More on Transfusion and Adverse Outcome

It's Time to Change

PREOPERATIVE anemia and perioperative allogeneic erythrocyte (RBC) transfusion have both been shown to be independently associated with adverse outcome, such as increased mortality, postoperative infections, lung and kidney injury, myocardial infarction, stroke, and increased length of hospital stay.[1–6] The relative contribution of each of these conditions, and their interactions, is difficult to specify. The study by Glance *et al.* in this issue of ANESTHESIOLOGY is important, because the authors studied more than 10,000 patients with preoperative anemia who underwent elective noncardiac surgery and received up to 2 units of RBCs intraoperatively. The study used records from the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) database.[7]

In an attempt to reduce confounders, the investigators included only patients within a preoperative hemoglobin range of 6–10 g/dl. In this hemoglobin range, according to American Society of Anesthesiologists guidelines, RBC transfusions may be administered on a clinical basis.[8] Thus, these RBC transfusions had likely occurred after limited blood loss. Observed outcomes thus may be attributed more clearly to RBC transfusion than if patients had started with normal preoperative hemoglobin and, as a consequence, had to have lost large amounts of blood during ill-controlled surgery before being transfused. In the latter case, it would be difficult to say whether the adverse outcomes were due to hemodynamic instability and other effects of acute blood loss or due to the RBC transfusion itself. Since in the study by Glance *et al.*[7] all patients were anemic preoperatively and may not have experienced massive blood loss before the index transfusion, the observed outcomes may be attributed quite clearly to the RBC transfusion administered. Also, the negative impact on outcome was substantial: Transfusion of only 1 or 2 units of RBCs resulted in more septic (odds ratio [OR]: 1.43), pulmonary (OR: 1.79), thromboembolic (OR: 1.77), and wound (OR: 1.87) complications and increased mortality (OR: 1.29).

The key strengths of this study lie in the number of the patients and the detailed data collection; the shortcomings are shared with many other transfusion cohort studies. Despite various efforts, it is always difficult to call transfusion as the cause of an adverse outcome, as opposed to some other associated patient comorbidity. A brief look at table 1 of the Glance *et al.* article indicates that the transfused cohort was generally in worse shape at baseline, compared with the not-transfused group (lower hematocrit, older age, more dependent, more comorbidities, etc.). Statistical methods are used to remedy this commonly seen disparity. Multivariate analysis can be used to adjust for confounders (the method used in the current study), or transfused patients can be matched against nontransfused patients (with varying degrees of complexity). Although these approaches often do marvels, they are not "cures," because they are ultimately limited by the available variables and their data. Do we have all the potential confounders captured in our dataset? How certain are we of the primary reasons behind giving transfusion to every single case? What was the tipping point that made the physician decide to give blood to this patient, but not the other patient? These questions are often impossible to answer accurately in cohort studies, and they undermine the validity of the results.

Although the multivariate adjustment used in this study is a valid method, more data on the models would have been helpful (*e.g.*, strength of association as indicated by pseudo-R-squared or the reasoning behind creating the specific hematocrit categories). In addition, use of a matching approach may have allowed for more transparent interpretation of the results (at expense of reduced sample size). Given the large sample size, it would have been interesting to see whether the transfused and not-transfused patients could have been effectively matched to each other based on the risk factors for receiving transfusions (and, possibly, known risk factors of each outcome), thus allowing a more direct comparison.

In addition, large database analyses do have limitations of their own. Problems with miscoding of procedures and diagnoses are well recognized.[9] This study by Glance *et al.*, however, relies on the NSQIP database, which is more accurate than other state or federal administrative datasets. Data are collected by trained surgical chart reviewers, and participating hospitals undergo interrater reliability audits.[10]‖ Still, for any particular study, a generalized database such as NSQIP will not provide all the information that one might wish for.

In the case of the present study, we do not know the extent of pre- or postoperative transfusion in the study patients; because of NSQIP data definitions, patients could have received up to 4 units preoperatively and 4 units postoperatively. Transfusion before or after surgery, but not during,

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‖ American College of Surgeons. Participation requirements. In: National Surgical Quality Improvement Program. Available at: https://acsnsqip.org/main/get_started_requirements.asp. Accessed July 20, 2010.

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◆ This Editorial View accompanies the following article: Glance LG, Dick AW, Mukamel DB, Fleming FJ, Zollo RA, Wissler R, Salloum R, Meredith W, Osler TM: Association between intraoperative blood transfusion and mortality and morbidity in patients undergoing noncardiac surgery. ANESTHESIOLOGY 2011; 114:283–92.

might decrease the detected effect of intraoperative transfusion; alternatively, those patients requiring pre- or postoperative transfusion might be more likely to receive blood intraoperatively. NSQIP does not record intraoperative nadir hematocrit or immediate postoperative hematocrit. Thus, we do not know if lower intraoperative hematocrit was associated with worse outcome. Because NSQIP data do not include a hospital identifier, the final results may have been confounded by hospital-based differences in practice, including differences in local transfusion triggers.[10]

Results of the present study are in line with previous studies in general,[3] cardiac,[1] orthopedic,[4] and trauma surgery.[5,6] Also, in a recent cohort data analysis in 239,286 elderly Veterans Administration patients with and without preoperative anemia RBC transfusions resulted in increased 30-day mortality (adjusted OR: 1.37 [1.27–1.48]).[11] Only in a 1-min subgroup of patients with a preoperative hematocrit of less than or equal to 24% (1.9% of the study population) did RBC transfusion result in a reduced mortality, whereas in patients with a preoperative hematocrit of greater than 30% (more than 80% of the study population), RBC transfusions actually increased mortality significantly (ORs: 1.37–1.59). Interestingly, in patients who eventually died, late postoperative complications, such as failure to wean from the ventilator and unplanned intubation indicative of lung injury, renal failure, and infectious complications, were very similar to the ones found in the article by Glance *et al.*,[7] and they were more frequent than in nontransfused patients.[11]

Another aspect of the study by Glance *et al.*[7] deserves mentioning, namely the fact that nonelective cases were excluded. Therefore, it should have been possible to treat preexisting anemia before surgery. This is important, because preoperative anemia is frequent,[2,11–13] easy to detect, and—in many situations—treatable at relatively low costs.[14] At least, in orthopedic surgery, there is strong evidence that preoperative treatment of anemia results not only in reduced RBC transfusion, but also in improved outcome.[15]

Where do we go from here? The call for prospective, randomized studies on the benefit or detriment of allogeneic RBC transfusions is the usual conclusion after studies of the likes of Glance *et al.* are published. This conclusion is certainly politically correct; however, if Glance *et al.* and the slew of others are correct—which is a valid possibility—can we take the responsibility to continue today's widespread transfusion practice, an approach that is putting patients at risk?

Contrarians to the above still overly rely on banked blood products, despite mounting evidence that patient blood management is achievable, avoids exposure to allogeneic blood products, improves patient outcome, and saves resources.[15,16] The ease of ignoring preoperative anemia as well as the simplicity of ordering and transfusing RBCs and thereby completely ignoring the burgeoning evidence of adverse transfusion outcome are not in the best interest of patients. Maintaining the clinical status quo under such circumstances would not be accepted in any other field of medicine in the context of current safety and quality standards.

Working on studies regarding benefit or detriment of allogeneic RBC transfusions is important, but more so is acting already today according to patient blood management principles; it is time for a change toward better patient care.

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References

1. Karkouti K, Wijeysundera DN, Beattie WS: Risk associated with preoperative anemia in cardiac surgery: A multicenter cohort study. Circulation 2008; 117:478–84
2. Beattie WS, Karkouti K, Wijeysundera DN, Tait G: Risk associated with preoperative anemia in noncardiac surgery: A single-center cohort study. ANESTHESIOLOGY 2009; 110:574–81
3. Bernard AC, Davenport DL, Chang PK, Vaughan TB, Zwischenberger JB: Intraoperative transfusion of 1 U to 2 U packed red blood cells is associated with increased 30-day mortality, surgical-site infection, pneumonia, and sepsis in general surgery patients. J Am Coll Surg 2009; 208:931–7
4. Pedersen AB, Mehnert F, Overgaard S, Johnsen SP: Allogeneic blood transfusion and prognosis following total hip replacement: A population-based follow up study. BMC Musculoskelet Disord 2009; 10:167
5. Charles A, Shaikh AA, Walters M, Huehl S, Pomerantz R: Blood transfusion is an independent predictor of mortality after blunt trauma. Am Surg 2007; 73:1–5
6. Chaiwat O, Lang JD, Vavilala MS, Wang J, MacKenzie EJ, Jurkovich GJ, Rivara FP: Early packed red blood cell transfusion and acute respiratory distress syndrome after trauma. ANESTHESIOLOGY 2009; 110:351–60
7. Glance LG, Dick AW, Mukamel DB, Fleming FJ, Zollo RA, Wissler R, Salloum R, Meredith W, Osler TM: Association between intraoperative blood transfusion and mortality and morbidity in patients undergoing noncardiac surgery. ANESTHESIOLOGY 2011; 114:283–92.
8. Practice guidelines for perioperative blood transfusion and adjuvant therapies: An updated report by the American Society of Anesthesiologists Task Force on Perioperative Blood Transfusion and Adjuvant Therapies. ANESTHESIOLOGY 2006; 105:198–208
9. Woodworth GF, Baird CJ, Garces-Ambrossi G, Tonascia J, Tamargo RJ: Inaccuracy of the administrative database: Comparative analysis of two databases for the diagnosis and treatment of intracranial aneurysms. Neurosurgery 2009; 65:251–6
10. Gombotz H, Rehak PH, Shander A, Hofmann A: Blood use in elective surgery: The Austrian benchmark study. Transfusion 2007; 47:1468–80
11. Wu WC, Smith TS, Henderson WG, Eaton CB, Poses RM, Uttley G, Mor V, Sharma SC, Vezeridis M, Khuri SF, Friedmann PD: Opera-

tive blood loss, blood transfusion, and 30-day mortality in older patients after major noncardiac surgery. Ann Surg 2010; 252: 11–7

12. Shander A, Knight K, Thurer R, Adamson J, Spence R: Prevalence and outcomes of anemia in surgery: A systematic review of the literature. Am J Med 2004; 116(Suppl 7A):58–69S
13. Goodnough LT, Vizmeg K, Sobecks R, Schwarz A, Soegiarso W: Prevalence and classification of anemia in elective orthopedic surgery patients: Implications for blood conservation programs. Vox Sang 1992; 63:90–5
14. Goodnough LT, Shander A, Spivak JL, Waters JH, Friedman AJ, Carson JL, Keating EM, Maddox T, Spence R: Detection, evaluation, and management of anemia in the elective surgical patient. Anesth Analg 2005; 101:1858–61
15. Spahn DR: Anemia and patient blood management in hip and knee surgery: A systematic review of the literature. ANESTHESIOLOGY 2010; 113:482–95
16. Moskowitz DM, Klein JJ, Shander A, Cousineau KM, Goldweit RS, Bodian C, Perelman SI, Kang H, Fink DA, Rothman HC, Ergin MA: Predictors of transfusion requirements for cardiac surgical procedures at a blood conservation center. Ann Thorac Surg 2004; 77:626–34

ANESTHESIOLOGY REFLECTIONS

The Boston Anesthesia System

To design the Boston Anesthesia System (BAS, *above*), biomedical engineer Jeffrey Cooper, Ph.D., orchestrated collaborations between Harvard's Massachusetts General Hospital (MGH) and the Massachusetts Institute of Technology (MIT). MIT engineers Edwin Trautman and Jeffrey Moore composed computer code for the 8-bit Intel 8080, the "chip" that computer-powered the BAS. Modified from a Volkswagen, a solenoid-operated automatic fuel injector metered liquid volatile inhalant into the N_2O–O_2 mixture resulting from an upstream pair of 8-element digital flow controllers. Magnetically keyed, disposable, prefilled agent-specific containers (labeled "Halothane" and "Enflurane," *above center*) were engineered to prevent user error. Respecting the BAS' mission of "supporting rather than preoccupying" the anesthesiologist, MIT/Harvard solid-state physicist Ronald Newbower and MGH anesthesiologist Reynolds Maier designed an array of safety monitors. Donated to the Wood Library-Museum in 2006, the BAS was hailed by Harvard professor Richard Kitz, M.D., as "a prototype of the first fully electronic, integrated, microprocessor-controlled anesthesia workstation." (Copyright © the American Society of Anesthesiologists, Inc. This image also appears in the *Anesthesiology Reflections* online collection available at www.anesthesiology.org.)

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