Elective Vascular Surgery Without Transfusion

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Although blood transfusion has helped make major vascular surgery possible, it has done so at a potential cost to our patients. Allogeneic red cell transfusions subject patients to the risks of transfusion reactions, disease transmission, and immunomodulation. These risks can be avoided in the majority of our patients through a better understanding of transfusion practices and the use of multiple alternatives to allogeneic blood.

Transfusion reactions, which occur in approximately 5% of transfusion recipients, are either hemolytic or febrile in nature.[1,2] Acute, intravascular hemolytic reactions occur as a result of ABO incompatibility and can be fatal.[3] Symptoms can take many forms including hemoglobinuria, fever, chills, coagulopathy, chest pain, and circulatory collapse. In the unconscious, anesthetized patient, acute reactions present either as sudden, hypotension in the euvolemic patient, or unexpected bleeding secondary to disseminated intravascular coagulation.[2] These reactions are the result of transfusion errors caused primarily by personnel outside the blood bank, the majority arising from failure to correctly identify either the patient or the unit before transfusion.[4,5] Prevention requires constant vigilance, particularly in settings where large volumes of blood are required in a short period of time; eg, the exsanguinating patient with a ruptured or torn aorta.

Delayed extravascular hemolytic reactions are caused by non-ABO, antigen-antibody incompatibility.[2] These may occur within three to ten days after transfusion as fever, malaise, hyperbilirubinemia, or a falling hematocrit. The exact incidence of these reactions is unknown and they are rarely recognized for what they are. Instead, a falling hematocrit in a recently transfused patient is attributed to recurrent or continued bleeding. A real danger exists in continuing to transfuse such patients with incompatible blood. In the worst case scenario, an acute hemolytic reaction can be precipitated if blood has not been recross-matched since the original transfusion. A febrile

response caused by circulating recipient antibodies to donor leucocyte or platelet contaminants is the most common form of transfusion reaction.[1] The incidence of these reactions can be diminished greatly by filtering leukocytes from blood, either in the blood bank before storage or at the time of transfusion.[5]

Graft-versus-host (GVH) disease, although rare, is of importance because it is usually fatal.[6] This disease typically results from the engraftment of immunocompetent T-lymphocytes in an immunosuppressed patient following transplantation or transfusion. Recent reports document GVH disease occurring in presumably immunocompetent patients following transfusion of directed-donor blood from immediate family members. Investigation of the donor-recipient relationship has shown that most are either first-degree relatives or share a human lymphocyte antigen (HLA) haplotype. Fortunately, pretransfusion gamma irradiation eliminates the offending lymphocytes at doses that do not adversely affect red cells. The vascular surgeon who wishes to use directed-donor blood (usually at the insistence of the patient's family) should check with the blood bank director as to the need for preoperative irradiation.

Blood can carry and transmit a wide variety of viral, parasitic, rickettsial, and bacterial diseases (Table I). Analysis of acquired immune deficiency syndrome (AIDS) cases in the United States as of 1991 showed that those caused by transfusion accounted for fewer than five per year of the overall total.[7] State-of-the-art human immunotrophic virus (HIV) testing now includes analyses for antibodies to HIV-1 as a first line of defense followed by detection of the HIV-1 antigen and culture techniques. These testing strategies coupled with improved screening have dramatically, but not completely, eliminated the presence of HIV in the blood supply.[8]

Hepatitis C virus still represents the greatest risk to patients, both in terms of disease transmission and mortality.[9] Cytomegalovirus (CMV), a relatively innocuous member of the herpes family, is so widespread that transfusion-transmitted CMV infection presents a small but troublesome risk. Vascular surgical patients at increased risk may include seronegative adults who need multiple transfusions; eg, ruptured abdominal aorta or blunt trauma victims. Exposure to some viruses can be reduced by screening blood, eliminating unnecessary transfusions, and removal of leukocytes from blood. The latter can be accomplished effectively by the use of filters designed to remove up to 99.9% of white cells.[10]

A variety of animal studies have demonstrated systemic immunosuppression caused by both cellular and humoral factors following allogeneic transfusion.[11-15] Decreases in natural killer cell numbers and function persisting for up to 30 days following whole blood transfusion in surgical patients have been documented.[16,17] Reductions in lymphocyte counts, particularly helper cells, were measured in 38 vascular surgery patients by Fernandez and colleagues.[18] These findings represent more than isolated changes in immune function mediators. In their review of 11 clinical studies, Triulzi and colleagues concluded that allogeneic transfusion was found to be an independent predictor of increased risk for postoperative infection.[19] Tartter's review of 40 retrospective studies reporting the influence of transfusion on tumor recurrence in cancer patients showed a similar positive association.[20] For the vascular patient, the preponderance of evidence favors an association, albeit not necessarily cause and effect, between transfusion and an adverse outcome in the form of an increased risk of postoperative infection. Given the dire consequences of infection in vascular surgical patients, especially those with intracavitary prostheses, prudent practice dictates avoiding allogeneic transfusion whenever possible.

Alternatives designed to limit the use of allogeneic blood transfusion in cardiovascular surgery can be divided conveniently into preoperative, intraoperative, and postoperative measures (Table II). Preoperative assessment of transfusion need begins with a complete evaluation of the patient, which should be conducted with the following goals in mind: (1) uncovering any factors that may lead to unexpected bleeding, (2) establishing the need for transfusion, and (3) determining the patient's ability to predonate blood. Each patient should be questioned about bleeding history, both personal and familial. A complete history is a more effective way of anticipating bleeding problems than routine screening using prothrombin times (PT) and partial thromboplastin times (PTT). These studies should be reserved for specific indications; eg, a history of liver disease or anticoagulant therapy.[21] Major coagulation disorders such as Hemophilia A or B are not absolute contraindications to surgery as long as hemostasis can be corrected to normal or near-normal levels through the use of Factor VIII and IX replacement therapy.[22] When feasible, patients should avoid the use of warfarin-based anticoagulants, aspirin, and nonsteroidal anti-inflammatory drugs well in advance of any planned surgery.

Preoperative measurement of hemoglobin and hematocrit will detect the presence of anemia, which should be corrected by iron supplementation and

Risks of allogeneic blood transfusion

Transfusion Reactions—5% of transfusions

Fatal hemolytic =	<1:1,000,000
Non-fatal hemolytic =	1:25,000
Fever/urticaria =	1:100

Disease transmission

HIV-1	1:40,000-150,000
Hepatitis B	1:250,000
Hepatitis C	1:500-3,000
HTLV I & II	1:5000-10,000
CMV	Varies; 1:2

Immunosuppression
Infection — 25% to 30% increase postoperatively
Cancer
Shortened survival
Shortened disease-free interval

Table 1.

attention to nutrition. Blood requirements vary with the type of problem encountered and operation needed as well as the general health of the patient. Patients undergoing surgery for aortic aneurysms and portal hypertension usually have blood losses of 500 to 1000 ml or more. An extra-anatomic bypass for aortoiliac occlusive disease should result in less blood loss than a transperitoneal procedure. Preoperative guidelines of transfusion need can be obtained from a review of the Maximum Surgical Blood Ordering Schedule (MSBOS), which estimates transfusion need according to surgical procedure. We have developed an algorithm that uses the MSBOS approach to assist the vascular surgeon in deciding blood requirements and the appropriate use of alternatives.[23]

Although much has been written about the ability of various indices and tests to assess risk and predict outcomes in patients undergoing major surgery, unfortunately, little is known about what preoperative information is useful in predicting transfusion need or the effect of transfusion on surgical outcome. Cardiac status should be evaluated through preoperative consultation and stress testing, when appropriate, to ensure that patients are able to mount the necessary cardiac responses to changes in perioperative hemoglobin level. Several studies have shown the benefit of optimizing cardiac status on outcome following vascular surgery, although an advantage was not directly correlated to transfusion need.[24-26] Most patients are able to undergo major surgery while anemic without adverse outcomes. Our initial study of anemic Jehovah's Witness patients defined risk factors associated with increased morbidity and mortality, but this was limited by small numbers and the co-mingling of emergency and elective patients.[27] A follow-up analysis of 59 Jehovah's Witness patients who underwent 63 vascular procedures showed that major operations could be conducted safely with no transfusion in the presence of anemia.[28]

Of the preoperative alternatives, autologous predonation of blood has had the greatest impact. In a study of 271 consecutive patients undergoing elective open heart surgery, Owings and colleagues showed that autologous predonation eliminated the need for allogeneic blood use in 73% of the group.[29] The amount of allogeneic blood given to the predonation group was significantly lower, 0.8 ± 1.5 units vs. 3.7 ± 3.6 units. Similar results have been reported by others.[30,31] The success of autologous predonation depends on a number of factors, including time, hemoglobin level, patient disease, and cooperation, from both the patient and physician. Successful autologous predonation requires intervention by the surgeon at least one month before scheduled surgery. The average donor can give three to four units of blood in this period with collection continuing up to 72 hours before surgery.[29,32] A preoperative delay of one month may not be possible or advisable for some patients, especially those with symptomatic or large aneurysms and those with esophageal varices and a history of recent bleeding. Autologous predonation is not an option for Jehovah's Witnesses.

Preoperative anemia (hemoglobin <11 g/dL) may eliminate a patient from consideration for autologous predonation. Preoperative administration of erythropoietin has been shown to increase the number of units donated from 4.1 to 5.4 in a prospective, randomized study of patients scheduled for orthopedic surgery, but this drug is not currently available for widespread use.[33] Predonation is contraindicated in patients with critical aortic stenosis or symptomatic coronary artery disease.[32] The majority of patients who are candidates for major vascular surgery also have coronary artery disease. Although Owings and coworkers reported that autologous predonation was safe in a group of patients with known coronary artery disease (ie, those scheduled for coronary artery bypass surgery) a small percentage of patients had hypotensive responses to blood withdrawal. Symptoms can be minimized in this group by infusing saline during phlebotomy and by limiting the total amount of blood collected at each session to 500 ml.

If the patient cannot or will not donate blood before hospitalization, the next best option is to collect and reinfuse the blood in the perioperative period through either acute normovolemic hemodilution or intraoperative autotransfusion. Acute normovolemic hemodilution is the process of removing and temporarily storing blood just before or immediately after the induction of anesthesia and replacing it with either crystalloid or colloid solutions. The removal of one to four units is possible in the patient with a normal hematocrit and results in a post-dilutional hematocrit of 20% to 30%.[34,35] The advantages of acute normovolemic hemodilution are an improvement in tissue perfusion secondary to decreased viscosity and loss of fewer red cells from bleeding. A decrease in viscosity produces an increase in cardiac output of 25% to 35%, primarily in response to an augmented venous return.

Hemodilution can be performed safely in most patients, with the only

Bloodless elective vascular surgery

PREOPERATIVE MEASURES	
	Check HGB/HCT Early
	Check Iron Stores
	Check Nutritional Status
	Limit Blood Drawing
	Schedule Autologous Predonation
INTRAOPERATIVE MEASURES	
	General Principles
	Hemodilution
	Platelet Sequestration
	Autotransfusion
	Blood Substitutes/Alternatives
	Drugs
POSTOPERATIVE MEASURES	
	Drugs
	Autotransfusion
	Blood Withdrawal
	Nutrition

Table 2.

contraindications being anemia, which limits the amount of blood that can be removed, and cardiac disease. Safety at low levels of hemoglobin has been demonstrated in a variety of healthy animal studies.[36,37] Studies of cardiac and vascular patients have shown that those with left ventricular dysfunction may be at greater risk of ischemia during hemodilution.[38,39]

Hemodilution can reduce homologous blood use in up to 90% of general surgery and cardiovascular patients.[35] Although studies limited to vascular procedures are few, benefits have been shown in both improved oxygenation and decreased reliance on banked blood.[40,41] Platelet or plasma sequestration, a hemodilution technique used successfully during open heart surgery to reduce homologous blood use by as much as 70%, has been adopted by vascular surgeons.[42-44] In this process, a unit of blood is removed preoperatively before heparin infusion. The collected blood is then separated using the Cell Saver® (Haemonetics, Braintree, MA) into a platelet rich plasma component and packed red cells. Red cells are given as needed during the procedure; the plasma component is reinfused at the conclusion of the procedure. Tawes and colleagues attained a 45% reduction in homologous blood need using plasma sequestration in 41 patients undergoing aortic procedures.[45] By using a similar approach combined with aortic aneurysm exclusion in 69 patients, Paty and colleagues limited the need for homologous transfusion to only 28% of their patients.[46]

Intraoperative autotransfusion can be performed safely with systems that either collect and reinfuse shed blood directly or more sophisticated devices that wash the blood before reinfusion. Each approach has its advantages and disadvantages. Systems that wash blood eliminate the risk of reinfusion of free hemoglobin, coagulation byproducts, and contaminants contained in plasma; however, they are expensive, time-consuming, and require technical expertise when compared to simpler, direct reinfusion devices.

Unwashed blood has been shown to be safe in major vascular cases with reinfusion volumes of up to five units.[47-50] Unfortunately, unwashed blood may contain vasoactive contaminants, activated clotting factors, fibrin degradation products and free hemoglobin, all of which can be dangerous.[51] Non-washed, unheparinized blood, in particular, has measurable amounts of fibrin degradation products, which, if infused in quantity, can produce clinically significant coagulopathies. Free hemoglobin in shed blood can damage renal tubules through the generation of free hydroxyl radicals, especially if circulation to the kidney is compromised or during acidosis and prolonged hypotension.

If the surgeon anticipates small volume losses of one to two units of blood, the use of an unwashed system appears to be safe. If blood losses are expected to be greater, or if they become larger than anticipated from bleeding, it is safest to rely on a system that washes salvaged blood before transfusion. Bear in mind that blood collected in a reservoir not designed for washing can be transferred easily to a system with such capabilities if blood loss becomes excessive. A contraindication to the use of autotransfused blood in elective vascular surgery, whether washed or not, is the presence of infection. The fear of producing bacteremia, sepsis, and death by reinfusing bacteria, endotoxin, or both, forms the basis for this prohibition. Although Boudreaux and colleagues have shown that the risk may be proportional to the amount of contamination, it makes sense to avoid autotransfusion in vascular grafting procedures where infection has life-threatening potential.[52]

Autotransfusion of shed blood is not limited to the operating room. Blood can be collected postoperatively from the chest cavity in patients who have undergone thoracic aortic procedures.[53,54] Results with postoperative autotransfusion have been mixed with little information available for vascular patients. Advocates of this approach in cardiac and orthopedic patients point to significant reductions in homologous blood use and the increased percentage of patients who avoid banked blood as reason enough for its use.[53] Others believe that the amount of blood recovered is inadequate to justify the risks involved.[54] In his review of postoperative salvage, Valeri supported its safety but could not find convincing evidence of efficacy in terms of reducing homologous blood use.[53] Finally, the surgeon should not rely upon postoperative blood salvage as a substitute for good intraoperative hemostasis or a decision to reexplore early when blood loss in the immediate postoperative hours is excessive.

Surgical blood loss can also be reduced by careful attention to operative detail. Dissection along anatomic, avascular planes is essential and requires a thorough knowledge of anatomy. All potentially vascular structures should be clamped and tied before being cut. Any vessel inadvertently cut or any unexpected bleeding, no matter how minor, must be controlled. Blood loss from many small bleeding points can add up quickly. A variety of cutting devices (eg, electrocautery) that decrease incisional blood loss are available to the surgeon.[55,56] Collagen hemostat pads, powders, and topical thrombin sprays are helpful in controlling oozing. Fibrin glue, made with highly concentrated human fibrinogen and clotting factors, has been shown by Tawes to be useful in controlling bleeding during vascular procedures.[57] The importance of minimizing operative blood loss is confirmed by our analyses of mortality, preoperative hemoglobin level, and blood loss during vascular surgery in the Jehovah's Witness.[58] Outcome was based more on the amount of blood lost during surgery than the starting hemoglobin level, with no deaths occurring if blood loss was less than 500 ml regardless of the preoperative hemoglobin level.

Both the retroperitoneal approach to the abdominal aorta and the exclusion-bypass technique have been reported as superior to traditional surgical approaches and handling of the aorta in terms of blood loss, although some controversy exists concerning the former. By substituting a retroperitoneal exclusion technique for a traditional transperitoneal approach, Leather and colleagues decreased blood loss to 900 ml, a reduction of almost one half.[59] Carrel and colleagues found a similar decrease from 1300 ml to 630 ml in 42 retroperitoneal operations compared to 121 transperitoneal cases.[60] In contrast, Cambria and colleagues found no significant transfusion advantage to using one approach over the other in a series of 69 patients randomized to either a retroperitoneal or transperitoneal operation.[61] Our report of Jehovah's Witnesses included 11 patients with abdominal aortic aneurysms who successfully underwent surgery using a transperitoneal approach, intraoperative autotransfusion, and no homologous blood.[58] All

survived with an average postoperative hemoglobin value of 8.9 g/dL. The common thread in these studies is attention to detail with a commitment to avoid blood loss and transfusion with alternatives such as autologous blood. We believe success in avoiding homologous transfusion in vascular surgery depends more on this factor than on a single technical innovation.

Woven Dacron® grafts with minimal porosity, gelatin-sealed grafts, and polytetrafluorethylene (PTFE) essentially eliminate blood loss from extravasation during aortic bypass and replacement, but their effect on reducing transfusion need is questionable. Reid and Pollock reported that gelatin-sealed grafts had "no measurable blood loss at implantation."[62] However, 47 patients still required transfusion for blood loss of greater than 750 ml or on clinical grounds. Fisher and colleagues' comparative analysis of double velour woven Dacron® grafts compared to PTFE using sophisticated blood loss measurement techniques concluded that neither graft had an advantage over the other in decreasing blood loss or preventing transfusion.[63] Their results may have been skewed by a significantly lower preoperative erythrocyte volume in the Dacron® group, which may have accounted for increased transfusion need. In the lower extremity, Hans and colleagues noted a greater blood loss with *in situ* femoral popliteal bypass versus reversed saphenous vein.[64] They attributed this to an increased operative time and more release of blood in testing the vein. By careful attention to detail and limiting bleeding from the anastomosed vein during *in situ* surgery, we have reduced blood loss in a small number of lower-extremity bypass cases to approximately 150 ml, a level below the need for transfusion.[58]

Pharmacologic prevention of blood loss holds promise for the future. Monitoring of heparin levels and reversal with protamine is standard practice in cardiac surgery and does not interfere with other blood conservation techniques. Desmopressin, Epsilon-amino caproic acid (EACA), and aprotinin, or Trasylol, a serine protease inhibitor, have been used successfully to reduce blood loss during cardiac surgery in a number of clinical trials.[65] Of the three, aprotinin is the most promising. Aprotinin is thought to work by inhibiting kallikrein and plasmin or by preserving platelet adhesion membrane receptors during cardiopulmonary bypass.[66] Results in over 200 patients from three controlled, prospective studies have documented decreases in both postoperative blood loss (up to 45%) and the need for allogeneic transfusion.[67-69] Moreover, aprotinin may have an important role in treating patients with aspirin-induced platelet abnormalities. No comparable experience using these drugs in vascular surgical patients exists.

Perfluorocarbon and hemoglobin-based blood substitutes are under investigation and currently have a limited role. Initial trials of Fluosol DA 20% (Green Cross, Osaka, Japan) in the Jehovah's Witness were disappointing.[70] Fluosol significantly increases dissolved oxygen content, but this addition appears to have little clinical effect on overall outcome. Poor results with Fluosol are attributable to its low concentration of perfluorocarbon and its rapid elimination from the circulation. Future formulations that address these problems may be more useful. We believe that perfluorocarbons will have a definite, but limited, role in future bloodless surgery as hemodilution agents, modifiers of reperfusion injury, or as temporary support in patients with well-defined critical oxygen deficits.

Erythropoietin holds much greater promise as an adjunct in bloodless surgery. Goodnough has shown that erythropoietin administered preoperatively can significantly increase the number of units of blood obtained through autologous predonation.[33] It follows from this finding that the time required for predonation can be decreased, thereby reducing the potential risk to patients with critical vascular lesions. Our study of erythropoietin in the anemic, postoperative patient showed that the drug accelerates recovery of hematocrit.

Postoperative blood conservation measures are primarily continuations of those taken both preoperatively and intraoperatively. These include attention to nutritional support and iron restoration as well as the use of Erythropoietin to stimulate red cell mass replacement. Following thoracic aortic surgery, mediastinal blood can be collected and reinfused using autotransfusion devices. Similarly, Desmopressin and Aprotinin can be given to patients postoperatively to control blood loss. However, it is important the surgeon understand that none of these above adjuncts are substitutes for early re-exploration in the patient who is bleeding actively.

Unfortunately, blood loss frequently continues in the postoperative period in the form of phlebotomy for laboratory tests.[71] Cookbook order sheets that include standing orders for frequent and often unnecessary laboratory tests should be avoided. Blood samples should be limited to essential studies, relying instead on noninvasive monitoring systems to gain information. For example, it is preferable to follow a patient's oxygen status with a transcutaneous oxygen monitor, checking blood gases only when acute changes occur, rather than drawing blood gases every six hours. When blood tests are necessary, pediatric collection tubes and microsamples should be used. Flush solutions should be returned to arterial and central lines to avoid wastage.

In the Intensive Care Unit patient, the first postoperative 24 to 48 hours are the most critical. The controlled setting of the operating room, where the patient is ventilated and anesthetized, is replaced by a period of increased stress and pain. Oxygen consumption, reduced intraoperatively by both anesthesia and ventilation, increases and may become directly dependent on delivery. In this setting, the surgeon may choose to maintain the most critically ill patients in an anesthetized, ventilated state to lessen oxygen consumption. Measures should be taken to prevent shivering, because the latter can increase oxygen consumption 35% to 40%.[72]

Neither hemoglobin concentration nor oxygen-derived variables are completely reliable as transfusion triggers in the postoperative period. Measures of the former may inaccurately estimate actual red cell mass.[73] Global estimates of oxygen delivery and consumption do not provide information on specific organ function; eg, the heart. A number of studies of surgical patients have demonstrated that most patients can tolerate hemoglobin values in the 7 to 8 g/dL range.[58,74-77] This does not necessarily mean that a *tolerable* hemoglobin level should automatically be considered an *acceptable* level for use as a transfusion trigger in all patients. Similarly, it is unnecessary and potentially risky to transfuse all patients to an optimal hemoglobin of 10 g/dL. Part of the problem with a hemoglobin-based trigger is its lack of generalizability.

Some patients can tolerate very low perioperative hemoglobin levels; others require supranormal values to survive, depending upon diagnosis and clinical condition. Two recent reports of an increased incidence of electrocardiographic evidence of myocardial ischemia in postoperative vascular patients with hematocrits below 29% are worrisome, although neither accounted for the presence or severity of underlying heart disease.[78,79] All of these studies are limited by small numbers.

The use of a minimally acceptable hemoglobin level as a transfusion trigger assumes that all patients are able to mobilize compensatory mechanisms equally and adequately. This may not be the case, especially in those vascular surgical patients with underlying coronary artery disease. Increased cardiac work puts demands on myocardial oxygen delivery, such that patients with quiescent coronary artery disease may develop arrhythmias or subendocardial ischemia. The heart is more dependent on delivery for its oxygen supply than other organs, extracting approximately one half its delivery. When hemoglobin falls, an increase in cardiac output requires a concomitant increase in coronary artery blood flow. In the presence of critical coronary artery stenoses, the heart may be unable to respond sufficiently to meet its oxygen (O_2) demands, leading to ischemia.[39] In the critically ill Intensive Care Unit patient where invasive monitoring is justifiable, measurements of CO_2 transport variables may be useful.

In summary, the decision to transfuse should be related to the specific patient's needs and condition. The presence of cardiac, pulmonary, and other atherosclerotic disease processes should be assessed and quantified when possible. Patients with coronary artery disease and pulmonary hypoxia will most likely require higher perioperative hemoglobin levels than those with normal hearts and lungs to avoid ischemia and undue cardiac stress. STI

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