“Can’t You Do Something To Stop This Bleeding?”

Systemic Strategies For Reducing Blood Loss in Surgery

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Surgical procedures account for the transfusion of nearly 15 million units of red blood cells and 1.5 million platelet (PLT) transfusions per year in the United States.¹ Although the risk for transmission of viral diseases with transfusion decreased with the advent of improved screening of blood for pathogens, other adverse effects remain. These include transfusion reactions, immunomodulation, acute lung injury, fluid overload, and, in some cases, mortality.²⁻⁴ In the current environment of health care, in which cost containment has become of utmost importance, any intervention that will reduce perioperative bleeding and transfusion should be welcome. This review examines the pharmacologic therapies commonly employed to decrease surgical bleeding and transfusions.
Perioperative bleeding often is exacerbated by abnormalities that develop as a result of surgical trauma, component transfusion, and the activation of inflammatory and fibrinolytic cascades (Figures 1 and 2). Surgical patients often are treated for chronic conditions with anticoagulant medications that further complicate perioperative management.\(^5\)\(^-\)\(^7\) Because abnormal bleeding frequently results from derangement of the coagulation system and pharmacologic interventions typically focus on major aspects of this system, it is important to have a basic knowledge of hemostasis. Clinicians also must understand that, although hypercoagulability may be the major hemostatic problem that anesthesiologists address in the operating room, patients become hypercoagulable after surgery as a result of surgical stress, and thrombosis is more likely to produce a catastrophic complication such as myocardial infarction or pulmonary embolism. Thus, therapies that decrease bleeding preoperatively should have a relatively short duration of action to avoid exacerbating a prothrombotic state.

**Pharmacologic Interventions**  
Pharmacologic interventions to reduce bleeding and transfusion have been studied most often in cardiac and orthopedic surgeries and aim to either prevent or
reverse defects associated with coagulopathy (Table). Most prospective studies have focused on the effectiveness of individual drugs given prophylactically, although some, like recombinant factor VIIa (rFVIIa; NovoSeven, Novo Nordisk) are given primarily as rescue treatment when bleeding is excessive. Pharmacotherapy for decreasing bleeding and transfusion may be loosely categorized as antifibrinolytic and procoagulant. Surgeons also use topical agents intraoperatively; however, topical therapy to decrease surgical bleeding is outside the scope of this review.

**Antifibrinolytics**

Antifibrinolytics are the most common class of drugs used to improve hemostasis. These agents may be classified into 2 groups—lysine analogs and serine protease inhibitors.

**Lysine Analogs**

Epsilon aminocaproic acid (EACA; Amicar, Pfizer) and tranexamic acid (TA; Cyklokapron, Pfizer) are synthetic lysine analogs that inhibit fibrinolysis. EACA and TA competitively bind to lysine-binding sites of plasminogen and plasmin. Blockade of these sites prevents activation of the proenzyme plasminogen to the active fibrinolytic enzyme plasmin. EACA binds to plasmin to a lesser degree at a higher dose, and inhibits plasmin from digesting fibrinogen and fibrin. TA is 10 times more potent than EACA and approximately 100 times more expensive in the United States, although both drugs are available in generic forms. TA also may improve hemostasis by preventing plasmin-induced PLT activation. EACA is approved by the FDA to enhance hemostasis when fibrinolysis contributes to bleeding. TA is approved for the short-term treatment or prevention of dental bleeding in hemophiliacs. Lysine analogs are water-soluble molecules that distribute readily into extravascular water spaces. EACA is largely excreted intact by the kidneys, and approximately 35% undergoes hepatic metabolism to the metabolite adipic acid. Renal clearance of the compound approximates endogenous creatinine clearance. The terminal elimination half-life of EACA is 1 to 2 hours. The pharmacokinetics of TA are similar to those of EACA.

![Figure 2. The fibrinolytic system.](image-url)
Dosage protocols for lysine analogs for bleeding prophylaxis have not been standardized. Dosing schemes vary widely, particularly for patients undergoing cardiac and orthopedic surgeries, and are not based on pharmacologic principles. Doses for EACA in cardiac surgery may involve the administration of a loading dose of between 75 and 150 mg/kg before cardiopulmonary bypass (CPB), followed by continuous infusion of 10 to 25 mg/kg per hour. Butterworth et al studied the pharmacokinetics of EACA in cardiac surgery with CPB and found that a loading dose of 75 mg/kg followed by maintenance infusion of 25 mg/kg per hour should produce adequate blood levels of the drug throughout surgery.11

In clinical trials of patients undergoing cardiac surgery, loading doses of TA have ranged from 10 to 30 mg/kg followed by infusion of 1 to 16 mg/kg per hour.12-19 Pharmacokinetic data suggest that the maintenance dose (mg/kg/h) should be close to or the same as the loading dose (in mg/kg) to obtain stable levels during CPB. The plasma level of TA required to inhibit fibrinolysis is unclear. Although many study protocols have used 100 mcg/mL as the minimal plasma concentration required for complete inhibition of fibrinolysis, more recent data suggest that much lower levels—17.5 mcg/mL in adults—are effective, and indicate that a lower dose should be effective. This finding is important given the association between high doses of TA and seizures.20

Efficacy

Numerous studies evaluating the effects of EACA and TA have been published across a variety of patient populations. A recent review found nearly 100 such studies of TA alone.21 Although most clinical research on TA and EACA has been conducted in patients undergoing cardiac and orthopedic surgeries, the drugs also have been evaluated in craniofacial, gynecologic, hepatic, urologic, and vascular surgeries.

TA and EACA repeatedly have been found to be effective in reducing bleeding and transfusion in adult and pediatric cardiac surgeries. A 2011 Cochrane review included more than 250 studies of TA and EACA, as well as aprotinin (Trasylol, Bayer), including 34 trials of TA and 11 of EACA in cardiac surgery.22 Despite large variability in dosing, both drugs had clinically significant efficacy in reducing transfusion by about 30%.

Trials of TA and EACA in orthopedic surgery have focused primarily on spine surgery and total knee and hip arthroplasty.23 In total joint arthroplasty, TA reduced the risk for transfusion by 53%, and EACA by 36%. Again, disparities in dosing protocols may explain the apparent difference in efficacy more than actual differences in the medication. A 2008 meta-analysis of the use of antifibrinolytic agents in spine surgery found a reduction of about 50% in the risk for transfusion among patients who received TA or EACA,24 although a recent randomized placebo-controlled study in adults undergoing spine surgery found no difference in transfusion associated with use of TA. Two other recent studies did find TA25 and EACA26 to be effective in pediatric spine surgery for scoliosis.

Efficacy almost certainly depends on the complexity of the surgery, and the baseline risk for bleeding and transfusion. Dosing regimens that can be predicted to produce subtherapeutic plasma levels also may play a role.

Two recent studies have shown marked decreases (66%-75%) in the incidence of transfusion in children undergoing surgery for craniosynostosis.27,28 Another recent study,29 which included open and minimally invasive craniosynostosis repair, did not find TA to be effective; in this trial, all patients were transfused.

Multiple studies have shown a decrease in transfusion requirements in liver transplant surgery in patients treated with EACA and TA. Concerns remain about thrombotic complications, particularly thrombosis of the freshly anastomosed hepatic artery. However, the data do not support any increased risk.30

TA also has been studied in trauma patients.31 CRASH-2 (Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage) is a large (>20,000 patients) placebo-controlled trial of the effects of TA on mortality, vascular occlusive events, and transfusions in trauma patients. The results show that the early administration of the drug to these patients reduces their risk for death from hemorrhage with no increase in vascular occlusive events. Use of TA also
was associated with a significant reduction in all-cause mortality, likely due to the decrease in bleeding and transfusion and transfusion-associated complications. Fewer data are available for other operations; TA and EACA appear to be effective in cesarean delivery, gynecologic surgery, radical prostatectomy, and tonsillectomy.32–35

Adverse Effects

EACA and TA have not been studied in large, multicenter randomized controlled trials (RCTs) powered to evaluate safety. However, in small studies the drugs appear generally not to promote severe adverse effects.36

Both EACA and TA can cause hypotension when given as rapid IV bolus. EACA can cause rhabdomyolysis, myonecrosis, anion gap acidosis, upper urinary tract thrombosis, and hyperkalemia.14,36 Lysine analogs have not been associated with an increase in incidence of renal dysfunction or mortality in cardiac surgery.37 Thromboembolic complications, such as reduced early graft patency, stroke, deep vein thrombosis, pulmonary embolus, and myocardial infarction, are theoretically possible. But focused reviews and meta-analyses have not found such association.37 Large retrospective studies have consistently reported an increased risk for seizures with higher doses of TA compared with other antifibrinolytics and placebo.38–40

Serine Protease Inhibitors

Aprotinin

Serine proteases are ubiquitous enzymes responsible for coordinating a wide variety of physiologic functions. The nonspecific serine protease inhibitor (serpin) aprotinin was in widespread use in cardiac surgery between FDA approval in 1993 and removal from the market in 2007. It also saw use in other surgical applications such as liver transplantation and orthopedic surgery. Although it was withdrawn from the United States market following a large Canadian trial showing an increase in mortality relative to lysine analog antifibrinolytics,41 the drug remains controversial. Both Canadian and European regulatory agencies recently withdrew their prohibition against the marketing of aprotinin.

Aprotinin inhibits several serine proteases, including trypsin, plasmin, plasma kallikrein, and tissue kallikrein. It also inhibits the contact phase activation of coagulation that initiates coagulation and fibrinolysis, and has minor inhibitory effects on the intrinsic pathway coagulation factors. Aprotinin also exerts an indirect preservative effect on PLT function during CPB.36

Aprotinin was extensively studied in cardiac surgery patients and found to significantly decrease blood loss and transfusion in adults and children. Comparison studies with the lysine analogs typically demonstrated superiority of aprotinin, particularly in high-risk patients. Multiple RCTs of aprotinin also demonstrated safety, but beginning in 2006, 3 retrospective studies found an increase in serious adverse events associated with the drug, resulting in an FDA advisory. When the Canadian prospective RCT showed an increase in mortality in patients treated with aprotinin, the FDA decided to remove the drug from the market.

Nafamostat

Nafamostat mesilate is a synthetic serpin used in Japan since 1981.42 It is not approved in the United States. Nafamostat inhibits thrombin, factors Xa and XIIa, kallikrein, plasmin, and complement factors (C1r, C1s). Nafamostat also preserves PLT function and attenuates systemic inflammatory response. The drug has been investigated as an anticoagulant in extracorporeal circuits and as a hemostatic agent in cardiac surgery. Several studies conducted in Japan reported a significant reduction in postoperative blood loss in cardiac surgery.43 Large RCTs are needed to define its role in the perioperative period.

Ecallantide

Ecallantide (Kalbitor, Dyax) is a recombinant human peptide derived from tissue factor pathway inhibitor. The drug is FDA-approved for the treatment of hereditary angioedema. Ecallantide inhibits plasma kallikrein with high affinity, and plasmin with lesser effect. Early clinical data demonstrated that ecallantide decreases blood loss and need for transfusion in patients undergoing cardiac surgery.44 However, a recent trial comparing ecallantide with TA in high-risk cardiac surgery patients showed TA to be superior in decreasing blood loss and transfusion, with higher 30-day mortality in the patients receiving ecallantide.45

Procoagulant Drugs

Desmopressin

Desmopressin acetate (DDAVP, Sanofi-Aventis) is a synthetic vasopressin analog that stimulates the release of factor VIII and von Willebrand factor from the endothelium into the plasma, where they enhance PLT aggregation.15 DDAVP is FDA-approved for treatment of hemophilia A and type I von Willebrand’s disease. The drug is contraindicated in type IIB von Willebrand’s as it will cause thrombocytopenia. The recommended dose of DDAVP is 0.3 mcg/kg, and it should be administered slowly to avoid inducing hypotension. DDAVP also has been used in patients with uremia, cirrhosis, or aspirin-associated bleeding.46,47

The effectiveness of DDAVP for the prevention or treatment of perioperative bleeding in patients without known PLT disorders is not well established. DDAVP has not been consistently shown to reduce perioperative blood loss, and is associated with thrombosis and myocardial infarction in unselected cardiac surgery patients.30 Selected patients with demonstrated PLT defects may be responsive to DDAVP.49 Evidence does not support its prophylactic use in hemostatically normal patients undergoing elective noncardiac surgical procedures.
Recombinant Factor VIIa Concentrate

rFVIIa is FDA-approved for the management of bleeding related to hemophilia in patients with factor inhibitors. rFVIIa enhances the natural coagulation pathway through the formation of tissue factor-factor VIIa complex at the site of endothelial damage. It binds to the phospholipid membranes of activated PLTs, where it activates factor X independent of the tissue factor pathway. The result is a massive rise in thrombin generation at the surface of the PLTs. Because of its short half-life (2.7 hours), rFVIIa must be given as boluses that may be repeated every 2 hours (until bleeding stops) or as a continuous infusion. Recommended doses range from 15 to 90 mcg/kg. Increasing doses are associated with improved effectiveness, but are likely to carry a higher risk for thrombosis, which, along with its high cost, are the major caveats for use of this compound.

The off-label use of rFVIIa may be effective in certain settings, such as in cases of intracranial hemorrhage, life-threatening bleeding, or as rescue therapy when excessive bleeding does not respond to routine hemostatic therapy. rFVIIa does not produce clots on its own. As a result, the drug should be administered only after patients have been transfused with adequate products to replenish clotting factors, including PLTs and fibrinogen. Although the literature is replete with case reports and small retrospective series showing apparently successful treatment of life-threatening bleeding, large, prospective studies demonstrating the safety and effectiveness of rFVIIa are lacking. Moreover, considerable evidence indicates that off-label use of the drug can cause catastrophic thrombotic complications. The application of rFVIIa for serious hemorrhage should be restricted to situations in which the risk for continued bleeding unresponsive to transfusion therapy clearly outweighs the risk for serious thrombotic complications.

Prothrombin Complex Concentrates

Prothrombin complex concentrates (PCCs) are pooled factor concentrates of human origin and contain the vitamin K-dependent clotting factors II, VII, IX, and X. Although originally developed and approved for treatment of hemophilia B (factor IX deficiency), PCCs most often are used to reverse the effects of warfarin anticoagulation. Two 4-factor PCCs are approved for use in the United States: Bebulin VH (Baxter) and Profilnine (Grifols). Compared with fresh frozen plasma, these drugs have smaller infusion volumes to reverse warfarin-induced coagulopathy, are more effective, and do not require cross matching. Although PCCs have been used to treat coagulopathic bleeding with some evidence of success, there is insufficient evidence of their safety and effectiveness in conditions other than bleeding resulting from warfarin anticoagulation or known factor deficiencies. Thrombosis and high cost also are major considerations for the use of PCCs.

Conclusions

Anesthesiologists often are asked by their surgical colleagues to administer medication to treat excessive bleeding. Although some agents may decrease blood loss in appropriate cases, it is important to understand the risks and limitations of each drug before it is given to a patient. It also is important to remind the surgeon to first rule out surgical bleeding; no drug is a substitute for surgical hemostasis. The majority of these drugs are used perioperatively outside their FDA indications, and may have unknown safety issues. The search for ideal pharmacologic agents to reduce perioperative bleeding continues, and to date no single universal pharmacologic agent is available to solve the problem of excess perioperative bleeding and transfusion. Although PCCs and rFVIIa may be useful in certain settings, the best data exist for the lysine analog antifibrinolitics. Large safety trials and dose-finding studies for EACA and TA are warranted. TA has emerged as a potential lifesaving drug for trauma patients, and the CRASH-3 study may show similar results for patients with traumatic brain injury.

References

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