Perioperative Blood Transfusions*

Indications and Options

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A reevaluation of the indications for and alternatives to transfusion of allogeneic blood was precipitated by transfusion-induced HIV. The transfusion trigger has shifted from an optimal hemoglobin level and hematocrit (10/30) to that level of hemoglobin necessary to meet the patient's tissue oxygen demands. This critical level can best be determined by physiologic measurements. A number of autologous blood options can reduce the patient's allogeneic blood needs. Pharmacologic measures to increase hemoglobin levels (erythropoietin) and to decrease blood loss at surgery are discussed as are the potential contributions of blood substitutes to transfusion support of the surgical patient.   *(CHEST 1999; 115:113S–121S)*

In the last 15 years, the perception of transfusion of allogeneic blood in the surgical setting has moved from a benign intervention, sometimes life-saving, to an outcome to be avoided. Whereas the transfusion of blood products in the surgical patient was once an uncomplicated aspect of the procedure, the recognition in the early 1980s that blood transfusions carried a risk of HIV infection forced a reevaluation of the indications for transfusing the surgical patient. Since then, an extensive literature has developed on the indications for, risks of, and alternatives to transfusion of allogeneic blood.

INDICATIONS FOR PERIOPERATIVE TRANSFUSIONS: THE TRANSFUSION TRIGGER FOR RBCs

The RBC transfusion trigger is a term used to describe the set of circumstances under which transfusion is reasonable and for which no further justification is needed. Prior to the 1980s, surgical patients were considered optimally treated if their hemoglobin level and hematocrit remained above 10 g/dL and 30%, respectively. The first published reference to the "10/30" rule was by Adams and Lundy[1] of the Mayo Clinic. Their recommendation was based on clinical experience. Later, *in vitro* and animal studies lent support to the concept that O_2 delivery (DO_2) peaks at a hematocrit of 30%[2] and the oxygen transport and survival in animals is maximized at hematocrits of between 30% and 40%.[3–5]

Despite contradictory observations that animals could survive at much lower hematocrits if their intravascular volume were kept normal[6] and that Jehovah's Witness patients often survived surgical procedures at lower preoperative and postoperative hemoglobin levels,[7,8] the "10/30" rule was considered the standard of care until the late 1980s. At this time, the concern for transmission of HIV forced a reexamination of indications for transfusions with an ultimate conclusion that an absolute number (hematocrit or hemoglobin level) was insufficient for the purpose of justifying blood transfusion in all patients.

If a simple laboratory value such as the hematocrit is no longer a suitable trigger for transfusion, what are the alternatives for identifying that set of circumstances under which transfusion is reasonable and no additional justification is required? Both signs and symptoms of anemia and physiologically defined measures of DO_2 to tissues have been suggested as more rational transfusion triggers.

SIGNS AND SYMPTOMS

The classic signs and symptoms of severe anemia (exertional dyspnea, chest pain, lethargy, hypotension, pallor, tachycardia, impaired consciousness) often occur when the level of hemoglobin is dangerously low. In a study by Carmel and Shulman,[9] exertional dyspnea did not occur until the hemoglobin concentration fell to < 7 g/dL. In another study, at levels < 6 g/dL, only 54% of patients experienced tachycardia, 32% had hypotension, 35% had impaired consciousness, and 27% had dyspnea.[10] The levels of anemia required to produce symptoms were even more severe in children. Therefore, relying on signs or symptoms of anemia to guide transfusion decisions would probably result in significant under-

transfusion. Moreover, in the anesthetized surgical patient, symptoms obviously would not be helpful.

Physiologic Transfusion Triggers

Measurements of tissue oxygenation are thought to be more accurate predictors of a patient's transfusion requirements in that they should correct for individual patient variables that affect the body's ability to compensate for severe anemia and blood loss. Although a hemoglobin level would serve well in predicting the need for transfusion in a uniform population with the same degree of underlying cardiac or pulmonary disease undergoing similar procedures, measurements of tissue oxygenation would be better suited to patients presenting with varying underlying conditions.

In vitro studies of isolated tissues and studies of normovolemic anemia in animals suggest that the minimal hemoglobin level at which tissue DO_2 is adequate is about 3 to 5 g/dL. Hemoglobin concentrations below this level are associated with cardiac decompensation in dogs and baboons.[11–13] A recent study in healthy humans found that acute normovolemic hemodilution to 5 g/dL was tolerated without signs of tissue hypoxia.[14] The duration of extreme anemia, even with normal blood volume maintained, is probably an essential factor. In pigs, when hematocrits were maintained at 10%, cardiac ischemia and death occurred in a significant fraction of animals over a 5-h study period.[15] The 3- to 5-g/dL hemoglobin concentration then might be accepted as the minimal level of hemoglobin to sustain life in an otherwise healthy animal.

There are a number of compensatory mechanisms that contribute to maintaining adequate tissue oxygenation that are activated in response to severe blood loss and anemia. These include the following: increased cardiac output; increased heart rate and left ventricular stroke volume; increased O_2 extraction ratio (O_2ER); reallocation of blood flow; and right shift in hemoglobin-oxygen dissociation curve.

The heart is more dependent on the delivery of oxygen than other organs. Under normal physiologic conditions (no anemia) the myocardium extracts about 50% of the oxygen delivered to it, more than any other organ. Any increase in work requires increased DO_2 via blood flow to the myocardium. In anemia, both the blood flow to the myocardium and the fraction of extracted O_2 (O_2ER) must increase to meet tissue O_2 demand. A healthy heart can compensate with increased blood flow and increased O_2ER to hemoglobin levels of 3 or 4 g/dL, after which myocardial ischemia occurs.[11–13] In a heart in which the vessels are stenosed as in atherosclerosis,

the increased blood flow is not possible and ischemia, particularly subendocardial, occurs at much higher hemoglobin concentrations. Pulmonary disease presents another complicating factor that prevents adequate compensation to severe anemia. Decreased ventilation and/or O_2 diffusion in the lung compounds the diminished O_2-carrying capacity of anemic blood leading to less oxygen delivered to tissues.[5] As one might imagine, both cardiac and pulmonary disease can occur with variable severity in different patients. Therefore, the impact of a given degree of anemia is unique to each patient given his or her unique set of underlying conditions. At present, to my knowledge, there are no uniformly available measurements of O_2 tissue delivery that can be utilized to guide transfusion therapy. The clinician is often left with the problem of a known compromised patient, but the degree to which the patient is unable to compensate to anemia is unknown. In this setting, physiologically based transfusion triggers should be helpful.

The factors that control oxygen delivery to the tissues are related in the Fick equation:

$$\dot{V}O_2 = \dot{Q}X(CaO_2 - C\bar{v}O_2)$$

where $\dot{V}O_2$ represents oxygen consumption, $\dot{Q}$ is cardiac output, and CaO_2 and $C\bar{v}O_2$ are arterial and mixed venous oxygen content, respectively. $\dot{V}O_2$ remains stable across a wide range of hemoglobin concentrations that affect CaO_2 and $C\bar{v}O_2$. The equation remains balanced due to compensatory increases in cardiac output and O_2ER. However, there is a critical hematocrit (10%) below which the ability to maintain $\dot{V}O_2$ rapidly deteriorates.[5]

DO_2 is the product of cardiac output and CaO_2. It represents oxygen content delivered to the tissues. The goal of transfusion therapy is to maintain DO_2 well above that critical value so that an appropriate reserve of O_2 is maintained should the patient require it because of blood loss or elevated $\dot{V}O_2$.

Possible Physiologic Transfusion Triggers

Mixed Venous O_2—$P\bar{v}O_2$

$P\bar{v}O_2$ should reflect tissue oxygenation. However, the $P\bar{v}O_2$ can underestimate the level of tissue hypoxia.[5] The rate of change in $P\bar{v}O_2$ is probably more significant than a static level, therefore a dropping value may be a more ominous sign of tissue hypoxia than a stable low level. Determining the $P\bar{v}O_2$ requires invasive monitoring and therefore is not available in some surgical settings. However, in most cardiovascular procedures, this measurement can be made.

Mixed Venous O_2 Saturation—$S\bar{v}o_2$

$S\bar{v}o_2$ is considered by some to be more useful as a marker of tissue oxygen levels. As the $P\bar{v}o_2$ drops below 30 mm Hg, the $S\bar{v}o_2$ declines precipitously related to the steep change in that portion of the hemoglobin-oxygen dissociation curve. $S\bar{v}o_2$ also declines rapidly when hematocrits fall below 20%.[5] In one recent clinical trial, $S\bar{v}o_2$ of < 55% was used as the transfusion trigger in patients undergoing cardiovascular surgery. Use of allogeneic blood was significantly reduced compared with what would have been used if a traditional hematocrit-based transfusing trigger had been followed.[16]

O_2 Consumption—$\dot{V}o_2$

A decrease in $\dot{V}o_2$ in postoperative and trauma patients correlates with a poor prognosis. Increasing Do_2 by improving volume and hemoglobin concentration increases $\dot{V}o_2$ and improves the mortality rate.[17] In this setting, intravascular volume as supplied by crystalloid or colloid solutions is more effective than RBCs for rapidly correcting Do_2. The $\dot{V}o_2$ can be misleading. The fall in $\dot{V}o_2$ seen in sepsis is out of proportion to decline in Do_2, probably due to decreased tissue perfusion. Therefore, in sepsis, transfusion does not necessarily improve $\dot{V}o_2$, but inotropic agents may benefit such patients. In ARDS, $\dot{V}o_2$ as calculated by the Fick equation does not correspond to $\dot{V}o_2$ measured directly by calorimetry, possible due to shunting around capillary beds.[5] Therefore, in some clinical situations, $\dot{V}o_2$ may not be a reliable guide to transfusion requirements.

Oxygen Extraction Ratio—O_2ER

O_2ER can be expressed: $(CaO_2 - C\bar{v}o_2)/CaO_2$.

When the O_2ER exceeds 50% in animal studies, lactate increases and cardiac decompensation is imminent. This occurs at hematocrits of around 10%. In dogs, reduction in coronary artery blood flow induced by surgical ligature results in the O_2ER reaching 50% at hematocrits > 20%.[5] Therefore, in compromised patients, the O_2ER may serve as a more accurate guide to transfusion than hemoglobin concentration.

The physiologic measurements listed above are attempts to make the transfusion decision more reliable and responsive to the patient's tissue oxygen needs. The advantage of using one or more of these measurements over a certain level of hemoglobin or hematocrit is that they should predict better the transfusion needs in the patient who cannot compensate normally to severe anemia and blood loss. One drawback applying to all is the requirement for invasive monitoring to acquire the measurements.

Robertie and Gravlee[3] in 1990 attempted to provide transfusion guidelines without invasive monitoring, taking into account underlying conditions that prevent adequate compensatory reactions to anemia: for well-compensated patients without heart disease, a trigger of 6 g/dL was proposed; for patients with stable coronary artery disease and < 300 mL blood loss anticipated, 8 g/dL; for older patients and those with postoperative complications who cannot increase cardiac output, 10 g/dL. These guidelines are similar to those proposed by others.[18] Today most hospitals are required to periodically monitor transfusion practices and apply a set of audit criteria to the use of all blood components. Several professional groups have published transfusion guidelines that may serve as models for individual hospitals to develop their own internal transfusion audit criteria.[19,20] For perioperative RBC transfusions, most guidelines are in agreement with those proposed by the National Institutes of Health consensus conference on perioperative blood transfusion.[21]

In 1988, the National Institutes of Health convened this consensus conference to address the issue of surgical blood transfusion. After hearing 2 days of presentations of data and opinion by experts, the panel made the following conclusions. (1) Available evidence does not support the use of a single criterion for transfusion such as a hemoglobin concentration of < 100 g/L (10 g/dL). No single measure can replace good clinical judgment as the basis for decision-making regarding perioperative transfusion. (2) There is no evidence that mild-to-moderate anemia contributes to perioperative morbidity. (3) Perioperative transfusion of homologous RBCs carries documented risks of infection and immune changes. Therefore, the number of homologous transfusions should be kept to a minimum. (4) There are being developed a variety of promising alternatives to homologous transfusion. These alternatives will reduce the use of homologous transfusion to some extent and their development should be encouraged. However, for the foreseeable future, homologous blood transfusions will continue to be the therapeutic mainstay. Therefore, primary attention should be devoted to the promotion of safe and effective transfusions from carefully selected volunteer donors. (5) Future research is necessary to define the best indications for RBC transfusion and the safest methods of blood conservation and delivery.

IS THERE A RISK OF UNDERTRANSFUSING?

The risk:benefit calculation underlying the shift in the thinking about the transfusion trigger is not

static. In the 15 years since the risk of HIV was appreciated in the blood supply, clinicians have refocused on the decision to transfuse to make sure that it is justifiable each time. In addition, unprecedented efforts have been made by government, private industry, and the blood banking community to make blood products as safe as possible. Indeed the risk of contracting an infectious disease from a blood transfusion has never been lower, thanks to extensive screening and laboratory testing of donors and their donations (Table 1).[22]

The lower the "risk" side of the risk:benefit equation for transfusion, the more we must pay attention to the risk of not transfusing. Several investigators have sought to quantify the risk of not transfusing. Kitchens[23] studied the rate of fatal complications due to anemia in 16 reports of the surgical outcome in Jehovah's Witness patients. All together, there were 1,404 procedures represented resulting in a mortality rate due to anemia of between 0.5 to 1.5%. While this was taken as support for the safety of not providing transfusions for surgical patients, these estimates can also be used as a baseline risk of death from not giving transfusions. The risk of fatal outcome due to blood products must then exceed this level to justify a policy of withholding all transfusions.

Except in the setting of surgery on Jehovah's Witness patients, however, one rarely has a clear-cut decision of transfusing or not transfusing any blood. More often, a hospital-wide transfusion trigger policy is in place that may support transfusions at very conservative (ie, low) hemoglobin concentrations. It is therefore more difficult to determine the risk of transfusing too conservatively vs more liberally. Investigators are beginning to evaluate current conservative transfusion guidelines to determine if undertransfusion is occurring.[24–26] Nelson et al[25] continuously monitored 27 high-risk patients using ambulatory ECG from the evening before surgery through 80 h postoperatively. Evidence of myocardial ischemia was present in 10 of 13 patients with hematocrits < 28%, 6 having a morbid cardiac event. Of 14 patients whose hematocrit remained > 28%,

only 2 demonstrated ischemia and none had a morbid event ($p < 0.001$, and $p < 0.0058$, respectively). To date and to our knowledge, other studies showing significant rates of undertransfusion are lacking.

Transfusion Options for the Surgical Patient

Allogeneic (Homologous) Blood

The vast majority of the nation's allogeneic blood supply is donated by volunteer, unpaid donors. In the 1970s, blood from unpaid donors was shown to carry a lower risk of hepatitis compared with blood from paid donors. Additional safeguards for the nation's volunteer blood supply now include rigorous questioning of prospective donors about HIV and hepatitis risk activities and an elaborate array of sensitive infectious disease screening tests designed to interdict hepatitis, HIV, syphilis, and human T-cell lymphotrophic virus transmissions. The risk of contracting HIV infection from a screened unit of blood is now on the order of 1 in 500,000 units compared with a risk estimated to have been 1 in 5,000 in 1983.[22] Similarly, the risk of hepatitis C virus infection has fallen dramatically from about 1 in 25 in the early 1980s to 1 in 103,000 today[22] (Table 1).

A major advantage of the volunteer allogeneic blood supply is that blood products are nearly always available on short notice in sufficient quantity to meet both elective and emergency surgical needs. US blood banks are required to have standard operating procedures for compatibility testing prior to issuing blood for transfusion, and hospitals are required by Joint Commission on Accreditation of Health Care Organizations and American Association of Blood Banks Standards to have procedures for identifying the correct patient for the transfusion and for administering the blood product.

Many hospitals issue blood for surgical procedures using a maximum surgical blood ordering schedule (MSBOS). This is a list of the procedures performed in a hospital together with the recommended quantity of RBC units to crossmatch, based on utilization data specific to that hospital. In general, the MSBOS should direct the blood bank to prepare units if there is a > 10% chance that blood will be required for a given procedure (based on local utilization data). Sufficient units should be crossmatched to meet the needs of 90% of patients undergoing the specific procedure. There should be a mechanism for the surgeon or anesthesiologist to override the MSBOS if special circumstances increase the risk of blood loss for a specific situation. Procedures for which blood use is unlikely, but still possible (< 10%), require only a type and screen. This results in the

Table 1—Residual Risk Estimates for Infectious Disease Transmission in Blood Transfusions*

Virus	Estimate of Residual Risk/10^6 U	Range
HIV	2.03	0.36–4.95
HCV	9.7	3.47–36.11
HBV	15.83	6.82–31.97
HTLV	1.56	0.50–3.90

*From Schreiber et al.[22] HCV = hepatitis C virus; HBV = hepatitis B virus; HTLV = human T-cell lymphotrophic virus.

patient having his ABO and Rh type determined and an RBC antibody screen performed on the serum. If RBC transfusions do become necessary, cross-matched blood can be made available in about 15 to 20 min.[27]

Autologous Blood

While fear of HIV transmissions reduced the use of allogeneic blood, the demand for autologous blood services mushroomed since the 1980s. Autologous blood transfusion has been available since at least the 1920s; it is only in the 1980s that it has assumed a major role in the management of blood needs in the surgical patient. There are a number of ways in which autologous blood can be harvested and used: predeposit (preoperative) autologous donation (PAD); acute normovolemic hemodilution (ANH); intraoperative cell salvage (ICS); and postoperative cell salvage. Each has advantages and disadvantages and must be considered in the context of the patient's medical condition, the planned procedure, and the time available prior to undergoing the procedure.

Perhaps the most widely used form of autologous transfusion is PAD. The patient who is scheduled for an elective procedure likely to require the transfusion of blood comes into the clinic, hospital, or blood center up to 6 weeks in advance of the surgery to donate blood to be stored for his or her own use. Normally, blood center programs schedule donors once per week for up to 6 weeks preceding surgery. American Association of Blood Banks and Food and Drug Administration (FDA) guidelines prohibit taking an autologous donation within 72 h of the planned surgery, and ideally, collections should end 2 to 3 weeks before surgery to allow the patient time to reestablish his or her vascular volume and to begin to regenerate RBCs prior to the surgery. Oral iron supplementation is standard during the phlebotomy sequence and continues postoperatively if necessary. Most patients are able to donate at least 2 U for their surgical procedures, and for most procedures, this is adequate to prevent the use of allogeneic blood. Most programs for PAD require testing of autologous predeposit blood for the same infectious disease markers used on allogeneic blood.[28] This is a requirement of FDA if the collecting facility is different from the facility where surgery will take place. Many programs allow release of infectious disease marker-positive units with appropriate biohazard labeling for the exclusive use of the patient/donor.[28] Most programs do not "cross over" or use autologous blood for other patients if the intended recipient does not require it.[28]

The main advantage of PAD is having standard units of properly stored and tested blood available at the time of surgery, thereby avoiding allogeneic transfusion. Drawbacks include the inability of programs to provide this kind of blood product on an immediate basis; therefore, it is not an option for emergent or semiemergent surgical procedures. The patient must be healthy enough to provide PAD units. Anemia and severe cardiac disease are the major medical contraindications for donating PAD units. In addition, patients who are confirmed positive for some infectious disease markers (HIV, hepatitis B surface antigen) are not able to participate in some PAD programs.[28]

The 6-week time frame during which most PAD blood is collected is related to the maximum allowed storage interval for liquid RBC units. If a large number of units is required for the surgery (≥ 6), often the patient cannot sustain adequate hemoglobin levels to allow collection every week. The ability to collect autologous blood prior to surgery has been shown recently to be augmented, particularly in patients with mild anemia, by exogenous erythropoietin.[29,30] However, attempts to show that erythropoietin-augmented PAD protocols reduce allogeneic blood transfusions have had mixed results.[31–34] Avoidance of allogeneic blood by erythropoietin treatment is most apparent in patients who are mildly anemic preoperatively and in whom adequate iron supplementation is maintained.

Perhaps the most troublesome aspect of PAD programs is the cost. Virtually all blood collection agencies that provide allogeneic and autologous blood collection services have found that the latter costs more.[35,36] Moreover, the most cost-efficient use of PAD has yet to be determined.[36]

PAD for some surgical procedures has not been shown to be cost-effective.[37–39] This is principally due to the wastage that occurs in units that are ordered for procedures that are unlikely to require blood transfusion. Careful ordering of autologous blood based on the hospital's MSBOS is a rational way to control the proliferation of PAD unit wastage and the related expense.

Acute Normovolemic Hemodilution

ANH is a form of autologous blood donation that occurs immediately preoperatively after anesthesia is induced and before surgery begins.[40–42] The concept is that the hemoglobin concentration in the patient is aggressively reduced under careful monitoring of cardiovascular function and tissue Do_2. The units of collected blood are set aside at room temperature to be reinfused at the end of the procedure. The volume is replaced with acellular fluid; either colloid

(at a 1:1 ratio with volume removed) or crystalloid (at a 1:3 ratio). Since the volume of blood loss at surgery is not affected by having diluted the patient's hemoglobin concentration, the blood that is shed results in reduced absolute RBC loss. ANH involving the removal of 2 to 3 U is most effective for patients with anticipated blood loss > 50% of estimated blood volume, a high initial hematocrit (> 42%), and the ability to tolerate dilutional anemia.[43] Some have advocated ANH as a replacement for PAD as a less costly alternative.[44]

Limited ANH has been shown to be safe for patients with severe left main coronary artery disease scheduled for semiemergent surgery. When preoperative hematocrits were reduced to no lower than 34%, no increase ST sement changes were noted relative to control subjects. Exposure to allogeneic blood was significantly decreased in the ANH group.[45]

ANH is not without risk. In a recent study of severe ANH in adolescent scoliosis patients, 75% hemodilution, while tolerated in terms of Do_2, resulted in significant dilutional coagulopathy with reduction of platelets, fibrinogen, and increases in prothrombin time and partial thromboplastin time.[46]

While an intriguing theory, in practice, ANH may have little impact on saving of the patient's RBCs. In a recent study using a computer model of hemoglobin lost and saved under ANH, taking into account that after the first unit taken, subsequent units will have a lower hemoglobin concentration because of ongoing dilution during the phlebotomy, a net volume of < 1 U of RBCs is saved.[42,47] In a systematic review of studies on ANH, Bryson et al[48] recently found that although overall, the use of ANH was associated with a decreased use of allogeneic blood, in those institutions in which blood transfusion was controlled by protocol, there was no difference in allogeneic blood use between patients undergoing ANH and control subjects.

Intraoperative Cell Salvage

Another form of autologous blood donation is ICS.[49] Shed blood at surgery is suctioned under low pressure into a reservoir, saline solution washed and filtered, or simply filtered and returned to the patient during the surgery. Large quantities of blood can be salvaged in this way reducing the requirement for allogeneic blood. Orthopedic, urologic, and vascular surgical procedures are appropriate for ICS. Contraindications include malignancy, particularly if the surgical field is likely to contain free tumor tissue or cells, and abdominal trauma resulting in leakage of bowel contents into the surgical field.

A major obstacle to utilizing ICS more widely is cost. Procedures most likely to provide a cost-beneficial use of ICS are limited to those that are likely to result in at least 2 U of shed RBCs (1,000 mL shed blood) and that have no contraindications. A special circumstance is liver transplantation in which ICS is often an economical way to provide blood transfusion support in the operating room, resulting in liters of salvaged washed blood that can be returned rapidly to the patient. Complications of ICS are rare if the procedure is performed properly. However, dilutional coagulopathy due to massive transfusion of washed RBCs without accompanying plasma or platelets can occur. More rarely, hemolysis of salvaged blood due to high-suction pressure and air emboli when product is directly infused from the cell saver to the patient without transferring into a blood bag are risks.

Aggressive attempts to limit allogeneic blood transfusion at surgery often involve combining several of these blood conservation strategies. An example is a report by Rosengart et al[50] in Jehovah's Witness patients presenting for a range of cardiac procedures. A vigorous combination of erythropoietin, aprotinin, ICS, and ANH resulted in only a 4% mortality, none due to anemia. Hematocrits at the time of hospital discharge in these patients were somewhat higher than in a control group of patients who received allogeneic transfusions according to hospital guidelines.

Pharmacologic Agents to Reduce Transfusion Requirements and Blood Loss

Erythropoietin

Erythropoietin, a potent stimulant of erythrocyte production and development, was recently approved by the FDA for the purpose of augmenting presurgical autologous blood donations. This drug has also been used in surgical patients with and without donations of autologous blood, as a means of limiting anemia and hastening postsurgical recovery of hemoglobin. Unfortunately, with few exceptions,[51] the results are disappointing, in that most trials of erythropoietin given prior to surgery do not result in reduction of allogeneic blood transfused, although most have documented a positive impact on reticulocyte count and preoperative hematocrit.[51–53]

Fibrin Sealant

Fibrin glue or sealant is a product containing human fibrinogen and usually bovine thrombin. These two components are combined at the time of use, in the presence of calcium, to form a flexible seal over suture lines. They are available as commer-

cial products in Europe, but are yet to be approved by the FDA. In the United States, many surgeons "home brew" their own fibrin glue by using single units of cryoprecipitate either from the patient (autologous) or from the donor supply. Bovine thrombin is added with calcium to make the fibrin glue. The commercial products have an advantage in that they have a higher concentration of fibrinogen than can be achieved in single units of cryoprecipitate. The commercial preparations are manufactured from pools of human plasma and undergo viral inactivation processes.

Antifibrinolytics: Lysine Analogs Epsilon Amino Caproic Acid and Tranexamic Acid

These drugs inhibit plasminogen and plasmin binding to fibrin. While not shown to be helpful once active pathologic bleeding is manifest, when used prophylactically, they do reduce blood loss.[54]

Desmopressin

This analog to vasopressin, a naturally occurring hormone, causes a 2- to 20-fold increase in circulating factor VIII levels and release of high-molecular-weight von Willebrand factor multimers from the endothelium. This results in a shortening of the bleeding time in uremic patients and in those with mild-to-moderate von Willebrand's disease. Unfortunately, in patients with normal hemostasis, desmopressin has not been particularly effective in reducing surgical blood loss.[54]

Aprotinin

Perhaps the most promising drug to come along in the last decade to reduce surgical blood loss is aprotinin, a naturally occurring serine protease inhibitor that probably affects hemostasis through several mechanisms: it is antifibrinolytic, inhibits kallikrein, inhibits plasmin and activated protein C, and possibly preserves platelet function. A number of controlled randomized studies support its use to reduce surgical blood loss in cardiac surgery, without compromising graft patency.[54]

BLOOD SUBSTITUTES

Since the 1960s, the military and private companies have sought to develop a substitute for RBCs, principally to duplicate their oxygen-carrying capacity. Such a substitute promises improved shelf life over that of RBCs, no need for compatibility testing and therefore immediate availability, and improved safety over RBCs due to viral inactivation that would occur as part of the manufacturing process. Two main classes of compounds are leading candidates for a RBC substitute: hemoglobin solutions and perfluorochemical solutions.

Hemoglobin Solutions

The hemoglobin molecule has a high O_2-binding capacity and unloads oxygen at P_{O_2} of 40 mm Hg. This feature makes hemoglobin an ideal substance to supply O_2 to tissues avoiding hypoxia. In developing hemoglobin solutions to serve as RBC substitutes, a number of factors must be considered.[55,56]

In the last decade, companies have used four different sources of hemoglobin: human, bovine, recombinant, and transgenic. At the present time, it is unclear which of these will ultimately prove to be the best source.

The major limiting factor recognized to date, toxicity, has less to do with the source of the hemoglobin then with the properties of the hemoglobin solution.[56] Unmodified tetrameric hemoglobin, which dissociates to dimeric form, is toxic to the kidney, GI tract, and causes vasoconstriction. This has led to modifications of the hemoglobin molecule to prevent its dissociation into the dimeric form. Modification strategies include the following: conjugating the tetrameric hemoglobin with a large molecule such as polyethylene glycol; cross-linking the tetramers using chemical cross-linking agents or genetically modifying the molecule to create a covalent bond between subunits; polymerizing the hemoglobin tetramers into varying molecular weight sizes using chemical cross-linking agents; and encapsulating tetrameric hemoglobin in liposomes to create artificial RBCs. Each of these modifications is designed to prolong the half-life to the hemoglobin molecules in circulation and to limit toxic reactions. Clinical testing must resolve which approach will best accomplish these goals.

The possible clinical indications for hemoglobin solutions are diverse. With respect to perioperative transfusion therapy, their potential role in acute blood loss and hemodilution is most important. Clinical trials of three hemoglobin solutions are ongoing. In one trial, patients experiencing acute blood loss after trauma, surgery, or both are given escalating doses of pyridoxilated polymerized stroma-free hemoglobin (Poly SFH-P). A unit of Poly SFH-P contains the oxygen-carrying capacity of 1 U of RBCs. In this initial trial, patients tolerated up to 6 U of the compound without toxic reactions and avoided allogeneic blood transfusion for 24 h after surgery. A second ongoing trial is a randomized controlled study of Poly SFH-P in patients suffering acute blood loss. They will receive up to 6 U of the

compound during acute bleeding. The end point is units of allogeneic blood avoided.[56]

This and other hemoglobin solutions are still encumbered by a short half-life in circulation (about 8 h for ultrapurified polymerized bovine hemoglobin).[57] It is difficult to envision total replacement of allogeneic blood transfusion by these compounds, but if widely used in acute surgical settings, they will clearly reduce allogeneic blood ordered.

A further use of hemoglobin solutions is in ANH. Instead of replacing the blood taken with crystalloid or colloid solutions, the replacement fluid may be part or wholly a hemoglobin solution. This would potentially maintain full tissue oxygenation during ANH, increasing the cushion of safety for the patient. No convincing data are available as yet supporting this indication for hemoglobin solutions.

Perfluorochemical solutions

In the 1960s, there was a great deal of excitement generated by demonstrations that rats and mice could be immersed in beakers of perfluorocarbon solutions and maintain oxygenation.[58] These solutions were given to laboratory animals IV in an attempt to show that they could substitute for RBCs. These early experiments demonstrated unacceptable toxic reactions in animals (gas embolism). The compounds were immiscible in water (or plasma) and would separate unless emulsified. Ultimately a clinically acceptable perfluorocarbon was developed, Fluosol-DA (Korea Green Cross Corporation; Seoul, Korea). This was used in transfusions of Jehovah's Witness patients, but did not offer a clear clinical benefit over colloid solutions. The requirement for high O_2 pressure, for thawing, emulsifying, and oxygenating prior to use made these solutions a cumbersome alternative for its other prime indication, as a perfusion solution for infusion distal to coronary artery angioplasty catheters. Its use remains inconsequential.[59]

Newer perfluorocarbons are now formulated that can carry more oxygen and are simpler to handle. These are undergoing FDA testing, not as blood substitutes, but as perfusion solutions.

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