Review

How low is too low? Cardiac risks with anemia

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Abstract

Despite the increasing availability of data supporting more restrictive transfusion practices, the risks and benefits of transfusing critically ill patients continue to evoke controversy. Past retrospective and observational studies suggested that liberal transfusion strategies were more beneficial in patients whose hematocrit levels fell below 30%. An expanding body of literature suggests that an arbitrary trigger for transfusion (the '10/30 rule') is ill advised. A recent randomized controlled trial provided compelling evidence that similar, and in some cases better, outcomes result if a restrictive transfusion strategy is maintained. The impact of this accumulating evidence on clinical practice is evident in large reports, which show that the average transfusion trigger in critically ill patients was a hemoglobin level in the range 8–8.5 g/dl. Based on the available evidence, transfusion in the critically ill patient without active ischemic heart disease should generally be withheld until the hemoglobin level falls to 7 g/dl. Transfusions should be administered as clinically indicated for patients with acute, ongoing blood loss and those who have objective signs and symptoms of anemia despite maintenance of euvolemia. The hemoglobin level at which serious morbidity or mortality occurs in critically ill patients with active ischemic heart disease is a subject of continued debate but it is likely that a set transfusion trigger will not provide an optimal risk–benefit profile in this population.

Keywords anemia, blood, cardiac disease, critically ill patients, hemoglobin, transfusion trigger

Introduction

For years many physicians firmly believed that a hemoglobin of 10 g/dl and a hematocrit of 30% represented desirable goals in anemic patients, especially those undergoing surgical procedures and those with cardiac disease. Despite the paucity of objective data to support this contention, the so-called '10/30 rule' persisted until recently [1]. Most authorities attribute this bias to a 1942 report by Adams and Lundy [2] in which they recommended a hemoglobin of 10 g/dl and a hematocrit of 30% in the perioperative setting based on their clinical experience. Recent studies [3–7] have provided compelling evidence against the 10/30 rule in critically ill patients as well as in the perioperative period. Despite these data, many clinicians continue to provide transfusion using a hematocrit of 30% as a 'transfusion trigger' [8]. However, current practice and available evidence is gradually shifting from transfusing to an arbitrary hemoglobin (10/30) to achieving a level of hemoglobin necessary to meet the patient's tissue oxygen demands [9,10].

The optimal hemoglobin level is more closely approximated by physiologic measurements [11]. In patients who are not critically ill, most studies have demonstrated that a substantially lower hemoglobin level (7 g/dl) can be tolerated if normovolemia is maintained. Experience in Jehovah's Witness patients has allowed an assessment of human tolerance of severe acute anemia and demonstrated the feasibility of survival in the case of very low hematocrit [12–18]. In a review of 61 medical and surgical reports published from 1970 to 1993, Viele and Weiskopf [17] identified 50 deaths attributed to anemia in untransfused Jehovah's Witnesses with hemoglobin concentrations of 8 g/dl or less, or hematocrit of 24% or less. Of the 50 deaths, 23 were thought to be primarily due to anemia. Except for three patients who died after

ICU = intensive care unit; RBC = red blood cell.

cardiac surgery, all patients whose deaths were attributed to anemia died with hemoglobin concentrations of 5 g/dl or less. There were 25 survivors with a hemoglobin of 5 g/dl or less.

Recently, Weiskopf and coworkers [19] conducted an interventional study to determine whether acute, severe isovolemic reduction in hemoglobin levels to 5 g/dl in healthy, resting individuals would result in inadequate cardiac compensatory mechanisms, and therefore compromise oxygen delivery. No evidence of inadequate oxygenation, as assessed by lack of change in oxygen consumption and plasma lactate concentration, was noted in the 11 preoperative patients and 21 nonsurgical volunteers with hemoglobin levels as low as 5 g/dl.

Anemia in the critically ill patient

Anemia in the setting of critical illness is quite prevalent, with 37–44% of patients receiving at least one blood transfusion during their intensive care unit (ICU) stay [20,21]. In one representative study [8], 85% of patients with an ICU length of stay greater than 1 week received at least one blood transfusion. In more than two thirds of these cases blood transfusion was not associated with acute blood loss. Concerns over the deleterious effects of anemia are increasingly being balanced by an increased awareness of the serious, well documented consequences of packed red blood cell (RBC) transfusion [22].

In a pivotal study published in 1999, Hebert and coworkers [3] prospectively randomized 838 critically ill ICU patients with hemoglobin under 9 g/dl to one of two transfusion strategies. The control group ('liberal strategy') received transfusion of packed RBCs when the hemoglobin fell below 10 g/dl. The study group ('restrictive strategy') received transfusion of packed RBCs when hemoglobin fell below 7 g/dl. The in-hospital mortality rate was significantly lower in the restrictive strategy group. The 30-day mortality rate was not significantly different between groups but was significantly lower with the restrictive strategy in patients who were less ill (Acute Physiology and Chronic Health Evaluation II score $\leq$20) and those who were younger (age $<$55 years). There was no difference in mortality between groups in patients with clinically significant heart disease. A restrictive strategy of RBC transfusion is at least as effective and possibly superior to a liberal transfusion strategy in critically ill patients, with the possible exception of patients with acute myocardial infarction and unstable angina.

Current evidence suggests that clinicians are reconsidering more conservative transfusion practices in light of these and similar data. Vincent and coworkers [20] conducted a cross-sectional study intended to evaluate transfusion practices in 146 European ICUs. They reported that pretransfusion hemoglobin concentrations (8.4 g/dl) are currently lower than those previously cited [20,23]. Data from a prospective, multicenter, observational trial [21] suggest a similar trend toward more restrictive transfusion practices in the USA. The mean pretransfusion hemoglobin was 8.6 ± 1.7 g/dl [21]. This shift toward restrictive transfusion policies may in part be related to the work published by the Canadian Critical Care Trials Group.

Anemia in the patient with cardiovascular disease

The hemoglobin concentration at which risk for death or serious morbidity occurs was investigated by Carson and colleagues [24] using a retrospective cohort of 1958 patients who underwent surgery and declined blood transfusion. The primary outcome variable was 30-day mortality. Cardiovascular disease was defined as a history of angina, myocardial infarction, congestive heart failure, or peripheral vascular disease. In patients with preoperative hemoglobin levels of 12 g/dl or greater the mortality rate was 1.3%, whereas patients with preoperative hemoglobin levels of less than 6 g/dl had a mortality rate of 33.3%. The authors concluded that low preoperative hemoglobin substantially increases the risk for death and serious morbidity [24].

The threshold for transfusion in the critically ill or perioperative patient with known coronary artery disease is still debated. The traditional belief is that anemic patients with coronary artery disease are at high risk for myocardial ischemia or infarction because they cannot increase oxygen extraction or augment coronary arterial flow. Retrospective studies to date in this population, including the study by Carson and colleagues [24], suggest that critically ill patients with cardiac disease had higher mortality when hemoglobin levels dropped from approximately 10 g/dl perioperatively to 6.0–6.9 g/dl. In fact, the adjusted odds of death in patients with cardiovascular disease increased five-fold (from 2.3 to 12.3).

There is little available evidence supporting the use of blood transfusions in the setting of acute myocardial infarction, excluding retrospective work based on a large administrative discharge database done by Wu and colleagues [25]. Ignoring the significant limitations of the study design and methods, Wu and coworkers reported that patients with lower hematocrit values on admission had higher 30-day mortality rates. At least one randomized controlled trial has suggested that lowering the hemoglobin threshold for transfusion in aortocoronary bypass grafting procedures to 8 g/dl postoperatively does not adversely affect outcome [26]. There is some suggestion that cardiac bypass patients with higher hematocrit levels postoperatively are more likely to sustain a postoperative myocardial infarction [6]. In this setting, both study groups consisted of patients whose surgical lesions were corrected, and as such, they may have behaved differently from patients with fixed cardiac disease. There is substantial evidence on the beneficial effect of β-blockade in patients who have or are at risk for coronary artery disease in reducing mortality as well as the incidence of cardiovascular

complications [27]. However, of the recent studies investigating anemia in cardiac disease, all have failed to control for confounding variables such as β-blockade and heart rate.

The investigators in the Transfusion Requirements in Critical Care (TRICC) trial [28] performed a subgroup analysis of the main study to include patients who were thought to be at increased risk for complications associated with anemia because of a diagnosis related to coronary artery disease. Those investigators analyzed 357 patients and found no significant difference in 30-day mortality between the restrictive and the liberal transfusion strategies. Other outcome measurements including multiorgan dysfunction scores, ICU and in-hospital length of stay were superior in the restrictive strategy group. Furthermore, there was a greater incidence of pulmonary edema, a common complication of blood transfusion, in the liberal transfusion strategy group (10.7% versus 5.3%) than in the restrictive group [3]. Intuitively, transfusion in the asymptomatic patient with ischemic heart disease and left ventricular dysfunction may actually be detrimental by precipitating pulmonary edema. In a subgroup with severe ischemic heart disease ($n = 257$), the absolute survival rate was lower in the restrictive strategy group than in the liberal strategy group, but this difference was not statistically significant. The authors concluded that a restrictive transfusion strategy appeared to be safe in most critically ill patients with cardiovascular disease, with the possible exception of patients with acute myocardial infarction and unstable angina. Because this conclusion was derived from a subgroup analysis, caution is warranted in the interpretation of these results.

The critically ill patient with active ischemic cardiac disease continues to represent a 'gray area' in the literature. Under these circumstances, it is prudent to recommend individualizing transfusion decisions to meet the patient's specific myocardial oxygen supply/demand, which may change during the course of their illness [29]. Arbitrary application of the 10/30 rule may result in avoidable adverse outcomes and as such can no longer be advocated as a transfusion trigger in any patient population.

Conclusion

Anemia in the setting of critical illness is prevalent. Based on the available data, it appears appropriate and safe to withhold transfusion based on the hemoglobin or hematocrit level until the patient's hemoglobin is 7 g/dl or less. Regarding patients with cardiac disease but without acute myocardial infarction or unstable angina, evidence from the TRICC study suggests that this approach is safe in this group as well, provided euvolemia is maintained. There is still controversy about this group of patients, however, and more trials addressing transfusion triggers in patients with coronary artery disease are needed. Given the well documented risks associated with blood transfusion [22], these data strengthen the contention that blood transfusion should be carefully considered and that the decision to transfuse RBCs cannot be justified by the 10/30 rule.

Competing interests

None declared.

References

1. McFarland JG: **Perioperative blood transfusions: indications and options.** *Chest* 1999, **Suppl:**113S-121S.
2. Adams RC, Lundy JS: **Anesthesia in cases of poor surgical risk. Some suggestions for decreasing the risk.** *Surg Gynecol Obstet* 1942, **74:**1011-1019.
3. Hebert PC, Wells G, Blajchman MA, Marshall J, Martin C, Pagliarello G, Tweeddale M, Schweitzer I, Yetisir E: **A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group.** *N Engl J Med* 1999, **340:**409-417.
4. Carson JL, Duff A, Berlin JA, Lawrence VA, Poses RM, Huber EC, O'Hara D, Noveck H, Strom BL: **Perioperative blood transfusion and postoperative mortality.** *JAMA* 1998, **279:**199-205.
5. Waggoner JR III, Wass CT, Polis TZ, Faust RJ, Schroeder DR, Offord KP, Piepgras DG, Joyner MJ: **The effect of changing transfusion practice on rates of perioperative stroke and myocardial infarction in patients undergoing carotid endarterectomy: a retrospective analysis of 1114 Mayo Clinic patients. Mayo Perioperative Outcomes Group.** *Mayo Clin Proc* 2001, **76:**376-383.
6. Spiess BD, Ley C, Body SC, Siegel LC, Stover EP, Maddi R, D'Ambra M, Jain U, Liu F, Herskowitz A, Mangano DT, Levin J: **Hematocrit value on intensive care unit entry influences the frequency of Q-wave myocardial infarction after coronary artery bypass grafting. The Institutions of the Multicenter Study of Perioperative Ischemia (McSPI) Research Group.** *J Thoac Cardiovasc Surg* 1998, **116:**460-467.
7. Carson JL, Willett LR: **Is a hemoglobin of 10 g/dL required for surgery?** *Med Clin North Am* 1993, **77:**335-347.
8. Corwin HL, Parsonnet KC, Gettinger A: **RBC transfusion in the ICU. Is there a reason?** *Chest* 1995, **108:**767-771.
9. Sehgal LR, Zebala LP, Takagi I, Curran RD, Votapka TV, Caprini JA: **Evaluation of oxygen extraction ratio as a physiologic transfusion trigger in coronary artery bypass graft surgery patients.** *Transfusion* 2001, **41:**591-595.
10. Stehling L, Simon TL: **The red blood cell transfusion trigger. Physiology and clinical studies.** *Arch Pathol Lab Med* 1994, **118:**429-434.
11. Greenburg AG: **A physiologic basis for red blood cell transfusion decisions.** *Am J Surg* 1995, **Suppl 6A:**44S-48S.
12. Majeski J: **Advances in general and vascular surgical care of Jehovah's Witnesses.** *Int Surg* 2000, **85:**257-265.
13. Grebenik CR, Sinclair ME, Westaby S: **High risk cardiac surgery in Jehovah's Witnesses.** *J Cardiovasc Surg* 1996, **37:**511-515.
14. Kitchens CS: **Are transfusions overrated? Surgical outcome of Jehovah's Witnesses.** *Am J Med* 1993, **94:**117-119.
15. Victorino G, Wisner DH: **Jehovah's Witnesses: unique problems in a unique trauma population.** *J Am Coll Surg* 1997, **184:**458-468.
16. Ott DA, Cooley DA: **Cardiovascular surgery in Jehovah's Witnesses. Report of 542 operations without blood transfusion.** *JAMA* 1977, **238:**1256-1258.
17. Viele MK, Weiskopf RB: **What can we learn about the need for transfusion from patients who refuse blood? The experience with Jehovah's Witnesses.** *Transfusion* 1994, **34:**396-401.
18. Spence RK, Alexander JB, DelRossi AJ, Cernaianu AD, Cilley J Jr, Pello MJ, Atabek U, Camishion RC, Vertrees RA: **Transfusion guidelines for cardiovascular surgery: lessons learned from operations in Jehovah's Witnesses.** *J Vasc Surg* 1992, **16:**825-829.
19. Weiskopf RB, Viele MK, Feiner J, Kelley S, Lieberman J, Noorani M, Leung JM, Fisher DM, Murray WR, Toy P, Moore MA: **Human cardiovascular and metabolic response to acute, severe isovolemic anemia.** *JAMA* 1998, **279:**217-221.
20. Vincent JL, Baron J-F, Reinhart K, Gattinoni L, Thijs L, Webb A, Meier-Hellmann A, Nollet G, Peres-Bota D: **Anemia and blood transfusion in critically ill patients.** *JAMA* 2002, **288:**1499-1507.

21. Corwin HL, Gettinger A, Pearl RG, Fink MP, Levy MM, Abraham E, MacIntyre NR, Shabot M, Duh M-S, Shapiro MJ: **The CRIT study: Anemia and blood transfusion in the critically ill: current clinical practice in the United States.** *Crit Care Med* 2004, **32:**39-52.
22. Fakhry SM, Rutherford EJ, Sheldon GF: **Hamatologic principles in surgery.** In *Textbook of Surgery: the Biological Basis of Modern Surgical Practice*, 16th ed. Edited by Townsend CM Jr, Beauchamp RD, Evers BM, Mattox KL. Philadelphia: W.B. Saunders Company; 2001:68-89.
23. Hebert PC, Wells G, Martin C, Tweeddale M, Marshall J, Blajchman M, Pagliarello G, Schweitzer I, Calder L: **A Canadian survey of transfusion practices in critically ill patients.** *Crit Care Med* 1998, **26:**482-487.
24. Carson JL, Duff RM, Berlin JA, Spence RK, Trout R, Noveck H, Strom BL: **Effect of anaemia and cardiovascular disease on surgical mortality and morbidity.** *Lancet* 1996, **348:**1055-1060.
25. Wu W-C, Rathore SS, Wang Y, Radford MJ, Krumholz HM: **Blood transfusion in elderly patients with acute myocardial infarction.** *N Engl J Med* 2001, **345:**1230-1236.
26. Bracey AW, Radovancevic R, Riggs SA, Houston S, Cozart H, Vaughn WK, Radovancevic B, McAllister HA Jr, Cooley DA: **Lowering the hemoglobin threshold for transfusion in coronary artery bypass procedures: effect on patient outcome.** *Transfusion* 1999, **39:**1070-1077.
27. Mangano DT, Layug EL, Wallace A, Tateo I: **Effect of atenolol on mortality and cardiovascular morbidity after noncardiac surgery.** *N Engl J Med* 1996, **335:**1713-1720.
28. Hebert PC, Yetisir E, Martin C, Blajchman MA, Wells G, Marshall J, Tweeddale M, Pagliarello G, Schweitzer I: **Is a low transfusion threshold safe in critically ill patients with cardiovascular diseases?** *Crit Care Med* 2001, **29:**227-234.
29. Walsh TS, McClelland DB: **When should we transfuse critically ill and perioperative patients with known coronary artery disease?** *Br J Anaesth* 2003, **90:**719-722.