

BLOOD TRANSFUSIONS

Preface

My Juju's Stronger Than Yours!

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Perhaps no single topic evokes as strong visceral reactions as transfusion of whole blood or fractionated blood component. Practitioners who share a common philosophy regarding such diverse topics as antimicrobial prescription, colloid versus crystalloid resuscitation, and the value of early enteral nutrition readily draw the proverbial line in the sand regarding optimal values of hemoglobin and hematocrit. This issue of *TraumaCare* explores the data that underpin this divisive topic, explores the physiologic rationale supporting transfusion triggers and practices, provides a rational guide for initiating component therapy, and details alternatives to transfusion therapy for the critically ill in the operating room and intensive care unit.

Despite the wealth of experience with whole blood and component therapy transfusion, there is little *compelling* evidence that increasing hemoglobin concentration, arteriolar oxygen content, or global oxygen delivery increases survival in patients other than in two very precisely defined patient populations: those with 1) active hemorrhage and 2) active cardiac ischemia. Otherwise, despite deeply entrenched notions of the benefit of transfusion for ventilator weaning, strength, hemodynamic performance, and microvascular flow, there are no prospective, randomized, controlled data to support the practice of maintaining a hemoglobin of 10 g/mL or hematocrit of 30%.

How can our profession engage in as costly a practice as component therapy without definitive data to support such a practice? Likely, we (medical professionals) have generally surrendered our clinical equipoise with regard to transfusion therapy and are loath to subject our patients to a clinical investigation that may withhold transfusion in a circumstance where we believe transfusion to be beneficial or even critical. Additionally, although the cost of component therapy has sharply escalated with the widespread use of leukoreduction, enhanced screening for blood-borne infection, and detergent-treated plasma to reduce infection transmission, these costs may be negligible in comparison to the cost for enhanced technology. The last decade witnessed the growth of near-universal CT scanning, magnetic resonance imaging, positron emission tomography, virtual colonoscopy and bronchoscopy, which detail only a few of the "standard" diagnostic tools that add to the spiraling cost of medical care *prior to definitive therapy*. Thus, the costs of component therapy appear minimal in comparison. Furthermore, increasingly toxic chemotherapeutic regimens, often in conjunction with bone marrow transplantation, require component therapy as a standard commensal of definitive therapy for the underlying malignancy. Hence, we have accepted component therapy as a supportive measure in much the same way as we use intravenous fluid, activated protein C, and increasingly, activated factor VIIa.

Nonetheless, deleterious effects of transfusion therapy have been elucidated. These untoward and unintended consequences span such diverse effects as immunosuppression, increased mortality, transfusion-related acute lung injury, alloimmunization, and reduced microvascular flow. These consequences are detailed throughout this issue of *TraumaCare* and provide a strong rationale for exploring alternatives to transfusion. Alternatives may include colloid resuscitation, acute normovolemic hemodilution, red cell scavenging, and pharmacologic adjuncts to enhance the clotting cascade.

It is my hope that the contents of this issue will provoke readers to critically explore their personal and institutional transfusion practices, explore alternatives to component therapy, and adopt practices that minimize or even eliminate component utilization, except in circumstances where that practice is supported by data.

Why Should Clinicians Be Concerned about Blood Conservation?

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Learning Objectives: 1) To fully understand the meaning and working of bloodless conservation. 2) To know the importance of implementing a blood conservation program. 3) To understand the various methods and techniques of decreasing allogeneic blood transfusion.

Abstract

A shrinking donor pool and an increased awareness of risks associated with allogeneic blood transfusion have contributed to the evolving and widening application of techniques for blood conservation. "Bloodless medicine and surgery" has moved beyond the concerns of just Jehovah's Witness patients. Risks associated with blood transfusions have been well documented, which, coupled with more stringent donor screening, has had significant impact on the availability and costs of blood supply. The challenge for clinicians is to prevent complications and unnecessary blood use. Although there is no single blood

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conservation strategy that will be applicable to all patients and populations, the aim of this review is to describe different approaches that clinicians might use in forming a comprehensive strategy for blood conservation. Ultimately, the success of a blood conservation program requires multidisciplinary teamwork involving the blood bank, pharmacy, administration, surgeons, hematologists, and anesthesiologists to ensure that goals of minimizing blood loss and avoiding transfusion are met.

For many of us, blood conservation seems to be an abstract concept only for consideration by health care providers caring for patients who refuse transfusion. Although “bloodless surgery” for Jehovah’s Witness patients provided some of the impetus for blood conservation techniques, all clinicians need to be concerned about reducing the amount of transfused blood product for more clinical and practical reasons. Blood conservation is no longer a niche practice, reserved for “bloodless surgery” programs and the treatment of Jehovah’s Witness patients. In reality, blood conservation—defined as the active attempt to eliminate or minimize the transfusion of allogeneic blood—likely represents a best practice that can significantly improve quality of care. Decreasing short-term complications as well as serious long-term sequelae should result in improved outcomes. Additional benefits include preservation of limited resources—donated human blood components—for when they are truly necessary, as well as the cost savings associated with minimizing allogeneic transfusion. Active efforts to conserve blood should ultimately become the standard of medical and surgical therapy.

Why Be Concerned with Blood Conservation?

Religious and Ethical Issues. In caring for Jehovah’s Witnesses who refuse allogeneic transfusion on religious grounds, clinicians are often challenged to provide the best care while respecting patients’ beliefs. Jehovah’s Witness patients abstain from the transfusion of major blood components (i.e., whole blood, red cells, white cells, platelets, plasma) based on interpretation of biblical scriptures concerning blood. Consequently, many institutions have developed bloodless medicine and surgery programs to serve the specific needs of this group.^{1,2} The transfusion of lesser blood components (e.g., isolated clotting factors, albumin, immunoglobulin preparations, hemoglobin-based blood substitutes) is considered a “conscience decision” and is left in the hands of the individual patient. Discussion of the complex legal and ethical issues surrounding the management of Jehovah’s Witness patients is beyond the scope of this article; however, familiarity with key elements of this issue, such as informed consent, proxy, and the management of children and pregnant patients, is crucial to their successful medical management.^{3,4} Safe bloodless management of Jehovah’s Witness patients is certainly an achievable goal, as evidenced by its successful application in such demanding cases as liver transplantation⁵ and open-heart surgeries.⁶

Patients may also refuse blood on nonreligious grounds, most typically because of fear of infectious complications such as human immunodeficiency virus (HIV). It is important to educate these patients on the real risks of blood transfusion before they commit to refusal to the point of death. Although we need to respect the patient’s right to self-determination, we must also ensure that a patient is sufficiently well informed to refuse transfusion under any circumstances. In our experience, many such patients will accept transfusion once they are aware of the real risks, especially if they are informed that other transfusion avoidance measures will be used.

Risk	Estimated Frequency (per unit)
Infection^{1,14}	
Viral	
HIV	1:1,500,000 – 1:4,700,000
Cytomegalovirus	1:100
Hepatitis B	1:31,000 – 1:205,000
Hepatitis C	1:500,000 – 1:3,100,000
Human T-cell lymphotropic virus types I and II	1:641,000
Malaria	1:4,000,000
Bacterial contamination ^{9,14}	
Packed red blood cells	1:30,000 – 1:143,000
Platelets	1:2000 – 1:3000
Blood transfusion reactions^{1,14,18}	
Hemolytic reactions	1:25,000
Fatal hemolytic reactions	1:160,000
Acute hemolytic reactions	1:13,000
Delayed hemolytic reactions	1:9,000
Allergic reaction (mild to severe)	1:2,338 – 1:30,281
TRALI	1:5,000-1:7,000

TRALI, transfusion-related acute lung injury.

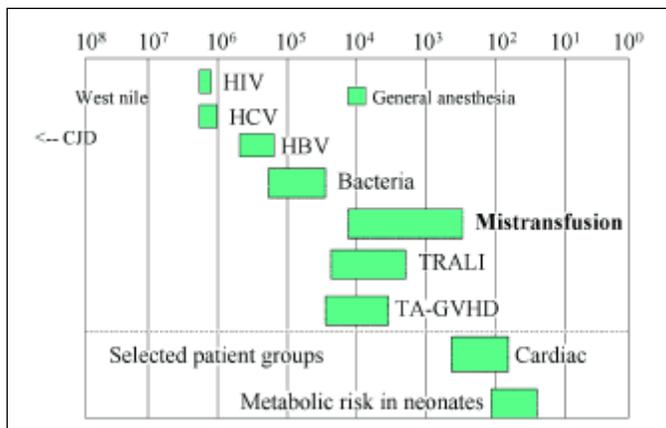


Figure 1. Paling Risk Scale for Major Transfusion Hazards*

*Estimated current risk of transfusion as shown on a Paling Scale. The vertical lines represent powers of 10. The horizontal bars are risk estimates taken from published literature. HIV, human immunodeficiency virus; HCV, Hepatitis C; HBV, Hepatitis B; TRALI, transfusion-related acute lung injury; TA-GVHD, transfusion-associated graft-versus-host disease. (Figure provided by Walter Dzik, MD, Massachusetts General Hospital.)

Infectious Considerations. With donor restrictions and technological advances in screening, viral transmission by blood transfusion is now a rare occurrence. For example, the risk of transmission of HIV or hepatitis from transfusion has declined by an estimated 10,000-fold. Furthermore, the risk of transfusion transmission of these and other viral infections, including human T-cell lymphotropic virus types I and II (HTLV-I and HTLV-II) continues to decline. These risks are listed in Table 1 and their decline is graphically illustrated in Figure 1.⁷ Risks of transfusion-transmitted Chagas disease, West Nile virus, and Parvovirus B19 are

variable, depending on their prevalence in the donor pool. Prions, such as variant Creutzfeldt-Jakob disease, are associated with a 6- to 7-year latency period; consequently, there may be delay before increased prevalence in donor pools is seen.⁸⁻¹⁰

By comparison, there has been little improvement in the risk of noninfectious blood transfusion hazards. Today, blood transfusion-related adverse outcomes are more likely to result from other risks, such as bacterial contamination, hemolytic reactions, or transfusion-related lung injury, than from the transmission of viral diseases.

Mistransfusion. Mistransfusion (i.e., failure to give the right blood product to the right patient) accounts for over 50% of all transfusion-related adverse occurrences.^{11,12} Fatal acute hemolytic reactions to transfusion occur in 1 in 160,000 transfusions.^{7,13,14} Approximately one-half of all acute hemolytic reaction-related deaths are attributable to ABO incompatibility, as a result of administrative (i.e., human) errors.^{11,13} These are most often related to mismatching of the patient and the blood unit, ranging from 1 in 14,000 to 1 in 18,000 transfusions.¹³ In addition, delayed transfusion reactions are seen in 1 in 9,000 patients; 0.5% of patients will develop some nonhemolytic clinical manifestations of blood transfusion reactions, even with white blood cell-reduced units.¹⁵ New technologies such as bar coding, radiofrequency identification, and embedded chips show promise in improving the accuracy of blood delivery.¹⁶ Nevertheless, assiduous attention to patient identification and clerical details can go a long way toward eradication of common transfusion errors.

Red Cell Contamination. Bacterial contamination accounts for over 10% of transfusion-associated deaths and the majority of infection-related deaths, according to a 1999 Food and Drug Administration report.¹⁷ *Yersinia enterocolitica* is the most common bacterial contaminant of red cells. In this situation, the contamination of the blood is directly related to the length of storage, with red cell contamination reportedly occurring in as few as 7 to 14 days. In the United States, red cell contamination is rare, occurring in <1 per million red cell units transfused.^{18,19} Gross contamination of red cell units should be suspected when the color of the blood in the blood bag appears much darker in comparison with the blood in the attached segmented tubing, a consequence of hemolysis and decreased oxygen supply.²⁰

Platelet Contamination. Platelet-related sepsis is seen in 1 in 2,000 to 1 in 3,000 transfusions, with the risk greater (at 1 in 400 units) in transfusion of pooled platelet concentrates from multiple donors compared with single-donor platelet transfusion. Because of the increasing risk of bacterial overgrowth with time, the shelf life of stored platelets should not exceed 5 days.^{19,21} In the face of associated risk:benefit ratio, prudence dictates that platelet transfusion should be conservative and targeted based on the individual patient's clinical profile.

Transfusion-Related Acute Lung Injury. Transfusion-related acute lung injury (TRALI) is an acute respiratory distress syndrome that, in its most serious form, is life-threatening and indistinguishable from adult respiratory distress syndrome. Its estimated frequency has been reported to be anywhere from 1 in 5,000 to 1 in 70,000 transfusions, and it is associated with 6% to 10% mortality rate.^{22,23} Transfusion-related acute lung injury is often underdiagnosed or misdiagnosed, as well as underreported.²⁴ A succinct summary of diagnosis and management has been recently presented by Toy and Gajic.²⁵ Reactive lipid products from donor cell membranes that arise during storage of blood products have been implicated in the pathophysiology of TRALI. Such substances are capable of neutrophil priming, with subsequent damage to the pulmonary-capillary endothelium in the recipient, especially during sepsis. Blood donor antibodies containing HLA or neutrophil antigenic specificity react with recipients' neutrophils, leading to

increased permeability of the pulmonary circulation. Risk factors include patient susceptibility (cardiac disease or hematologic malignancy), age of blood products, and increased levels of bioactive lipids in blood components.²⁶

Transfusion-Mediated Immunomodulation. Allogeneic transfusions are associated with alterations in a variety of clinical outcomes, including reduced organ allograft rejection, reduced spontaneous abortions, increased postoperative infection and multiorgan failure, and increased tumor recurrence.^{8,10,27} Immunomodulation resulting from transfusion is a contributory mediator in these effects; both cellular and humoral immunity are adversely affected. After packed red blood cell transfusions, there is decreased production in interleukin-2 and increased production of prostaglandin-E₂. A decrease in CD4 helper cells is seen, along with an increase in B cells and CD8 suppressor cells. Immunosuppressive effects of allogeneic blood are related to leukocytes and subsequent sensitization.²⁸

In addition, transfusion-associated graft-versus-host disease is a rare complication that can be seen in immunocompromised patients. This reaction results from the transfusion of immunocompetent T cells capable of engrafting and initiating an immune response against recipient antigen; gamma radiation abolishes the proliferative activity of the lymphocytes in donor blood.

The immunosuppressive potential of blood transfusion is well documented in renal transplants, in which it reduces risk of rejection, but links between blood transfusion and increased risk of infection and multiorgan failure or increased risk of tumor recurrence are more controversial. In separate studies, postoperative infection rates were increased in transfused patients undergoing cardiac surgery, hip fracture repair, intra-abdominal surgery, and trauma.^{14,29-31} Braga and colleagues³² found that transfusion of >1,000 mL of blood was an independent risk factor in the development of postoperative infection in patients undergoing surgery for gastrointestinal cancer. Moore et al³³ found a linear trend between the number of units of packed red blood cells transfused and the incidence of multiple organ failure in trauma patients.

Perioperative blood transfusion has been implicated in decreased survival in various types of cancer, including colorectal, esophageal, liver, gastric, renal, and breast carcinoma.³⁴⁻⁴⁰ On the other hand, other studies have found no relationship between earlier-than-expected cancer recurrence and allogeneic perioperative blood transfusion in non-small cell lung cancer, laryngeal cancer, or gynecologic cancer.⁴¹⁻⁴³ Transfusion of even a small number of packed red cell units has been shown to increase proinflammatory mediators postoperatively in cardiac surgery patients and may contribute to poorer postoperative performance.⁴⁴

Other Noninfectious Hazards of Transfusion. After transfusion of multiple units of stored blood, electrolyte abnormalities such as hyperkalemia (secondary to increasing potassium in stored cells) and hypocalcemia (resulting from the binding of calcium by citrate-based anticoagulants) are common and may have clinical consequences. Fluid overload remains a significant problem after transfusion, and suggests invasive hemodynamic monitoring when significant blood loss is anticipated. Coagulopathies result from dilution with large volumes of transfused fluids and blood products. Stored packed red blood cells undergo a shift in the oxygen-hemoglobin dissociation curve secondary to changes in the level of 2,3-diphosphoglycerate, which renders the transfused product less than an ideal oxygen-delivery solution.⁴⁵ Red cells stored for more than 15 days lose adenosine triphosphate, thus causing a decrease in deformability that affects the transportation of oxygen in microcirculation.⁴⁶ Neonates are at risk for hypoglycemia, hypocalcemia, and cardiac events after transfusion.^{47,48}

Cost. Blood products are expensive. There are 12 to 14 million units of blood transfused each year in the United States at a cost of approximately \$2 billion. These costs have been driven up by the price of testing. Technologies that can further improve the safety of the blood supply, such as leukoreduction, and developing pathogen-reduction strategies may push these costs even higher. Decreasing federal reimbursement further increases the direct costs of transfusion. Indirect costs (e.g., increased length of hospital stay secondary to acute complications such as infection, delayed healing, or prolonged mechanical ventilation) occur and may be significant.⁴⁹

Safe Blood as a Limited Resource. Allogeneic blood is by no means a limitless resource. Although advanced testing technology has improved the safety profile of allogeneic blood dramatically, it has also caused the donor pool to shrink. This is especially severe in areas with high prevalence of communicable diseases such as HIV. The ban on the importation of blood products from countries with Creutzfeldt-Jakob disease prevalence has had a significant impact on the supply to the United States.⁵⁰⁻⁵² The available blood supply in the United States is often measured in days or less. Wasteful use of this precious resource can result in lack of availability when needs are acute and severe, such as in massive trauma, natural disaster, or terrorist actions. We must continue to encourage voluntary blood donation to maintain adequate supplies of banked blood for those times in which nothing else will do. Widespread institution of measures to limit use of banked blood can have a tremendous impact on the blood supply.

The supply of safe blood in developing countries is at a critical level. Of the 81 million units of blood collected annually, only 39% supplies the low- and middle-income countries that possess 89% of the world's population.⁵³ Lack of healthy donors diminishes the supply chain. The World Health Organization reports that of 178 countries surveyed, only 39 have 100% voluntary unpaid donors (the safest source), 20 do not have 100% screening for HIV, 24 do not have 100% screening for hepatitis B, 37 do not have 100% screening for hepatitis C, and 24 do not have 100% screening for syphilis. Some countries have no screening at all for some of these diseases. The populations most vulnerable to blood-borne pathogens in these areas include women with complications of pregnancy, children with life-threatening anemia, and trauma patients.^{11,54,55}

Improved blood banking techniques and transfusion services, application of rigorous testing, and drives to increase the healthy volunteer donor pool, in addition to active blood conservation measures, should help improve the availability of infection-free blood. National and international hemovigilance programs will monitor both the safety of the blood supply and of transfusion practice.^{11,54,56}

Why Be Concerned with Blood Conservation?

As clinicians, it is important for us to realize that we can all have an impact on blood conservation. Anesthesiologists administer about half the blood given in the United States, and can therefore have a profound effect on the amount of allogeneic blood products used. Surgeons can use techniques and technologies that can save blood throughout the surgical continuum. Although this article will focus on perioperative management, there are many opportunities to modify transfusion practice in medical management, for example, in the treatment of hemoglobinopathies, coagulopathies, and cancer.

Preoperative Management. Options for blood conservation should be considered as soon as surgery is contemplated. This is especially important in the case of a patient who states his or her intent to refuse transfusion under any circumstances. Planning may involve multiple specialties (surgery, anesthesiology, and hematology) to ensure proper patient preparation. Suboptimal initial hemoglobin

levels can be augmented using several techniques. Recombinant human erythropoietin can be very effective at restoring a patient's hemoglobin to physiologically normal levels preoperatively, as well as restoring those levels more rapidly postoperatively. Clinicians are advised to refer to manufacturer's recommendations and specific literature for detailed dosage regimens. Correction of nutritional deficiencies of iron, folate, and vitamin B12, as well as intravenous iron therapy, with or without supplementation with vitamin C, can enhance red cell production as well.⁵⁷⁻⁶¹

Autologous Predonation. Although well accepted by patients and many surgeons, and routine with certain cases, autologous preoperative blood donation (APBD) remains a controversial technique. APBD decreases patient exposure to allogeneic blood, but is not without its own disadvantages, including inconvenience to the patient, who must make additional trips to the hospital for collection, as well as the cost of processing the blood. More importantly, patients who undergo APBD will often come for their surgery already anemic, increasing the likelihood of transfusion therapy.⁶²⁻⁶⁴ This superficially seems to be acceptable because patients would be transfused with their own blood; but when we consider that the most common cause of hemolytic transfusion reactions is clerical error, it becomes apparent that reinfusion of predonated blood is not completely risk-free. Changes in blood during storage may make patients susceptible to complications such as TRALI, even when the stored blood is their own.⁶⁵ Preoperative anemia will also decrease the effectiveness of intraoperative cell salvage. The improved safety profile of banked blood may seem to decrease the need for techniques such as APBD, but the shrinking donor pool and the need to preserve available blood supply compel us to consider its ongoing utility in clinical practice, even as we continue to explore improved regimens.⁶⁶

Surgical Considerations. Timing of surgery can become critical in the success of blood conservation efforts. Oftentimes, we try to perform an operation as soon as possible after diagnosis, or as soon as the operating room (OR) schedule will accommodate our patient. There may be times when our patient may be better served by using the aforementioned techniques to augment the preoperative hemoglobin to a level that will increase the safety margin, and decrease the likelihood of perioperative blood exposure. Ongoing preoperative losses may be minimized. For example, agents that induce amenorrhea can aid in restoring hemoglobin preoperatively in the patient with ongoing uterine bleeding.^{67,68}

Alternatively, delay may not be in the best interest of certain patients. A different approach may need to be taken with patients who are bleeding but refuse transfusion. For example, patients with gastrointestinal bleeding are frequently brought to the OR based on how much blood they need over a period of time. In a patient refusing transfusion, this may result in bringing a patient to the OR with a hematocrit already in the range where transfusion might be needed. Further intraoperative blood loss could then result in critical postoperative anemia.

Surgical techniques with decreased blood loss compared with conventional procedures should be considered. Laparoscopic procedures often provide precise control of bleeding, even for major surgery. Invasive radiologists can often minimize or prevent bleeding with selective embolization of vessels. Staging complex procedures with recovery time between phases can allow for restoration of hemoglobin and the avoidance of blood transfusion.

Intraoperative Measures. Intraoperatively, blood conservation efforts involve measures to decrease blood loss and measures to salvage shed blood. Meticulous surgical technique and maintenance of a dry operative field are the hallmarks of transfusion-free surgery. In addition to technical prowess, there are devices and techniques that can help achieve the desired bloodless field. Advanced cutting and coagulation devices, such as the harmonic scalpel, appear to offer advantages over electrocautery in terms of blood loss, surgical

duration, and exposure to transfusion.^{69,70} The harmonic scalpel uses ultrasonic energy to cut and coagulate by forming a coagulum of denatured proteins. Other advantages include precision, and as compared with electrocautery, relatively low temperatures and elimination of electrical current going through the patient.

The argon beam coagulator likewise offers rapid control of bleeding tissues and may reduce blood loss in varied scenarios, including hepatic, splenic, and obstetric procedures.⁷¹⁻⁷³ Energy from the ionized argon beam seals the tissue and the gas flow at the tip clears blood and fluid from the target site. This occurs at a lower temperature and with less tissue damage than with electrocautery.

Coagulation. Assiduous attention to normothermia in the perioperative period cannot be overemphasized. This is essential for normal function of the coagulation cascade. Hypothermia has been shown to increase blood loss and rate of transfusion in major laparotomies.⁷⁴

A number of hemostatic adjuncts are available that may help to limit total intraoperative blood loss. Topical absorbable hemostatic agents, including gelatin sponge, oxidized cellulose, collagen, and thrombin preparations, can augment standard methods of hemostasis, such as electrocautery and mechanical ligatures. Platelet gel can be manufactured from the patient's own blood in the OR, using standard cell salvage machinery or newer and simpler devices that use filtration or centrifugation to sequester a platelet-rich plasma fraction. Gel is then manufactured by adding calcium and thrombin to the concentrate.^{75,76} Taking advantage of its platelet-derived growth factors, platelet gel has been applied in a wide range of clinical healing uses, from bony reconstruction to plastic surgery, otolaryngology, and burns.⁷⁷⁻⁷⁹

Agents that enhance coagulation are continually being evaluated in the context of various surgical procedures. Aprotinin has been demonstrated to effectively decrease blood loss in certain cardiac procedures^{80,81} and possibly in certain orthopaedic⁸² and transplant⁸³ surgeries. Its mechanism is the inhibition of serine proteases, such as plasmin. Potential side effects of concern include thromboembolic events and allergic reactions,⁸⁴ especially with repeat exposure.

Epsilon aminocaproic acid seems to achieve its antifibrinolytic properties primarily through inhibition of plasminogen activators and secondarily through antiplasmin activity. Fibrinolytic bleeding may occur during cardiac surgery or portocaval shunt procedures and in patients with aplastic anemia, abruptio placentae, hepatic cirrhosis, and neoplasms, especially of the prostate, lung, stomach, or cervix.⁸⁵ Tranexamic acid, another antifibrinolytic, has been studied in similar circumstances and has often been found to be effective in reducing transfusion without an overwhelming risk of thromboembolic complications.⁸⁶ These antifibrinolytics may find additional uses, including reduction in early rebleeding after aneurysmal subarachnoid hemorrhage.⁸⁷

Desmopressin is a vasopressin analog that, in addition to its usefulness in diabetes insipidus, has been found to be useful in patients with uremia or cirrhosis, as well as those with von Willebrand syndrome or on antiplatelet medications. Its effectiveness as a hemostatic adjuvant results from increased factor VIII and von Willebrand factor activities. In major surgeries, it often found to be a less effective hemostatic agent than antifibrinolytics or aprotinin.^{80,88}

Recombinant factor VIIa (rFVIIa; Novo-Seven, Novo Nordisk, Bagsvaerd, Denmark) is a procoagulant initially developed for hemophilia treatment, which has been successfully used to minimize bleeding in a variety of surgical situations, including trauma. The mechanism is unclear and its use is being studied in many scenarios to determine optimal applications, dose, and timing. It certainly seems to be effective as a salvage treatment.^{89,90} Further outcome studies may show that earlier usage, despite the expense, can be an effective way to stem surgical blood loss and reduce allogeneic transfusion.

Hemodilution. Of the two types of hemodilution, autologous normovolemic and hypervolemic, autologous normovolemic hemodilution (ANH) is more widely used and studied. This technique involves collection of a significant amount of blood (typically two to four units) into anticoagulant-containing bags at the outset of a surgery via a venous or arterial line, and intravenous replacement with crystalloids or colloids to maintain normovolemia. The patient's own whole blood is then available for transfusion later in the case.⁹¹ The collected blood can additionally be separated into red cells and platelet-poor and platelet-rich plasma fractions, using cell salvage equipment, allowing directed component therapy when bleeding ensues. There is conflicting evidence on the overall efficacy of ANH with respect to blood savings and transfusion avoidance.⁹² A recent meta-analysis of ANH supports only modest benefits from ANH compared with standard therapy and other blood-conservation techniques.⁹³ ANH can be used in Jehovah's Witness patients as long as the process is adapted to effect a continuous system of blood withdrawal and reinfusion between collected blood and the patient.⁵

Hypervolemic hemodilution (HHD) is a simpler, although less-studied, technique. By using volume expansion, generally with colloids for the lasting effect, the hematocrit is diluted, and any blood lost will therefore contain less red cell mass. Studies comparing ANH and HHD showed similar reductions in perioperative allogeneic transfusion.^{94,95} HHD may be simpler, quicker, and less expensive to perform, although caution is warranted in patients who are prone to congestive heart failure or fluid overload. Further controlled testing should be done to establish the efficacy and applications for these hemodilution techniques.

Controlled hypotension, even to moderate degrees, can significantly help to stem blood loss from the surgical field. This can be achieved readily with routine anesthetic techniques. Greater degrees of controlled hypotension may require the use of vasodilators and invasive monitoring techniques; thus, caution is warranted in patients with cardiac or cerebrovascular disease.⁹⁶ Additionally, ischemic injury must be prevented with hypotensive techniques, especially in the presence of anemia. This is true for both peripheral structures and sensitive areas, such as the eyes. Several cases of blindness caused by retinal ischemia have been reported in this setting.^{97,98} Regional anesthesia can also aid in a similar fashion, especially in lower-extremity surgeries; in these cases, the increase in venous capacitance created by the sympathetic blockade helps limit surgical blood loss.⁹⁹

Cell Salvage. Cell salvage can be a very effective method of transfusion avoidance, and is probably at least as effective as predonation.¹⁰⁰ Shed blood is collected from the operative field and mixed with an anticoagulant, generally via a suction catheter. It is then concentrated and washed or filtered, depending on the particular cell salvage device in use, before the processed red cell solution is returned to the patient. Current devices do an excellent job at removing potentially harmful contaminants such as potassium, fat, and free hemoglobin from the salvaged blood. Washed blood should generally be returned via a 40-micron blood filter. Air embolism is a complication that can occur from using a pressure bag on an air-containing reinfusion bag. This can be avoided by using transfer bags for reinfusion of processed blood, or by using reinfusion equipment with air detection and removal technology.¹⁰¹

Several widespread assumptions result in limitation of use of cell salvage for many cases. It is commonly believed that cell salvage should not be used in cases where malignancy is present. Although it is well documented that cell salvage devices do not completely remove cancer cells from processed blood, the use of a leukocyte-depletion filter in the reinfusion line can eliminate malignant cells in the product. This has been demonstrated in vitro with several types of malignant cell lines including breast, colon, lymphoma, and lung.¹⁰²⁻¹⁰⁵ No increase in cancer spread or recurrence rate has been shown in malignancy patients who have received salvaged blood.¹⁰⁶⁻¹⁰⁸

Nevertheless, many clinicians await clear-cut outcome data and consider malignancy to be a contraindication to cell salvage. These issues should be addressed with a patient during the informed consent discussion, should intraoperative cell salvage be planned during a cancer surgery.¹⁰⁹ Bacterial contamination of the surgical site is generally believed to be a contraindication to use of cell salvage. In vitro testing has demonstrated between 97.6% and 100% bacterial removal rate, using cell salvage plus leukocyte-depletion filtration. This should allow for a significantly increased safety margin during those contaminated cases in which salvaged blood is considered to be a useful, or the only, option.¹¹⁰

Cesarean sections have been considered to be a taboo when it comes to cell salvage, because of fear of embolization of amniotic material, but recent studies demonstrate that after leukocyte-depletion filtration, the reinfusion product has a particulate contaminant concentration equivalent to that in maternal venous blood.^{109,111} Clinical studies should begin to clarify this issue in the near future, and case reports exist demonstrating uneventful cell salvage and reinfusion.¹¹² It is probably prudent to use normal saline to rinse the field of amniotic fluid into a separate suction canister prior to collection of blood into the cell salvage device.

Safe and successful use of cell salvage has also been reported in a sickle cell disease patient, another diagnosis commonly considered to be a contraindication to its use.¹¹³ Risk versus benefit is a common consideration in cell salvage use.

Case selection and cost should be considered carefully in using cell salvage. Although many studies¹¹⁴⁻¹¹⁶ and mathematical models¹¹⁷ point to its effectiveness, other studies question whether transfusion is indeed prevented, and whether the benefits substantiate the cost.¹¹⁸

Postoperative Blood Conservation. Blood conservation (via collection equipment ranging from simple filtration/reinfusion devices to advanced centrifugal blood collection and washing devices) can and should continue into the postoperative period, when a significant number of transfusions occur. Important considerations include maintenance of normal physiologic parameters (especially pH and temperature) to optimize coagulation. Postoperative blood salvage would be beneficial and the cost would be justified for procedures associated with significant postsurgical drainage, for example, total joint replacement.¹¹⁹⁻¹²¹

In providing nonallogeneic transfusion management of postoperative anemia, clinicians should focus on the treatment of symptomatic, potentially severe anemia, and the restoration of normal blood counts. Treatment options should maximize oxygen delivery and minimize oxygen demand. In severe cases, adequate tissue oxygenation should be ensured with arterial blood gas analysis and potentially with the use of a pulmonary artery catheter. Hyperbaric therapy may have a role in the treatment of critical anemia.^{122,123} Common-sense interventions, such as the minimization of blood draws for laboratory testing (i.e., decreased frequency and/or use of pediatric sample sizes), can have a significant effect on perioperative blood conservation.¹²⁴ In addition, and as previously discussed in this article, restoration of normal hemoglobin and hematocrit can be accelerated with use of recombinant erythropoietin and nutritional support.⁵⁷⁻⁶¹ It is hoped that oxygen-carrying hemoglobin or nonhemoglobin substitutes will someday become mainstream treatment for severe anemia.

Blood Conservation in Nonsurgical Management.

Commitment to blood conservation should extend beyond the surgical suite. In addition to issues such as transfusion triggers, alternative therapies for conditions routinely treated with allogeneic blood products (e.g., hemoglobinopathies, coagulopathies, renal failure, and oncologic disorders) should be developed. Treatments such as hydroxyurea for sickle cell disease, and erythropoietin for anemia, as well as hemostatic agents for coagulopathies, can reduce or eliminate patient exposure to banked products.¹²⁵⁻¹²⁷

Transfusion “Trigger:” One of the most basic questions in blood conservation is, “When should I transfuse?” The formerly ubiquitous “10 and 30 rule” for hemoglobin and hematocrit seems to have been largely supplanted by more restrictive approaches.¹²⁸ Tolerance of anemia must take into account each patient’s individual clinical picture. The evidence-based guidelines published by the American Society of Anesthesiologists in 1996 state: “(1) transfusion is rarely indicated when the hemoglobin concentration is greater than 10 g/dL and is almost always indicated when it is less than 6 g/dL, especially when the anemia is acute; (2) the determination of whether intermediate hemoglobin concentrations (6–10 g/dL) justify or require RBC [red blood cell] transfusion should be based on the patient’s risk for complications of inadequate oxygenation; (3) the use of a single hemoglobin ‘trigger’ for all patients and other approaches that fail to consider all important physiologic and surgical factors affecting oxygenation are not recommended; (4) when appropriate, preoperative autologous blood donation, intraoperative and postoperative blood recovery, acute normovolemic hemodilution, and measures to decrease blood loss (deliberate hypotension and pharmacologic agents) may be beneficial; (5) the indications for transfusion of autologous RBCs may be more liberal than for allogeneic RBCs because of the lower (but still significant) risks associated with the former.”¹²⁹

Adherence to these recommendations can take us far in our quest for blood conservation. It is important that we distinguish the effects of anemia from that of hypovolemia in our decision to transfuse. Red blood cell substitutes may someday radically change the lower limits of tolerable anemia in our patients.

Red Blood Cell Substitutes. Oxygen-carrying blood substitutes are generally divided into two types: fluorocarbon-based synthetic oxygen carriers and stroma-free, cross-linked human or nonhuman hemoglobin preparations. These compounds could play an obvious role in cases of acute massive blood loss, such as trauma, as well as in major surgeries, with or without associated hemodilution,¹³⁰ and successful outcomes have been achieved in patients refusing transfusion.^{131,132} The perfluorocarbon emulsions are easy to produce, have a long shelf life, and have minimal infectious or immunogenic effects. Potential disadvantages include the requirement for a high F_{iO_2} and rapid plasma clearance. Hemoglobin-based oxygen carriers are notable for high oxygen-carrying capacity, an appreciable oncotic effect, and prolonged shelf life; disadvantages include a short plasma half-life, potential renal toxicity, hypertensive effects, and the potential for immunologic effects.¹³³ Further clinical trials to establish the optimal dosage, efficacy, safety, and effect on outcome are indicated before oxygen-carrying blood substitutes are implemented in routine clinical practice.

Summary

Why be concerned with blood conservation? Because there are significant issues surrounding the use of allogeneic blood products and because we can all potentially do something about it. The purpose of this article is to highlight the importance of implementing a blood-conservation program in clinical practice and to introduce some of the many ways to achieve decreased allogeneic transfusion. A degree of determination and shift in thinking on the part of clinicians must occur to truly commit to practicing blood conservation. Choosing a single approach (for example, preoperative autologous donation or intraoperative cell salvage) would represent a step down the right path. A comprehensive approach to minimizing transfusion might encompass optimization of preoperative hemoglobin, careful planning of the procedure, consideration of preoperative donation, and the use combined modalities throughout the perioperative period. As physicians, we all need to examine our

practices to see which of these techniques fit, taking into account costs, potential blood savings, and most importantly, the benefits to our patients.

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Appendix

Resources for Additional Information on Blood Conservation

The following organizations and their associated websites are excellent sources for blood-conservation information. They both have active memberships and offer updated reviews of the current literature, newsletters, and continuing education meetings.

1. Society for the Advancement of Blood Management, www.sabm.org
2. Network for Advancement of Transfusion Alternatives, www.nataonline.com

Anemia: Risks, Tolerance, and Pharmacologic Adjuvants for Treatment

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Learning Objectives: 1) To understand the physiology of anemia, the reserve of the oxygen-delivery system, the clinical risks of anemia, the impact of directed therapy of anemia, the risks of red blood cell transfusions, the pharmacology of pharmaceutical agents used to treat anemia, and 2) to review clinical outcome measures in blood conservation techniques.

Abstract

Anemia has been identified as a risk factor for poor outcomes across diverse populations of medical and surgical patients. Even in low-risk, community-dwelling adults, anemia imparts a survival disadvantage. Red blood cell transfusions are still commonly used to correct anemia in many clinical situations, but evidence is emerging that transfusions may confer an additional risk rather than provide a benefit. In clinical practice, consistency is lacking with regard to hemoglobin thresholds that trigger the administration of transfusions; moreover, transfusions are often administered without sufficient justification. Because of the potential for risk, transfusions should be avoided whenever possible, but the degree of acute anemia that may be tolerated without negative impact on morbidity and mortality is still uncertain and varies by clinical circumstance. Consideration of therapy with erythropoietic agents and supplemental iron to reverse declining hemoglobin levels instead of transfusions may be a reasonable alternative. Several studies in high-risk patients indicate that this approach has the potential to provide clinical benefit. Prospective and well-designed clinical trials are needed to identify the ideal hemoglobin concentration and confirm that outcomes are improved when that concentration is achieved. Other strategies to limit blood loss and preempt the development of anemia and anemia-related morbidity are also needed.

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