RED CELL TRANSFUSION THERAPY IN CHRONIC ANEMIA

Ennio C. Rossi, MD

Blood transfusion became an effective form of therapy during the early part of this century. The discovery of blood groups and compatibility testing greatly reduced the number of transfusion "accidents," whereas the introduction of anticoagulants made transfusions readily available. Blood transfusion was prescribed liberally during those early days, and eventually the blood's ability to transmit hepatitis and the human immunodeficiency virus (HIV) became evident. Although hepatitis stimulated some concern, it has been the potential transmission of HIV that has focused attention upon the issue of blood utilization.

The use of blood and blood products has decreased since the advent of HIV. However, the blood-prescribing practices of physicians remain somewhat erratic. Stehling and colleagues found that the use of blood by anesthesiologists was based more on habit than data, whereas Goodnough et al noted highly variable transfusion practices during coronary artery bypass surgery in tertiary care teaching hospitals. Salem-Schatz et al found, especially among senior physicians, "widespread deficiencies in physician's knowledge of transfusion risks and indications," whereas Mozes et al noted a tendency to overestimate the risk of withholding transfusion. Stricter transfusion guidelines are being put in place, and the Joint Commission on Accreditation of Healthcare Organizations has established blood usage review as an important hospital medical staff quality assurance function.

In 1988, the National Heart, Lung, and Blood Institute held a Consensus Development Conference on Perioperative Red Cell Transfusion. Two important conclusions emerged from that conference: (1) the only indication for red cell transfusions is to increase the oxygen-carrying capacity in anemic patients; and (2) red cell transfusions should not be used to expand volume, enhance wound healing, or improve general well-being.

The decision to transfuse should not be "triggered" by a threshold hemoglo-
bin concentration, but it should be the result of thoughtful clinical assessment. This principle should also guide our transfusion decisions in chronic anemia.

ANEMIA

When the hemoglobin concentration, red blood cell count, or packed cell volume is less than normal, anemia is present. However, the definition of "normal" is ambiguous. The "normal" value in children varies during growth and development, women have lower values than men, and individuals living at high altitudes normally have higher hemoglobin concentrations. The range of normal is variable, and any line that attempts to separate "normal" from "anemia" is unavoidably arbitrary. Early anemia is usually asymptomatic. As the anemia intensifies and becomes chronic, symptoms may occur. The correct evaluation of these symptoms is an important part of the decision-making process for transfusion.

THE RELATIONSHIP OF ANEMIA TO SYMPTOMS

Anemia is not usually associated with symptoms until the hemoglobin concentration declines to 7 to 8 g percent. Elwood et al studied the relationship of symptoms to hemoglobin concentration in 880 women with mild anemia ranging between 8 and 12 g percent. The frequency of six symptoms—irritability, palpitations, dizziness, breathlessness, fatigue, and headache—was assessed with survey instruments that permitted respondents to select among five grades of severity, ranging from mild ("I only feel tired after a very hard day") to severe ("I always feel very tired all day long"). A second survey contained questions similar to the Cornell Medical Index used to assess psychoneurosis. When the "classical" symptoms of anemia were plotted against hemoglobin concentration, no correlations were detected. However, when symptom grades were compared with "neurotic" grades, statistically significant positive correlations were observed for all six symptoms. The lack of correlation between symptoms and hemoglobin concentration was confirmed by a randomized clinical trial of iron versus placebo (Table 1). Even though the hemoglobin concentration rose only in those individuals who received iron, the symptom patterns were indistinguishable, because both the treatment and placebo groups reported improvement.

As the hemoglobin concentration falls below 8 g percent, it is evident that, at some point, symptomatology related to diminished oxygen-carrying capacity must be encountered. This can be inferred from the study by Levine et al of the

<table>
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<tr>
<th></th>
<th>Iron</th>
<th>Placebo</th>
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<tr>
<td>Initial hemoglobin concentration (gram percent)</td>
<td>10.6 ± 0.1</td>
<td>10.6 ± 0.1</td>
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<tr>
<td>Increase to hemoglobin following treatment</td>
<td>2.3 ± 0.2</td>
<td>0.3 ± 0.1</td>
</tr>
<tr>
<td>Increased well-being</td>
<td>53%</td>
<td>58%</td>
</tr>
<tr>
<td>Decreased fatigue</td>
<td>40%</td>
<td>47%</td>
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physiologic effects of acute (euvolemic) anemia. After preliminary hemodynamic measurements, adult baboons were exchange transfused to a final hematocrit of 15% with hetastarch in saline. Comparison of hemodynamic measurements before and after exchange was quite revealing (Table 2). Despite reductions in red cell mass, arterial oxygen content, and oxygen delivery, increases in heart rate, cardiac output, and oxygen extraction successfully maintained oxygen consumption at the pre-exchange level of 7 cc/kg/min. Thus, in a healthy animal, cardiovascular compensatory mechanisms can maintain adequate oxygen consumption even after an acute, 55% decrease in red cell mass.

When the anemia is chronic and the decrease in red cells occurs gradually, other compensatory mechanisms are involved. This is clear if we consider how remarkably symptom-free some patients with sickle cell anemia may be, even with hemoglobin concentrations as low as 5 to 6 g percent. The resting pulse rate may be within the normal range, and diminished oxygen-carrying reserve may become evident only during significant exertion. In great measure this is due to increased red cell 2,3-diphosphoglycerate (2,3-DPG), which facilitates oxygen delivery to the tissues.

**CHRONIC ANEMIA AND 2,3-DPG**

Hemoglobin normally leaves the lungs fully saturated with oxygen, which it releases to the tissues in proportion to the partial pressure of oxygen (PO₂) it encounters. The binding of oxygen by hemoglobin is influenced by a number of variables. The oxygen dissociation curve, which plots the percent hemoglobin–O₂ saturation against the PO₂, can be used to express the effects of these variables. The oxygen dissociation curve of hemoglobin is sigmoidal, whereas the curve for myoglobin is hyperbolic. The difference is attributable to the four heme groups in hemoglobin (as opposed to only one in myoglobin) and heme-heme interaction. As each heme group is oxygenated, it produces a conformational change in the hemoglobin molecule that increases the oxygen affinity of the other heme groups. In the tissues, the cooperation of heme-heme interaction produces the reverse effect—the release of oxygen from the first heme group decreases affinity and facilitates oxygen release from the remaining heme groups. Thus, heme-heme interaction favors oxygen binding in the lungs and oxygen release in the tissues.³⁴

The concentration of 2,3-DPG within the red cell is an important variable affecting hemoglobin/oxygen affinity. 2,3-DPG binds to hemoglobin and reduces

<p>| Table 2. THE EFFECT OF HEMATOcrit REDUCTION UPON HEMODYNAMIC MEASUREMENTS* |
|---------------------------------|-----------------|-----------------|-----------------|</p>
<table>
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<th></th>
<th>Before Dilution</th>
<th>After Dilution</th>
<th>Percent Change</th>
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<tbody>
<tr>
<td>Hematocrit (%)</td>
<td>33</td>
<td>15</td>
<td>-55</td>
</tr>
<tr>
<td>Arterial O₂ content (cc/dL)</td>
<td>14</td>
<td>6.4</td>
<td>-55</td>
</tr>
<tr>
<td>O₂ delivery (cc/kg/min)</td>
<td>18.9</td>
<td>11.1</td>
<td>-41</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>110</td>
<td>141</td>
<td>+28</td>
</tr>
<tr>
<td>Cardiac output (L/min)</td>
<td>2.5</td>
<td>3.3</td>
<td>+32</td>
</tr>
<tr>
<td>O₂ extraction (%)</td>
<td>38.2</td>
<td>59.9</td>
<td>+57</td>
</tr>
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oxygen affinity. This reduction facilitates oxygen unloading in the tissues without hampering, at normal atmospheric pressure, oxygen binding in the lungs. In chronic anemia, red cell 2,3-DPG increases as the hemoglobin concentration decreases. As the hemoglobin declines, increasing 2,3-DPG progressively diminishes oxygen affinity, thus enhancing oxygen unloading in tissues. Through this mechanism the red cell adapts to chronic anemia and becomes a more efficient oxygen carrier. The effectiveness of this mechanism is affirmed by the remarkable tolerance patients have for chronic anemia.

TOLERANCE TO CHRONIC ANEMIA

For many decades conventional wisdom required a hemoglobin concentration of 10 g percent before a patient could undergo general anesthesia and surgery. Even though supportive data were negligible to nonexistent, the practice has continued through habit and tradition. Recently, the evaluation of surgical outcomes in Jehovah’s Witness patients has challenged this conclusion. Spence and colleagues analyzed the results of 113 operations in 107 consecutive Jehovah’s Witness patients who underwent major elective surgery. Despite hemoglobin concentrations as low as 6 g percent, there was no mortality provided estimated blood loss was less than 500 mL. They concluded that mortality in elective surgery depended more upon estimated blood loss than preoperative hemoglobin concentration. A recent review of cumulative experience in Jehovah’s Witness patients confirmed the low mortality, and it suggested that physicians have been overly concerned about the risk of not transfusing patients.

Recently, a threshold hemoglobin concentration, below which failure to transfuse increases the risk of death, was identified in a study of pediatric transfusion practice in Kenya. The rate of HIV-seropositivity in “healthy” blood donors in Central Africa is between 5% and 20%, and transfusion accounts for 40% of HIV infections in children over 1 year of age. Because of these conditions, acceptable blood is not readily available, and many transfusions that are ordered cannot be given. When the survival rates of transfused and not-transfused children were compared, an increased risk of death for lack of transfusion began to appear at 3.9 g percent (4.7 g percent, if respiratory distress was present). However, the vast majority of these children were acutely ill with malaria. In chronic anemia, an even lower threshold for increased deaths owing to the failure to transfuse would be expected (Table 3).

Reflection upon the compensatory mechanisms that increase the human tolerance to chronic anemia should permit us to develop reasonable transfusion strategies that meet, but do not exceed, the needs of patients.

Table 3. HEMOGLOBIN LEVEL AND SYMPTOMS*

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<th>Hemoglobin (gram percent)</th>
<th>Symptoms</th>
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<tr>
<td>9 to 11</td>
<td>Little to no dysfunction</td>
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<tr>
<td>7.5</td>
<td>Exertional dyspnea</td>
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<tr>
<td>6.0</td>
<td>Some weakness</td>
</tr>
<tr>
<td>3.0</td>
<td>Dyspnea at rest</td>
</tr>
<tr>
<td>2.0 to 2.5</td>
<td>Cardiac failure</td>
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TRANSFUSION STRATEGIES IN CHRONIC ANEMIA

The decision to transfuse should not be predicated exclusively on the hemoglobin concentration. It should be based upon clinical assessments of the patient’s oxygen requirement, the proportion of cardiopulmonary reserve employed to meet that requirement, and the potential for medical reversal of the anemia without transfusion. With that in mind, we can consider examples of anemia that rarely, occasionally, or frequently require transfusion (Table 4).

Anemias in which Transfusion is Rarely Required

Red blood cell transfusion is rarely if ever indicated in anemias correctable by medical means. Nutritional anemias due to vitamin B₁₂, folic acid, or iron deficiency should be treated with the appropriate hematocytic agent and transfusions should be avoided. However, on rare occasions, one may encounter a patient who tests the tolerable lower limit of hemoglobin concentration. In the past, this has been classically an elderly patient with florid pernicious anemia.

The demeanor of an 85-year-old woman with florid pernicious anemia can sometimes belie the ominous portents of a hemoglobin concentration of 3.5 g percent and resting pulse of 90. She may appear calm and composed, in contradiction to the attending staff who may be anxious and apprehensive. Because anemia develops very gradually, adaptive mechanisms may have had sufficient time to establish a surprising level of compensation. On the other hand, full realization that cardiopulmonary reserve is stretched to its near-limit does justify a degree of apprehension. Should this patient be transfused? If not at 3.5 g percent, would 3.0 g percent be the level to impel action? This is not an easy decision and heavy weights must be placed on both sides of the risk/benefit scale. The obvious benefit of transfusion must be balanced against the risk of precipitating congestive heart failure. Under most circumstances we can await the beneficial effects of vitamin B₁₂. If, however, the scale tips in favor of transfusion, a partial exchange procedure⁶ or slow infusion with hemodynamic monitoring⁷ may be the most prudent way to administer the blood. In any event, the decision to transfuse a patient with a medically correctable anemia will usually prompt a request for justification from most hospital transfusion committees.

Anemias in which Transfusion is Occasionally Required

Hypoproliferative anemia can be a difficult problem in medical management. Although recombinant human erythropoietin has reduced or abolished the

<table>
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<th>Table 4. TRANSFUSION STRATEGIES IN CHRONIC ANEMIA</th>
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<tr>
<td>Chronic Anemia</td>
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<tr>
<td>Nutritional anemias</td>
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<tr>
<td>Vitamin B₁₂ deficiency</td>
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<tr>
<td>Folic acid deficiency</td>
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<tr>
<td>Iron deficiency</td>
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<tr>
<td>Hypoproliferative anemias of various forms</td>
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<tr>
<td>Congenital hemolytic anemia in aplastic crisis (e.g., sickle cell anemia)</td>
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transfusion requirement of dialysis patients\(^a\) (and may prove effective in other forms of marrow failure), some patients with medically refractory hypoproliferative anemia will eventually require red cell transfusion. The decision to initiate chronic transfusion therapy should be made with care and deliberation. An unnecessarily high transfusion threshold will needlessly expose the patient to the risks of disease transmission and iron overload.

In an individual with adequate cardiopulmonary reserve, hemoglobin concentrations of 9 to 11 g percent are not associated with serious disability. Exertional dyspnea may be noted at 7.5 g percent, and some weakness may appear at 6 g percent (see Table 3). In the presence of coronary disease or some other condition that diminishes cardiopulmonary reserve, inadequate oxygen delivery may dictate the need for transfusion at higher hemoglobin levels. However, as a general rule, living with some symptoms is usually preferable to a program of chronic transfusion therapy with its attendant risks.

Anemias in which Transfusion is Frequently Required

Red blood cell transfusion is always mandated when the reduction in red cell mass is greater than the capacity for cardiopulmonary accommodation. In hypoproliferative anemia this threshold is approached gradually, and the decision for transfusion can be made with thoughtful deliberation. However, in chronic hemolytic anemia an emergency transfusion may be required whenever erythropoiesis abruptly ceases in the face of continuing hemolysis. "Aplastic crises" are seen in a variety of congenital hemolytic disorders, and they occur with some frequency in sickle cell anemia. In these patients the sudden disappearance of reticulocytes should alert us to aplasia, the impending precipitous decline in hemoglobin, and the probable need for transfusion.\(^{25}\)

CONCLUSION

The sole indication for red blood cell transfusion in patients with chronic anemia is to increase oxygen-carrying capacity. The decision should be based upon the patient's oxygen requirement and cardiopulmonary reserve. Nutritional deficiencies or effective alternative therapy (such as erythropoietin) should be ruled out, and symptoms ascribable to inadequate oxygen delivery should be in evidence.\(^1\) The age-old "transfusion trigger" of 10 g percent is no longer defensible.\(^{26}\) However, we should not discard one "trigger" merely to propose another.\(^{14}\) Rather, we should recognize that the decision to transfuse requires a clinical assessment and evidence of inadequate tissue oxygenation correctable by the infusion of red blood cells.

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