

TRANSFUSION POLICIES IN ANEMIA

In search of the transfusion threshold

JEFFREY L. CARSON & RICHARD C. REYNOLDS

Division of General Internal Medicine, UMDNJ-Robert Wood Johnson Medical School, New Brunswick, New Jersey, USA

Introduction

Every medical decision involves weighting the risk versus benefit. The risks related to red blood cell transfusion include the adverse effects of allogeneic blood and the risks of anemia. The potential benefits of blood transfusion are reduction of mortality and morbidity and improvement in functional recovery. In this lecture, I will focus on risks related to anemia and what is known about the benefits of allogeneic transfusion. I will complete the presentation with a description of a new clinical trial called FOCUS.

Risk from anemia

Animal data

The heart is the most vulnerable to the effects of anemia. The heart extracts a high percentage of oxygen. When anemia develops coronary blood flow must increase to maintain oxygen delivery. Blood flow increases because of decreased blood viscosity that results from anemia.

A series of experiments have been performed in canines to evaluate the effect of anemia (Table I). After hemodilution, healthy animals survive hemoglobin concentrations between 3 and 5 gdl⁻¹ [1–3]. However, myocardial ischemia is detectable by electrocardiograph changes at hemoglobin concentrations below 5 gdl⁻¹. At hemoglobin levels around 3 gdl⁻¹, severe physiologic derangement develops. This is manifested by anaerobic metabolism (lactate production) myocardial dysfunction, and death. Some animals survive with hemoglobin levels as low as 1 to 2 gdl⁻¹.

Animals with experimentally induced coronary artery disease poorly tolerate anemia. In the presence of coronary stenosis from 50% to 80%, myocardial ischemia and/or reduced cardiac function develop at hemoglobin levels between 7 to 10 gdl⁻¹. This

finding suggests animals with coronary artery disease are less tolerant of anemia than animals with normal hearts.

Human data

Studies in patients who decline blood transfusion for religious reasons provide critical insights into risks associated with anemia. In a small study of 125 patients, [4] mortality rose with lower preoperative hemoglobin levels and greater operative blood loss. The fatality rate was 61.5% in patients with preoperative hemoglobin concentrations below 6 gdl⁻¹, but only 7.1% in patients with preoperative hemoglobin concentrations greater than 10 gdl⁻¹. In this small case series, patients with a hemoglobin level above 8 gdl⁻¹ and operative blood loss below 500 ml, none of the patients died.

The largest study in patients who refused blood transfusion confirmed animal data that patients with cardiovascular disease are more susceptible to anemia than as patients without cardiovascular disease. In a cohort study in 1,958 adult surgical patients who underwent a surgical procedure in an operating room, [5] mortality rose as preoperative hemoglobin levels fell. However, patients with cardiovascular disease had a much higher risk of death as the hemoglobin concentration fell below 10 gdl⁻¹ than patients without cardiovascular disease (Figure 1).

A recent study combined data from two cohorts of Jehovah's Witness patients and examined the morbidity and mortality associated with postoperative hemoglobin concentrations below 8 gdl⁻¹ [6]. Of 2083 consecutive patients, 300 (15%) had postoperative Hgb levels <8 gdl⁻¹. None of the patients with postoperative hemoglobin levels between 7.1–8.0 died although 9.4% had significant morbidity. The 30 day mortality was 34% when the postoperative hemoglobin level fell to 4.1–5.0 gdl⁻¹.

Table I. Effects of anemia in animals undergoing hemodilution.

| Group | Event | Hemoglobin Concentration (gdl ⁻¹) |
|-------------------------|--------------------------------|---|
| Normal | ST segment changes | <5 |
| | Lactate production | <3 |
| | Decreased ventricular function | <3 |
| | Death | <3 |
| Coronary Artery Disease | ST segment changes | 7-10 |

The effect of anemia was assessed in normal volunteers undergoing isovolemic anemia to 5 gdl⁻¹. Transient electrocardiogram changes occurred with hemoglobin levels between 5-7 gdl⁻¹ in 5.7% of volunteers [7,8]. Subtle changes in cognition were found in young volunteers with hemoglobin levels between 5-7 gdl⁻¹ [9]. Fatigue developed when the hemoglobin level fell to 7 gdl⁻¹ and increased as the hemoglobin level dropped to 5 gdl⁻¹ [10]. Heart rate is linearly related to hemoglobin concentration [11]. These studies suggest that important clinical effects can be measured in young, normal humans with hemoglobin levels between 5-7 gdl⁻¹. It is unclear how these results relate to sick patients undergoing surgery but it seems possible such patients would be even less tolerant of anemia.

Efficacy of transfusion

Clinical trial data

Clinical trials are essential to establish efficacy of any treatment including blood transfusion. Unfortunately, there is limited evidence. Of the 10 randomized clinical trials, all but one was too small to evaluate clinical outcomes [12]. A meta-analysis that combined the results of these trials, [12] found the Transfusion Requirements in Critical Care (TRICC) trial contributed 83% of the information for the analysis of mortality in the meta-analysis [13]. The other trials were too small to reliably evaluate the effect of transfusion thresholds on clinical events.

The TRICC trial evaluated two transfusion triggers in 838 volume resuscitated patients admitted to intensive care unit [13,14]. In the restrictive arm of

the trial, patients were randomized to a transfusion strategy in which blood was administered when the hemoglobin concentration fell below 7.0 gdl⁻¹ (and maintained between 7.0 to 9.0 gdl⁻¹). In the liberal transfusion group, patients were transfused to maintain hemoglobin concentration between (10.0 gdl⁻¹ and 12.0 gdl⁻¹). Surprisingly, the 30-day mortality was slightly lower (not significant) in the restrictive transfusion group than the liberal group (18.7% vs. 23.3%). Overall, these findings were not statistically significant, although in patients less than 55 years of age and with Apache scores less than 20 (less ill patients), mortality was significantly better in patients randomized to the restrictive transfusion group. The results were different in patients with cardiovascular disease. In patients with ischemic heart disease (defined as myocardial infarct, angina, congestive heart failure, and cardiogenic shock), the liberal transfusion group had a small and non-significant improved outcome.

Observational studies

The seven large observational studies that evaluated the transfusion thresholds came to different conclusions and must be interpreted very cautiously. Studies in critically ill patients [15,16], patients undergoing coronary artery bypass surgery, [17] and surgical patients undergoing hip fracture repair [18] came to different conclusions. A very large study in acute myocardial infarction suggested [19] mortality was reduced by transfusion in patients with hematocrit levels less than 33%. However, a more recent analysis of clinical trials in acute coronary syndrome found that blood transfusion increased mortality [20]. Three small studies found higher rates of cardiac events in anemic patients. Thus, there is great heterogeneity of the study populations and results. Furthermore, the results of these observational studies should be interpreted very cautiously because statistical approaches to adjusting for differences between patients receiving transfusion versus those not transfused may not be successful. This point is emphasized by the results of recent clinical trials evaluating hormone replacement therapy where the results on cardiovascular risk were opposite of observational studies. Similarly, the

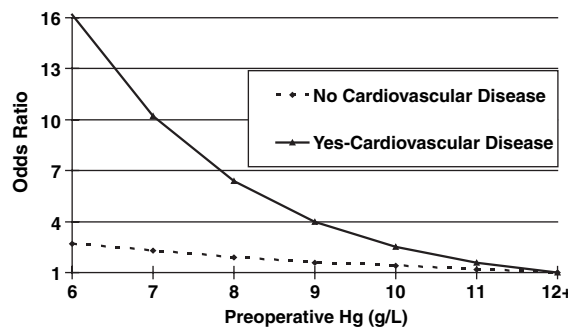


Figure 1. Odds of death in patients who decline blood transfusion stratified by presence of cardiovascular disease [5].

TRICC investigators found difference in their clinical trial than their observational study [15].

FOCUS: A new clinical trial

Given the limited high quality evidence, we have initiated a new NIH funded trial called FOCUS. The transfusion trigger trial for Functional Outcomes in Cardiovascular Patients Undergoing Surgical Hip Fracture Repair (FOCUS) is a randomized clinical trial designed to test the hypothesis that higher blood transfusion threshold improves functional recovery and reduces morbidity and mortality. Patients who undergo surgery for hip fracture, have a history of cardiovascular disease, and have a postoperative hemoglobin level less than 10 gdl^{-1} within 3 days of surgery are eligible. Patients will be randomized to receive enough blood to raise the hemoglobin level above 10 gdl^{-1} any time the hemoglobin level is detected to be below 10 gdl^{-1} during the hospitalization or to receive transfusion if symptoms of anemia develop. Transfusion is permitted but not required if hemoglobin level is less than 8 gdl^{-1} . The primary outcome is ability to walk 10 feet (or across a room) without human assistance at 60 days. The most important secondary outcome is postoperative unstable angina, myocardial infarction or death. Medical records will be reviewed while the patient is in the hospital. Patients will be telephoned at 30 and 60 days after entry into the study to determine functional capacity and vital status. Long term mortality will be determined by searching vital statistic registries in US and Canada. The pilot study for the trial has been published [21].

Summary

We have very limited data to guide the transfusion decision. The best evidence suggests that mortality and morbidity rises as the blood count falls but that in patients without cardiovascular disease a 7 gdl^{-1} level is tolerated in most patients. Below $5\text{--}6 \text{ gdl}^{-1}$, the mortality and morbidity rises rapidly. In patients with cardiovascular disease, animal and human studies suggest that a higher hemoglobin concentration may be necessary but there is limited evidence from clinical trials to inform this question. We expect that results from the new clinical trial called FOCUS will provide important new information to help guide transfusion decisions.

References

- [1] Wilkerson DK, Rosen AL, Sehgal LR, et al. Limits of cardiac compensation in anemic baboons. *Surgery* 1988;103:665–70.
- [2] Hagl S, Heimisch W, Meisner H, et al. The effect of hemodilution on regional myocardial function in the presence of coronary stenosis. *Basic Res Cardiol* 1977;72:344–64.
- [3] Anderson HT, Kessinger JM, McFarland WJ, Jr., et al. Response of the hypertrophied heart to acute anemia and coronary stenosis. *Surgery* 1978;84:8–15.
- [4] Carson JL, Poses RM, Spence RK, et al. Severity of anaemia and operative mortality and morbidity. *Lancet* 1988;1:727–9.
- [5] Carson JL, Duff A, Poses RM, et al. Effect of anaemia and cardiovascular disease on surgical mortality and morbidity. *Lancet* 1996;348:1055–60.
- [6] Carson JL, Noveck H, Berlin JA, et al. Mortality and morbidity in patients with very low postoperative Hb levels who decline blood transfusion. *Transfusion* 2002;42:812–8.
- [7] Leung JM, Weiskopf RB, Feiner J, et al. Electrocardiographic ST-segment changes during acute, severe isovolemic hemodilution in humans [In Process Citation]. *Anesthesiology* 2000;93:1004–10.
- [8] Weiskopf RB, Viele MK, Feiner J, et al. Human cardiovascular and metabolic response to acute, severe isovolemic anemia [see comments]. *JAMA* 1998;279:217–21.
- [9] Weiskopf RB, Kramer JH, D P, et al. Acute severe isovolemic anemia impairs cognitive function and memory in humans. *Anesthesiology* 2000;92:1646–52.
- [10] Toy P, Feiner J, Viele MK, et al. Fatigue during acute isovolemic anemia in healthy, resting humans. *Transfusion* 2000;40:457–60.
- [11] Weiskopf RB, Feiner J, Hopf H, et al. Heart rate increases linearly in response to acute isovolemic anemia. *Transfusion* 2003;43:235–40.
- [12] Carson JL, Hill S, Carless P, et al. Transfusion triggers: A systematic review of the literature. *Arch of Int Med* 2001.
- [13] Hebert PC, Wells G, Blajchman MA, et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group [see comments]. *N Engl J Med* 1999;340:409–17.
- [14] Hebert PC, Wells G, Marshall J et al. Transfusion requirements in critical care. A pilot study. Canadian Critical Care Trials Group [published erratum appears in *JAMA* 1995 Sep 27;274(12):944]. *JAMA* 1995;273:1439–44.
- [15] Hebert PC, Wells G, Tweeddale M, et al. Does transfusion practice affect mortality in critically ill patients? Transfusion Requirements in Critical Care (TRICC) Investigators and the Canadian Critical Care Trials Group. *Am J Resp & Crit Care Med* 1997;155:1618–23.
- [16] Vincent JL, Baron JF, Reinhart K, et al. Anemia and blood transfusion in critically ill patients. *JAMA* 2002;288:1499–507.
- [17] Spiess BD, Ley C, Body SC, et al. 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 Thorac Cardiovasc Surg* 1998;116:460–7.
- [18] Carson JL, Duff A, Berlin JA, et al. Perioperative blood transfusion and postoperative mortality. *JAMA* 1998;279:199–205.
- [19] Wu WC, Rathore SS, Wang Y, et al. Blood transfusion in elderly patients with acute myocardial infarction. *N Engl J Med* 2001;345:1230–6.
- [20] Rao SV, Jollis JG, Harrington RA, et al. Relationship of blood transfusion and clinical outcomes in patients with acute coronary syndromes. *JAMA* 2004;292:1555–62.
- [21] Carson JL, Terrin ML, Barton FB, et al. A pilot randomized trial comparing symptomatic vs. hemoglobin- level-driven red blood cell transfusions following hip fracture. *Transfusion* 1998;38:522–9.