AANA Journal Course

Update for Nurse Anesthetists

1

6 CE Credits*

Toward Reducing Perioperative Transfusions

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Even though the supply of blood products has never been safer, disease transmission remains the chief patient concern about transfusions. The primary concerns for anesthetists center on risks associated with blood transfusions, such as transfusion-related acute lung injury, anaphylactic transfusion reaction, clerical errors resulting in ABO incompatibility, and blood products contaminated with infectious organisms. These concerns, combined with patients' religious tenets and other factors, have contributed to renewed efforts to minimize blood transfusion without negative patient consequences. Achieving this goal requires a concerted effort by surgeons, perioperative nurses, and anesthesia providers.

Keywords: Acute normovolemic hemodilution, aprotinin, erythropoietin, preoperative autologous donation, transfusion triggers.

Objectives

At the completion of this course the reader should be able to:

1. State the 2 primary reasons patients cite for refusing blood product transfusions.
2. Define transfusion triggers.
3. List 3 types of interventions to reduce blood product transfusions.
4. List 3 drugs that may be administered to help reduce the need for blood product transfusions.
5. List 3 ways anesthetists may affect the need for blood product transfusions.

Introduction

Quickly, what is the most frequent, and probably the most ancient (oldest), tissue transplanted? Based on the 2 criteria set forth in this question, heart, kidney, lungs, and corneas do not qualify. All of these tissues are transplanted infrequently, at best, and have been carried out for around 50 to 75 years. By far, the most frequent tissue transplantation is the transfusion of blood products, although few healthcare providers consider blood product transfusion a form of tissue transplantation. Transfusions save many lives each year. More than 11.4 million units of blood products are transfused each year in the United States alone, which computes to the need for a blood product transfusion about every 3 seconds.

Fewer than 40 years after Sir William Harvey's discovery of the circulation of blood, the first blood transfusion, from dog to dog, was performed in Oxford, England, and was deemed a success because neither dog died.[1] In 1667, a dog-to-human transfusion was performed, and in 1668, a lamb-to-human transfusion was performed. Both of these transfusions were dismal failures. By 1677, transfusions from animals to humans had been outlawed.[2]

Documentation of a human-to-human transfusion was reported in Philadelphia, Pennsylvania, in 1795, but no other data were reported regarding the success or failure of the transfusion.[1] In 1818, further human-to-human transfusions were reported by a physician who claimed to have a 50% success rate. Transfusion success rates increased dramatically after the ABO blood groups were discovered in 1901.[1] This success rate advanced significantly with the discovery of the Rh groups; when combined with blood type determination before actual need, there was a reduction in transfusion reactions.

The supply of donated allogeneic blood in the United States and most developed countries is exhaustively tested to minimize the potential of disease transmission. The supply of blood products has never been safer with regard to disease transmission. The possibility of contracting human immunodeficiency virus via transfusion is approximately 1:1.4 million to 1:2.4 million units of transfused blood products, and the possibility of contracting the hepatitis C virus via transfusion is approxi-

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Human immunodeficiency virus	1:1.4 x 10^6 to 1:2.4 x 10^6
Hepatitis B	1:58,000 to 1:149,000
Hepatitis C	1:872,000 to 1:1.7 x 10^6
Bacterial infection	1:2,000
Donor screening error (Malaria, *Trypanosoma cruzi*, babesiosis, Creutzfeldt-Jakob disease)	1:4 x 10^6
Transfusion service error	1:14,000
Transfusion-related acute lung injury (all components)	1: 2,000
Fatal hemolytic reaction	1:600,000
Leukocytic target organ injury	1:2,000
Anaphylactic reaction	1:20,000 to 1:50,000

Table 1. Blood Transfusion Risks*[2,3]
* In units of red blood cells transfused.

mately 1:872,000 to 1:1.7 million units of transfused blood products (Table 1).[2,3] With the greater safety provided by advances in pathogen testing and increased knowledge of and crossmatching for more antibodies, transfusions have become commonplace.

In addition to the slight risk of disease transmission, potential harm may come as the result of clerical error during the processing of donated blood or in the time immediately before initiation of the transfusion. Clerical error, or transfusion service error, can result in ABO incompatibility. Current estimates are that this form of error occurs at a rate of 1:14,000 units of blood transfused. There are numerous complications associated with blood product transfusions (Table 2). Despite the safety record of blood products, disease transmission remains the primary patient concern about blood transfusion.

Along with concerns about disease transmission, religious beliefs may require the refusal of blood products. The most well-known such belief system is that of Jehovah's Witnesses, who rely on a strict, literal interpretation of various verses from *The Holy Bible*, in which blood is termed the source of life and once lost cannot be returned.

Replacing the Losses

Determination of the A, B, and O blood type groups was discovered in 1901 and used in transfusion administrations by 1907.[1] Transfusion reactions continued to occur until the Rh factor was discovered in 1939, which significantly reduced the occurrence of transfusion reactions. In 1942, the first laboratory indicator of when a patient should receive a transfusion was proposed by Adams and Lundy.[4] They suggested that to maintain a minimal physiologic oxygen carrying capacity, a patient should be given a transfusion when the hemoglobin concentration dropped to 10 g/dL and/or the hematocrit value fell to 30%. This assertion lacked strong scientific foundation.

The notion of a "transfusion trigger" is open to subjective interpretation. Transfusion triggers are indicators to guide anesthetists, surgeons, and others regarding the potential need to replace blood volume losses. Such values are but one of several parameters to be considered (Table 3). Recent recommendations from the American Society of Anesthesiologists (ASA) strongly recommend transfusion of red blood cells for patients whose hemoglobin concentration is 6 g/dL or less, whereas transfusion for a patient whose hemoglobin concentration is 10 g/dL or more is not warranted unless the patient has evidence of inadequate perfusion and/or oxygenation of vital organs and/or significant comorbidities.[5] Patients whose hemoglobin concentration falls between these parameters do not necessarily require transfusion of red blood cells. However, other factors must be considered with each patient, individually, including comorbidities, mixed venous saturation, arterial oxygen saturation, estimated blood volume losses, and the anticipated volume of continued blood loss. The ASA guidelines provide similar recommendations for platelets, fresh frozen plasma, and cryoprecipitate (Table 4).

Acute renal failure
Air embolism
Anaphylactic transfusion reaction, immediate or delayed
Bacterial sepsis due to contamination
Cardiovascular stress
Febrile reaction
Hemolytic reactions
Hypothermia
Immunosuppression
Transfusion-associated circulatory overload
Transfusion-related acute lung injury

Table 2. Complications Associated With Blood Product Transfusions

Hemoglobin concentration ≤ 7 g/dL for patients older than 65 years with cardiovascular or pulmonary disease
Hemoglobin concentration between 7 and 10 g/dL; benefit of transfusion is unclear
Hemoglobin concentration ≤ 6 g/dL for patients undergoing cardiopulmonary bypass
Acute blood loss > 1,500 mL or > 30% of estimated blood volume
Evidence of rapid blood loss without immediate control

Table 3. ASA Guidelines for Packed Red Cell Transfusions[5]

Strategies to Reduce the Rate of Transfusion

The myriad of potential complications associated with transfusions, the risk of disease transmission, religious

Platelets
Platelets count ≥ 100 x 10^9/L, transfusion not warranted
Platelets count ≤ 50 x 10^9/L, transfusion appropriate
Platelets count < 100 x 10^9/L but > 50 x 10^9/L, transfusion decision should consider prophylactic therapy, potential for platelet dysfunction, anticipated or current or active bleeding into a confined space, presence of potent antiplatelet agents, cardiopulmonary bypass, and microvascular bleeding
Fresh frozen plasma
Excessive microvascular bleeding in the presence of a prothrombin time (PT) 1.5 times normal *or* international normalized ratio (INR) > 2.0 *or* activated partial thromboplastin time (aPTT) > 2 times normal
Excessive microvascular bleeding due to coagulation factor deficiency when PT or INR and/or aPTT cannot be obtained quickly
Reversal of warfarin therapy
Correction of known coagulation factor deficiencies for which specific concentrates are not available
Heparin resistance (antithrombin III deficiency) in a patient requiring heparin
Cryoprecipitate
Obtain fibrinogen concentration if possible
Fibrinogen concentration ≥ 159 mg/dL, does not usually warrant cryoprecipitate
Fibrinogen concentration < 80 to 100 mg/dL, usually warrants cryoprecipitate administration
Fibrinogen concentration > 80 to 100 mg/dL but < 150 mg/dL, may need cryoprecipitate administration depending on anticipated or current bleeding and potential for bleeding into a confined space

Table 4. ASA Guidelines for Transfusion of Platelets, Fresh Frozen Plasma, and Cryoprecipitate[5]

tenets, and personal control of treatments and interventions challenge healthcare providers to find ways to minimize, if not eliminate, the possibility of receiving a transfusion. There are numerous interventions intended to reduce blood loss and to reduce the potential for receiving a transfusion. The interventions are generally classified as preoperative, intraoperative, and postoperative.

• *Preoperative Interventions.* Ideally, patients should be interviewed several days before the scheduled surgery. In addition to their medical history, anesthetists must obtain a complete pharmacological history, including prescribed medication(s), over-the-counter medications, and herbal remedies and supplements. There are numerous agents known to significantly alter coagulation pathways (Table 5). For elective and/or nonemergency surgical procedures, patients should be counseled during the preanesthesia interview or with written instructions from the surgeon to discontinue all agents known to alter coagulation for a period of 7 to 10 days before surgery. It is also prudent to delay or reschedule an elective or nonemergency procedure until the anticoagulation effects of a medication have worn off if the agent was not discontinued as requested. If the surgical procedure cannot be delayed for a sufficient time and significant bleeding is anticipated, administration of antifibrinolytic agents may be warranted. In addition, administration of vitamin K and other reversal agents, such as prothrombin complex concentrate or recombinant activated factor VII, may be required.

• *Antifibrinolytics.* Some patients may receive antifibrinolytic medications prophylactically; however, antifibrinolytic agents are not considered a part of a routine preoperative regimen. Typically, antifibrinolytic agents are reserved for patients scheduled to undergo a procedure associated with heavy blood loss and/or whose hemoglobin concentration is within the "window" for transfusion consideration and/or whose religious tenets forbid receiving blood products.

The antifibrinolytic agents currently available are aprotinin, aminocaproic acid, and tranexamic acid. Aprotinin has been the most extensively studied. Aprotinin is also called bovine antitrypsin. It was discovered in the 1930s.[6,7] Aprotinin inhibits several proteases, including trypsin, chymotrypsin, cathepsin, elastase, kallikrein, plasmin, protein C, thrombin, and urokinase; however, its action related to blood loss reduction has not been fully delineated.[8] Currently, the hypothesis for the role of aprotinin in reduced blood loss focuses on inhibition of fibrinolysis, inhibition of the release of inflammatory cytokines, and promotion of platelet adhesion. Aprotinin seems to strengthen clots by inhibition of kallikrein and plasmin.[9] Bleeding is also believed to be reduced by inhibition of activated protein C, the action of which is to help prevent intravenous thrombosis, thereby accelerating coagulation.[9] Determining the optimal dosing regimen and administration schedule (Table 6)[10,11] for aprotinin is difficult in part due to its pharmacokinetic profile, the numerous proteases in the body it

Prescription medications		
Abciximab	Etodolac	Oxaprozin
Antithrombin III	Fenoprofen	Piroxicam
Clopidogrel	Flurbiprofen	Sulindac
Diclofenac	Fondaparinux	Tinzaparin
Diclofenac/misoprostol	Indomethacin	Warfarin
Diflunisal	Lepirudin	
Enoxaparin	Meloxicam	
Over-the-counter medications		
Acetylsalicylic acid	Ketoprofen	
Ibuprofen	Naproxen	
Herbal supplements		
Chamomile	Garlic	Gingko
Echinacea	Ginger	Ginseng
Feverfew		

Table 5. Medications and Herbal Supplements That Prolong Coagulation

inhibits, and its lengthy half-life: the initial half-life is 150 minutes, and the terminal half-life is 10 hours.

The decision to use aprotinin must be carefully considered before administration. Aprotinin can have *very* serious side effects, including instigation of cardiovascular and/or cerebrovascular thrombosis, myocardial infarction, heart failure, encephalopathy, renal failure, and anaphylaxis.[12] In fact, use of aprotinin is associated with a dose-dependent double to triple risk of renal failure for patients undergoing primary or complex coronary artery surgery. According to some authorities, the potential for multiorgan damage from administration of aprotinin is significant and greatly increases the overall risk of mortality.[12] In October 2007, the Data Safety Monitoring Board recommended that use of aprotinin in a Canadian study, the Blood Conservation Using Antifibrinolytics: A Randomized Trial in a Cardiac Surgery Population, should be halted. The board's recommendation was prompted by questions and concerns raised with regard to multiorgan failure due to administration of aprotinin and preliminary findings in the study that suggested that use of aprotinin increases the risk of death.[13] On November 5, 2007, the US Food and Drug Administration (FDA) requested that Bayer Pharmaceutical Corporation suspend the marketing of aprotinin based on these concerns. The agency equivalent to the FDA in Germany demanded that Bayer withdraw the drug completely from the German market.[14,15]

A fatal anaphylactic reaction to aprotinin can occur at any point during a dosing regimen. The risk of anaphylaxis increases substantially on reexposure and peaks during the period of 4 to 30 days after the initial exposure. Patients reexposed to aprotinin within 6 months have a 4.1% incidence of an anaphylactic reaction; if reexposure occurs between 6 and 12 months, the incidence declines to 1.9%, and the incidence falls further to 0.4% if the reexposure occurs more than 12 months after initial exposure.[16]

First regimen	
1.4-mg intravenous (IV) *test dose*	
Wait 10 minutes, then	
280 mg IV, infused during 20-30 minutes, then	
70-mg/h IV infusion intraoperatively	
Second regimen	
1.4-mg IV *test dose*	
Wait 10 minutes, then	
140 mg IV, infused during 20-30 minutes, then	
35 mg/h IV infusion intraoperatively	

1 mL = 1.4 mg = 10,000 kallikrein inhibitor units. Dosing regimens are established by the plasma concentrations necessary to inhibit numerous serine proteases within the coagulation cascade. As of November 2007, aprotinin has been withdrawn from the market by the manufacturer, Bayer Pharmaceuticals, Inc, because of concerns about multiorgan failure and mortality associated with the use of aprotinin.

Table 6. Aprotinin Dosing Recommendations[10,11]

If, for any reason, the use of aprotinin is judged unfavorably, other medications, such as aminocaproic acid and tranexamic acid, desmopressin acetate, phytonadione, and vasopressin may be used. Aminocaproic acid and tranexamic acid result in reduced blood loss similar to that observed with aprotinin but without the degree of potential adverse effects.[12] Both of these drugs contribute to reduced blood loss by inhibition of plasminogen activators and by interfering with fibrinolysis.[17]

Desmopressin acetate contributes to reduced operative blood loss by producing an increase in plasma levels of factor VIII and von Willebrand factor. Phytonadione is an important cofactor for the production of active coagulation factors II, VII, IX, and X. Vasopressin produces vasoconstriction by directly stimulating smooth muscle V_1 receptors; constriction of arteries and arterioles will reduce

the blood flow within the operative field, to a degree, to help lessen surgical wound blood loss. Vasopressin is one of the body's stress hormones. Surgery is an extreme stressor for the body and may induce release of vasopressin from the pituitary. Previous studies have demonstrated that blood obtained during times of stress clots more quickly. The more rapid clotting occurs due to elevated plasma concentrations of factor VIIIc and von Willebrand factor, both produced by vasopressin. Like endogenous vasopressin, exogenous vasopressin would be anticipated to contribute to the increase in plasma concentrations of both of these coagulation factors.[18-20]

• *Erythropoiesis-Stimulating Agents.* Another pharmacological intervention designed to reduce the potential for blood transfusion is to increase the patient's native hemoglobin. The most effective means is by administration of an erythropoiesis-stimulating agent (ESA): recombinant human erythropoietin (rHuEPO), epoetin alfa, or darbepoetin alfa. The ESAs act on the bone marrow to stimulate production of red blood cells. Use of rHuEPO prophylactically to reduce the potential for blood transfusion was approved by the FDA in 1996.[21] Epoetin alfa is also approved for preoperative prophylactic use to reduce the potential for transfusions. Darbepoietin alfa is used to treat anemia that may result from chronic disease, such as rheumatoid arthritis or infections, or chemotherapy. Currently, darbepoetin alfa is not approved by the FDA for use as a preoperative prophylactic ESA.

Administration of ESAs is not an innocuous undertaking. Each has a relatively long half-life: rHuEPO, 8.5 hours; epoetin alfa, 4 to 13 hours; and darbepoetin alfa, 21 to 49 hours, depending on the route of administration. Each of the ESAs can result in serious side effects, including severe hypertension, stroke, seizures, myocardial infarction, congestive heart failure, vascular access thrombosis, pure red cell aplasia, allergic reactions, and immunogenicity. Side effects more commonly produced by ESAs include hypertension, fatigue, dyspnea, nausea, vomiting, diarrhea, arthralgia, tachycardia, asthenia, edema, fever dizziness, paresthesias, and cough.

Prophylactic administration of epoetin alfa has 2 recommended regimens: 300 U/kg, subcutaneously, daily for 15 days, beginning 10 days preoperatively and continued for 4 days postoperatively. The alternative regimen consists of subcutaneous injection of 600 U/kg, weekly, beginning 21 days preoperatively, repeated at 14 and 7 days preoperatively, and completed with the last injection the day of surgery. The dosing regimen for darbepoetin alfa for chemotherapy-related anemia recommends 2.25 µg/kg, subcutaneously, every 3 weeks to help the patient achieve a target hemoglobin concentration of 12 g/dL. As mentioned, preoperative prophylactic use of darbepoetin alfa to reduce the potential for blood transfusion would likely be considered "off-label" use, but it may theoretically be used for this purpose.

Administration of ESAs is contraindicated in patients with hypersensitivity to one of the drugs or this class of drugs, uncontrolled hypertension, latex sensitivity, and hypersensitivity to albumin, and ESAs should not be used in neonates or patients with antibody-mediated anemia. Administration of ESAs must be undertaken with caution in patients with hypertension, iron deficiency anemia, folate or B_{12} deficiency, congestive heart failure, coronary artery disease, seizure disorder, hematological disorder, sickle cell disease, hemolytic anemia, porphyria, or pure red cell aplasia because any of these conditions may be exacerbated by the use of ESAs.

The response to erythropoietin has been documented as 30% to 70% effective.[1] In 2001, Nieder et al[22] used "standard" and "low-dose" regimens, 600 U/kg and 300 U/kg, respectively, in men undergoing radical retropubic prostatectomy. The standard dose resulted in a 4.5% increase in the hematocrit value, whereas the low-dose regimen produced a 4.7% increase in the hematocrit value.[22] These 2 dosing regimens were used in patients undergoing hip joint total arthroplasty. Both regimens demonstrated statistically significant increases in erythrocyte production and a reduction in the need for allogeneic blood transfusion: only 11.4% of patients receiving the standard dose and 22.8% of patients receiving the low dose required transfusion compared with 44.9% of patients in the placebo group.[23]

Administration of an ESA works in 2 ways in concert with relatively invasive interventions to reduce the potential need for red blood cell transfusion, one preoperative autologus donation (PAD), the other intraoperative, acute normovolemic hemodilution. The increased red blood cell mass stimulated by ESAs can help a patient who chooses PAD as a preparation for upcoming surgery. PAD does not carry the age and weight limitations or restrictions imposed for allogeneic blood donations. To better tolerate the PAD regimen, the patient should have a hemoglobin concentration of 11 g/dL or more and/or a hematocrit of 33% or more before initiation of the donation process.[24] During PAD, the patient can donate as much as 10.5 mL/kg, and the donations may occur more frequently than once per week; however, the last scheduled donation should not be done fewer than 72 hours before the scheduled surgery to allow sufficient time to restore intravascular volume. PAD has distinct advantages and disadvantages (Table 7).

• *Intraoperative Interventions.* The intraoperative invasive intervention that may occur preoperatively occurs immediately before the operation, acute normovolemic hemodilution (ANH), first proposed in the 1970s. This intervention is decidedly less costly (monetarily) than PAD because the blood is collected immediately before surgical incision. As the blood is collected in the storage/ transfusion bag(s), it is immediately replaced by infusing crystalloid and/or colloids at a rate sufficient to maintain nor-

Advantages
Prevention of disease transmission
Prevention of red blood cell alloimmunization
Blood supply supplementation
Provision of compatible blood to patients with alloantibodies
Prevention of some adverse transfusion reactions
Provision of reassurance to patients about blood risks
Disadvantages
Unchanged risk of bacterial contamination
Unchanged risk of ABO incompatibility error
Higher cost than allogeneic blood
Wastage of unused blood
Increased incidence of adverse reactions to autologous donation
Risk of perioperative anemia and increased likelihood of transfusion

Table 7. Advantages and Disadvantages of Preoperative Autologous Donation

motension.[25] Colloids are reportedly preferred to crystalloids because of their ability to preserve tissue oxygenation.[26,27] The blood collected during ANH does not require testing for infectious agents and typically is not associated with waste, storage time, transfusion mishaps, loss of clotting factors, or loss of 2,3-diphosphoglycerate. With ANH, the patient's hemoglobin concentration can be safely drawn down to 7 to 9 g/dL, which still allows for some operative blood losses before replacement of the losses may become necessary—a safety margin of sorts. The stored blood can be returned to the patient during or at the completion of the surgical procedure. Both PAD and ANH have the potential for waste because any blood not returned to the patient must be discarded—it cannot be donated for use by any other patient.

The simplest and least costly intervention to reduce the potential for blood transfusion works in conjunction or concert with PAD or ANH. That intervention is to accept lower hemoglobin levels. In the past, the triggers for transfusion were a hemoglobin concentration of 10 g/dL and/or a hematocrit value of 30%, which endured for more than 50 years without evidence of efficacy.[28] In recent years, reducing the hemoglobin transfusion trigger to concentrations between 6 and 9 g/dL has become more accepted.

Intraoperative interventions to reduce blood losses can be aided by actions of anesthetists. The choice of anesthetic technique can contribute to the reduction of operative blood losses. Epidural and spinal anesthesia produce reduced arterial and venous pressures, which contribute to reduction of operative blood losses.[29]

Controlled hypotension may significantly reduce operative blood loss, but patients should be healthy enough to tolerate this technique. Vital organ ischemia is a very real concern in the decision to use controlled hypotension, particularly in patients with atherosclerosis or impaired autoregulation.[30] For patients healthy enough to tolerate controlled hypotension, this technique has demonstrated reduction of estimated blood losses by 35% to 83%.[31]

Because even mild hypothermia is associated with decreased platelet function, maintenance of normothermia should be an anesthetic goal for every patient.[32,33] In addition, maintaining normal physiologic parameters, such as normocarbia and normal acid-base balance, should be targeted because variations in these parameters are influential in contributing to reduced intraoperative blood loss.

• *Postoperative Interventions.* Salvage of shed blood is a type of autologous blood donation. The blood shed during surgery is collected, washed, and concentrated before reinfusion. This form of autologous transfusion has been accepted by some patients of the Jehovah's Witness faith because of the continuous loop or "closed circuit" formed in the recovery to reinfusion process. This salvage technique can be used in conjunction with PAD or ANH to reduce the amount of blood donation required preoperatively, reducing the risks associated with PAD and allogeneic transfusions and the waste of blood collected and not reinfused. Similarly, blood collected via surgically placed drains can be collected into specialized containers and reinfused during the postoperative period.

Conclusion

Despite the ever-increasing safety of the supply of blood products, disease transmission is listed as the primary patient concern regarding transfusions. Blood transfusions are undoubtedly lifesaving, but there continue to be substantial associated risks. During the last 10 to 20 years, the goal to reduce transfusions of blood products has gained momentum. To achieve a true reduction in the number of transfusions, the traditionally accepted paradigms for transfusion will inevitably have to change. Changing the paradigms will push everyone involved outside their comfort zones. However, through education, implementation of sound interventions, such as ANH and PAD, and lowering the transfusion thresholds, the goal of dramatically reducing the rate of blood transfusions may be accomplished.

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