ABSTRACT

Increasing concerns over the widespread use of blood transfusions have prompted interest in blood conservation strategies, including various pharmacologic agents, as well as numerous devices and techniques. This article explores the currently available blood conservation strategies and the evidence supporting their efficacy in various acute clinical settings. Pharmacologic agents, which include antifibrinolytic agents, desmopressin, erythropoiesis-stimulating agents, parenteral iron, vitamin K, and recombinant activated factor VII, can either reduce or stop bleeding, or decrease the likelihood of transfusion by raising hemoglobin. Other strategies, which have mostly been used to reduce transfusion requirements in surgical or trauma cases, include acute normovolemic hemodilution, cell salvage, reduction of blood loss during diagnostic testing, and potentially red-cell substitutes. Also included is a discussion on areas of controversy related to blood conservation and examples of successful institution-based blood management programs.


Although blood transfusion can be a life-saving treatment for acute blood loss or severe symptomatic anemia, the many potential associated harms and supply limitations have been well documented and, therefore, its use in many nonacute hematologic states (eg, mild-to-moderate anemia) is strongly debated. As a result, several available blood conservation strategies (Table) have been used in an attempt to avoid or minimize transfusions in selected patients, and upon further investigation, these strategies may be offered to patients with chemotherapy-induced anemia (CIA).

PHARMACOLOGIC STRATEGIES TO REDUCE BLOOD TRANSFUSION

Pharmacologic agents used in blood conservation can either reduce or stop bleeding or decrease the likelihood of transfusion by raising hemoglobin (Hb). These include antifibrinolytic agents, desmopressin (DDAVP), erythropoiesis-stimulating agents (ESAs), parenteral iron, vitamin K, and recombinant activated factor VII. Although some of these drugs may in theory be used in malignancy-influenced bleeding, the current supporting evidence comes primarily from studies examining them peroperatively, in critical care settings, in trauma, or in those with congenital bleeding disorders.

ANTIFIBRINOLYTIC AGENTS

These agents (ie, tranexamic acid, epsilon aminocaproic acid, and aprotinin) inhibit the breakdown of blood clots and are used in a variety of conditions to reduce bleeding. Epsilon aminocaproic acid inhibits fibrinolysis via inhibition of plasminogen
### Table. Summary of Clinical Recommendations and Evidence Base for Blood Conservation Strategies to Reduce the Need for Blood Transfusions in Critically Ill Patients

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<td>Tranexamic acid or epsilon aminocaproic acid</td>
<td>Improved hemostasis</td>
<td>• Reduced risk of recurrent bleeding and death associated with gastrointestinal bleeding*&lt;br&gt;• Reduced risk of perioperative bleeding and need for reoperation in cardiac surgery patients&lt;br&gt;• Under investigation for use in trauma patients</td>
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<td>Aprotinin</td>
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<td>Desmopressin</td>
<td>Improved hemostasis and increased factor VIII and von Willebrand levels</td>
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<td>Recombinant activated factor VII</td>
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<td>Artificial oxygen carriers (modified hemoglobin substitutes or perfluorocarbons)</td>
<td>Increased oxygen transport without blood transfusion; increased ability to perform acute normovolemic hemodilution</td>
<td>• Possible reduction in need for transfusion*&lt;br&gt;• Prolonged shelf-life&lt;br&gt;• Products can be stored at room temperature&lt;br&gt;• No risk of disease transmission&lt;br&gt;• No immunologic effects</td>
<td>RCT&lt;br&gt;Case report&lt;br&gt;Case report&lt;br&gt;Case report&lt;br&gt;Case report</td>
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<td>Postoperative blood recovery techniques (cell salvage)</td>
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<td>Reduction of iatrogenic blood loss from diagnostic testing</td>
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<td>Erythropoietin</td>
<td>Increased production of red blood cells in bone marrow</td>
<td>• Increase in hemoglobin level and possible reduced need for transfusion&lt;br&gt;• Possible reduction in mortality among trauma patients*</td>
<td>RCT; meta-analysis&lt;br&gt;RCT subgroup analysis</td>
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<tr>
<td>Restrictive red blood cell transfusion trigger†</td>
<td>Raised hemoglobin threshold for red blood cell transfusion</td>
<td>• Reduced need for blood transfusion without increase in morbidity or mortality in most critically ill patients</td>
<td>RCT</td>
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*Further results from recent phase III RCT are required to determine benefits and harms.  
†For example, a change in hemoglobin threshold for transfusion of 70 g/dL.  
RCT = randomized controlled trial.  
inhibitors and, to a lesser degree, through antiplasmin activity. Tranexamic acid is similar to epsilon aminoacaproic acid, but it is approximately 10 times more potent. Aprotinin (no longer available in clinical practice) also limits the action of plasmin, but has a somewhat different mode of action. In some studies, perioperative use of antifibrinolytic agents was shown to reduce the need for blood transfusions and re-operation, but the benefits are less clear in other trials.

DDAVP

This agent is a synthetic analogue of arginine vasopressin that induces the release of stored factor VIII and von Willebrand factor from endothelial cells. DDAVP has been shown to be effective in controlling and preventing bleeding in patients who have congenital platelet disorders (eg, mild hemophilia A and von Willebrand’s disease) and in those who have platelet dysfunction associated with renal failure. Because a meta-analysis of DDAVP in the treatment of perioperative bleeding showed a nonsignificant reduction in blood loss without evidence of a reduction in transfusion need, DDAVP may not be effective in improving hemostasis or in reducing acute blood loss in critically ill patients who do not have specific bleeding disorders.

RECOMBINANT-ACTIVATED FACTOR VII (RECOMBINANT FACTOR VIIa)

A recombinant coagulation factor concentrate, this product is specifically approved for patients with factor deficiencies (hemophilia), but because it is also known to enhance thrombin generation, it has been suggested to provide hemostasis in various other clinical situations, including obstetrical bleeding, trauma, and perioperative bleeding. In fact, a substantial portion of this product’s usage is currently off-label, and as such, a consensus panel has developed recommendations for appropriate clinical situations related to off-label use of recombinant factor VII. The major categories of off-label use included closed-space (including intracranial) bleeding, surgical bleeding, and other bleeding causes (eg, postpartum, multiple trauma, and active gastrointestinal bleeding).

ESAs

The currently US Food and Drug Administration-approved ESAs, epoetin alfa and darbepoetin alfa, share a similar mechanism of action, which involves stimulation of erythropoiesis via binding to the erythropoietin receptor on erythroid progenitors. The major difference between these agents is in their pharmacokinetics, with darbepoetin alfa (compared with epoetin alfa) exhibiting a longer serum half-life (t1/2) but a lower binding affinity for the erythropoietin receptor in vitro, taking 3 to 5 times longer to reach peak serum concentrations. The effectiveness of ESAs, along with supplemental parenteral iron, as a blood conservation strategy in patients with CIA is well documented, with multiple studies demonstrating their ability to significantly raise Hb levels and reduce transfusion requirements. George M. Rodgers, III, MD, PhD, provides a more detailed discussion on the efficacy and safety of ESA and parenteral iron therapy in the management of CIA.

BLOOD CONSERVATION DEVICES/TECHNIQUES

In an effort to minimize reliance on blood transfusions, many techniques and devices have been used over the decades in various clinical scenarios (eg, trauma and surgery) to diminish blood loss. This section focuses on some of the major strategies in use today.

ACUTE NORMOVOLEMIC HEMODILUTION

As a blood conservation method in surgery, acute normovolemic hemodilution (ANH) was re-introduced in the 1970s in response to the growing awareness of transfusion-related risks and religious objections to transfusion. The strategy involves removing a portion of a patient’s blood immediately prior to surgery, and simultaneously replacing it with an acellular fluid (eg, crystalloid or colloid) to maintain normovolemia. The patient’s blood becomes diluted and the amount of actual red blood cell (RBC) and plasma loss during surgery is reduced. In the meantime, the collected blood is properly stored and re-infused into the patient after cessation of major blood loss or when transfusion is needed. Because ANH blood does not have testing requirements and involves collection and storage of units at the patient’s bedside, ANH can be performed on the day of the procedure, and it is therefore more advantageous than preoperative autologous blood donation (PABD). The latter procedure requires the patient to make preoperative visits to the hospital to donate his or her own blood, has testing requirements, and because the units are not stored solely in the operating room, is associated with potential errors leading to ABO-incompatible blood transfusions and the risk of bacterial contamination.
In regard to efficacy of ANH, many studies have shown inconclusive results, whereas others have demonstrated some benefits. For example, one retrospective analysis of 800 patients concluded that ANH reduced the need for allogenic blood transfusion in patients undergoing orthopedic surgery and other smaller studies found ANH to be comparable to PABD in reducing the need for allogenic blood trans-fusions in various surgical procedures. Other studies have associated ANH with either a slight or non-significant reduction in the risk of allogenic transfusion in the perioperative period, but most are limited by design flaws. ANH appears to be more effective in procedures with larger anticipated blood loss.

**RBC Salvage**

Similar to ANH, RBC salvage has been available for over 2 decades and is based on the concept of collecting blood for later retransfusion to the donor. This form of autologous transfusion involves aspiration of shed blood from the surgical field into a closed suction device, filtration, and eventual transfer into an anticoagulant-containing reservoir. If immediate volume replacement is necessary (e.g., trauma), the “unprocessed” blood can be readministered from the reservoir to the patient. For hemodynamically stable patients, the collected blood may be centrifugally washed to remove debris and contaminants before reinfusion (“processed blood”). Intraoperative cell salvage has been shown to reduce the risk of transfusions and is, thus, considered a reasonable alternative or additional method of volume/blood management in patients undergoing high blood loss surgical (e.g., cardiothoracic or vascular) procedures.

**Reducing Blood Loss During Diagnostic Testing**

Depending on institutional practices and the patient’s illness, blood samples for diagnostic testing can be taken up to 24 times per day, with indwelling central venous or arterial catheters contributing substantially to increased blood loss. Numerous studies dating back to the 1980s have reported significant volumes of blood loss (e.g., 41 mL/day per patient) among patients admitted to various intensive care units (e.g., cardiothoracic, general surgical, and medical-surgical). This increased diagnostic-related blood loss places the most acutely ill patients, including those receiving myelosuppressive chemotherapy, at an increased risk of anemia. Approaches to reducing iatrogenic blood loss have included use of small-volume (pediatric) blood collection tubes, reduction of discarded blood from catheter collections, alterations in test-ordering behavior, and point-of-care microanalysis.

**Areas of Controversy**

The benefits/efficacy of the various blood conservation strategies described previously appear to be arguable, because the current evidence is based on limited, and at times conflicting, studies and very diverse settings (e.g., trauma, congenital bleeding disorders, and perioperative). Likewise, certain related risks are somewhat unclear and may pose patient harm. As a result, the risk versus benefit of blood conservation strategies has always been under scrutiny and is, therefore, one of the main controversies in this area of medicine.

The common concern with the majority of pharmacologic agents used in blood conservation is the risk of thrombosis, which is inherent to the coagulation-promoting mechanism of action. Both DDAVP and recombinant factor VII have been associated with rare but serious thrombotic events, including acute cerebrovascular thrombosis and acute myocardial infarction, most commonly in patients with hypercoagulability states. The antifibrinolytic agent aprotinin is associated with an increased risk of thrombosis, cardiac complications, renal toxicity, and death, as suggested by a large observational study of patients undergoing coronary artery bypass grafting surgery. More than 4000 patients were given either aprotinin, aminocaproic acid, or tranexamic acid for reduction in perioperative bleeding. Use of aprotinin (but not aminocaproic acid or tranexamic acid) was associated with a doubling in the risk of renal failure requiring dialysis, a 55% increase in the risk of myocardial infarction or heart failure, and a 181% increase in the risk of stroke or encephalopathy. Another study has also suggested an association between aprotinin and renal toxicity among patients undergoing cardiac surgery with cardiopulmonary bypass. As a result of these data, worldwide marketing of aprotinin has been suspended.

Erythropoiesis-stimulating agents have also been associated with thrombotic complications and, in more recent studies, with an increased risk of tumor progression and death in oncology patients. Although most of the adverse outcomes appear to be related to Hb concentrations greater than 12 g/dL, the increased risk of tumor progression and mortality have not been
excluded when ESAs are dosed to a target Hb level lower than 12 g/dL. ESAs should, therefore, be adjusted to maintain the lowest Hb level needed to avoid the need for blood transfusions and should only be used for treatment of anemia related to myelosuppressive chemotherapy (see Dr Rodgers’ article).9

The major risks relating to cell salvage include air embolism, induction of an inflammatory state (eg, febrile reactions), sepsis, hemolysis, and coagulopathy. Use of cell salvage during oncologic surgery is quite controversial, because it has a theoretical risk of introducing tumor cells from the operative field into the patient’s vasculature. However, because recent studies have not found an increase in local recurrence or metastatic disease among patients who were treated with cell salvage, some surgeons have become more comfortable with using this blood conservation strategy in oncology.22,23

Most of the controversy surrounding ANH is related to the lack of a definitive verdict on its efficacy, rather than on its risk (which appears to be minimal). Essentially, investigators conducting ANH trials have not been able to reach conclusive results because of numerous limitations in trial design, including lack of blinding and widely accepted standards for ANH procedure, as well as too many variables (eg, changing transfusion protocols/criteria).10 Moreover, performing an accurate meta-analysis on ANH is nearly impossible because of significant differences between existing studies. Although ANH does not easily lend itself to conventional research methods, recent studies are using more rigorous designs and will perhaps ultimately reach a more definitive conclusion.

**AREAS OF DEVELOPMENT**

In recent years, there has been increasing interest in the development of red-cell substitutes, including cell-free (modified) Hb solutions and perfluorocarbon emulsions (synthetic oxygen carriers).11 Hb substitutes may delay or reduce exposure to allogenic transfusions by replacing blood products and improving oxygen delivery during acute blood loss. These products, which are currently being investigated in patients with acute trauma and in those undergoing surgery (with or without ANH), have several potential advantages, including availability without the need for cross-matching, long shelf life, storage at room temperature, and reduced risk of disease transmission.1,11 Disadvantages include a relatively short half-life after administration, interference with Hb measurements, renal toxic effects, and adverse effects on vascular tone resulting in increased blood pressure. Some of the newer products in development have longer half-lives and appear to be less toxic and vasoconstricting, but previous studies have linked one of these agents (diaspirin cross-linked Hb) with increased mortality in trauma patients.

Perfluorocarbons appear promising because they can transport both oxygen (at twice the rate of Hb) and carbon dioxide, and they have a long half-life. So far, patients who received perfluorocarbons (along with ANH) in studies of elective surgery had less transfusion requirements, but because perfluorocarbons require delivery of 100% oxygen, they may not be applicable in pre-hospital situations.1

**INSTITUTION-SPECIFIC PROTOCOLS**

According to recent guidelines on perioperative blood transfusion and blood conservation in cardiac surgery, there is still marked variability in transfusion practices and blood conservation interventions, essentially because accurate and timely information on platelet and coagulation status of surgical/intensive care unit patients is difficult to obtain, and because process variability is difficult to control.2 As a result of these shortcomings, several investigators have examined the value of transfusion algorithms using institution-derived transfusion practices, in conjunction with accurate point-of-care testing to guide responses to bleeding and to direct blood transfusion. In most studies, the combination of point-of-care testing and transfusion algorithms was found to be both cost-effective and efficacious in limiting nonautologous blood product transfusions and providing adequate hemostasis. Moreover, the guidelines contend that a multifaceted approach to blood conservation “produces the best results.”2

In the spirit of using this approach to standardize transfusion practices, several institutions have developed evidence-based blood management guidelines. Englewood Hospital and Medical Center initially developed a bloodless medicine and surgery program for Jehovah’s Witnesses and other patients who refused blood products. But because the majority of Englewood’s patients who were managed with blood conservation strategies had outcomes that were comparable to those of transfusion-treated patients, the
program was expanded. Englewood’s current program incorporates medications that enhance Hb production, ANH, cell salvage, staging of difficult procedures, and a greater tolerance of acute anemia. As a result of these interventions, use of allogenic blood at Englewood has decreased by approximately 50%, with surgery-related mortality rates remaining low.

As another example, the pharmacy department at Swedish Medical Center has established a blood management department, with the goals of conserving blood utilization, improving patient outcomes, and reducing hospital costs. A multidisciplinary team (eg, physicians, nurses, and pharmacists) created new transfusion guidelines (advocating transfusions only in the presence of decreased tissue perfusion) and order forms (standardizing blood component ordering across all services). The pharmacy department also developed a learning module on anemia and offered anemia consultations to inpatients scheduled for surgery or those at high risk of anemia. Pharmacists reviewed relevant patient laboratory values (eg, complete blood count and iron studies) and either made therapeutic recommendations or referred patients to hematologists. Since implementation of this program, Swedish Medical Center has experienced an overall reduction in use of transfusions and reduced length of stay among patients undergoing elective orthopedic surgeries.

CONCLUSIONS

The increased scrutiny of blood transfusions has caused many healthcare providers to examine more closely the various blood conservation strategies that were at one point only considered for those patients who had religious or other objections to transfusions. Although most of the currently published studies involving blood conservation have been focused on nonanemia indications, future studies will likely examine more diverse uses and offer more definitive results.

REFERENCES

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