Permissive anemia: How low should we go?

Glenn J. R. Whitman, MD

From the Department of Surgery, Johns Hopkins School of Medicine, Baltimore, Md.

Disclosures: Author has nothing to disclose with regard to commercial support.

Received for publication Aug 3, 2015; accepted for publication Aug 3, 2015; available ahead of print Aug 28, 2015.

Address for reprints: Glenn J. R. Whitman, MD, Department of Surgery, Johns Hopkins School of Medicine, 1800 Orleans St, Zayed Tower/Suite 7107, Baltimore, MD 21287 (E-mail: gwhitman@jhmi.edu).

J Thorac Cardiovasc Surg 2015;150:1330-1

0022-5223/\$36.00

Copyright © 2015 by The American Association for Thoracic Surgery

<http://dx.doi.org/10.1016/j.jtcvs.2015.08.008>

Since 1999, blood transfusion triggers have been of interest, in particular as a result of the Transfusion Requirements in Critical Care trial in which a transfusion trigger of 7 g/dL versus 9 g/dL was shown to be equivalent in a critical care population.¹ It was not for another 10 years before a randomized trial examined transfusion triggers in cardiac surgery.² At that time, 3 articles appeared in the same issue of the *Journal of the American Medical Association*. Bennett-Guerrero and colleagues³ showed huge disparities in transfusion rates of between 5% and 95% for isolated coronary artery bypass surgery in 2009. With no perceptible difference in outcome, this represented a huge opportunity to standardize care and improve blood use. In that same issue, Hajjar and colleagues,² using a randomized controlled trial to examine the effect of 2 transfusion triggers in cardiac surgery (hematocrit 24% vs 30%), showed no difference in morbidity or mortality at 30 days.² Finally, an accompanying editorial suggested that blood use and transfusion rates would soon be used as a metric to determine the quality of a cardiac surgery program.⁴

Since that time, Dr Ad and colleagues have published several articles on restrictive blood transfusion strategies in cardiac surgery. In their current article in the *Journal*, Ad and colleagues⁵ compare the postdischarge course of asymptomatic patients, presumably with no coronary artery disease, who underwent isolated valve procedures between 2008 and 2014, and were discharged with a hemoglobin level less than 8 g/dL (N = 153) or greater than 8 g/dL (n = 891). On multivariate analysis, discharge hemoglobin did not predict discharged to home status, 30-day mortality, 30-day readmission rate, or 1-year survival. Furthermore, the authors propensity matched the anemic group to 152 patients with a hemoglobin level greater than 8 g/dL at the time of discharge. Despite discharge hemoglobin levels of 7.5 versus 9.6 g/dL in the 2 groups, a 2.1 g/dL difference (more than in any other study to date), they found no difference in any of their outcome variables. After recognizing that the transfusion rates were equivalent in the 2 propensity-matched groups (by definition), Ad

Glenn J. R. Whitman, MD

Central Message

"To know that we know what we know, and to know that we do not know what we do not know, that is true knowledge." —Nicolaus Copernicus

See Article page 1322.

See Editorial page 1032.

and colleagues⁵ went on to compare the transfused and nontransfused patients in the propensity-matched groups (n = 304). Although addressing a different hypothesis, the data showed that transfusion exposure decreased 1-year survival by 7%, adjusted for discharge hemoglobin concentration. It is a weak conclusion, because the propensity matching was not in an effort to find similar transfused and nontransfused patients, but similar patients with a discharge hemoglobin level less than or greater than 8 g/dL. Nevertheless, it is worthy of note and consistent with the growing conviction that blood transfusions are harmful, particularly when arguably unnecessary.

Ad and colleagues' recommendations as written in their perspective seem almost incontrovertible, "...the practice of blood transfusion after valve surgery to correct lower hemoglobin levels in asymptomatic patients before discharge should be eliminated."⁵ In fact, there continues to be a need for caution regarding this recommendation, a hesitancy acknowledged by the authors themselves. They themselves point out in their "Study Limitations" section, "future studies utilizing a random control design are warranted to evaluate the association between discharge hemoglobin levels and outcomes in asymptomatic patients."⁵

Until recently, every randomized controlled trial looking at hemoglobin transfusion triggers has shown no difference or, in fact, a benefit to restrictive therapy. However, the waters muddled for cardiac surgery in 2015 when Murphy and colleagues⁶ published their results from the Transfusion Indication Threshold Reduction (TITRe2) trial, which randomized patients undergoing open surgery to transfusion triggers between 7.5 and 9 g/dL, finding a significant difference in mortality at 90 days, 4.2% versus 2.6%, in favor of the liberally transfused group. Of note, only 31% of patients were free of coronary artery disease, and in that important respect, it is different from this current study. Further evidence that discharge anemia may be associated with worse outcomes was seen in an analysis of 153,000 patients recently discharged from the Cleveland Clinic. Risk-adjusted 30-day readmissions increased up to 3.5-fold in the group of more than 25,000 patients discharged with a hemoglobin level less than 9 g/dL.⁷ This should give us pause.

Of concern in this trial by Ad and colleagues⁵ is that the predicted Society of Thoracic Surgeons/European System for Cardiac Operative Risk Evaluation mortality rate of the group discharged with a hemoglobin level less than 8 g/dL was approximately twice that of the group discharged with a hemoglobin level greater than 8 g/dL. One would have expected the opposite, that the healthier patients with a lower predicted risk would have been the ones discharged with lower hemoglobin levels. Despite this fact, the providers caring for the sicker group with a higher expected mortality thought it was acceptable to discharge them more anemic.

Although the multivariate and propensity matching analysis failed to show discharge hemoglobin as a predictor of inferior outcomes, this reader cannot help but think that there was some unmeasured variable that allowed physicians to accept a greater discharge anemia in the higher-risk group. From the foot of the bed, physicians simply may be very good at predicting who can and who cannot tolerate anemia. In this respect, the exemplary statistical analysis exhibited by this article may have missed an important, unmeasured, and illusory variable. And as stated, therein lies the crucial need for a randomized trial before we adopt a policy ignoring discharge anemia as an important factor in the care of patients with valvular heart disease.

References

1. Hebert PC, Wells G, Blajchman MA, Marshall J, Martin C, Pagliarello G, et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. *N Engl J Med*. 1999;340:409-17.
2. Hajjar LA, Vincent JL, Galas FR, Nakamura RE, Silva CM, Santos MH, et al. Transfusion requirements after cardiac surgery: the TRACS randomized controlled trial. *JAMA*. 2010;304:1559-67.
3. Bennett-Guerrero E, Zhao Y, O'Brien SM, Ferguson TB Jr, Peterson ED, Gammie JS, et al. Variation in use of blood transfusion in coronary artery bypass graft surgery. *JAMA*. 2010;304:1568-75.
4. Shander AS, Goodnough LT. Blood transfusion as a quality indicator in cardiac surgery. *JAMA*. 2010;304:1610-1.
5. Ad N, Holmes SD, Shuman DJ, Speir AM, Pritchard G, Halpin L. Should asymptomatic patients discharged with lower hemoglobin expect worse outcomes after valve surgery? *J Thorac Cardiovasc Surg*. 2015;150:1322-9.
6. Murphy GJ, Pike K, Rogers CA, Wordsworth S, Stokes EA, Angelini GD, et al. Liberal or restrictive transfusion after cardiac surgery. *N Engl J Med*. 2015;372:997-1008.
7. Koch CG, Li L, Sun Z, Hixson ED, Tang A, Chagin K, et al. Magnitude of anemia at discharge increases 30-day hospital readmissions. *J Patient Saf*. September 2, 2014 [Epub ahead of print].