



## THE TRANSFUSION TRIGGER UPDATED: CURRENT INDICATIONS FOR RED CELL THERAPY

Recent studies have called into question the traditional concept of the transfusion trigger. Until the mid-1980s, this value, defined as the hemoglobin or hematocrit laboratory level at which most patients need red blood cell transfusion, was approximately 10/30; most medical or surgical patients were transfused at that level. During the past 15 to 20 years, a number of studies suggested that otherwise "healthy" adults could tolerate a greater degree of anemia without compromise. A number of transfusion guidelines published in the late 1990's have been summarized and were reviewed in *Blood Bulletin* (Vol. 2, #3 1999).

Clinical transfusion therapy relies on clinical experience and investigation. The most highly regarded investigative studies are randomized clinical trials of various transfusion triggers; observational studies are also valuable. Both are reviewed in this issue of *Blood Bulletin*.

**Observational studies.** Several studies have been conducted involving Jehovah's witnesses who have undergone surgery and refused transfusion for religious reasons. An analysis of approximately 2000 adult patients undergoing surgery, excluding open heart procedures, in 12 hospitals between 1981 and 1994 demonstrated increasing risks as the hemoglobin falls.<sup>1</sup> A separate analysis of 300 patients with postoperative hemoglobin of 8.0g/dL or below was performed.<sup>2</sup> The subset included 70% females, with a mean age of 57 years. The overall mortality rate was 16%. Those with postoperative hemoglobin levels of 7.1-8g/dL had no deaths (upper 95% CI 3.7%), but 9.4% (CI 4.4-17%) had a morbid event, defined as a myocardial infarction, congestive heart failure, arrhythmia, or infection (bacteremia, pneumonia, or deep wound) that occurred within 30 days of surgery. Patients with a postoperative hemoglobin of 4.1 to 5g/dL had a mortality rate of 34.4% (CI 18.6-53.2%), and 57.7% (CI 36.9-76.6%) had a morbid event. Adjustment for age, cardiovascular disease, and Acute Physiology and Chronic Health Evaluation II (APACHE II) score showed that for those with postoperative hemoglobin <8g/dL, every gram decrease in hemoglobin resulted in a 2.5 times higher risk of death (CI 1.9-3.2).

Thus, patients with cardiovascular disease (defined as the preoperative presence of angina, congestive heart failure, or atherosclerosis) had a higher risk of death with low preoperative hemoglobin, or a decline of hemoglobin level during surgery.<sup>1</sup> These studies quantify the increased risk associated with cardiovascular disease regarding tolerance of anemia, but do not provide guidance about a transfusion trigger, since these patients did not receive transfusions.

### Prescribing red blood cell transfusions requires clinical decision making.

- The lower limit or "transfusion trigger" for general medical and surgical patients approximates hemoglobin/hematocrit levels of 7.0g/dL and 21%, respectively. Below these levels, morbidity and mortality increase.
- Some patient subsets, such as elderly patients suffering from acute myocardial infarction, appear to have better outcomes when transfusions increase the hematocrit to 30 to 33%.

**Current data suggest that restraining transfusions favors positive patient outcomes—except when significant underlying cardiac disease is present.**

**Controlled trials.** Ten controlled trials conducted over 40 years and involving 1780 patients were included in a review of randomized clinical trials involving transfusion.<sup>3</sup> Outcomes measured included proportion of patients transfused, volume of blood transfused, morbidity, mortality, and length of hospital stay. Five studies involved surgical patients, three addressed trauma patients or other acute blood loss situations, and two were performed in ICU patients.

The use of a restrictive transfusion trigger overall (a lower hemoglobin/hematocrit concentration, although defined differently in the various studies) reduced the probability of transfusion by 42%, and resulted in an average saving of nearly 1 unit (0.93) per transfused patient. There was no increase in cardiac events, including infarction, or in the hospital length of stay. Mortality was lower with the restrictive strategy, though this was not statistically significant overall. Importantly, no functional status measurements were used. However, most of the data on clinical outcomes were generated by a single trial.<sup>4</sup> Several other studies stated that restrictive strategies might not be appropriate for several subsets of patients, including those with significant cardiac disease.

**The largest controlled trial.** A study by Hebert and colleagues in Canada involving a randomized clinical trial of 838 adult ICU patients with euvolemia delved into transfusion trigger issues and deserves particular attention.<sup>4</sup> Patients were randomized to either a restrictive

(continued on reverse)

transfusion regimen, in which transfusions were given when the hemoglobin dropped below 7g/dL and the concentration was maintained between 7.0 and 9.0g/dL, or to a more liberal strategy—transfusion when the hemoglobin fell to below 10.0g/dL and maintained between 10.0 and 12.0g/dL. Overall 30 day all-cause mortality was similar in the two groups (18.7 vs. 23.3 %). In patients who had an APACHE II score of  $\leq 20$ , however, the restrictive strategy group had less mortality (8.7 vs. 16.1 %,  $p=0.03$ ). In those less than 55 years old, the restrictive strategy was better: 5.7% compared to 13.0% mortality ( $p=0.02$ ). In those with clinically significant cardiac disease, there was no difference (20.5% and 22.9%,  $p=0.69$ ). Patients in the restrictive group received an average of  $2.6 \pm 4.1$  units vs.  $5.6 \pm 5.3$  in the liberal group. Significant exclusions affecting generalizability of the study include active blood loss at the time of enrollment, chronic anemia, or admission following a routine cardiac surgical procedure.

**Patients with cardiovascular disease.** An analysis of the 357 patients in the above study who had cardiovascular disease showed similar 30-day and other mortality rates in the two groups.<sup>5</sup> In the restrictive group, those with severe ischemic heart disease had higher (but statistically insignificant) mortality. The authors assert that the trigger of 7g/dL is as appropriate in cardiac patients as in other patients. A separate analysis showed that hemoglobin concentrates and transfusion did not affect the duration of mechanical ventilation in patients requiring this intervention.<sup>6</sup>

While these reports showed no difference in outcomes between the restrictive and liberal strategies (or possible benefit of restricting transfusion in some subnets), a large multicenter observational study of European ICU's<sup>8</sup> showed 33% higher mortality among transfused patients versus non-transfused patients—even when all other variables were controlled, including scores of acuity and organ dysfunction. However, these results should be interpreted with caution because of the heterogeneity of the patient population.

In certain patient populations, higher transfusion triggers may lead to improved outcomes. An analysis of nearly 79,000 Medicare beneficiaries with acute myocardial infarction showed that transfusion was associated a lower short-term mortality rate if the hematocrit at admission was 30% or lower and transfusion might be effective in patients with a hematocrit as high as 33%.<sup>8</sup>

In another study of 32 patients with low-level anemia (hemoglobin 10-11.5g/dL) randomized to treatment with erythropoietin (epo) or placebo, the group receiving epo had less mortality and strikingly better functional outcomes than the group not treated.<sup>9</sup> This small study and the large observational study by Wu<sup>8</sup> identified patients benefiting from higher hemoglobin concentrations.<sup>9</sup> In a third study, anemia increased the risk of 1-year mortality with acute MI, although confounding factors such as demographics and co-morbid conditions may have explained the effect.<sup>10</sup>

Thus, it appears that a subset of cardiac patients will benefit from more liberal transfusion—while general surgical and medical patients may benefit from a more restrictive strategy.

What might be the cause of poorer outcomes of transfusion in patients without cardiovascular disease? One study cites immunomodulation, but gives no specific examples.<sup>6</sup> This and another study suggest that leukocyte content and the age of red cells transfused may influence outcomes.<sup>6, 11</sup> However, a recent study of 1200 ICU patients showed that mortality was similar in patients receiving epo or transfusion, at a trigger of approximately 8.5g/dL,<sup>12</sup> casting doubt on the potential role of leukocytes or red cell age. If one assumes excess mortality in the transfused group, as suggested by the Hébert and Vincent studies, this effect is not ameliorated by epo.<sup>13</sup>

Clearly, randomized controlled trials and observational studies have provided additional data for making clinical decisions. Results of further studies will provide additional information to enhance the clinical use of blood transfusion.

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