REVIEW ARTICLE

DRUG THERAPY

Prevention and Treatment of Major Blood Loss

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In a medical setting, surgery is the most common cause of major blood loss, defined as a loss of 20% of total blood volume or more. In particular, cardiovascular procedures, liver transplantation and hepatic resections, and major orthopedic procedures including hip and knee replacement and spine surgery, are associated with severe bleeding. Excessive blood loss may also occur for other reasons, such as trauma. Indeed, bleeding contributes to approximately 30% of trauma-related deaths.[1] Bleeding in critical locations, such as an intracerebral hemorrhage, may also pose a major clinical challenge.

Severe bleeding often requires blood transfusion. Even when the benefits of transfusion outweigh the risks (e.g., mismatched transfusion, allergic reactions, transmission of infections, and acute lung injury),[2] strategies to minimize the use of limited resources such as blood products are essential. The most obvious and probably the most effective strategy is to improve surgical and anesthetic techniques. For example, liver transplantation, a procedure that once required transfusion of large amounts of blood products, now has relatively small transfusion requirements in most instances.

Ruling out abnormalities of hemostasis in a patient with bleeding is also essential, because such problems can often be corrected by replacing the defective components of the hemostatic system. However, cases of excessive blood loss in which no surgical cause or abnormalities in hemostasis can be identified require pharmacologic strategies, which can be broadly divided into preoperative prophylaxis for operations that confer a high risk of bleeding and interventions for massive, refractory bleeding. The medications that have been most extensively evaluated as hemostatic agents include the antifibrinolytic lysine analogues aminocaproic acid and tranexamic acid; aprotinin, a bovine-derived protease inhibitor; and desmopressin, a synthetic analogue of the antidiuretic hormone that raises the plasma levels of factor VIII and von Willebrand factor.[3] In addition, recombinant activated factor VII appears to be efficacious in an array of clinical situations associated with severe hemorrhage.[4] The safety of aprotinin, the most widely used of these agents, has been questioned because of concerns about renal and cardiovascular adverse events.[5]

Most trials of hemostatic agents have been designed to assess therapeutic efficacy, but they were not optimally designed to assess potential toxic effects, so definitive safety data are lacking for all hemostatic agents. Many trials of these agents have used perioperative blood loss and other measures that are not the most clinically relevant end points, and many published trials were not powered to assess more clinically relevant outcomes such as mortality or the need for reoperation. We review the therapeutic benefits of hemostatic drugs and consider the risk of adverse events. In particular, we consider thrombotic complications, which constitute a major concern when agents that potentiate hemostasis are administered.

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ANTIFIBRINOLYTIC AGENTS

Approximately 5% of patients undergoing cardiac surgery require reexploration because of excessive blood loss; indeed, bleeding during and after cardiac surgery is an established marker of increased morbidity and mortality.[6-8] Pharmacologic strategies are therefore often used to minimize blood loss during cardiac surgery. Aprotinin (a direct inhibitor of the fibrinolytic enzyme plasmin) is the only drug reported to minimize transfusion requirements in coronary-artery bypass grafting and approved by the Food and Drug Administration (FDA). Aminocaproic acid and tranexamic acid are also used, but they have not been approved by the FDA for this indication. The mechanism of action of these agents is illustrated in Figure 1. Table 1 lists the most frequently used dosages of antifibrinolytic agents.

EFFICACY OF ANTIFIBRINOLYTIC AGENTS

After the first study in 1987,[9] more than 70 randomized, controlled trials that included from 20 to 796 patients (median, 75) confirmed and established the efficacy of aprotinin for limiting the requirements for transfusion of red cells, platelets, and fresh-frozen plasma in patients undergoing cardiac surgery. We examine in depth four trials chosen for their size and design.

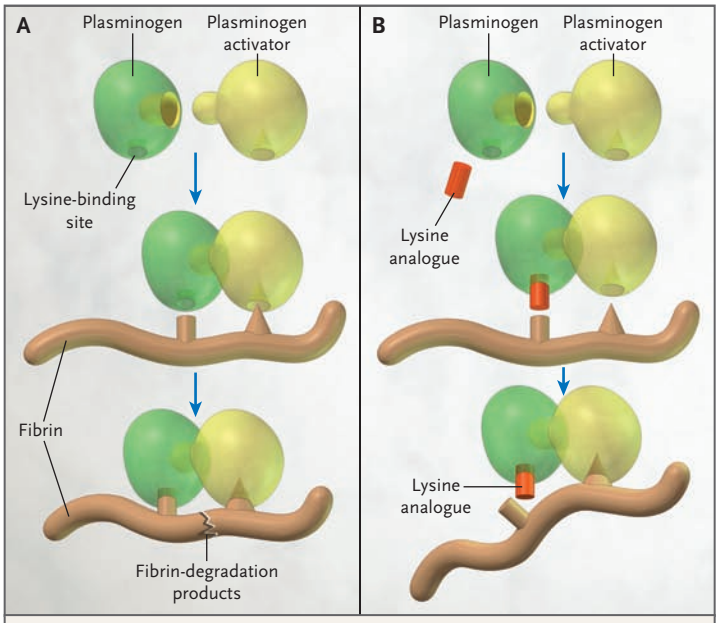

Figure 1. Mode of Action of Lysine Analogues (Aminocaproic Acid and Tranexamic Acid).

Activation of plasminogen by endogenous plasminogen activators results in plasmin, which causes degradation of fibrin. Binding of plasminogen to fibrin makes this process more efficient and occurs through lysine residues in fibrin that bind to lysine-binding sites on plasminogen (Panel A). In the presence of lysine analogues, these lysine-binding sites are occupied, resulting in an inhibition of fibrin binding to plasminogen and impairment of endogenous fibrinolysis (Panel B).

In a study of 796 patients who were randomly assigned to receive aprotinin or placebo during primary coronary-artery bypass grafting, aprotinin was associated with reduced blood loss (mean [±SD], 664±1009 ml, vs. 1168±1022 ml in the placebo group). Aprotinin also was associated with a decreased rate of use of any blood product (40%, vs. 58% in the placebo group).[10] In a randomized, placebo-controlled trial involving 704 patients, treatment with aprotinin was associated with a decrease in mean perioperative blood loss (832±50 ml, vs. 1286±52 ml in the placebo group) and a reduction in the proportion of patients requiring any transfusion (35% vs. 55%).[11] Two trials recruited patients who were at increased risk for bleeding because they were undergoing repeat cardiac surgery.[12,13] On average, patients who received aprotinin needed between 1.6 and 2 units of blood products, whereas patients who received placebo needed between 10 and 12 units.[12,13] Similar findings with aprotinin have been reported in many other placebo-controlled trials, with a reduction in perioperative blood loss ranging from 50 to 1350 ml (median reduction, 400 ml) and a reduction by a factor of 1.5 to 3 in the proportion of patients requiring any transfusion.[14-25]

Randomized trials of tranexamic acid or aminocaproic acid are much less numerous than trials of aprotinin.[26-31] In the largest trial of tranexamic acid, 210 patients were randomly assigned to receive tranexamic acid (at a dose of 10 g) or placebo. Administration of tranexamic acid resulted in a 69% reduction in red-cell transfusions, and the proportion of patients requiring any blood product was 12.5% in the tranexamic acid group as compared with 31.1% in the control group.[31]

There have also been meta-analyses and systematic reviews of the efficacy of antifibrinolytic agents.[32-36] Table 2 summarizes the results of a Cochrane review. As compared with placebo, the use of aprotinin or tranexamic acid, but not of aminocaproic acid, reduced the need for blood transfusion by 30% and saved approximately 1 unit of blood per operation.[36] There was no difference in efficacy between low-dose and high-dose regimens of aprotinin (Table 1), whereas the large

variations in dosages of tranexamic acid and aminocaproic acid precluded the evaluation of the relationship between dosage and efficacy. In terms of more clinically relevant events, the relative risk of reoperation for excessive bleeding was significantly reduced among patients who received aprotinin, as compared with those who received placebo, although mortality was not affected. There was a significant reduction in these events with either tranexamic acid or aminocaproic acid.[36]

Thus, the results of controlled trials and reviews indicate that antifibrinolytic drugs are effective hemostatic agents in cardiac surgery. Reductions in both transfusion requirements and reoperation for bleeding appear to be confirmed by the narrow confidence intervals of the odds ratios that are indicators of the relative risks (Table 2). There are not enough efficacy data to draw definitive conclusions regarding the use of antifibrinolytic agents in other situations.

SAFETY OF ANTIFIBRINOLYTIC AGENTS

There have been criticisms that many trials of the efficacy of aprotinin in cardiac surgery were unnecessarily carried out (and reported) after the transfusion-sparing efficacy was unequivocally established and that such studies should have focused instead on the more cogent and unsettled issue of safety.[37,38] Adverse events, particularly thrombotic complications, are expected when a major regulatory system such as the fibrinolytic system is pharmacologically inhibited; this is especially true in patients undergoing cardiac surgery, because they often have underlying atherothrombotic disease.

Table 3, which summarizes the risks of complications when antifibrinolytic agents are administered, shows that none of the adverse events examined was significantly increased.[36] However, a few early studies indicated that the use of aprotinin could lead to an increase in cases of postoperative renal dysfunction, possibly through the inhibition of kallikrein and other endogenous vasodilators, with a resultant reduction of renal blood flow.[24,39,40]

The risk of serious adverse events associated with aprotinin was recently highlighted by the results of a nonrandomized, observational study involving 4374 patients who underwent elective coronary-artery bypass surgery.[5] That study, which compared aprotinin, aminocaproic acid, and tranexamic acid with no treatment, used the propensity-score adjustment method to balance the covariates and thus reduce bias that could arise if sicker patients selectively received one agent over another. The results indicated that, as compared with no treatment, aprotinin (but neither aminocaproic acid nor tranexamic acid) doubled the risk of severe renal failure, increased the risk of myocardial infarction or heart failure by 55%, and was associated with a nearly doubled increase in the risk of stroke or other cerebrovascular events. That study confirmed that the three antifibrinolytic agents reduced blood loss to a similar degree, but adverse events were much more frequent with aprotinin than with the other agents. Much debate followed the publication of the study,[41-44] which was criticized on the grounds that it was observational, was carried out in many different countries and institutions, and was poorly controlled with respect to known determinants of outcome such as the use or nonuse of antithrombotic and inotropic drugs, the duration of cardiopulmonary bypass, and the amounts of blood transfused.

However, other recent studies have also reported adverse renal effects of aprotinin. A review of randomized trials conducted from 1991 to 2005

Table 1. Mechanism of Action and Intravenous Doses of Antifibrinolytic Agents Used in Cardiac Surgery to Minimize Blood Loss and Transfusion Requirements.

Agent	Mechanism of Action	Recommended Dosages
Aprotinin	Directly inhibits the fibrinolytic enzyme plasmin, plasma and tissue kallikrein, trypsin, and activated coagulation factor XII	High (total, 700 mg or more); low (any dose smaller than 700 mg) Loading dose at induction of anesthesia, 280 mg Maintenance dose during surgery, 70 mg/hour Pump priming dose, 280 mg (optional)
Aminocaproic acid	Inhibits binding of plasmin to fibrin by occupying the lysine-binding sites of the proenzyme plasminogen	Total, 10–30 g Loading dose at induction of anesthesia, 1–15 g Maintenance dose during surgery, 1–2 g/hr
Tranexamic acid	Acts like aminocaproic acid but is approximately 10 times more potent than aminocaproic acid on a molar basis	Total, 3–10 g Loading dose at induction of anesthesia, 2–7 g Maintenance dose during surgery, 20–250 mg/hr

Table 2. Results of the Cochrane Review of the Effect of Antifibrinolytic Agents on Clinical Events among Patients Undergoing Major Surgical Procedures.*

Comparison	Event	No. of Trials	No. of Patients Who Received Drug/ No. of Controls	Relative Risk of Event (95% CI)
Aprotinin vs. control	Need for allogeneic transfusion	61	4055/2972	0.70 (0.64–0.76)
	Need for reoperation because of bleeding	29	1758/1142	0.40 (0.25–0.66)
	Death	28	2828/2085	0.87 (0.63–1.19)
Tranexamic acid vs. control	Need for allogeneic transfusion	18	758/584	0.66 (0.54–0.81)
	Need for reoperation because of bleeding	9	423/351	0.72 (0.29–1.79)
	Death	11	419/346	0.43 (0.15–1.18)
Aminocaproic acid vs. control	Need for allogeneic transfusion	4	106/102	0.48 (0.19–1.19)
	Need for reoperation because of bleeding	5	306/316	0.32 (0.07–1.39)
	Death	4	288/296	1.66 (0.46–6.01)
Tranexamic acid vs. aprotinin	Need for allogeneic transfusion	7	202/272	1.21 (0.83–1.76)

* Most of the patients were undergoing cardiac surgery. Data are from Henry et al.[36] CI denotes confidence interval.

reported that patients who received aprotinin had a 9% rate of renal failure (defined as the need for dialysis or a postoperative increase in the serum creatinine level of at least 2.0 mg per deciliter [176.8 μmol per liter]) and that renal dysfunction (defined as an increase in creatinine of 0.5 to 1.9 mg per deciliter [44.2 to 168.0 μmol per liter]) occurred in 12.9% of patients receiving aprotinin as compared with 8.4% of controls (relative risk, 1.47; 95% confidence interval [CI], 1.12 to 1.94; P<0.001).[41] An observational survey commissioned by the manufacturer showed similar rates of renal dysfunction and renal failure among 67,000 patients who received aprotinin.[45]

Although Mangano et al.[5] and the authors of previous systematic reviews report that aminocaproic acid and tranexamic acid appear to be relatively safe,[32-36] the numbers of trials and study participants were much smaller for these drugs than for aprotinin. Thus, confidence with regard to safety issues is not solid, especially with respect to thrombosis. Most important, trials comparing aprotinin with lysine analogues have been too few and too small.[46-49] An independently funded, randomized clinical trial with three study groups is being conducted in Canada. The Blood Conservation using Antifibrinolytics: A Randomized Trial in a Cardiac Surgery Population (BART) study, which is still enrolling patients, plans to enroll 2970 patients undergoing high-risk cardiac surgery to determine whether aprotinin is superior to aminocaproic acid or tranexamic acid in reducing the risk of massive postoperative bleeding.[50] Secondary end points are mortality from all causes and adverse events such as cardiovascular disease and renal failure.[50]

On the basis of all the data reported thus far, there is abundant, solid evidence that aprotinin reduces perioperative and early postoperative blood loss and transfusion requirements in patients undergoing cardiac surgery. However, despite the large number of clinical trials involving this agent, its effectiveness in decreasing the need for reoperation has been reported only in reviews,[36] and evidence of its effect on mortality is lacking. It is regrettable that the inexpensive lysine analogues have been less thoroughly investigated as of this writing, because it appears likely that these agents are at least as efficacious as aprotinin. The uncertainty about aprotinin's safety remains a substantial concern. Until the results of the Canadian trial are available,[50] aprotinin remains the hemostatic agent of choice. However, it should be used only when excessive perioperative and early postoperative blood loss is predicted (e.g., in the case of a complex operation or special clinical circumstances such as the use of antiplatelet agents).

Evidence of the efficacy of lysine analogues is not as solid as that for aprotinin, so these agents should be used only as a second choice in high-risk cardiac surgery. There is definitely no role for either aprotinin or other hemostatic agents in noncomplex coronary-artery bypass surgery, even though in many cases an off-pump procedure is used, which reduces blood loss and transfusion requirements.[51,52] The FDA has warned that it is

Table 3. Results of the Cochrane Review of the Effect of Antifibrinolytic Agents on Adverse Events among Patients Undergoing Major Surgical Procedures.*

Comparison	Event	No. of Trials	No. of Patients Who Received Drug/ No. of Controls	Relative Risk of Event (95% CI)
Aprotinin vs. control	Myocardial infarction	20	1871/1117	0.97 (0.69–1.36)
	Stroke	8	605/373	0.43 (0.16–1.19)
	Any thrombotic event	15	1305/745	0.64 (0.31–1.31)
	Renal failure or dysfunction	13	2210/1566	1.19 (0.79–1.79)
Tranexamic acid vs. control	Myocardial infarction	8	391/316	0.69 (0.21–2.29)
	Stroke	6	406/306	2.27 (0.65–7.99)
	Any thrombotic event	12	561/449	0.98 (0.49–1.94)
	Renal failure or dysfunction	2	121/119	0.87 (0.08–9.78)
Aminocaproic acid vs. control	Myocardial infarction	3	267/277	0.90 (0.30–2.76)
	Stroke	4	288/296	0.26 (0.03–2.36)
	Any thrombotic event	2	97/97	0.20 (0.01–4.14)

* Most of the patients were undergoing cardiac surgery. Data are from Henry et al.[36] CI denotes confidence interval.

important to monitor patients receiving aprotinin for renal, cardiac, and brain toxic effects and that aprotinin should be used only when the clinical benefit of reducing blood loss is essential to medical management and outweighs any risk.[53]

RECOMBINANT ACTIVATED FACTOR VII

Recombinant activated factor VII (rFVIIa) is thought to act locally at the site of tissue injury and vascular-wall disruption by binding to exposed tissue factor, generating small amounts of thrombin that are sufficient to activate platelets[4] (Fig. 2). The activated platelet surface can then form a template on which rFVIIa directly or indirectly mediates further activation of coagulation, ultimately generating much more thrombin and leading to the conversion of fibrinogen to fibrin.[54,55] Clot formation is stabilized by the inhibition of fibrinolysis due to rFVIIa-mediated activation of thrombin-activatable fibrinolysis inhibitor.[56]

EFFICACY OF rFVIIa

Initially, rFVIIa was licensed for the treatment of bleeding in patients with hemophilia who had antibodies inactivating factor VIII or IX.[4] More recently, this agent has been used extensively in patients with major hemorrhage from surgery, trauma, or other causes.[57] A small, controlled clinical trial showed that rFVIIa could minimize perioperative blood loss and transfusion requirements in patients undergoing transabdominal prostatectomy, an operation that is often associated with major blood loss.[58] In that trial, 36 patients were randomly assigned to receive a single preoperative injection of rFVIIa (20 or 40 μg per kilogram of body weight) or placebo. Administration of the active drug resulted in a significant reduction of blood loss (50%) and eliminated the need for transfusion, which was required in approximately 60% of patients who received placebo.[58]

Additional studies have focused on patients undergoing orthotopic liver transplantation. An open-label pilot study involving six patients showed a marked reduction in transfusion requirements among those who received a single dose of rFVIIa (80 μg per kilogram) as compared with matched historical controls.[59] However, a subsequent randomized, placebo-controlled trial evaluating two different doses of rFVIIa (60 and 120 μg per kilogram) showed no reduction in transfusion requirements among 182 liver-transplant recipients, although red-cell transfusion was averted in 8.4% of patients who received rFVIIa but in none of the patients in the placebo group.[60] Two randomized, controlled trials of rFVIIa (up to 100 μg per kilogram at every second hour of surgery) in patients with cirrhosis or normal liver function who were undergoing major liver resection did not show a significant effect of rFVIIa on either the volume of blood products administered or the percentage of patients requiring transfusion.[61,62]

In addition, rFVIIa was evaluated in a randomized, controlled study involving 20 patients undergoing noncoronary cardiac surgery requiring cardiopulmonary bypass.[63] Administration of rFVIIa at a dose of 90 μg per kilogram after discontinuation of bypass significantly reduced the need for blood transfusion (relative risk of any transfusion,

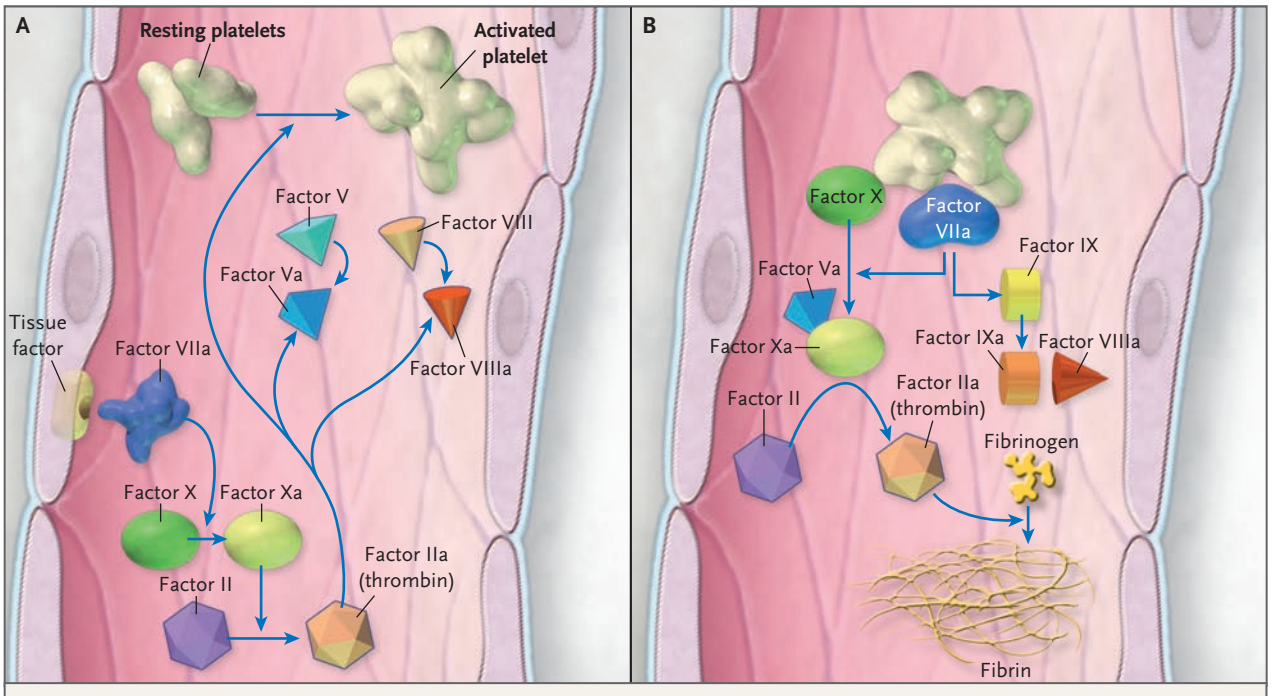

Figure 2. Mechanism of Action of Recombinant Factor VIIa.

When the vessel wall is disrupted, subendothelial tissue factor becomes exposed to circulating blood and may bind factor VIIa (Panel A). This binding activates factor X, and activated factor X (factor Xa) generates small amounts of thrombin. The thrombin (factor IIa) in turn activates platelets and factors V and VIII. Activated platelets bind circulating factor VIIa (Panel B), resulting in further factor Xa generation as well as activation of factor IX. Activated factor IX (factor IXa) (with its cofactor VIIIa) yields additional factor Xa. The complex of factor Xa and its cofactor Va then converts prothrombin (factor II) into thrombin (factor IIa) in amounts that are sufficient to induce the conversion of fibrinogen to fibrin.

0.26; 95% CI, 0.07 to 0.90). In addition, a propensity score–matched, case–control study involving 51 patients with massive blood loss after cardiac surgery showed a significant decrease in blood loss and requirements for blood products after the administration of rFVIIa (at a dose of 35 to 70 μg per kilogram).[64] In this study, however, the incidence of acute renal dysfunction among patients receiving rFVIIa was 2.4 times that in the control group, although there were no significant differences between the two groups with regard to other adverse events.[64]

Several case reports and case series suggest that rFVIIa is also useful in reducing major blood loss in patients with trauma.[65] A placebo-controlled trial involving 143 patients with severe blunt trauma showed that three successive doses of rFVIIa (200, 100, and 100 μg per kilogram) significantly reduced red-cell transfusion (mean reduction, 2.6 units) and reduced the proportion of patients in whom massive transfusion, defined as more than 20 units of red cells, was required (14% of treated patients vs. 33% of controls).[66] However, a parallel trial involving 134 patients with penetrating trauma showed no significant effects.[66]

Studies have also evaluated rFVIIa for the treatment of spontaneous intracranial hemorrhage, a condition for which there is a paucity of effective therapeutic options.[67] A dose-finding trial involving 400 patients showed that as compared with placebo, rFVIIa was associated with a slower increase in the size of intracerebral hematoma. More important, there was a 35% reduction in mortality and an improved disability score at 90 days in patients who received rFVIIa.[67] Unfortunately, these promising early results were not confirmed in a subsequent phase 3, randomized, controlled trial involving 821 patients.[68] A preliminary report indicated that there was a significant reduction in the size of the intracerebral hematoma but with no effect on mortality and severe disability on day 90, the primary end point of the study.[68] The manufacturer has not sought regulatory approval for rFVIIa for the treatment of intracerebral hemorrhage.

This agent has also been studied in patients

with bleeding esophageal varices and portal hypertension, a combination that constitutes another major clinical challenge. In a randomized, controlled trial involving 245 patients with cirrhosis and upper gastrointestinal bleeding (66% of whom had bleeding varices) who were being treated with standard endoscopic and pharmacologic interventions, the administration of rFVIIa (eight consecutive doses of 100 μg per kilogram within 30 hours after the initiation of treatment) was not more effective than placebo with respect to the primary composite end point (failure to control bleeding within 24 hours and failure to prevent rebleeding or death within the first 5 days).[69] However, in a subgroup of patients with more severe cirrhosis (classified as Child class B or C), rFVIIa was associated with a decrease in the proportion of patients reaching the composite end point (8%, vs. 23% in the control group; P=0.03). Furthermore, none of the patients treated with rFVIIa had rebleeding within 24 hours, whereas rebleeding occurred in 11% of patients in the control group (P=0.01).[69]

Many case reports and case series have examined the use of rFVIIa in patients with excessive or life-threatening blood loss occurring in an array of clinical settings.[57] However, no randomized, controlled clinical trials have been completed, which is not surprising, given the difficulty of performing meaningful studies in such heterogeneous situations. Many reports claim that the use of rFVIIa resulted in rapid reduction of blood loss or a decrease in transfusion requirements after other therapeutic measures had failed. Although many of these reports appear to be compelling, it is difficult to assess the usefulness of rFVIIa properly, since publication bias in case reports and series is likely.

SAFETY OF rFVIIa

Controlled clinical trials have shown that the incidence of thrombotic complications among patients who received rFVIIa was relatively low and similar to that among patients who received placebo.[70] However, most studies of rFVIIa involved patients who had impaired coagulation or who were at low risk for thrombosis. In one trial involving patients with conditions such as intracerebral hemorrhage and a much higher risk of thrombosis, 7% of patients receiving rFVIIa had serious thromboembolic events — mainly myocardial infarction or ischemic stroke — as compared with 2% of those receiving placebo.[67] Midway through this trial, an exclusion criterion changed. Initially, only patients with thrombotic disease within 30 days before enrollment were excluded, but at the midpoint, all patients with any history of thrombotic disease were excluded, which may have obscured safety concerns associated with the use of rFVIIa. A review based on the FDA MedWatch database indicated that thromboembolic events have occurred in both the arterial and venous systems, particularly in patients with diseases other than hemophilia in whom rFVIIa was used on an off-label basis.[71] A total of 54% of the thromboembolic events were arterial thrombosis (in most cases, stroke or acute myocardial infarction); venous thromboembolism (in most cases, venous thrombosis or pulmonary embolism) occurred in 56% of patients. In 72% of the 50 reported deaths, thromboembolism was considered the probable cause. It is not clear to what extent the clinical conditions requiring the use of rFVIIa may have contributed to the risk of thrombosis.[71] These findings provide evidence of an increased risk of thrombotic complications that may offset the potential benefit of rFVIIa in patients with severe blood loss.

The availability of rFVIIa has expanded the treatment options for acute hemorrhage in patients with conditions other than hemophilia. This agent is not a panacea, but it has efficacy in patients with trauma and excessive bleeding that is resistant to other treatments. However, the promising results obtained so far must be substantiated by confirmatory trials, and studies of the cost-effectiveness of this expensive agent are also warranted. The many published cases of dramatic success in patients with various types of acute hemorrhages, albeit convincing and rewarding for the involved clinicians, should be viewed with caution in terms of constituting clinically directive evidence. Attempts are being made to improve the potency and efficacy of rFVIIa further by engineering the molecule through DNA technology, but clinical trials designed to establish increased efficacy and safety remain to be performed.[72,73]

OTHER INTERVENTIONS

Desmopressin was originally developed and licensed for the treatment of inherited defects of hemostasis.[74-76] This drug, given by slow intravenous infusion at a dose of 0.3 μg per kilogram, acts by releasing ultralarge von Willebrand factor multimers from endothelial cells, leading to an in-

crease in plasma levels of von Willebrand factor and associated factor VIII and an enhancement of primary hemostasis.[77,78] The strongest evidence of efficacy is in the prevention and treatment of bleeding in patients with mild hemophilia A and von Willebrand's disease.[75,76] In 1986, Salzman et al.[79] showed that as compared with placebo, desmopressin reduced blood loss and transfusion requirements by approximately 30% during complex cardiac surgery. Subsequent attempts to reproduce these findings were variable; most did not confirm the marked benefit originally reported.[80-82] Overall, there have been 18 trials of desmopressin in a total of 1295 patients undergoing cardiac surgery. These trials show a small effect on perioperative blood loss (median reduction, 115 ml). Several reviews suggest that although desmopressin helps to reduce perioperative blood loss, its effect is too small to influence other, more clinically relevant outcomes such as the need for transfusion and reoperation.[33,83-85] In addition, desmopressin does not reduce blood loss or transfusion requirements during elective partial hepatectomy, another operation often associated with major blood loss.[86] A report that desmopressin reduced blood loss associated with posterior spinal surgery for idiopathic scoliosis[87] was not confirmed.[88-90]

Although desmopressin can shorten the skin-bleeding time in patients with uremia,[91] the current widespread use of recombinant erythropoietin has made this abnormality of hemostasis much less frequent than it was previously.[92] The beneficial effect of erythropoietin on hemostasis is based on the increase in red-cell mass, which affects the blood–fluid dynamics, leading to a more intense interaction between circulating platelets and the vessel wall.

Thus, there is little evidence that desmopressin is efficacious in conditions other than mild hemophilia A and von Willebrand's disease. The use of desmopressin in some patients who have bleeding as a consequence of inherited and acquired defects of platelet function may be considered. This drug has been shown to shorten the skin-bleeding time in patients with cirrhosis of the liver and in those with some types of inherited platelet disorders.[93] However, the use of desmopressin for these indications is not supported by sound clinical evidence based on relevant end points.[94] The most common adverse effects of desmopressin, facial flushing and transient hyponatremia, are usually mild. There have been reports of arterial thrombotic events, not only in patients with atherothrombosis but also in patients with bleeding disorders and in a blood donor.[95-100] A systematic review showed that for patients with acute myocardial infarction who underwent cardiac surgery, the frequency of these adverse events among patients who received desmopressin was twice that among patients who received placebo, with no improvement in clinical outcomes.[33] However, another review, evaluating 16 trials of desmopressin in cardiac surgery and in other high-risk operations, showed that the rate of thrombosis did not differ significantly between patients who received desmopressin and patients who received placebo (3.4% vs. 2.7%).[101]

Hemostatic agents for topical use (particularly "fibrin sealants" composed of human fibrinogen, human or bovine thrombin, and in some instances human factor XIII and bovine aprotinin) have been licensed in Europe.[102,103] In several poorly controlled studies involving small series of patients, the efficacy of these agents has been reported for indications such as cardiovascular and thoracic surgery, liver and spleen lacerations, and bleeding at cannulation sites and suture lines. Methodologically sound clinical trials would be required to show the efficacy and safety of these drugs.

CONCLUSIONS

The available data broadly indicate that aprotinin, lysine analogues, and rFVIIa are potent hemostatic agents but that desmopressin is less efficacious. Aprotinin and lysine analogues are used almost exclusively for prophylaxis against anticipated major blood loss, whereas rFVIIa is used not only to prevent but also to treat excessive bleeding. The role of antifibrinolytic agents in the treatment of massive refractory hemorrhage has not been established to date. The choice among hemostatic agents is ultimately based on the clinician's sense of the expected therapeutic efficacy, the safety profile, and the costs — a balance that may vary depending on the characteristics of individual patients and specific clinical settings. The use of any drug that potentiates hemostasis inevitably carries a risk of thrombosis, particularly in patients with atherosclerosis or risk factors for thrombosis.

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