Tighten Your Belts! Reduce Your Transfusion Costs with Preoperative Management of Anemic Patients

Thomas R. Vetter, MD, MPH

CURRENT BEST PRACTICES IN PERIOPERATIVE PATIENT-CENTERED BLOOD MANAGEMENT

Blood management has been defined by the Society for Advancement of Blood Management as “the timely application of evidence-based medical and surgical concepts designed to maintain hemoglobin concentration, optimize hemostasis and minimize blood loss in an effort to improve patient outcome.”1 Formalized blood management is being driven by, and gaining momentum because of, known and unknown blood risks; preservation of a local, regional and national blood supplies; and escalating blood product costs.2,3

Approximately 15 million packed red blood cell (PRBC) units are transfused annually in the United States and 85 million are transfused annually worldwide.4,6 However, blood transfusion practices vary widely and often do not follow current evidence-based best practices.7 Furthermore, while blood transfusion is a mainstay of treating surgical blood loss, it is not without risk, especially in developing countries with inadequate screening of donor blood.7,8 An increasing number of patients thus refuse blood products, seek autologous donation, or request so-called “bloodless surgery” due to the perceived risk of blood transfusion.9

Known risks of allogeneic transfusions include transmissible infectious agents, transfusion reactions, and effects on immunomodulation (e.g., postoperative infection and tumor progression).1,5 Not surprisingly, the risks associated with allogeneic PRBC transfusions differ significantly among countries with a low versus high human development index (HDI): an index based on life expectancy, literacy, enrollment in further education, and per capita income.9 In countries with a low HDI, the risk of infection (human immunodeficiency virus, hepatitis B, hepatitis C, and malaria) is increased, whereas in countries with a high HDI, immunological reactions (hemolytic transfusion reactions, alloimmunization and immunosuppression) are predominant.8

Published data also support a major association between intraoperative blood transfusion and morbidity and mortality in patients undergoing noncardiac surgery.10 A recent retrospective analysis examined the association between blood transfusion and 30-day morbidity and 30-day mortality, in patients undergoing general, vascular, or orthopedic surgery. Compared with patients who were not transfused, patients receiving one or two units of erythrocytes were significantly more likely to have pulmonary complications (adjusted odds ratio, aOR of 1.76), sepsis (aOR of 1.43), thromboembolic complications (aOR of 1.77), and wound complications (aOR of 1.87).10

Intraoperative blood transfusion was also associated with a significantly increased risk of death (aOR of 1.29), with a similar increased risk of 30-day composite morbidity (aOR of 1.23 and NNH of 3) and 30-day mortality (aOR of 1.32 and NNH of 11) were observed in the 2005–2006 American College of Surgeons (ACS) National Surgical Quality Improvement Program (NSQIP) database of general surgery patients.11 While these data are disconcerting, such association does not equate to causation. Nevertheless, efforts to reduce or to eliminate the need for surgical blood transfusion are very critical.12

The most important predictor of blood transfusion in surgery is the preoperative circulating erythrocyte mass, as estimated by the patient’s hemoglobin (Hgb).3 Thus not surprisingly, preoperative anemia is also an independent predictor of postoperative morbidity and mortality.13–15 Based upon the 2008 ACS NSQIP database, preoperative anemia was independently associated with an increased risk of 30-day morbidity (aOR of 1.35) and 30-day mortality (aOR of 1.42) in patients undergoing major noncardiac surgery.15 Of note, this significantly increased risk of morbidity and mortality was present with mild anemia (hematocrit > 29% and < 39% in men and > 29% and < 36% in women) and moderate-to-severe anemia (hematocrit ≤ 29% in men and women).15 An even stronger association between anemia (Hgb < 13.0 g/dL for men and < 12.0 g/dL for women) and increased 90-day mortality (aOR of 2.36) was observed in a retrospective Canadian health system cohort of noncardiac surgery patients.13

Preoperative anemia is a common condition among surgical patients; however, its reported prevalence varies widely, ranging from 5% to 75% depending on the type of surgery, the patient’s age, gender, co-morbidities, as well as the criteria used for defining anemia.16,17 The most frequent causes for existing preoperative anemia are iron deficiency and anemia of chronic disease.18,19 In a national audit of patients undergoing elective orthopedic surgery in the United States, 35% were found to have Hgb of < 13 g/dL at the time of preadmission testing.20–22 A recent systematic review observed an average 24% prevalence of preoperative anemia in total joint replacement patients, resulting in a 45% perioperative transfusion rate.23

Lastly, with the ageing of the population in the United States, and other developed countries, voluntary blood donation pools and rates continue to decrease,24 which will likely increase the occurrence of acute blood shortages and elective surgery cancellations.18,25,26 This shrinking donor availability, combined with measures to reduce the risks of infection transmission (e.g., increasingly restrictive donor screening criteria) have increased the direct costs of blood products.26,27 It has been estimated that the total cost per unit of PRBC is in excess of $1000 ($250 acquisition cost X 4), resulting in annual hospital expenditures of $1.63 to $6.03 million.28

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Given these various motivating factors, patient blood management (PBM) (i.e., “blood conservation”) is thus being widely advocated.26,29,30 PBM has been defined by Society for Advancement of Blood Management as “the appropriate provision and use of blood, its components and derivatives, and strategies to reduce or avoid the need for a blood transfusion.”1 This concerted effort is better termed, patient-centered blood management,31 to reflect the increasing emphasis on patient-centeredness in other areas of medicine and the consumer-perspective of health care.32–34

PBM incorporates an evidence-based approach that is multidisciplinary (anesthesiology, critical care medicine, surgery, and transfusion medicine) and multiprofessional (physicians, nurses, pump technologists, and pharmacists).3,20,35,36 PBM focuses on the treatment of the individual patient and comprises goal-directed transfusion therapy and appropriate pharmacotherapy.18,37 PBM is fundamentally based on three strategies or pillars: (1) optimizing of the patient’s (preoperative) erythrocyte mass, (2) minimizing diagnostic, therapeutic, or intraoperative blood loss, and (3) increasing individual clinician’s tolerance towards anemia and adherence to valid blood transfusion triggers by prudently capitalizing on physiologic tolerance of anemia.18,26

**FUNDAMENTALS OF A PREOPERATIVE ANEMIA MANAGEMENT PROGRAM**

A key to achieving such optimal surgery-related patient-centered blood management is a formal preoperative anemia management program (PAMP). Commensurate with the promulgated principles and the above first strategy or pillar of PBM, a formal PAMP primarily identifies surgical patients who are anemic and thus at risk for transfusion and implements a preoperative management plan aimed at reducing or eliminating the presence and/or risk of anemia and the need for allogeneic transfusion, hence reducing the inherent risks, inventory pressures, and the escalating costs associated with transfusion.3,18,26

To this end, a multidisciplinary panel of physicians was recently convened by the Network for Advancement of Transfusion Alternatives with the aim of developing practice guidelines for the detection, evaluation, and management of preoperative anemia (primarily in elective orthopedic surgery) and formulating recommendations using the GRADE working group methodology.16,20 Based upon a systematic literature review and critical evaluation of the evidence, this Network for Advancement of Transfusion Alternatives panel made a series of recommendations (Table 1).

### Table 1. Network for Advancement of Transfusion Alternatives (NATA) recommendations for the detection, evaluation, and management of preoperative anemia.16,20

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>GRADE</th>
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<tr>
<td>Elective orthopedic surgical patients should have an Hgb level determination</td>
<td>Grade 1C</td>
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<td>further laboratory testing for differential diagnosis in those with anemia.</td>
<td></td>
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<tr>
<td>Nutritional deficiencies should be treated prior to increasing Hgb before</td>
<td>Grade 1C</td>
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<td>surgery to be within the normal range.</td>
<td></td>
</tr>
<tr>
<td>Erythropoiesis-stimulating agents be used for anemic patients in whom</td>
<td>Grade 1C</td>
</tr>
<tr>
<td>nutritional deficiencies have been excluded, corrected, or both</td>
<td></td>
</tr>
<tr>
<td>Intravenous iron administration during the preoperative period for patients</td>
<td>Grade 2A</td>
</tr>
<tr>
<td>undergoing orthopedic surgery who are expected to develop severe postoperative anemia</td>
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**Hgb:** hemoglobin

**Strength of recommendation:** Is risk/benefit clear?

Yes strong recommendation = Grade 1: “We recommend”

No weak recommendation = Grade 2: “We suggest”

**Quality of evidence**

High-quality evidence = A (meta-analyses, randomized controlled trials)

Moderate-quality evidence = B (randomized controlled trials with limitations, observational studies with large effects)

Low- or very low-quality evidence = C (observational studies, randomized controlled trials with major limitations)

**Development and Implementation of an Anesthesiology-Based Preoperative Anemia Management Program**

A patient-centered approach to blood management has been advocated by the American Society of Anesthesiologists.31 However, currently, the presence of preoperative anemia is commonly accepted de facto by anesthesiologists. The planned surgery is typically performed as scheduled, without any preemptive corrective action, but instead simply with a lower clinician threshold for intraoperative PRBC transfusion as the default therapy.18,26 This phenomenon is especially noteworthy given the ethical and medico-legal requirement to inform such anemic patients preoperatively on their risks versus benefits with regard to anesthesia and surgery and to plan concomitant diagnostic and treatment measures.18 In order to meet with these requirements, it has been proposed that patients should be initially seen in an outpatient preoperative clinic as soon as possible, but at least three to four weeks before their planned surgery so that appropriate anemia management can be initiated.35 At many institutions (including mine), this hiatus is not feasible, primarily due to a wide patient catchment area and resulting patient inconvenience. This has prompted implementing at our institution a more compressed 12 to 16 day preoperative PRBC transfusion regimen (Figure 1), which is currently the subject of a prospective conjoint randomized controlled clinical trial and formal health care economic evaluation.

A number of studies have demonstrated the safety and efficacy of the preoperative use of an erythropoietic stimulating agent (ESA) like recombinant human erythropoietin (Table 2), especially in the orthopedic population, for reducing the need for red cell transfusion. Of note, the reported side effect profile and adverse event rate (e.g., deep venous thrombosis) in the active treatment versus control groups has been comparable.25,37–46 There is less pain with the subcutaneous injection of epoetin alfa as compared to darbepoetin alfa.47,48 Moreover, epoetin alfa is less expensive and more effective than darbepoetin alfa for an equipotent longitudinal regimen.
The United States Food and Drug Administration (FDA) currently requires all ESAs to be prescribed and used under a risk management program, known as a risk evaluation and mitigation strategy, to ensure the safe use of these drugs. The ESAs included in this risk evaluation and mitigation strategy are marketed under the names Epogen®, Procrit®, and Aranesp®. Per the FDA: “Healthcare professionals who prescribe ESAs for anemia not caused by cancer chemotherapy are required to provide a copy of Medication Guide to each patient or their representative when an ESA is dispensed.” Furthermore: “Healthcare professionals who use ESAs only for non-cancer uses are not required to enroll in the ESA APPRISE Oncology program.”

Patients should receive iron supplementation (Table 3), preferably IV, throughout the presurgical use of an ESA to optimize red blood cell production and to avoid iatrogenic functional iron deficiency.20,26,37,49 Large, single, total replacement doses of all parenteral iron preparations (including


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iron sucrose) are conventionally given by IV infusion over one hour. These high doses have an increased incidence of side effects. However and alternatively, low doses (100 mg to 200 mg) of iron sucrose have been reportedly given safely as a two-minute slow IV push. Ferumoxytol can be given over 20–60 seconds. Iron sucrose was initially approved by the FDA in 2000 and for nondialysis-dependent iron deficiency in 2005. Of note, despite its apparent clinical advantages, ferumoxytol has yet to be FDA approved for treatment of nondialysis dependent iron deficiency.

The conventional wisdom that surgical patients should be transfused to maintain a Hgb of 10 g/dL and a hematocrit of 30% is no longer valid for most patients. Present clinical practice guidelines now recommend restrictive red cell transfusion practices, with the goal of minimizing exposure to allogeneic blood (from an unrelated donor). Specifically, the American Association of Blood Banks has recently recommended adhering to a more restrictive transfusion strategy (7 to 8 g/dL) in hospitalized, stable patients (Grade: strong recommendation; high-quality evidence).

Pertinent to an anesthesiology-based PAMP, a reasonable intraoperative blood conservation protocol applies the same restrictive transfusion trigger (Hgb < 8 g/dL), but also takes into consideration the patient’s intraoperative estimated allowable blood loss and hemodynamic stability. Specifically, if the patient has lost > 30% of his/her estimated blood volume (based upon ideal body weight for height) and requires the administration of an IV medication (vasopressor) for hypotension, the patient will be transfused with 1 (one) unit of PRBCs. Repeat transfusion with PRBCs will occur based on these same criteria. Likewise pertinent to an anesthesiology-based PAMP, consistent with these American Association of Blood Banks guidelines, in postoperative surgical patients, transfusion should be considered at a Hgb concentration of 8 g/dL or less for symptoms of chest pain, orthostatic hypotension or tachycardia unresponsive to fluid resuscitation, or congestive heart failure (Quality of evidence: high; strength of recommendation: strong). However, continuous appropriate training, education, and awareness are needed to avoid local guideline-based protocol violations and to limit unnecessary further exposure to allogeneic blood transfusion and its related risks.

### ROLE OF AN ANESTHESIOLOGY-BASED PREOPERATIVE ANEMIA MANAGEMENT PROGRAM IN A PERIOPERATIVE SURGICAL HOME MODEL

Varied and fragmented care plans, undertaken by different practitioners, currently expose surgical patients to lapses in expected standard of care, increase the chance for operational mistakes and accidents, result in unnecessary and potentially detrimental care, and adversely affect the patient health care experience. Standardization of perioperative processes is increasingly recognized as needed to optimize not only resource utilization and quality but also patient safety, well-being, and satisfaction. Likewise, the medical community and the public are increasingly embracing shared decision-making, a process by which health care choices are made jointly by the practitioner and the patient. Like the Medical Home model that has been implemented in the primary care practice setting, the Perioperative Surgical Home has thus been proposed by the American Society of Anesthesiologists and other stakeholders as an innovative, patient-centered continuity of care model that emphasizes shared decision-making.

In the Perioperative Surgical Home model, anesthesiologists serve as the surgical patient’s primary perioperativist, providing highly integrated, continuity of care throughout the preoperative, intraoperative, and postoperative periods. This broadening of anesthesiologists’ scope of practice should promote such standardization and shared decision-making, thus likely improving clinical outcomes and decreasing unnecessary resource utilization. A patient-centered, anesthesiology-based PAMP a logical component of such a multifaceted Perioperative Surgical Home.

While a preanesthetic patient assessment has been a longstanding required element of any anesthetic, it has been historically performed in close proximity to the scheduled surgery and has routinely only collected a limited set of clinical data, including laboratory testing. In patients with a greater chronic disease burden, such a preanesthetic assessment may fail to detect some of the patient’s underlying conditions, delay diagnosis, and result in unnecessary further exposure to allogeneic blood transfusion and its related risks.

### Table 2. Commercially available erythropoietic stimulating agents (ESA)

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<thead>
<tr>
<th>ESA</th>
<th>Equipotent Dose</th>
<th>Equipotent Dose</th>
<th>Equipotent Dose</th>
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<tbody>
<tr>
<td>Darbepoetin alfa</td>
<td>200 mcg</td>
<td>100 mcg</td>
<td>60 mcg</td>
</tr>
<tr>
<td>Epoetin alfa (Eprex®)</td>
<td>40,000 units</td>
<td>20,000 units</td>
<td>10,000 units</td>
</tr>
<tr>
<td>Epoetin alfa (Procrit®)</td>
<td>40,000 units</td>
<td>20,000 units</td>
<td>10,000 units</td>
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### Table 3. Contemporary commercially available intravenous iron (IV Fe) preparations

<table>
<thead>
<tr>
<th>IV Fe</th>
<th>Typical lower, split dose, rate of administration</th>
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<tr>
<td>Iron sucrose (Venofer®)</td>
<td>100 mg, 200 mg, or 300 mg over 2 to 30 minutes</td>
</tr>
<tr>
<td>Ferric carboxymaltose (Ferinject®)</td>
<td>500 mg or 1000 mg over 15 minutes</td>
</tr>
<tr>
<td>Ferumoxytol (Feraheme®)</td>
<td>510 mg in &lt; 60 seconds</td>
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*May not be available in the United States

**Approved by the United States Food and Drub Administration in 2009; post-marketing trials continue to be published (but no preoperative data)
Minimizing the need for surgical transfusions has not only physiologic but also economic benefits. Preoperative treatment of anemia with recombinant human erythropoietin [e.g., epoetin alfa (PROCRIT®), manufactured by Amgen Inc., Thousand Oaks, CA for Janssen Products, LP, Horsham, Pennsylvania] and IV Fe [e.g., iron sucrose (Venofer®), American Regent, Inc., Shirley, NY] have been advocated to reduce the need for allogeneic transfusion. Such treatment is covered by the Center for Medicare & Medicaid Services and commercial payers (e.g. Blue Cross and Blue Shield).

A retrospective review of University of Alabama Hospital administrative and clinical data from 2011 revealed a cross-sectional 39% prevalence of preoperative non-macrocytic anemia (Hgb ≤ 12.5 g/dL and mean corpuscular volume < 100 fL in females and males) among 358 total hip arthroplasty patients, resulting in 352 PRBC units being transfused in the 128 preoperatively anemic patients (Vetter et al., 2012 American Society of Anesthesiologists Annual Meeting). Of note, despite receiving a PRBC transfusion, the preoperatively anemic patients had a mean Hgb of 8.8 gm/dL (SD 1.1) at time of hospital discharge. The local direct (wholesale) cost of epoetin alfa (PROCRIT®) is $381/dose (40,000 IU) and the direct (wholesale) cost of iron sucrose (Venofer®) is $63/dose (200 mg), the latter with an estimated administration cost of $50/doze. The estimated total cost of a PRBC unit at University of Alabama Hospital is $1000 ($250 acquisition cost X 4). Treating these 128 anemic total hip arthroplasty patients with preoperative ESA + IV Fe therapy (three weekly doses/patient) and postoperative IV Fe (single dose/patient) (applying the protocol in Figure 1) would cost $178,560 versus $352,000 for the estimated total cost of the 352 transfused PRBC units, a net annual savings of $173,440. Further savings would be realized by inclusion of other elective major surgical procedures (e.g. total knee arthroplasty) or if the third dose of epoetin alfa is not needed on the day of surgery.

The Patient Protection and Affordable Care Act of 2010 seeks to reign in spiraling health care costs by fundamentally transforming health care delivery via (a) new care models that deliver more cost-effective and coordinated care and (b) incentive-based reimbursement. In this new health care paradigm, providers, including anesthesiologists, will be paid not just for the quantity but the quality and value of the services they provide. Value-based purchasing of health care, pay for performance, and a changing payment paradigm that includes bundled payments and/ or accountable care arrangements are all powerful motivators to improve health care delivery and outcomes, particularly in the perioperative setting. Hospital-physician collaborations will continue to evolve toward greater economic integration, including major financial gain and risk sharing. A greater level of payment will be based on the reduced resources used by those care delivery teams achieving superior outcomes, thereby fostering innovation and reducing waste. To be successful, the nascent Perioperative Surgical Home model, including for example, a comprehensive Preoperative Assessment, Consultation, and Treatment Clinic and a robust PAMP will need to create strategic added value for a hospital and health system as well as payers. This added value will strengthen the position of anesthesiologists as they navigate and negotiate in the face of finite and more likely decreasing fiscal resources (i.e., making do with less).

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