

Recombinant Human Erythropoietin

Efficacy and Safety Considerations for Maximizing Blood Conservation in Cardiac Surgery

BLOOD products transfused to patients undergoing cardiac surgery consume approximately 15% of the banked blood supply in the United States.¹ Cardiac surgical patients known to be at particular risk for receiving allogeneic blood transfusions in the perioperative period include patients with preoperative anemia and patients undergoing surgeries other than primary coronary artery bypass grafting operations.¹ In this issue of *ANESTHESIOLOGY*, Yoo *et al.* report results of a single-center randomized controlled trial (RCT) of preoperatively anemic valvular heart surgery patients who a day before surgery received either 500 IU/kg of IV recombinant human erythropoietin α (rhEPO) plus iron supplement ($n = 37$), or a placebo bolus of normal saline ($n = 37$).² Interestingly, despite the short interval between rhEPO administration and initiation of surgery (16–24 h), subjects in the rhEPO group were significantly less likely than subjects in the placebo group to receive packed erythrocyte (PRBC) transfusions during the perioperative period spanning surgery and the first 4 postoperative days (59% compared with 86%; $P = 0.009$).² Furthermore, subjects in the rhEPO group who received PRBCs were transfused with significantly fewer units than subjects in the placebo group (1.6 ± 0.9 units/patient *vs.* 3.7 ± 2.1 units/patient; $P = 0.004$).²

The results of this RCT are encouraging regarding potential for rhEPO to be used as an effective component of multimodal efforts to minimize perioperative blood transfusions in anemic patients undergoing valvular heart surgeries. A key strength of the study by Yoo *et al.* is that it enrolled patients known to be at increased risk for receiving perioperative PRBC transfusions (*i.e.*, preoperative anemia and need for valvular surgery). Prior studies of rhEPO have enrolled populations of primarily coronary artery bypass graft surgery



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patients who were not selected for having preoperative anemia.^{3–6} Still, 59% of the patients in the rhEPO intervention group received perioperative PRBC transfusions, suggesting that the work by Yoo *et al.* should provide a starting point for future studies designed to test alternative rhEPO blood conservation approaches that could reduce PRBC use even further. Mitigating allogeneic PRBC transfusions, particularly in higher risk cardiac surgical groups, is important for reducing risks of transfusion-related infections and immunologic reactions, and for decreasing consumption of a limited health care resource.⁷ Furthermore, observational studies suggest that PRBC transfusion should be limited as much as possible because it is associated with increased morbidity and mortality after cardiac surgery.^{8–11} Subjects in the rhEPO group of the Yoo *et al.* study received a mean of 1.6 units of PRBC, so it is plausible that additional blood conservation measures could reduce need for transfusion in considerably more of these higher-risk patients.

Consistent with the 2011 Update to the Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists Blood Conservation Clinical Practice Guidelines, subjects in both arms of the Yoo *et al.* study intraoperatively received the lysine analog tranexemic acid, and a red cell salvage device was utilized, allowing reinfusion of salvaged red blood cells.^{1,7} However, the prime volume used in the cardiopulmonary bypass (CPB) circuit in the study was 1.6 l, suggesting that perioperative transfusion might be further reduced by implementing other recommendations from the Society of Thoracic Surgeons and Society of Cardiovascular Anesthesiologists Blood Conservation Clinical Practice Guidelines, such as retrograde autologous CPB circuit prim-

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◆ This Editorial View accompanies the following article: Yoo Y-C, Shim J-K, Kim J-C, Jo Y-Y, Lee J-H, Kwak Y-L: Effect of single recombinant human erythropoietin injection on transfusion requirements in preoperatively anemic patients undergoing valvular heart surgery. *ANESTHESIOLOGY* 2011; 115:929–37.

ing and vacuum-assisted venous drainage used in conjunction with minicircuits.¹ Also, subjects in this study were transfused for hemoglobin levels less than 7 mg/dL while on CPB and hemoglobin levels less than 8 mg/dL after separating from CPB and during the first 4 postoperative days.² The Society of Thoracic Surgeons and Society of Cardiovascular Anesthesiologists Blood Conservation Clinical Practice Guidelines suggest that these transfusion thresholds could be dropped to as low as less than 6 g/dL during CPB in patients who have limited comorbidities, and to less than 7 mg/dL in most patients during the period after CPB.⁷ It would be interesting to investigate if rhEPO continues to significantly impact PRBC transfusion rates when coupled with additional recommended blood conservation measures, and to assess if the 59% PRBC transfusion rate in the rhEPO intervention group drops substantially.

Although the 2011 Updated Society of Thoracic Surgeons and Society of Cardiovascular Anesthesiologists Blood Conservation Clinical Practice Guidelines state that “it is reasonable to use preoperative erythropoietin plus iron, given several days before cardiac surgery, to increase red cell mass in patients with preoperative anemia (Class IIa recommendation),” the guidelines do not provide recommendations regarding the dose, route (subcutaneous *vs.* IV), timing, or contraindications to administration of perioperative rhEPO.¹ Although there are at least 13 previous RCTs that have investigated if receiving perioperative rhEPO significantly decreases transfusions in cardiac surgical patients, the timing, route of administration, and dose of rhEPO varied substantially between these studies.^{3,5,6} Yoo *et al.*'s preoperative 500 IU/kg IV rhEPO intervention on day 1 significantly decreased overall perioperative transfusion rates in anemic patients undergoing cardiac valve surgery, but the subjects in both the rhEPO and placebo arms of the study were still anemic on the day of surgery and underwent similar rates of intraoperative PRBC transfusion. The bulk of the between-group differences in PRBC transfusions occurred during postoperative days 1–4.² Between-group differences in post-CPB reticulocyte decline were not significant until postoperative day 2, and absolute reticulocyte counts were not significantly higher in the rhEPO group until postoperative day 4.² Yoo *et al.* are correct that a single IV rhEPO dose given the day before surgery is convenient, but, unlike many coronary artery bypass grafting surgeries, cardiac valve surgeries are often scheduled electively, and, for many patients, preoperative planning might permit rhEPO to be administered at an earlier preoperative time point (such as 3–4 days before surgery). A prior RCT that assessed rhEPO given at a dose of 100 IU/kg IV 4 days before coronary artery bypass grafting surgery found that preoperative hemoglobin was significantly higher in the rhEPO group compared with the control group.⁶ With the objective of also addressing the

likelihood of intraoperative transfusion, it seems warranted to conduct future large studies of preoperatively anemic subjects in order to compare perioperative transfusion rates for subjects receiving a single dose of rhEPO 3–4 days before valve surgery with rates in subjects receiving a single dose of rhEPO 1 day before surgery. Furthermore, since Yoo and colleagues argue that preoperative day 1 rhEPO administration is well timed to mitigate blunted erythrocyte production after CPB, an additional study arm could allow comparison of transfusion rates in subjects receiving single preoperative boluses of rhEPO to transfusion rates in subjects who receive rhEPO boluses at both earlier and later preoperative time points. Future studies could also directly compare efficacy of subcutaneous *versus* IV rhEPO dosing, as subcutaneous administration would be most practical for outpatient preoperative administration.

Although it would be helpful for future studies to enroll large enough numbers of subjects to permit comparison of alternative preoperative rhEPO regimens for efficacy in reducing perioperative PRBC transfusions, it is also important that additional studies are designed with the statistical power needed to evaluate the safety of rhEPO use in cardiac surgical patients. Erythropoietin-stimulating agents are not approved by the Food and Drug Administration for use in cardiac surgical patients, and, in fact, the Food and Drug Administration states that “Epopogen is not indicated for use in patients undergoing cardiac and vascular surgery.”¹² Although rhEPO is approved by the Food and Drug Administration to treat anemic patients with renal disease or cancer, or to reduce allogeneic blood transfusions in patients scheduled to undergo elective noncardiac, nonvascular surgeries, this approval is accompanied by a Food and Drug Administration-required Boxed Warning in prescribing information that states that erythropoietin-stimulating agents increase the risk of death, myocardial infarction, stroke, venous thromboembolism, thrombosis of vascular access, and tumor progression and recurrence.^{12*} These adverse events have been identified mainly in nonsurgical patients receiving repeated doses of rhEPO over a longer timeframe than would generally be proposed for anemic patients scheduled for cardiac surgery.¹² However, a multicenter RCT of spine surgery patients who received preoperative rhEPO (600 IU/kg subcutaneous weekly for 3 weeks before surgery without prophylactic anticoagulation) *versus* placebo reported significantly higher incidence of postoperative deep vein thrombosis in the rhEPO group (4.7% *vs.* 2.1%).¹³ Yoo *et al.*'s study did not assess for development of postoperative deep vein thrombosis or thromboembolic events, and, like previous studies of rhEPO in cardiac surgical patients, this study was not sufficiently powered to assess differences in development of thrombotic or other adverse cardiovascular outcomes. The authors did identify significantly reduced acute kidney injury in the rhEPO group, suggesting that future larger studies of clinical cardiovascular outcomes might actually identify organ protective benefits of perioperative rhEPO administration. Fu-

* United States Food and Drug Administration: http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/103234Orig1s5166_103234Orig1s5266lbl.pdf. Accessed July 13, 2011.

ture larger RCTs that evaluate subjects for adverse events during the short and intermediate postoperative periods should be able to evaluate whether there is a clinically relevant risk or benefit of rhEPO administration and related PRBC transfusion reduction that extends to thrombotic and cardiovascular outcomes after cardiac surgery.

In summary, Yoo *et al.*'s findings suggest that preoperative rhEPO may be a useful tool for reducing need for PRBC transfusions in cardiac surgical patients at higher risk for requiring allogeneic blood transfusions. However, use of rhEPO should be considered only as an adjunct, and not a replacement, for other well-established and effective strategies for blood conservation in cardiac surgical patients. Most importantly, future studies are needed to address both the safety and potential benefits of using rhEPO in cardiac surgical patients. These studies will hopefully identify a perioperative rhEPO regimen that provides a favorable balance between medical benefits, risks, and health care costs.

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