ELSEVIER

SEMINARS IN PERINATOLOGY

Transfusion Therapy in Postpartum Hemorrhage

Anand Padmanabhan, MD, PhD, Joseph Schwartz, MD, and Steven L. Spitalnik, MD

Postpartum hemorrhage (PPH) is an obstetric emergency that can occur following vaginal or cesarean delivery. Rapid diagnosis of PPH using laboratory and clinical parameters is an important first step in its management. Traditional blood components, including packed red blood cells, platelets, plasma, and cryoprecipitate, should be used in patients with significant bleeding. Recent studies underline the utility of transfusing these components in defined ratios to prevent dilutional coagulopathy. Disseminated intravascular coagulation (DIC) should be considered in severely bleeding obstetric patients and should be treated aggressively using blood components. Newer hemostatic agents, such as activated factor VII, will play significant roles in patients with bleeding that is refractory to standard therapy. Implementation of an obstetric bleeding protocol that integrates new knowledge in coagulation should aid physicians in improving outcomes for the mother and her fetus.

Semin Perinatol 33:124-127 © 2009 Elsevier Inc. All rights reserved.

KEYWORDS postpartum hemorrhage, blood transfusion, factor VII, dilution coagulopathy, disseminated intra vascular coagulation, hemorrhage protocol

Postpartum hemorrhage (PPH), a major cause of maternal morbidity and mortality, causes approximately 140,000 deaths annually worldwide.[1-3] In primary PPH, bleeding occurs within 24 hours of delivery, whereas secondary PPH occurs 24 hours to 12 weeks postdelivery.

Pregnancy is associated with increases in multiple coagulation factors, including fibrinogen, factors VII, VIII, IX, X, XII, and von Willebrand factor, decreases in anticoagulant protein S, and an increase in activated protein C resistance. Fibrinolytic activity decreases associated with decreased tissue plasminogen activator activity and increases in thrombin-activable fibrinolysis inhibitor and plasminogen activator inhibitor levels.[4] In addition, myometrial contraction and local and systemic coagulation factors play a role in producing hemostasis.[5-7] These physiological alterations may prepare the pregnant woman for the potentially severe hemorrhage during parturition. Placental separation causes severe blood loss at the rate of approximately 700 mL/min.[4] Disruptions in hemostasis can, therefore, result in brisk, massive hemorrhage.

A commonly used definition of PPH is blood loss >500 mL after vaginal delivery or >1000 mL after cesarean section.[8] However, physicians typically underestimate, rather than overestimate, blood loss,[2] often resulting in delays in the initiation of blood transfusion and other resuscitative efforts. Another definition of PPH uses laboratory tests: a 10-point or greater decline in postpartum hematocrit as compared with antepartum levels. However, this may not reflect the current hematological status of the patient and seldom helps in patient management in real time.[9] A third approach monitors the patient for signs and symptoms of bleeding. Thus, hypotension, tachycardia, pallor, diaphoresis, oliguria, anuria, and altered consciousness can reflect severe bleeding, but these symptoms occur only after >15% of the patient's blood volume is lost.[10] Although none of these approaches alone is a sensitive indicator of PPH, an integrated approach may identify bleeding earlier. This assessment should also aim to rapidly establish the bleeding source. Bleeding from a specific, localized site is likely a surgical issue, whereas generalized oozing likely results from systemic coagulopathy. In addition, an initial surgical bleed can progress to a generalized coagulopathy if the bleeding is not arrested quickly. Typically, blood transfusion is considered when >30-40% of the patient's blood volume is lost (>1.5-2 L of blood in a 70 kg patient).[11] Smaller blood losses should be treated with crystalloid/colloid infusions; blood transfusion is indicated in specific circumstances, such as pre-existing anemia or reduced cardiovascular reserve. It is a good

The Section of Transfusion Medicine and Cell Therapy, Department of Pathology and Cell Biology, Columbia University Medical Center, College of Physicians and Surgeons of Columbia University, New York, NY.

Address reprint requests to Steven L. Spitalnik, MD, Department of Pathology and Cell Biology, Columbia University Medical Center, College of Physicians and Surgeons of Columbia University, 630 W 168th Street, New York, NY 10032. E-mail: ss2479@columbia.edu

0146-0005/09/$-see front matter © 2009 Elsevier Inc. All rights reserved.
doi:10.1053/j.semperi.2009.01.002

practice to draw laboratory tests at least every 30 minutes to guide transfusion therapy.

Blood Component Therapy

Transfusion rates in the postpartum period are estimated at 0.4% to 1.6%.[12] Blood transfusion should be used for replacement of oxygen-carrying capacity and hemostatic function, not for volume replacement. Packed red blood cell (pRBC) transfusions restore the oxygen-carrying capacity of blood. Although the effects of oxygen deprivation do not become evident until the hemoglobin concentration falls between 5 g/dL and 6 g/dL,[13] a higher threshold should be entertained in bleeding obstetric patients with associated comorbidities or with an extremely brisk bleed. Despite the absence of well-designed trials, a platelet count of >50,000/μL in a bleeding patient is generally considered adequate for hemostasis.[14] Plasma transfusions should be used to prevent dilutional coagulopathy and in situations where the PT/PTT is >1.5 times mean control levels.[15] Cryoprecipitate, an excellent source of factor VIII, fibrinogen, and von Willebrand factor, is especially useful in treating hypofibrinogenemia (typically, <100 mg/dL in a bleeding patient) and disseminated intravascular coagulation (DIC).[16] Given the time required for laboratory testing, clinical judgment often determines the triggers and patterns of transfusion in the acute setting of PPH.

Currently, there is no uniform consensus on the optimal ratio of blood products to transfuse into severely bleeding patients. Although there are very limited data in the obstetric literature, numerous recent efforts have been made to refine our understanding of blood transfusion for trauma. The recent trauma experience has largely been drawn from the war theaters in Afghanistan and Iraq. Recommendations for the ratios of pRBC, plasma, and platelet transfusions vary widely, ranging from 1:10 to 2:3 for plasma:pRBCs and from 6:10 to 12:10 for platelets:pRBCs.[17-19] Empiric plasma and platelet replacement has been based on the "washout" equation,[18,20,21] a mathematical model of exchange transfusion. This assumes a stable blood volume and calculates the exponential decay of each blood component when bleeding and replacement rates are constant and equal. In severely bleeding patients, this model probably does not mirror reality. A computer simulation model combining hemodilution and hemodynamic parameters indicates that replacement of 2 U plasma for every 3 U pRBCs, and 8 U of platelets for every 10 U of pRBCs prevents the PT from becoming subhemostatic (the sentinel event in dilutional coagulopathy).[19] Another mathematical model of whole-blood loss during hemorrhagic shock suggests a unit-for-unit coadministration of plasma and RBCs during resuscitation to reverse dilutional coagulopathy.[22] In addition, the ratio of fibrinogen to pRBCs transfused affects survival in casualties receiving massive transfusion.[23] Thus, in patients with combat-related trauma requiring massive transfusion, a high plasma:pRBCs transfusion ratio (1:1.4) was independently associated with improved survival.[24] The "bloody vicious cycle" of hypothermia, metabolic acidosis, and coagulopathy is thought to be linked to the high risk of mortality in massively transfused patients.[25-28] Based on these accumulating data, the US Army Surgeon General distributed a policy recommending that a 1:1 plasma:RBC ratio be transfused into all patients with significant trauma.[24] It may be possible to extend these conclusions to massive PPH, which is often accompanied by hypothermia, acidosis, and dilutional coagulopathy.

Disseminated Intravascular Coagulation (DIC)

Amniotic fluid embolism and abruptio placentae can cause DIC.[29] Initiation of DIC is mediated by the tissue-factor VII pathway (the "extrinsic" arm of the coagulation pathway).[30] In DIC, anticoagulant systems, including antithrombin III, protein C, and tissue factor pathway inhibitor, are impaired,[31] and fibrinolysis is inhibited by rises in plasma plasminogen activator inhibitor-1, which is considered the primary inhibitor of the fibrinolytic system.[32] DIC can result in severe end organ injury due to clot formation in the microvasculature, and a generalized systemic coagulopathy due to consumption of clotting factors and platelets. The use of fibrinogen, an acute phase reactant, as a diagnostic indicator of DIC is limited with a sensitivity of only 28%.[33] An algorithm developed for the diagnosis of DIC using platelet counts, fibrin-related markers (ie, D-dimers or fibrin degradation products), prolonged prothrombin time, and fibrinogen levels was validated with sensitivity and specificity of ~95%.[34,35] With continued bleeding and clinical and/or laboratory suspicion of DIC, transfusions of pRBCs, platelets, plasma, and cryoprecipitate need to be initiated early and aggressively. With severe transfusion-refractory and DIC-associated bleeding, factor VIIa (NovoSeven; Novo Nordisk, Bagsvaerd, Denmark) may be considered, although it is generally thought to be contraindicated in DIC; this is discussed further below.

Activated Factor VII (Factor VIIa; NovoSeven)

Activated factor VII is a recombinant activated coagulation factor approved by the FDA for use in patients with congenital hemophilia with inhibitors, in patients with congenital factor VII deficiency, and in patients with acquired hemophilia.[36] However, factor VIIa has been used off-label in numerous trauma and surgical settings[37,38] and in patients with severe PPH.[39-44] Although considered contraindicated in hypercoagulable states, such as DIC, it has been used in obstetric DIC without apparent adverse events.[39,45] The mechanism of action of pharmacologic doses of recombinant factor VIIa has been studied in cell-based models. Factor VIIa binds to thrombin-activated platelets in a tissue factor-independent manner through low-affinity binding. The bound factor VIIa activates FX on the activated platelet surface independent of the presence of FVIII or FIX, thereby aiding in clot formation.[46] Factor VIIa may be considered as salvage treatment in patients with massive PPH, for whom the only remaining option is hysterectomy. Should factor VIIa be used in the