) g/dL, comparable to the transfusion threshold used in the study by Corwin et al.²⁷ These studies strongly suggest that clinicians have not incorporated the results from the TRICC trial into practice. Additional high-quality clinical trials that replicate the findings from the TRICC trial will be needed to convince clinicians that the lower transfusion threshold is safe. Unfortunately, there are no other adequately powered trials evaluating transfusion triggers in ICU or other settings.^{30,31}

Third, Corwin et al²⁷ also may have been able to achieve the transfusion reduction by decreasing the transfusion threshold to 7g/dL.²⁶ This is a less expensive approach to reduce the use of allogeneic blood than administering erythropoietin. However, as pointed out by the authors, the transfusion thresholds included in their study represent the predominant current practices in ICUs in the United States and Europe.

Should erythropoietin be used in all patients admitted to intensive care for longer than 3 days? A formal cost-effectiveness analysis is needed, although the results are likely to depend largely on the parameters identified in prior work evaluating the cost-effectiveness of HIV-testing protocols for donated blood,^{32,33} in which the most important variable is the amount one is willing to pay to reduce the very small risk of transfusion to (almost) zero. The costs involved are straightforward on the surface. Ten patients had to be treated with 3 doses of rHuEPO at \$1200 per patient (\$400 per dose) to save the cost of 1 patient being transfused (at \$400 per unit of blood) during a 28-day period. The known adverse effects of allogeneic blood are so low that they only minimally affect cost^{32,33}; rHuEPO also had few adverse effects in this study.²⁷ If transfusion avoidance and the pursuit of zero risk from infectious diseases transmitted by blood transfusion, regardless of cost, the standard used for nucleic acid amplification testing, is applied, then this treatment would be cost-effective.³² From a clinical standpoint, the effectiveness of the treatment in improving clinical outcomes has not been established. This study did not answer that question.

During the past 20 years nearly all the work to improve blood management has focused on reducing risk and transfusion avoidance. While the search and testing for new infections that threaten the blood supply must continue, it is time to devote more effort in defining how to optimally use blood transfusions and drugs such as erythropoietin to maximize outcomes in specific patient populations. Clinical trials are needed to replicate the findings of the TRICC trial

in other study populations in whom blood transfusion is frequently administered, such as surgical patients.³⁴ It is time to move from the concept of a transfusion trigger of “how low can you go” to evaluating the use of blood and blood-related products to minimize mortality and morbidity, including organ dysfunction, and improve patient outcomes.

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