Novel Concepts in Treatment and Prevention of Bleeding

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Perioperative patients often may have complex underlying hemostatic disorders because of tissue injury associated with surgery, an underlying disease state, or clot prevention therapy. Patients after trauma or complex injuries may also have coagulopathies attributable to multiple factors including hemorrhage, surgical injuries, or preexisting therapy including drugs that affect their hemostatic system. Hemostasis is a multifaceted inflammatory cascade with humoral and cellular elements that can be activated by multiple pathways (1–3). Patients after cardiopulmonary bypass also can develop major hemostatic alterations. Excessive postoperative bleeding can be attributable to multiple factors including hemodilution and activation of the coagulation, fibrinolytic, and inflammatory pathways (4–5).

Understanding hemostasis is also far more complex than knowing intrinsic and extrinsic hemostatic activation pathways taught in medical school. Hemostatic function involves multiple factors including release of tissue factor, generation of factor VIIa, platelet activation, and the complex cellular and humoral amplification that follows. Multiple causes are also involved in the pathogenesis of bleeding, but the interaction of platelets with coagulation factors including fibrinogen and the role of vascular injury together are three key elements in clotting (5–10).

Approaches to reduce bleeding and transfusion requirements in surgical 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, pentasaccharide (fondaparinux), platelet inhibitors (thienopyridines-clopidogrel or IIb/IIIa receptor antagonists), or new direct thrombin inhibitors (ximelagatran) also may potentiate bleeding. This review will focus on novel pharmacologic therapies and newer therapeutic approaches for bleeding.

Anticoagulation: New and Old Agents

Patients presenting for surgery may also be anticoagulated for deep vein thrombosis prophylaxis, to prevent pulmonary embolism, or for atrial fibrillation. Anticoagulation is based on inhibiting both thrombin activation and platelet activation (1–3). Thrombin is a potent procoagulant that forms fibrin from soluble fibrinogen, activating factors V and VIII and activating platelets. Activated platelets adhere to injured vascular endothelia, express IIb/IIIa receptors, aggregate, and further enhance generation of thrombin (6,7). Because of the complex humoral amplification system linking hemostatic and inflammatory responses, there are multiple pathways to produce thrombin and prothrombotic effects (8–10).

Unfractionated heparin is the most commonly used anticoagulant to prevent clotting, especially during surgery (11–13). Unfractionated heparin is a diverse mixture of polysaccharide chains ranging in molecular weight from approximately 3000 to 30,000 daltons. Heparin binds to antithrombin III enhancing the rate of thrombin-antithrombin III complex formation but also inhibits other steps in coagulation through acceleration of the reactions between antithrombin and thrombin or factor Xa (13). One of the advantages of heparin anticoagulation is that it can be reversed immediately by removing heparin from antithrombin III with protamine (14). Unfractionated heparin is also an important cause of heparin-induced thrombocytopenia.

Low molecular weight heparins are purified fragments of unfractionated heparin with a mean molecular weight of approximately 5000 (13). Both unfractionated heparin and low molecular weight heparins exert their anticoagulant activity by activating antithrombin (previously known as antithrombin III). Low molecular weight heparins have a longer half-life and dose-independent clearance; the recovery of anti-factor Xa activity approaches 100%, compared with approximately 30% with unfractionated heparin (13). The plasma half-life of low molecular weight heparins is two to four times as long as that of unfractionated heparin, ranging from 2–4 h after IV injection and from 3–6 h after subcutaneous injection (13). The inhibitory activity of low molecular weight heparins against factor Xa persists longer than their inhibitory activity against thrombin, reflecting the more rapid clearance of longer heparin chains. In contrast, unfractionated heparin is eliminated in two phases in a

dose-dependent fashion: a rapid, saturable phase reflecting hepatic uptake and a slower phase corresponding to renal clearance (13).

Newer agents include fondaparinux and ximelagatran. Fondaparinux is a synthetic antithrombotic agent with specific anti-factor Xa activity (15). Its pharmacokinetic properties allow for a simple, fixed-dose, once-daily regimen of subcutaneous injection, without the need for monitoring (15). In a dose-ranging trial involving patients with symptomatic proximal deep vein thrombosis, 7.5 mg of fondaparinux appeared to have efficacy and safety similar to those of a low molecular weight heparin (dalteparin) (15). Ximelagatran is an oral anticoagulant that directly inhibits thrombin and is not yet approved in the United States (16). Ximelagatran is the first orally available direct thrombin inhibitor. Ximelagatran is a prodrug for the active metabolite melagatran. Clinical studies have demonstrated ximelagatran to be comparable in efficacy to warfarin and low molecular weight heparins for prophylaxis of venous thromboembolism and comparable to warfarin for stroke prevention in the setting of atrial fibrillation. Adverse effects with ximelagatran mainly involve bleeding complications, which are more frequent than with placebo but are comparable to those occurring with standard anticoagulant treatment (i.e., warfarin and low molecular weight heparins) (16).

Reversing Anticoagulation

Unfractionated heparin, but not low molecular weight heparin, can be reversed by protamine, a basic polypeptide isolated from salmon sperm that neutralizes heparin by a nonspecific acid-base interaction (polyanionic-polycationic) (17). Anaphylaxis is one of the complications of protamine (18,19). Warfarin reversal can be performed with vitamin K or more acutely with fresh-frozen plasma. The other anticoagulants can potentially be reversed by other agents (e.g., recombinant factor VIIa).

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 clinical trials have been with the hemoglobin-based oxygen carriers that use purified and modified hemoglobins (20–22). Because free hemoglobin can produce potential adverse effects, the hemoglobin-based oxygen carriers have been structurally modified 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 (21–23). Only Hemopure is licensed for use (21). Hemopure is the only agent that has been approved, in South Africa. Hemopure uses glutaraldehyde to polymerize bovine hemoglobin followed by extensive purification and viral inactivation steps to produce Hemopure. Current studies have reported this agent for perioperative use as a oxygen bridge, decreasing the need for allogeneic red blood cells (24–26). In 1997, a veterinary formulation of their hemoglobin-based oxygen carrier, Oxyglobin, was licensed by the United States Food and Drug Administration for use in animals. One of the mechanisms by which hemoglobin-based oxygen carriers may be effective in reducing transfused blood may be a result of the fact that in hemorrhagic conditions; replenishing lost iron is difficult. 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 hemoglobin-based oxygen carrier solutions may be transient, they are rapidly metabolized, and free iron is potentially scavenged by multiple mechanisms to stimulate erythropoiesis and reticulocytosis. This may explain why patients were discharged with similar hematocrits in both groups despite the reduction in transfused allogenic packed erythrocytes in the hemoglobin-based oxygen carrier treated patients.

Aprotinin

Aprotinin is a broad-spectrum serine protease inhibitor isolated from bovine lung that inhibits multiple proteases including XII, kallikrein, plasmin, and protease activated receptors. 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) by 31%–81% and decreases the need for allogeneic transfusion by 35%–97% and the proportion of patients requiring transfusion of allogeneic blood by 40%–88% (27–29). Aprotinin's mechanism of action is complex and may also involve reduction of the inflammatory response (30). Multiple mechanisms are responsible for aprotinin's ability to reduce bleeding after cardiopulmonary bypass. Aprotinin is the most potent antifibrinolytic agent. The propagation of the "intrinsic" fibrinolysis through factor XII-mediated kallikrein activation and the generation of plasmin through "extrinsic" or t-PA-mediated activation of plasminogen is effectively inhibited by approximately 4 μmol/L of aprotinin, which is maintained in plasma with the high-dose regimen (31).

Aprotinin has also been studied in clinical trials in vascular, liver transplantation, and orthopedic surgery (32–43). Aprotinin decreased intraoperative 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 reducing the need for blood transfusion as compared with a placebo group. Samama et al. (42) 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], 2,023 mL [633–4,113] compared with placebo: 3,577 mL [1,670–21,758 mL]). The total number of homologous and autologous units was also decreased in the large-dose aprotinin group (2 U [0–5 U] compared with placebo: 4 U [0–42 U]).

Antifibrinolytic Agents and Desmopressin

Antifibrinolytic agents are synthetic lysine analogues that include ϵ-aminocaproic acid (Amicar) and tranexamic acid. These molecules inhibit fibrinolysis by attaching to the lysine-binding site of the plasminogen molecule, displacing plasminogen from fibrin. Levi et al. (29) performed a meta-analysis of all randomized, controlled trials of the three most frequently used pharmacological strategies to decrease perioperative blood loss (aprotinin, lysine analogues [aminocaproic acid and tranexamic acid], and desmopressin). Studies were included if they reported at least one clinically relevant outcome (mortality, re-thoracotomy, proportion of patients receiving a transfusion, or perioperative myocardial infarction) and perioperative blood loss. In addition, a separate meta-analysis was done for studies on complicated cardiac surgery. Seventy-two trials (8409 patients) met the inclusion criteria. Treatment with aprotinin decreased mortality almost twofold (odds ratio, 0.55; 95% confidence interval [CI], 0.34–0.90) compared with placebo. Treatment with aprotinin and with lysine analogues decreased the frequency of surgical re-exploration (odds ratio, 0.37; 95% CI, 0.25–0.55 and odds ratio, 0.44; 95% CI, 0.22–0.90, respectively). These two treatments also 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 analogues 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.

Recombinant Coagulation Products

Coagulation products that are recombinant are used to manage bleeding in patients with hemophilia, von Willebrand's disease, or acquired inhibitors to antihemophilic factor (e.g., AHF concentrates, factor IX concentrates, factor VIIa concentrate, factor IX complexes, anti-inhibitor coagulant complexes). These commercially available products are used to manage acute bleeding or to prevent excessive bleeding during cardiac and non-cardiac surgery in patients 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 the treatment of bleeding and to secure hemostasis in complex clinical situations (44,45).

Recombinant factor VIIa produces a prohemostatic effect by forming a complex with tissue factor that is expressed locally at the site of injury and locally initiates hemostatic activation. Tissue factor is a membrane-bound glycoprotein that is expressed on subendothelial cells after tissue injury and loss of endothelial protective mechanisms. Circulating FVIIa accounts for approximately 1% of circulating FVII and is inactive until bound with tissue factor (46). When rFVIIa is administered, it binds to tissue factor that activates factor X to factor Xa, leading to the generation of thrombin (FIIa) and subsequent fibrin formation and platelet activation (47,48). Administering rFVIIa to patients with multiple hemostatic abnormalities may result in additional thrombin generation both on the surface of activated platelets but also at the local site of injury (49–52). rFVIIa has been used in patients with cirrhosis, with normalization of prothrombin time (53).

Multiple publications are appearing reporting the off label application of rFVIIa in surgical patients. Slappendel et al. (54) reported that rFVIIa decreased postoperative bleeding after hip arthroplasty in a patient with alcohol-induced cirrhosis. Svartholm et al. (55) reported that rFVIIa diminished intraoperative bleeding associated with severe necrotizing pancreatitis after standard therapeutic measures had failed. Other publications have reported the cessation of bleeding following major trauma with refractory hemorrhage and coagulopathy (56,57). Other reports have described the successful treatment of patients with refractory bleeding following cardiac surgery (58–62). Although rFVIIa has been reportedly used to treat a wide variety of coagulation defects, it is currently approved for patients with hemophilia who have inhibitors. 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 μg/kg is usually the initial starting dose in patients with hemophilia, lower doses of 30–45 μg/kg have been reported to be effective in surgical patients (57–63). Additional studies are needed to further evaluate dosing, safety, and efficacy in perioperative use of rFVIIa.

The Future

The potential for bleeding in perioperative patients after cardiac 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 also 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 should be considered as potential therapies.

Suggested Web site: www.bleedingweb.com.

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