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Restrictive or liberal approach to red blood cell transfusion for cardiac surgery

Among the largest group of recipients of red blood cell transfusions are patients undergoing cardiac surgery. Whether a restrictive approach to intraoperative and postoperative transfusion in cardiac surgery is superior to a more liberal approach with regard to patient outcomes is unclear. The authors conducted a study to determine whether a restrictive transfusion approach applied throughout the perioperative period would be noninferior to a liberal approach in terms of major morbidities and mortality. They conducted a multicenter, randomized, controlled trial with patients undergoing cardiac surgery who had a moderate to high risk of death. The Transfusion Requirements in Cardiac Surgery (TRICS) III trial enrolled patients 18 years of age or older who had a European System for Cardiac Operative Risk Evaluation (EuroScore I) of six or higher on a scale of zero to 47, with higher scores indicating a higher risk of death after cardiac surgery. The patients were randomized to a restrictive red blood cell transfusion threshold (transfuse if the hemoglobin level is less than 7.5 g/dL) or a liberal red blood cell transfusion threshold (transfuse if the hemoglobin level is less than 9.6 g/dL in the operating room or ICU or is less than 8.5 g/dL in the non-ICU ward). The primary outcome was death from any cause, myocardial infarction, stroke, or new onset renal failure with dialysis by discharge or day 28, whichever came first. The results showed that the primary outcome occurred in 11.4 percent of patients in the restrictive-threshold group and 12.5 percent of those in the liberal-threshold group. Furthermore, mortality was three percent in the restrictive group and 3.6 percent in the liberal group. Red blood cell transfusions occurred in 52.3 percent of patients in the restrictive group and 72.6 percent in the liberal group. The investigators found no significant differences between groups with regard to the other secondary outcomes. They concluded that for patients undergoing cardiac surgery who were at moderate to high risk for death, a restrictive strategy for transfusion was noninferior to a liberal strategy for the outcomes evaluated. The investigators noted that these same outcomes were achieved in the restrictive group with fewer units of blood being transfused.

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AAV5-factor VIII gene transfer in severe hemophilia A

Hemophilia A is an X-linked genetic mutation that encodes coagulation factor VIII. Patients with severe hemophilia A (factor VIII activity level of less than 1 IU/dL) have a propensity for spontaneous bleeding in joints and soft tissue. This may cause debilitating arthroplasty and increase the risk of intracerebral hemorrhage. The standard-of-care treatment for hemophilia A is to give the patient exogenous factor VIII before bleeding occurs. However, due to the short half-life of available factor VIII, the patient often requires several infusions weekly. The construction of the vector-mediated gene therapy AAV5-hFVIII-SQ showed promise in a dose-dependent increase in factor VIII expression in mouse and nonhuman primate models. The authors performed a phase one-two dose-escalation study of factor VIII gene transfer from a single intravenous infusion of AAV5-hFVIII-SQ in nine men with hemophilia A. They enrolled subjects into one of three dose cohorts—low, intermediate, and high dose—and followed them for 52 weeks. The results showed that factor VIII levels remained at 3 IU or less per deciliter in the recipients of the low

or intermediate dose. However, in the high-dose cohort, the factor VIII activity level was more than 5 IU/dL between weeks two and nine after gene transfer in all seven participants. Additional encouraging results showed that in six subjects, the factor VIII level increased to a normal value (50–150 IU/dL) that was maintained at one year after receipt of infusion. In the high-dose group, the median annualized bleeding rate decreased from 16 events before the study to one event after gene transfer. In all participants, the need for factor VIII for bleeding ceased by 22 weeks. The only significant adverse event observed was progression of pre-existing chronic arthropathy in one subject. The primary adverse event was asymptomatic elevation of the serum alanine aminotransferase level to 1.5 times the upper limit of the normal range or less. No neutralizing antibodies to factor VIII were detected in the subjects. The authors concluded that this study presents exciting findings about the infusion of AAV5-hFVIII-SQ, including the sustained normalization of factor VIII activity at one year in the six of seven subjects who received a high dose. This resulted in a profound decrease in the use of exogenous factor VIII, as well as stabilization of bleeding episodes. The authors noted, however, that due to the small size of the study, no definitive safety conclusions can be drawn.

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