Multidisciplinary Approach to the Challenge of Hemostasis

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A multidisciplinary panel consisting of experts chosen by the 2 chairs of the group representing experts in anesthesiology, blood banking, hematology, critical care medicine, and various surgical disciplines (trauma, cardiac, pediatric, neurologic, obstetrics, and vascular) convened in January 2008 to discuss hemostasis and management of the bleeding patient across different clinical settings, with a focus on perioperative considerations. Although there are many ways to define hemostasis, one clinical definition would be control of bleeding without the occurrence of pathologic thrombotic events (i.e., when balance among procoagulant, anticoagulant, fibrinolytic, and antifibrinolytic activities is achieved). There are common hemostatic challenges that include lack of scientific evidence and standardized guidelines for the use of therapeutic drugs, need for reliable and rapid laboratory tools for measuring hemostasis, and individual variability. Clinically meaningful and accurate real-time laboratory data reflecting a patient's hemostatic status are needed to guide treatment decisions. Current available routine laboratory tests of hemostasis (e.g., platelet count, prothrombin time/international normalized ratio, and activated partial thromboplastin time) do not reflect the complexity of in vivo hemostasis and can mislead the clinician. Although point-of-care coagulation monitoring tests including measures of thromboelastography/elastometry provide insight into overall hemostatic status, they are time-consuming to perform, complex to interpret, and require trained personnel. There is a particular need to develop laboratory tests that can measure the effects of anticoagulant and antiplatelet agents for individual patients, predict bleeding complications, and guide therapy when and if treatment with blood products or pharmacologic drugs is required. Formation of an organization comprised of specialists who treat bleeding patients will foster multidisciplinary collaborations and promote discussions of the current state of hemostasis treatment and future priorities for hemostasis research. Controlled trials with clinically meaningful end points and suitable study populations, as well as observational studies, investigator-initiated studies, and large registry and database studies are essential to answer questions in hemostasis. Because of the complexities of maintaining hemostatic balance, advances in hemostasis research and continuing communication across specialties are required to improve patient care and outcomes.

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Management of the bleeding patient remains a major challenge in surgery and medicine. Advances and controversies in managing hemorrhage have triggered renewed interest across multiple disciplines in understanding hemostasis and how to best use new therapeutics and conventional blood products.[1–3] This article summarizes proceedings, findings, and recommendations from a hemostasis advisory panel held in Scottsdale, AZ in January 2008 sponsored by Novo Nordisk that included hemostasis experts from anesthesiology, blood banking and hematology, critical care medicine, as well as surgical specialists in trauma, cardiac, neurology, obstetrics, vascular, and pediatric

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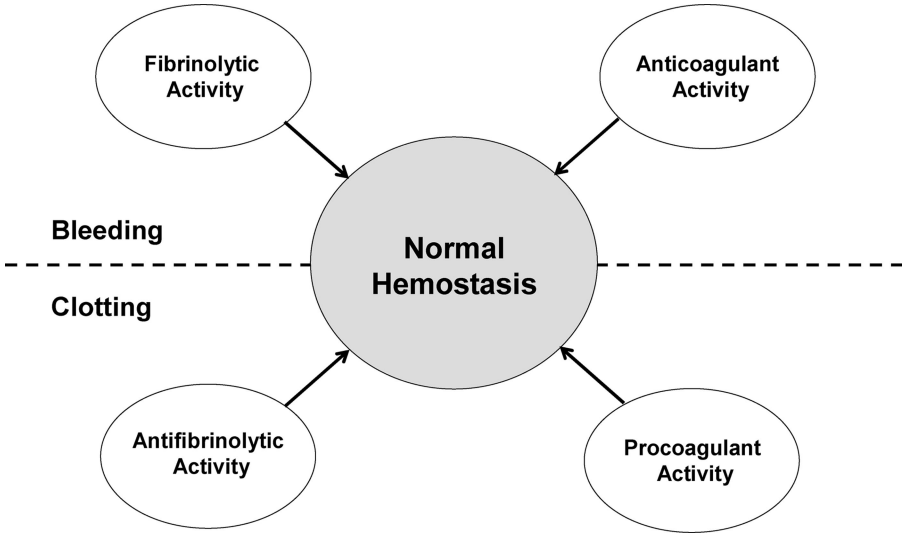

Figure 1. Normal hemostasis is a result of interaction among physiologic systems that promote bleeding (anticoagulant and fibrinolytic) or clotting (procoagulant and antifibrinolytic).

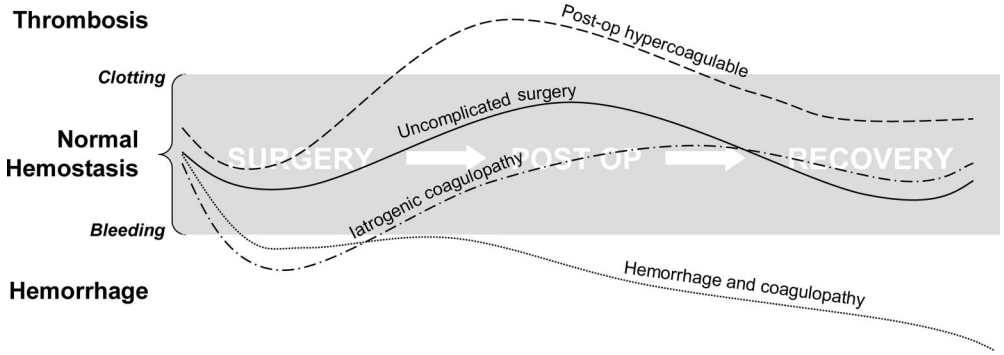

Figure 2. Examples of thrombosis and hemorrhage risks associated with surgery. The solid line represents the hemostasis profile for a normal, uncomplicated surgery (minor risk of thrombosis or hemostasis). The dashed line represents a procedure with a greater risk of postoperative thrombosis (e.g., central nervous system surgery). The dotted dashed line represents iatrogenic coagulopathy (e.g., cardiovascular surgery), and the dotted line represents uncontrolled hemorrhage with coagulopathy (e.g., major trauma, postpartum hemorrhage, or any complicated surgical procedure).

surgery chosen by the 2 external cochairs, Jerrold H. Levy (Emory University School of Medicine) and Craig Kessler (Georgetown University), in consultation with Jeffrey Lawson (Duke University) and Aryeh Shander (Englewood Hospital) to attempt to achieve a multidisciplinary balance based on their publications, contributions to the literature, and/or involvement in transfusion decisions or administration. The multidisciplinary panel met with the goals of creating a broad definition of hemostasis that transcended individual specialty-specific definitions and identifying challenges in managing bleeding and thrombotic complications of therapy. The panel arrived at a common understanding of hemostasis through a review of the mechanisms of hemostasis and discussions of the specialty- and circumstance-specific challenges and perspectives on hemostasis. From this common understanding arose common definitions of clinically meaningful end points, cross-specialty study design characteristics, and high-priority areas for research collaboration. For this article, specific individuals with their expertise wrote the individual sections, and the first author (JHL) edited and revised the article and subsequent revisions.

WHAT IS HEMOSTASIS?

There is no universally accepted definition of hemostasis. The most simplistic definition is the "cessation of bleeding"; however, ultimately death leads to the cessation of bleeding, and death is not an ideal example of hemostasis. An alternative 1-dimensional view is the mechanistic concept that hemostasis represents the platelet and coagulation cascades involved in the cessation of bleeding. A more refined clinical definition of hemostasis is bleeding control without the induction of pathologic thrombotic events such as myocardial infarction, stroke, arterial thrombosis, or deep vein thrombosis. Hemostasis can be considered as control of bleeding within the finely tuned balance of procoagulant, anticoagulant, fibrinolytic, and antifibrinolytic activities (Fig. 1).[4]

MECHANISMS OF HEMOSTASIS

Physiology of Bleeding

Understanding the physiology of bleeding and clotting in surgical patients is critical to achieving a

balance between hemorrhage and pathologic thrombosis (Fig. 2). The hemostatic mechanism has been previously described as a cascade of reactions occurring in sequence beginning with contact activation triggered by tissue factor and/or collagen and proceeding by the extrinsic, intrinsic, and final common pathways to the formation of thrombin, which converts fibrinogen to fibrin to form a clot. However, the regulation of coagulation is more complex than suggested by this model and is better described as a "symphony" of coagulation in which multiple systems are interacting simultaneously in concert with cellular surfaces of platelets and the vascular endothelium.[4] However, a major limitation of current therapies is conventional clotting tests that do not demonstrate or provide complete information about the physiologic processes of coagulation. Thus, determining appropriate therapy can be confusing. A better understanding of the in vivo regulatory mechanisms and pharmacologic modulation of thrombin generation may help control bleeding without potentially increasing prothrombotic risks.[5,6]

Currently, a cell-based model of coagulation is most often used to understand hemostasis. This model can be divided into initiation, amplification, and propagation phases.[5,6] In the initiation phase, injury or exposure to a signaling molecule changes the resting endothelium into an activated surface, which favors localized coagulation. Endogenous heparin molecules are removed from the endothelial cell surface, and the anticoagulant molecules thrombomodulin and antithrombin are downregulated. Tissue factor is exposed, and the composition of the endothelial surface phospholipids is altered. Tissue factor binds and activates factor VII (FVII). Activated FVII (FVIIa) activates factor IX and factor X, which in turn convert prothrombin (factor II) to thrombin and factor V to factor Va, to initiate clot formation. During amplification and propagation of the thrombus, activated platelets adhere to the endothelium, factors V, XI, and VIII are activated, and a positive feedback loop increases generation of thrombin. In addition to converting fibrinogen to fibrin, thrombin has multiple other hemostatic roles including further platelet activation. Many coagulation factors are serine proteases, and the coagulation process is regulated by serine protease inhibitors including protein C and S, tissue factor pathway inhibitor, and antithrombin. These agents inhibit clotting and localize clot formation to the site of injury. The fibrinolytic system is also activated in parallel, and it removes the clot in coordination with wound healing and tissue remodeling.

The cell-based model of coagulation also demonstrates the dynamic balance among hemostatic cascades. Additional factors including inflammation, surgical stress, shock, trauma, or underlying illness may affect the hemostatic balance by influencing endothelial or platelet function. As illustrated in Figure 1, managing hemostasis in clinical settings requires keeping a balance between pathologic bleeding (trauma, surgery, and hemophilia) and clotting (stroke, myocardial infarction, and thrombosis) for each moment of their clinical course. Early after injury or surgery, the balance shifts toward a net procoagulant activity to promote clot formation and hemostasis. However, once anatomic hemorrhage is controlled, the balance should shift toward a net anticoagulant activity to prevent uncontrolled clot formation and to promote recovery (Fig. 2). Certain patients undergoing cardiac surgery may have the additional insult of cardiopulmonary bypass (CPB), in which exposure to foreign materials (plastic tubing) and mechanical agitation can damage or consume the plasma components of the hemostatic system.[4] Use of anticoagulant medications on a chronic basis (warfarin and clopidogrel) or during hospital admission (heparin) can further affect the hemostatic balance.

Endothelial Biology

The endothelium plays a crucial anticoagulant role in maintaining the blood in a fluid state and in promoting limited clot formation when there is a breech in the integrity of the vascular wall. Endothelial cells express tissue factor pathway inhibitor, heparin, thrombomodulin, endothelial protein C receptor, tissue-type plasminogen activator, ecto-ADPase, prostacyclin, and nitric oxide to inhibit clot formation. After vascular injury, endothelial cells express tissue factor and secrete plasminogen activator inhibitor, von Willebrand factor, and protease activated receptors. Endothelial-derived anticoagulant and procoagulant molecules are unevenly distributed throughout the vasculature.[7] Endothelial cells display heterogeneity in structure and function such that each blood vessel is a complex palate of cells with different genes expressed in response to changes in the local microenvironment.[7] When there is a change in the systemic balance of coagulation, as in response to surgical stress or trauma, the endothelium responds, and affects the hemostatic balance between bleeding and clotting. Because of endothelial cell heterogeneity, the endothelium modulates almost all disease processes. The endothelium can be thought of as a metabolically active input-output device whose functions vary in response to the environment (Fig. 3). This property makes the endothelium a promising, and necessary, target for therapeutics affecting hemostasis.

HEMOSTATIC CHALLENGES FOR CLINICIANS

Most hemostatic issues facing clinicians are shared among specialties and include the following: lack of evidence and standardized guidelines for using biologics (blood products and protein derivatives) and pharmacologic agents; lack of accurate, meaningful, and rapid laboratory tools for evaluating the hemostatic system; individual variation by specific pathology or anatomic disruption; difficulty in assessing continued bleeding in anatomic regions that cannot be

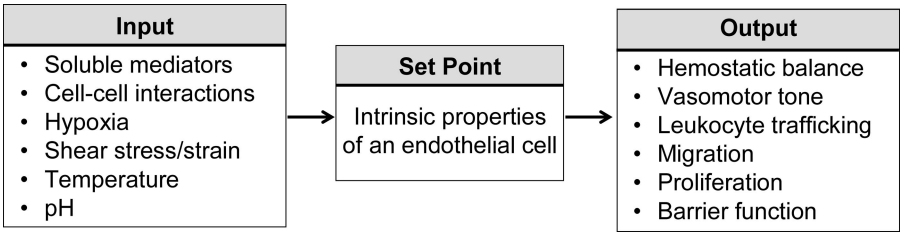

Figure 3. Model of an endothelial cell as an input-output device. Input comes from the extracellular environment and includes soluble mediators such as growth factors, cytokines, chemokines, lipopolysaccharide, and reactive oxygen species, as well as other inputs. Genetic and environmental intrinsic properties of each endothelial cell serve as a set point, which channels the flow of information and links the input and output. (Adapted with permission from Aird.[50])

directly inspected; and variable impact of pretreatment with anticoagulants or antiplatelet drugs. Specific hemostatic issues of the individual specialties will be considered below.

Cardiac/Vascular Surgery

Cardiac/vascular surgery patients represent a well defined but complex hemostatic challenge because of multiple factors including tissue injury, the use of heparin with protamine reversal, and preexisting antiplatelet and antithrombotic therapies. Cardiac surgery is further complicated by the use of CPB, which activates inflammatory, hemostatic, and fibrinolytic pathways.[8] Complex cardiac surgical procedures (e.g., repeat, combined, and aortic root procedures) are increasingly performed on patients at the extremes of age with underlying medical conditions. These patients have more extensive surgery, prolonged CPB times, and increased risk of bleeding. In addition, more patients receive anticoagulants and antiplatelet drugs preoperatively without clear therapeutic approaches for reversal or management (e.g., clopidogrel).[8]

With the withdrawal from marketing of aprotinin for use in high-risk cardiac surgery, there is an increasing need to further develop therapeutic approaches to manage refractor bleeding in cardiac surgery. Several studies suggest that transfusions are associated with worse outcomes in a dose-dependent manner, and there are adverse consequences to massive transfusion (beyond 4–5 U).[9–11] Koch et al.[9] reported an observational cohort study of 11,963 patients who underwent isolated coronary artery bypass from 1995 to 2002 of which 5814 (48.6%) were transfused. Transfusion of red blood cells (RBCs) was associated with a risk-adjusted increased risk for every postoperative morbid event: mortality (odds ratio [OR], 1.77), renal failure (OR, 2.06), prolonged ventilatory support (OR, 1.79), serious infection (OR, 1.76), cardiac complications (OR, 1.55), and neurologic events (OR, 1.37). Each unit of RBCs transfused was associated with incrementally increased risk for adverse outcome. Karkouti et al.[10] defined massive transfusion as receiving at least 5 U of RBCs within 1 day of surgery. Of 9215 patients analyzed, 1.8% (n = 169) died and 9.7% (n = 890) had massive transfusions/blood loss. After adjusting for multiple potential confounders (including perioperative adverse events), massive transfusions/blood loss was associated with an 8.1-fold (95% confidence interval, 3.9–17.0) increase in the odds of death. Overall, multiple studies continue to suggest that transfusions are important risk predictors in adverse outcomes, especially in cardiac surgery.

Trauma Surgery and Resuscitation

For the bleeding trauma patient, the approach is to control anatomic hemorrhage and initiate effective resuscitation. Acute, fatal hemorrhagic shock is characterized by progressive metabolic acidosis, hemodilution, and hypothermia, the so-called "lethal triad." Coagulopathy at this stage is difficult to reverse, even with massive transfusion that can also cause more coagulopathy, especially if "unbalanced" components such as only packed RBCs (PRBCs) are transfused without hemostatic factors. Many severely injured patients are coagulopathic at hospital admission (before fluid resuscitation even begins) as the result of tissue hypoperfusion triggering the release of inflammatory mediators. Hemodilution only compounds this problem. The role of blood loss, dilution, hypothermia, acidosis, fibrinolysis, inflammation, and other pathways as contributors to the coagulopathy of trauma remains to be fully elucidated.[12–15] On the basis of retrospective studies, some recommend that early resuscitation in hemodynamically unstable patients should be aimed at preserving hemostasis, and a transfusion protocol with a ratio of RBCs, plasma, and platelets in a 1:1:1 proportion should be used. This approach may improve outcomes,[2,16,17] but there is some controversy regarding this strategy of empiric fixed therapy because the current resuscitation approach is multifactorial. Clinical and laboratory variables are needed to identify the patients most likely to have abnormal hemostasis on admission and to complement early diagnosis of continuing hemorrhage, and thus identify those patients who would most benefit from directed therapy or possibly from a 1:1:1 resuscitation strategy.

Neurocritical Care

Intracranial bleeding caused by trauma, stroke, or severe coagulopathy presents unique clinical issues as a result of the consequences of the hemorrhage. Extraaxial bleeding, as represented by subdural and epidural hematomas, may cause brain herniation and

secondary brain injury from mass effect with resultant increased intracranial pressure and decreased cerebral perfusion. Intraaxial bleeding, as may happen with hypertensive intracerebral hemorrhage (ICH), may result in tissue destruction due to the impact of the initial hemorrhage, and in these circumstances, intervention regarding hemostasis may be too late. However, there is increasing recognition in both traumatic brain injury (TBI) and stroke that continuing hemorrhage may be a major contributor to secondary brain injury and worsened patient outcome. Growth of an initial hematoma is a common occurrence after head trauma, and this usually occurs in areas of previously contused brain. Likewise, growth of primary ICH due to continued bleeding is now recognized as common early after onset. Finally, bleeding from a ruptured aneurysm or arteriovenous malformation presents a risk for recurrent hemorrhage, often with catastrophic consequences.

The initial cause of bleeding in stroke and trauma is reasonably well understood and thought to result from primary rupture of an arteriole or vein from chronic injury from hypertension, weakening from a vascular anomaly, or stress from traumatic forces. However, the mechanisms of secondary and continuing hemorrhage remain poorly understood. Coagulopathy from warfarin or heparin use, liver failure, or even antiplatelet use may worsen hemorrhage in all of these contexts. However, the relative contribution of endothelial injury and circulating hemostatic abnormalities in "noncoagulopathic" patients remains a central question regarding the mechanisms of continued intracranial hemorrhage. The clinical observation that patients with severe brain trauma may present with a normal systemic coagulation profile but quickly develop abnormal coagulation variables and worsened cerebral bleeding has led to the recognition that the brain is rich in tissue factor, and TBI may alter systemic, and presumably local, hemostasis.[18] In addition, findings of increased hemorrhage in the setting of large craniectomy for severe brain trauma suggest that cerebral vascular autoregulation may also play a role. Thus, continuing intracranial bleeding after trauma and stroke may represent an interplay of endothelial, hemostatic, and physiologic factors.[19]

The challenges of acute cerebral bleeding share many features with other aspects of surgical and medical bleeding, but also pose unique problems. Surgical hemostasis is a major priority for patients undergoing an operation to evacuate a hematoma or treat a vascular anomaly. The ability to identify the contributions of abnormal hemostasis and endothelial injury in continuing hemorrhage in TBI or ICH (or even aneurysmal rerupture in subarachnoid hemorrhage) would suggest potential targets for intervention to limit these processes. However, the 2 factors that complicate our understanding and treatment of hemostasis in acute central nervous system (CNS) disease are (1) the time course of continuing or recurrent hemorrhage, and (2) the fact that the intracranial vault is a small closed space. Most early hematoma expansion in both TBI and ICH occurs within 4 to 6 hours after the initial hemorrhage, at least in patients who are not taking warfarin or antiplatelet drugs at the time of injury. Furthermore, the ability of the brain to tolerate any amount of additional hemorrhage may be limited. Thus, efforts to diagnose and intervene regarding the hemostatic system in acute CNS hemorrhage must focus on the ability to target abnormalities immediately to avoid any additional hemorrhage, essentially from the time point of initial patient evaluation.

Obstetrics and Postpartum Hemorrhage

At the end of pregnancy, uterine blood flow is approximately 800 to 1000 mL/min, and after delivery of the placenta, the uterus must rapidly establish hemostasis. This process occurs via uterine involution, vasoconstriction, and localized thrombosis. If hemostatic events are not well orchestrated, excessive bleeding can result, often with disastrous consequences, as evidenced by the fact that postpartum hemorrhage is the leading cause of maternal mortality worldwide.[20] Given the increasing rate of cesarean delivery (approximately 30% of deliveries in the United States [US]) and the epidemic of maternal obesity, postpartum hemorrhage will continue to dominate maternal morbidity and mortality in the foreseeable future. Coagulopathy and transfusion rates range from 1% to 25% for first cesarean deliveries, and up to 15% to 67% for patients who have had multiple operative deliveries.[21] Factors associated with postpartum hemorrhage are multiple and include disorders associated with abnormal labor patterns, large or multiple fetuses, preeclampsia, lacerations, multiple gestation, history of antepartum or intrapartum hemorrhage, placental disorders such as placenta previa or placenta accreta, and general anesthesia.[22,23] Inherited and acquired bleeding disorders, as well as anticoagulation, contribute to postpartum hemorrhage.[24] Recurrence rates of bleeding are alarmingly high, occurring in approximately 15% for second and 22% for third and subsequent pregnancies.[25] Early and late postpartum hemorrhage (>500 mL and >1000 mL for vaginal and cesarean delivery) occur in 4% to 6% and 1% to 3% of pregnancies, respectively.[24] The early (primary) form occurs within 4 hours of delivery, and uterine atony is the cause in 75% to 90% of cases. Late (secondary) postpartum hemorrhage occurs between 24 hours and 6 weeks postpartum, and occurs in 1% to 3% of pregnancies.[26] Massive postpartum hemorrhage refers to blood loss requiring replacement of 50% of circulating blood volume in <3 hours or loss of >150 mL/min.[27]

Optimal management of postpartum hemorrhage is not clearly defined at this time. A recent Cochrane review regarding the treatment of postpartum hemorrhage found that there were no adequate studies concerning medical and surgical interventions, except

for uterotonic drugs.[28] Published guidelines provide an overview for the management of the third stage of labor.[29] Although a list of treatment options is available, there is a lack of specific guidelines for postpartum hemorrhage management. Potential treatment options include the following: medical maneuvers consisting of uterotonics, prostaglandins, intravascular volume replacement, a range of blood products, and recombinant FVIIa (rFVIIa, off-label use); interventional radiology procedures of embolization and balloon catheterization of pelvic vessels; and surgical maneuvers consisting of uterine compression via intracavitary balloon inflation, uterine compression sutures, ligation sutures of a variety of pelvic vessels (uterine, ovarian, and hypogastric arteries), and hysterectomy. Treatment of massive postpartum hemorrhage with investigational use of rFVIIa was associated with a reduction in maternal mortality in a retrospective cohort study of 34 patients.[30] Thromboembolic events have been reported with off-label use of rFVIIa in postpartum hemorrhage.[31]

Despite the significance of postpartum hemorrhage to maternal health, several knowledge gaps are recognizable. There is a lack of a clear understanding of the molecular underpinnings of its pathophysiology, contribution of undiagnosed bleeding disorders, lack of reliable biomarkers, and lack of adequate clinical trial data to guide physicians in managing their patients.

Neonatal and Pediatric Surgery

Neonatal and pediatric patients undergoing major surgery with loss of multiple blood volumes are at significant risk for coagulopathy. The hemostatic system is not fully mature by 6 months of age, which may result in an increased bleeding tendency and reduced risk of thrombosis.[32] Infants are especially susceptible to adverse effects of transfusion, including dilutional coagulopathy, hyperkalemia, citrate intoxication, and other metabolic derangements caused by a small blood volume relative to the quantity of transfused products. Plasma and cryoprecipitate may reach the circulatory limits of these patients but still not provide sufficient factors to reverse or treat a coagulation defect. We speculate that hemostatic agents such as rFVIIa or prothrombin complex concentrates may produce better clotting profiles than blood products in this population because of their ability to acutely modify hemostasis because of the small circulating blood volumes. However, controlled studies are needed but difficult to perform in this patient population.

LABORATORY EVALUATION OF HEMOSTATIC FUNCTION

The ideal laboratory test to evaluate hemostasis in the bleeding surgical or medical patient should reflect the dynamic status of bleeding and be accurate and available in real time to enable the physician to make treatment decisions rapidly. Testing should be specific for different physiologic mechanisms to target specific treatments to correct deficits in hemostasis. The test result should have meaningful clinical implications and closely reflect the patient's hemostatic status. Other characteristics of the ideal test include reproducibility, resistance to effect of preanalytic variables, and ease of use in point-of-care settings such as the operating room, emergency department, and intensive care unit.

The commonly available routine laboratory tests of hemostasis, including platelet count, prothrombin time (PT)/international normalized ratio (INR), and activated partial thromboplastin time (aPTT) give information about the levels of platelets or soluble clotting factors in plasma but do not reflect the complexity of hemostasis in vivo.[33] Hence the PT, aPTT, and INR that provide information on the ability to clot, and which were developed for adjusting warfarin dosing, are poor predictors of bleeding despite their widespread use.[34] Platelet count can be an indicator of bleeding risk, but it provides no information on platelet functionality. Additional limitations to the predictive value of routine coagulation testing include preanalytic variables such as differences in anticoagulants used in sample tubes and differences in sample handling (e.g., placing on ice, which activates factor XII in vitro versus immediate analysis).[35] Finally, modest differences in body temperature between 35°C and 37°C affect coagulation factor activation and platelet function, which is not reflected in the PT and aPTT testing performed at 37°C in the laboratory.[33]

Point-of-care coagulation monitoring tests based on the viscoelastic properties of whole blood include thromboelastography (TEG®, Haemoscope Corp., Niles, IL) and rotation thromboelastometry (ROTEM®, Pentapharm GmbH, Munich, Germany). These tests have been available for several decades in Europe and the US but are being increasingly considered for use in operating rooms. Similar to the activated clotting time used to monitor heparin levels in the operating room, TEG®/ROTEM tests are rapid, point-of-care whole blood clotting tests. Unlike the activated clotting time, viscoelastic method examinations are designed to evaluate overall hemostatic status including platelet function and fibrinolysis. The TEG®/ROTEM tests graphically display the viscoelastic changes in the clot as it develops and resolves and measured parameters include the clotting time, clot kinetics, clot strengthening, amplitude, maximal strength, and clot lysis.[36] The literature shows that these viscoelastic tests have been effective in guiding transfusion therapy and reducing the overall use of blood products.[37] However, the tests take significant time to perform, especially for assessments of fibrinolysis, are complex to interpret, and require specially trained laboratory personnel to guarantee consistent quality of performance. Given these constraints, the viscoelastic tests are superior to standard INR/PT and platelet count monitoring frequently used to monitor coagulation function in the clinical setting.[38] However, any transfusion algorithms

based on point-of-care testing results have consistently been found to reduce transfusion rates because they reduce empiric transfusions.

Laboratory assessment tools are urgently needed that can identify the balance between bleeding and coagulation rapidly and reliably enough to guide treatment and transfusion decisions. There is also interest in a method to measure the effect of anticoagulants or antiplatelet drugs in an individual patient to predict bleeding complications from surgery or impact of these drugs on risk of continued hemorrhage. Important questions include: (1) At what point does bleeding become uncontrolled, requiring more aggressive treatment with blood products or drugs? and (2) How can laboratory testing be used to signal this transition? Especially valuable across all surgical disciplines and procedures would be a point-of-care laboratory test that could be used in high-risk patients to indicate deterioration during surgery and guide appropriate interventions to prevent massive bleeding. There is also need for more rapid, specific, and accurate tests for factor deficiencies, qualitative platelet defects, and fibrinolytic activity.

HEMOSTATIC BALANCE AND TREATMENT OPTIONS

Significant, unexpected blood loss coupled with fluid resuscitation producing a dilutional coagulopathy may represent a final common pathway toward fatal hemorrhage in many surgical or trauma cases. Adverse effects related to transfusion occurring days or months after surgery are likely to be underrecognized, as suggested by studies of increased complications in cardiac surgery patients receiving older versus more recently donated banked blood.[39] In fact, a recently published review of a large United Kingdom database over a 7-year period determined that RBC transfusion in patients having cardiac surgery was strongly associated with infection and ischemic postoperative morbidity, hospital stay, increased early and late mortality, and hospital costs.[40]

There are clinical challenges in finding and maintaining the hemostatic balance. For example, which patients are likely to have excessive bleeding or be at risk of thrombosis? What is the best way to tailor resuscitation strategies to optimize the patient's own adaptive physiologic responses to bleeding or surgical stress? What blood products or other biological or pharmacologic agents are available to help manage hemostasis, and more importantly, when should they be given and in what doses? More studies are necessary to define the role of transfusion of blood products such as plasma, platelets, cryoprecipitate, or factor concentrates to replace losses and boost clotting, lysine analogs to inhibit fibrinolysis, desmopressin to increase platelet adhesion and promote clotting, rFVIIa to increase thrombin generation, and topical agents such as recombinant human thrombin.[41] Even more ambitiously, there is a need to elucidate the complex interaction between coagulation and inflammation so that patients can be optimally guided through both the short-term (acute hemorrhage) and long-term (multiple organ system failure) consequences of injury and disease. Reaching further, does the answer lie in gene expression at the level of the endothelium?

RESEARCH CHALLENGES

To foster cross-specialty collaboration in hemostasis research, a "hemostasis community" should be organized, composed of all specialists who treat bleeding patients and share an interest in hemostasis research. The multidisciplinary hemostasis community can discuss the current status of hemostasis and set future research priorities based on input from experts in basic science mechanisms of hemostasis (endothelial biology and proteomics) and clinical approaches to bleeding patients (trauma, medical, and surgical subspecialties).

Applicability of Treatment Paradigms

An example of an area of controversy suited to examination by the multidisciplinary hemostasis community is if, when, and how to apply an empiric 1:1:1 resuscitation ratio of RBCs, plasma, and platelets in massive transfusion. The early use of prethawed AB plasma and platelets in a 1:1 ratio with type O PRBCs is becoming widely accepted among trauma surgeons treating severely injured patients, although the evidence is still controversial and incomplete.[16] This represents a change in approach versus the standard practice for at least the past 20 years of using large volumes of crystalloid and PRBCs to maintain normal blood pressure, followed by plasma and platelets only later in the course of resuscitation when laboratory variables such as PT/PTT and platelet count have become abnormal.[42,43] Retrospective evidence suggests that less-aggressive fluid resuscitation and early administration of RBCs with plasma and platelets in a 1:1:1 ratio decreases overall mortality.[2,17]

Questions remain about how applicable this approach is to bleeding patients in other circumstances such as elective surgery or acute CNS hemorrhage, and how we can determine, either by clinical or laboratory evidence, when the patient is coagulopathic and requires aggressive plasma or other pharmacologic hemostatic support with hemostatic agents. In trauma, there is often a period of unobserved blood loss and patients present to the hospital already in hypotensive shock with deranged coagulation systems. These patients are intensely vasoconstricted in reaction to hypotension and pain. In elective surgery, catastrophic bleeding may occur but usually blood loss is observed, and there can be immediate intervention to stop bleeding. These patients are anesthetized and vasodilated when hemorrhage occurs, and this difference in endothelial "tone" may have profound

Table 1. Recommendations for Potential Meaningful Clinical End-Points of Investigations of Perioperative Hemostasis

Mortality (a 20% reduction should be targeted)
Long-term functional outcome
Re-operation for bleeding (30% reduction)
Decrease or avoidance of transfusion of allogeneic blood products
Decreased donor exposure
Decreased transfusion of non-red cell blood products
Decreased massive transfusion (>5 or >10 units red cells)
Reduction in chest tube drainage
Reduced morbidity due to acute respiratory distress syndrome, multiorgan dysfunction/failure, infection, acute coronary syndrome, deep venous thrombosis or pulmonary embolism
Reduced time to clotting
Improved safety or quality of life profile
Improved cost-effectiveness

implications for the subsequent course of resuscitation and the design of trials to study hemostasis.

In CNS hemorrhage, bleeding is usually indirectly observed by intermittent neuroimaging studies (e.g., computed tomography [CT]) or inferred from repeated clinical neurologic examination. In this setting, by the time hematoma enlargement is observed on follow-up head CT scanning or by clinical neurologic deterioration, the window for successful intervention may have passed. CT angiography is being explored as a marker for risk of active continuing bleeding.

Defining Clinically Meaningful End Points

To design clinical trials that are feasible, relevant to clinical practice, and if applicable, acceptable to regulatory agencies, meaningful clinical end points must be defined (Table 1). In the wake of recent experience with aprotinin in cardiac surgery and rFVIIa in acute ICH, measuring only intermediate end points such as reduced blood loss, amount of units transfused, or hematoma expansion is important, but may not be sufficient for future trials of hemostatic agents.[11,44]

Clinical studies of bleeding patients and potential hemostatic agents need a design that accounts for confounding variables that exist in these clinical scenarios. The studies should include provisions to collect samples concurrently for gene expression and proteomic analysis and for measurements of individual coagulation factors and inflammatory mediators. This approach will allow investigators to link clinical data and outcomes with hemostatic mechanisms, thus elucidating the physiology of hemostasis, and may also provide new end points for future studies.

Suitable Study Populations

Clinical hemostasis studies are needed that include patients across multiple surgical disciplines including trauma, cardiac and vascular surgery, emergency general surgery, obstetrics, and neurocritical care. Characteristics of a desired study population include sufficient numbers of patients, ability to consent patients (which can be difficult in trauma and acute stroke situations), bleeding that is quickly identifiable, rapidly available laboratory testing and imaging, and the potential for significant positive impact on both bleeding and clinical outcomes. To avoid bias in favor of or against any given interventions, consideration must be given to selecting groups that will distinguish between variability in patient response to treatment and outcomes driven more by the severity of the underlying disease process.

Study Design Options

Controlled, randomized, double-blind clinical trials of therapeutics or interventions are the "gold standard" for comparing treatments or treatment versus placebo. However, this type of data and study design may not be feasible to all investigative questions. Further, specific well-controlled results from clinical trials may be restricted to the study conditions, are often labeled for use based on the defining trial, and may not be more widely applicable to all clinical situations that are actually encountered by clinicians. For those Food and Drug Administration–approved hemostatic agents that are in use, large, well-conducted prospective cohort and observational studies should also be included. In trauma patients, studies would be useful to determine the impact on outcome of timing of resuscitation and transfusion in the first 6 hours after arrival in the emergency department. What blood products or other hemostatic agents should be given? What should be the timing and their temporal order, and what is their association with survival? What laboratory testing should be performed, and how are the results useful in guiding therapy? Such studies would provide data on the safety and efficacy of treatments used in large numbers of bleeding patients in real-world clinical settings.[45] Such an observational trial in trauma patients is starting within the next several months at 10 large trauma centers across the US.

Although there are many caveats with database analysis, a well-conducted trial using registry data can shed light on outcome measures and help focus questions to be answered by randomized trials. The advantage of registry information is the close reflection of clinical practice. Registries use patient outcome and other clinical end point data in large databases collected at multiple sites. One of the largest registries is the one from the Society of Thoracic Surgeons, which contains data on >3 million cardiothoracic surgery cases collected at 848 sites since 1994.[46] The Society of Thoracic Surgeons' registry data should be expanded to include outcomes (blood loss, discharge hemoglobin/hematocrit, morbidity, and mortality) related to the use of different pharmacologic agents, including dosing and timing information. Similar data are collected in the National Trauma Database.

In addition to existing registries, new registries are needed for other categories of bleeding patients. A high priority is formation of a massive transfusion registry and/or surgery disaster registry. Patients

could be entered based on number of RBC units transfused (e.g., >4 U) or on entry into a defined massive transfusion protocol. Such a registry should include massive transfusion patients irrespective of the type of surgery or trauma. Other potential registries include a database to enroll patients with postpartum hemorrhage to define current management and outcomes, and provide data for future improvement, and an active registry of patients with bleeding complications while taking anticoagulants or antiplatelet agents.

Investigator-initiated studies in hemostasis must be funded by industry and government agencies. Possible areas of interest include cardiac perioperative use of rFVIIa for prophylaxis, active bleeding, and salvage use in patients requiring massive transfusion. Different interventions would include transfusion of platelets and/or prothrombin complex concentrates versus rFVIIa or no agent with crossover if bleeding continues, to address the question of whether these treatments really affect bleeding. Both adults and children undergoing cardiac surgery should be studied because bleeding and response to treatment may differ by age group and the type of surgery performed. For postpartum hemorrhage, blood products (conventional therapy) can be compared with other biological or hemostatic agent administration versus using an early interventional angiographic approach to embolize arteries supplying the uterus.

Finally, laboratory-based studies are needed to develop a time course analysis of hemostasis using currently available biomarkers and new molecules as they are identified. Knowing the timing of changes that hemostatic components undergo in the course of developing coagulopathy would allow the development of new hypotheses for accurately timing administration of therapeutics in massive hemorrhage. Newer techniques such as proteomics will be crucial to providing a totally new understanding of hemostasis with the goal of individualized patient management.[47] Genomic analysis may help answer the question of whether there are individual genetic differences/polymorphisms/markers among patients that can affect hemostatic response to surgery, trauma, or hemorrhagic stroke.[48] Results from early studies on the proteomics and genomics of hemostasis are promising and may provide insights into mechanisms and treatment options. Ultimately, such studies may also provide new useful biomarkers for monitoring the status of clotting pathways. A list of proposed multidisciplinary research study proposals by the discussion and writing group is provided in Table 2.

Table 2. Multidisciplinary Research Study Proposals

1. Observational followed by randomized studies in trauma patients to determine the timing of resuscitation and transfusion in the first 6 hours after arrival in the emergency department versus outcome.
2. Expand the Society of Thoracic Surgeons registry data to include outcomes (blood loss, discharge hemoglobin/hematocrit, morbidity and mortality) related to the use of different pharmacologic agents, including dosing and timing information.
3. Formation of a massive transfusion registry and/or surgery disaster registry.
4. Perioperative use of recombinant activated Factor VII (rFVIIa) for active bleeding, including salvage use in patients requiring massive transfusion in cardiac surgery compared with prothrombin complex concentrates or other therapeutics as a registry.
5. Laboratory-based studies to develop a time course analysis of hemostasis using currently available biomarkers and new molecules as they are identified.
6. Registries and pilot studies regarding bleeding complications in patients taking warfarin or antiplatelet agents at the time of traumatic brain injury or intracranial hemorrhage.

CONCLUSION

In many clinical settings, maintaining hemostatic balance is poorly understood and remains complex. Limited evidence is available to guide treatment of these patients. Current laboratory tests are not sufficient to guide optimal biological or pharmacologic therapy. Blood product transfusion, the mainstay of treatment for bleeding, is often given without a full appreciation of the benefits, risks, and costs.[49] Increasingly, practitioners cannot afford to guess between 2 unsatisfactory approaches to the bleeding patient: (1) overtreat with blood products, antifibrinolytics, and hemostatic agents only to risk increased postoperative morbidity and mortality due to thrombotic complications; or (2) undertreat or postpone administration of hemostatic agents only to see bleeding increases and the patient experience deleterious effects such as reoperation, multiorgan failure, continued CNS bleeding, or death from exsanguination. Advances in hemostasis research in each specialty may have beneficial implications for patients in other disciplines. Ongoing communication among advocates for hemostasis research from all disciplines is critical to improving treatment and patient outcomes.

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