New Concepts in the Treatment and Prevention of Bleeding

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Perioperative patients may have complex underlying hemostatic disorders because of surgery, underlying diseases, or potentially acquired abnormalities. Coagulation disorders occur commonly in this patient population because of hemorrhage with dilutional changes, surgical injuries, or preexisting therapies, including drugs that affect their hemostatic system (1,2). Hemostasis is a multifaceted inflammatory cascade with humoral and cellular elements that can be activated by multiple pathways (3,4). Postoperative surgical patients, including patients following cardiopulmonary bypass (CPB), develop major hemostatic alterations which produce excessive postoperative bleeding; causes that include hemodilution and activation of the coagulation, fibrinolytic, and inflammatory pathways (2,4–6). Further, CPB has been referred to as a systemic inflammatory response syndrome (SIRS) with many of the hemostatic changes occurring similar to patients with SIRS due to sepsis (7). However, many surgical patients develop complex bleeding disorders irrespective of the surgical procedure because of massive hemorrhage and/or tissue injury (1).

Hemostasis is also a far more complex system than intrinsic and extrinsic hemostatic activation as taught in medical school (8,9). Multiple factors are responsible for creating clot, including release of tissue factor, thrombin generation, platelet activation, and the complex cellular and humoral amplification that follows (9–11). Multiple factors are also involved in the pathogenesis of bleeding, but the interaction of platelets with coagulation factors including fibrinogen following vascular injury are three key elements for clotting to occur (9,10,12).

Approaches to reduce bleeding and transfusion needs in the intensive care unit and critically ill patients are based on either preventing or reversing the defects associated with coagulopathies, whether they are preexisting or acquired. The increasing use of new anticoagulants (r-hirudin, bivalirudin, argatroban), low-molecular-weight heparins (LMWH), heparinoids (Orgaran), pentasaccharide (fondaparinux), or platelet inhibitors (thienopyridines-clopidogrel or IIb/IIIa receptor antagonists) also may potentiate bleeding (13,14). This review will focus on current pharmacologic therapies, patients at risk, and therapeutic pharmacologic approaches for bleeding.

ANTICOAGULATION: THROMBIN INHIBITORS

Patients may present perioperatively receiving anticoagulation therapy for multiple reasons, including atrial fibrillation, venous thrombosis prophylaxis, prosthetic valves, or for coronary artery disease. Anticoagulation is based on inhibiting both thrombin activation and platelet activation (14–17). Thrombin is a potent procoagulant that generates fibrin from soluble fibrinogen, activating factors V and VIII, and activating platelets (9). Activated platelets adhere to injured vascular endothelia, express IIb/IIIa receptors, aggregate, and further enhance generation of thrombin (18). Because of the complex humoral amplification system linking both hemostatic and inflammatory responses, there are multiple pathways to produce thrombin and prothrombotic effects.

Unfractionated heparin is the most commonly used anticoagulant to prevent clotting, especially during surgery. It is a mixture of 3000–30,000 Da fragments (19). Heparin binds to antithrombin III (AT III) increasing the rate of thrombin-AT III complex formation; it also inhibits other steps in coagulation, through acceleration of the reactions between antithrombin and thrombin or factor Xa (19). One of the advantages of heparin anticoagulation is that it can be reversed immediately by removing heparin from AT III with protamine (20). Unfractionated heparin is also an important cause of heparin-induced thrombocytopenia.

Like unfractionated heparin, LMWH are glycosaminoglycans (20). LMWH are fragments of unfractionated heparin purified to a mean molecular weight of about 5000 (16). LMWH have a longer half-life, and dose-independent clearance; the recovery of antifactor Xa activity approaches 100%, compared with about 30% with unfractionated heparin. The plasma half-life of LMWH is longer than unfractionated heparin, ranging 2–4 h after IV injection, and 3–6 h after subcutaneous injection. Fondaparinux is a synthetic pentasaccharide with once-daily dosing, and a long half-life.

Whenever stopping or reversing anticoagulation therapy, the risks of bleeding versus procoagulant effects of agents need to be considered. Unfractionated heparin but not LMWH can be reversed by protamine, a basic polypeptide isolated from salmon sperm that neutralizes heparin by a nonspecific acid–base interaction (polyanionic–polycationic). Anaphylaxis is one

of the complications of protamine. Warfarin reversal can be performed with vitamin K, or more acutely with fresh frozen plasma. The other anticoagulants are not readily reversible.

ANTICOAGULATION: PLATELET INHIBITORS

In patients with myocardial ischemia and or atherosclerotic vascular disease, inhibiting platelet activation is the cornerstone of therapy (21). Although aspirin is used extensively, it is a relatively weak antiplatelet agent (22). Aspirin irreversibly inhibits platelet cyclooxygenase and thromboxane A2, a potent platelet activator, but has no effect on other mechanisms and aspirin resistance may occur in up to 30% of patients. Clopidogrel is more potent than aspirin, and inhibits platelets by selectively and irreversibly binding to the P2Y12 receptor to inhibit the adenosine diphosphate-dependent pathway of glycoprotein IIb/IIIa-receptor activation (22–24). Antiplatelet therapy with aspirin and clopidogrel is standard care following revascularization by percutaneous coronary intervention with stent insertion. This so-called dual therapy is recommended for up to 4 weeks after intervention for bare-metal stents and for 6–12 mo after intervention for drug-eluting stents (21). Studies have shown that anyone undergoing bypass grafting who recently received clopidogrel are at increased risk for substantial perioperative bleeding. Although IIb/IIIa receptor antagonists are also used in acute coronary syndromes and are potent platelet inhibitors, clopidogrel is the major agent used with the least knowledge available about how to manage these patients or monitor its effects.

Vicenzi noted a 45% complication rate and a mortality of 20% reported in patients undergoing noncardiac surgery after coronary artery stenting (25). Discontinuation of antiplatelet drugs appeared to be of major influence on outcome. They prospectively evaluated 103 patients receiving stents within 1 yr before noncardiac surgery. Antiplatelet drug therapy was not, or only briefly, interrupted. Heparin was administered to all patients. Of 103 patients, 44.7% suffered complications after surgery; 4.9% of the patients died. All but two (bleeding only) adverse events were of cardiac nature. Most complications occurred early after surgery. The risk of suffering an event was 2.11-fold greater in patients with recent stents (<35 days before surgery) compared with percutaneous cardiac intervention more than 90 days before surgery (25).

The clopidogrel package insert suggests that if a patient is to undergo elective surgery and an antiplatelet effect is not desired, it should be stopped 5 days before surgery. However, if patients bleed, therapy or monitoring its effects has not been established. Further, risk versus benefit of stopping clopidogrel needs to be weighted against the risk of stent thrombosis, and the need for surgical intervention as well.

BLOOD SUBSTITUTES (HEMOGLOBIN-BASED OXYGEN CARRIERS)

Although three different classes of blood substitutes have been studied, including the perfluorocarbons, modified hemoglobins, and liposome-encapsulated hemoglobin, most of the clinical trials have been with the hemoglobin-based oxygen carriers that use purified and modified hemoglobins (26). Because free hemoglobin in the plasma can produce potential adverse effects, the hemoglobin-based oxygen carriers have been structurally adapted to prevent potential problems and to promote oxygen uptake and delivery. Nine different hemoglobin-based oxygen carriers have been studied over the past 20 yr, and four have been tested in phase III clinical trials. Only Hemopure is licensed for use outside this country. Hemopure uses glutaraldehyde to polymerize bovine hemoglobin followed by extensive purification and viral inactivation steps to produce Hemopure, a substitute with <3% hemoglobin tetramers. The current studies have evaluated this hemoglobin-based oxygen carrier for perioperative use to better decrease the need for allogeneic RBC transfusions. One of the mechanisms by which hemoglobin-based oxygen carriers may be effective in reducing transfused blood may be a result of its ability to restore lost iron following hemorrhage. Giving either oral or IV iron to patients is not well tolerated; free iron is toxic; and iron-containing parenteral solutions, usually bound to dextrans, have the potential to produce anaphylactic reactions. Although the oxygen-carrying capacity of most HBOC solutions may be transient, they are rapidly metabolized, and free iron is potentially scavenged by multiple mechanisms to subsequently stimulate erythropoiesis and reticulocytosis. This may explain why patients were discharged with similar hematocrits in both groups, despite the decrease in transfused allogenic packed erythrocytes in the HBOC-treated patients (27).

ANTIFIBRINOLYTIC AGENTS, APROTININ, AND DESMOPRESSIN

Antifibrinolytic agents are synthetic lysine analogs that include ε-aminocaproic acid (EACA, Amicar) and tranexamic acid. These molecules inhibit fibrinolysis by attaching to the lysine binding site of the plasmin-(ogen) molecule, displacing plasminogen from fibrin. Because fibrinolysis exhibits a major cause of bleeding, these agents have been reported to be effective in multiple surgical procedures (28).

Levi et al. reported a meta-analysis of all randomized, controlled trials of the three most often used pharmacological strategies to decrease perioperative blood loss in cardiac surgery (aprotinin, lysine analogs [aminocaproic acid and tranexamic acid], and desmopressin) (29). Studies were included if they reported at least one clinically relevant outcome (mortality, rethoracotomy, proportion of patients receiving a transfusion, or perioperative myocardial infarction) as well as

perioperative blood loss. In addition, a separate meta-analysis was done for studies on complicated cardiac surgery. A total of 72 trials (8409 patients) met the inclusion criteria. Treatment with aprotinin decreased mortality almost twofold compared with placebo. Treatment with aprotinin and with lysine analogs decreased the frequency of surgical reexploration (0.37 and 0.44 respectively). These two treatments also significantly decreased the proportion of patients receiving any allogeneic blood transfusion. The use of desmopressin resulted in a small decrease in perioperative blood loss, but was not associated with a beneficial effect on other clinical outcomes. Aprotinin and lysine analogs did not increase the risk of perioperative myocardial infarction; however, desmopressin was associated with a 2.4-fold increase in the risk of this complication. Studies in patients undergoing complicated cardiac surgery showed similar results.

Desmopressin

Desmopressin acetate (DDAVP) is a synthetic analog of vasopressin that increases plasma levels of factor VIII and stimulates vascular endothelium to release the larger multimers of von Willebrand factor (vWF) (30). vWF mediates platelet adherence to vascular subendothelium by functioning as a protein bridge between glycoprotein Ib receptors on platelets and subendothelial vascular basement membrane proteins. DDAVP shortens the bleeding time of patients with mild forms of hemophilia A or von Willebrand disease (vWD) (30,31). Which patients might benefit from use of DDAVP? Patients with mild to moderate forms of hemophilia or vWD undergoing surgery are likely to benefit from its use. In addition, patients with uremic platelet dysfunction and patients with chronic liver disease undergoing major surgery may benefit. Mongan and Hosking reported that patients with a thromboelastogram (TEG) taken after protamine administration and with maximal amplitude $<$50 mm benefit from the effects of DDAVP (32). DDAVP administered IV at a dose of 0.3 mg/kg achieves maximal increases in levels of factor VIII and vWF in 30–60 min with no further increases achieved by higher doses. It should be diluted and given over 15–30 min to avoid hypotension. Side effects include hyponatremia with repeated dosing. Unfortunately, most studies do not demonstrate consistent efficacy of DDAVP (33).

Aprotinin

Aprotinin is a broad-spectrum serine protease inhibitor that inhibits factor XII, kallikrein, plasmin, and PAR1 receptors (34). In cardiac surgery when used prophylactically, multiple randomized, placebo-controlled trials on aprotinin safety and efficacy have demonstrated that aprotinin therapy reduces bleeding (i.e., mediastinal and chest tube drainage) and decreases the need for allogeneic transfusion, and the proportion of patients needing transfusion of allogeneic blood (35,36). Sedrakyan reported data from 35 CABG trials (n = 3879) confirming that aprotinin reduces transfusion requirements (relative risk 0.61) relative to placebo, with a 39% risk reduction, and was not associated with increased or decreased mortality (relative risk 0.96), myocardial infarction (relative risk 0.85), or renal failure (relative risk 1.01) risk, but it was associated with a reduced risk of stroke (relative risk 0.53). Aprotinin's mechanism of action is complex and may also involve reduction of the inflammatory response (37). Multiple mechanisms are responsible for aprotinin's ability to reduce bleeding after CPB and in other surgical procedures.

Aprotinin has also been studied in clinical trials in vascular, liver transplantation (38), and orthopedic surgery (28). Aprotinin decreased intra- and postoperative bleeding and blood transfusion in these settings. In orthopedic surgery, aprotinin moderately decreases blood loss and transfusion requirements during total hip replacement. One or two packed red cell units per patient may be saved when aprotinin is used. In a double-blind study in high-risk septic and cancer patients undergoing pelvic and hip surgery, aprotinin proved to be effective in significantly reducing the need for blood transfusion as compared with a placebo group. Samama et al. evaluated two doses of aprotinin with placebo after major orthopedic surgery and reported blood loss decreased in the Large-Dose Aprotinin group (calculated bleeding, whole blood, hematocrit 30%, median [range], 2023 mL [633–4113] as compared with placebo, 3577 mL [1670–21,758 mL]). The total number of homologous and autologous units was also significantly decreased in the Large-Dose Aprotinin group (2 U [0–5 U] as compared with placebo, 4 U [0–42 U]) (39).

APROTININ AND RECENT CONTROVERSIES

The NEJM reported an observational, nonrandomized database and subjected it to extensive statistical analyses (40). The FDA in an advisory reported that "Neither study was randomized, and both compared Trasylol to products that are not FDA approved for use in the management of cardiac surgery patients." The underlying question to any analysis using nonrandomized patients is why a patient receives a particular therapy (41–43). In observational studies, clinicians control the treatment assigned. The different groups evaluated may have large differences in their observed covariates, and these differences can lead to biased estimates of treatment effects (42). Propensity scoring reduces bias but does not eliminate it, and thus sicker patients receive different treatments. Factors that influence outcomes, including bypass times, exact aprotinin dosing, platelet transfusions, or anticoagulation, are not reported (40). Aprotinin is given to higher risk patients also at high risk for other complications. The association identified in the NEJM between patients in whom aprotinin was used and the

patients who had complications, but does not prove a cause-and-effect. The recent NEJM revisited these issues in November (Volume 355, November 30) with letters to the editor, a comment from the FDA, and a comment from the Editor. I would encourage everyone to read the original study and letters to the editor that followed. Current guidelines can be found at the FDA's Website (http://www.fda.gov/cder/drug/infopage/aprotinin/default.htm).

RECOMBINANT COAGULATION PRODUCTS

Coagulation products that are recombinant are used to manage bleeding in patients with hemophilia, vWD, or acquired inhibitors to antihemophilic factor (e.g., AHF concentrates, factor IX concentrates, factor VIIa concentrate, factor IX complexes, anti-inhibitor coagulant complexes) (44,45). These commercially available products are used to manage acute bleeding or to prevent excessive bleeding during cardiac and noncardiac surgery inpatient with hematologic disorders. Recombinant activated factor VIIa (rFVIIa; NovoSeven®, Novo Nordisk) has been used as a novel and effective treatment for patients with hemophilia with inhibitors for treating bleeding, and to secure hemostasis in complex clinical situations (46).

Recombinant factor VIIa produces a prohemostatic effect by forming a complex with tissue factor (TF) that is expressed locally at the site of injury, and locally initiates hemostatic activation (10). TF is a membrane-bound glycoprotein that is expressed on subendothelial cells after tissue injury and loss of endothelial protective mechanisms (47). Circulating FVIIa accounts for nearly 1% of circulating FVII, and is inactive until bound with TF (10). When rFVIIa is administered, it binds to TF that activates factor X to factor Xa, leading to the generation of thrombin (FIIa) and resulting fibrin formation and platelet activation (11). Giving rFVIIa to patients with multiple hemostatic abnormalities may result in added thrombin generation both on the surface of activated platelets and at the local site of injury (48).

Multiple publications are appearing reporting rFVIIa in surgical patients and cardiac surgical patients, including a recent reported analysis of the clinical studies (49). Other publications have reported the cessation of bleeding following major trauma with refractory hemorrhage and coagulopathy. Other reports have described the successful treatment of patients with refractory bleeding following cardiac surgery. Although rFVIIa has been reportedly used to treat a wide variety of coagulation defects, it is approved for patients with hemophilia who have inhibitors. We have reported its use in Jehovah Witnesses (50) and in complex patients with multifactorial bleeding (51). Further, therapeutic doses of recombinant factor VIIa are not established; different doses have been used during surgery in patients with hemophilia and inhibitors, and with refractory bleeding following cardiac surgery. Although 90 $\mu g \cdot kg^{-1}$ is usually the initial starting dose in patients with hemophilia, lower doses of 30–45 $\mu g \cdot kg^{-1}$ have been reported in surgical patients to be effective (52). Additional studies are needed to further evaluate dosing, safety, and efficacy in perioperative use of rFVIIa. However, guidelines are reported by Goodnough et al. (52) and Despotis et al. (53) for off label use in patients with life threatening hemorrhages.

THE FUTURE

The potential for bleeding after cardiac surgery and noncardiac surgery represents an ongoing problem for clinicians, and creates a need for multiple pharmacologic approaches. Current and future pharmacologic approaches to attenuating hemostatic system activation must be defined to decrease coagulopathy and the potential need for allogeneic blood administration, and to provide a mechanism to specifically produce hemostatic activation in the bleeding patient. Novel anti-inflammatory strategies are under investigation in cardiac surgery, targeting multiple pathways (i.e., kallikrein, complement, reperfusion injury) to reduce the bleeding. The increasing use of clopidogrel and newer anticoagulants will continue to pose new paradigms and potential problems in managing cardiac surgical patients. Newer therapies including recombinant factor VIIa as a therapy for refractory bleeding need to be considered as potential therapies.

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