Hemostatic agents

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Hemostasis is defined as "the stoppage of bleeding, hemorrhage, or blood flow through a blood vessel or body part." Hemostatic agents improve hemostasis by improving primary hemostasis, stimulating fibrin formation, or inhibiting fibrinolysis.[1] Although transfusion of platelets (PLTs) and hemostatic factors are mainstays of therapy, pharmacologic agents are important adjuncts as blood products become increasingly in short supply, and alternative therapies need to be considered. Multiple pharmacologic approaches with hemostatic agents to treat or prevent bleeding are based on either preventing or reversing the defects associated with preexisting or acquired coagulopathy, with patients often presenting with multiple problems. The increasing use of drugs in cardiovascular medicine that inhibit PLT function or thrombin including clopidogrel, low-molecular-weight heparins, fondaparinux, and melagatran present the clinician with agents that may not be readily reversible with standard therapies.[2] Therapeutic approaches for pharmacologic management with hemostatic agents are listed in Table 1. Newer therapies including the potential use of recombinant activated factor (F) VIIa as a therapy for refractory bleeding will also be considered.

ABBREVIATIONS: CABG = coronary artery bypass grafting; CPB = cardiopulmonary bypass; DDAVP = 1-desamino-8-D-arginine vasopressin; DVT = deep vein thrombosis; EACA = epsilon-aminocaproic acid; MI = myocardial infarction; rFVIIa = recombinant activated factor VIIa; TA = tranexamic acid; TF = tissue factor.

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TRANSFUSION 2004;44:58S-62S.

APROTININ

Aprotinin is a serine proteinase inhibitor that inhibits a broad spectrum of proteases including plasmin, trypsin, kallikrein, chymotrypsin, activated protein C, and thrombin.[3-5] Aprotinin has been studied extensively in cardiac surgery and has been reported in other studies including orthopedic surgery and hepatic transplantation. Aprotinin is the only Food and Drug Association-approved pharmacologic treatment to reduce blood transfusion in coronary artery bypass grafting (CABG) associated with cardiopulmonary bypass (CPB). Multiple studies have reported aprotinin's efficacy that includes nearly 45 studies involving 7000 patients.[2,5] Other agents have been reported in the literature from smaller, not always well-designed, studies of variable design that have been considered in meta-analysis. In higher-risk, repeat CABG patients, multiple studies reported that aprotinin was effective in decreasing blood loss and blood transfusion requirements. Although a retrospective analysis of an early study suggested a higher risk for myocardial infarction (MI) and graft closure, two additional prospective studies reported by Levy and colleagues[6] in repeat CABG patients and by Alderman and colleagues[7] in primary CABG patients did not support earlier reports. In one study of repeat CABG surgery in 287 patients, there was a significant difference in total blood product exposures among treatment groups (high-dose aprotinin, 2.2 ± 0.4 U; low-dose aprotinin, 3.4 ± 0.9 U; pump-prime only, 5.1 ± 0.9 U; placebo, 10.3 ± 1.4 U). There were no differences among treatment groups for the incidence of perioperative MI.[6] Further, a meta-analysis of pharmacologic strategies in cardiac surgery reported treatment with aprotinin decreased mortality almost twofold (odds ratio [OR], 0.55; 95% confidence interval [CI], 0.34-0.90) compared to placebo and decreased the frequency of surgical reexploration (OR, 0.37; 95% CI, 0.25-0.55). Any hemostatic agent that decreases bleeding and transfusion requirements has the potential to affect graft patency. Aprotinin is the only agent examined in multiple studies. Three studies found no significant difference in the patency of grafted vessels when examined postoperatively.[8-10] The effects of aprotinin on graft patency, MI, and blood loss in patients undergoing primary CABG with CPB

TABLE 1. Hemostatic agents

Aprotinin
Desmopressin
FEIBA (FVIII inhibitor bypassing activity)
Fibrin glue
rFVIIa
Lysine analog antifibrinolytics (EACA, TA)

were reported by Alderman and coworkers.[7] Patients were randomly assigned to receive aprotinin (n = 436) or placebo (n = 434). Graft angiography was obtained a mean of 10.8 days after the operation. Electrocardiograms, cardiac enzymes, and blood loss and replacement were evaluated. In 796 assessable patients, aprotinin reduced thoracic drainage volume by 43 percent ($p < 0.0001$) and requirement for red blood cell (RBC) administration by 49 percent ($p < 0.0001$). Among 703 patients with assessable saphenous vein grafts, occlusions occurred in 15.4 percent of aprotinin-treated patients and 10.9 percent of patients receiving placebo ($p = 0.03$). After adjusting risk factors associated with vein graft occlusion, the aprotinin versus placebo risk ratio decreased from 1.7 to 1.05 (90% CI, 0.6-1.8). These factors included female sex, lack of prior aspirin therapy, and distal vessel quality. At US sites, there were no differences in graft patency, and occlusions occurred in 9.4 percent of the aprotinin group and 9.5 percent of the placebo group ($p = 0.72$). At Danish and Israeli sites, where patients had more adverse characteristics, occlusions occurred in 23.0 percent of aprotinin-treated and 12.4 percent of placebo-treated patients ($p = 0.01$). Aprotinin did not affect the occurrence of MI (aprotinin, 2.9%; placebo, 3.8%) or mortality (aprotinin, 1.4%; placebo, 1.6%).[7]

APROTININ STUDIES IN CHILDREN

Miller and associates[11] reported the hemostatic and economic effects of aprotinin in children undergoing reoperative cardiac procedures with CPB. Decreased blood product transfusions, shortened skin closure times, and shortened durations of intensive care unit and hospital stays were found in the aprotinin groups, most significantly in the high-dose group with a resulting average decrease of nearly $2,500 in patient charges.

META-ANALYSIS

Levi and associates[5] reported a meta-analysis of all randomized, controlled trials of the three most often used pharmacologic strategies to decrease perioperative blood loss (aprotinin, lysine analogs [aminocaproic acid and tranexamic acid], and desmopressin). Studies were included if they reported at least one clinically relevant outcome (mortality, rethoracotomy, proportion of patients receiving a transfusion, or perioperative MI) in addition to perioperative blood loss. In addition, a separate meta-analysis was performed for studies on complicated cardiac surgery. They identified 72 trials (8409 patients) that met the inclusion criteria. Treatment with aprotinin decreased mortality almost twofold (OR, 0.55; 95% CI, 0.34-0.90) compared to placebo. Treatment with aprotinin and with lysine analogs decreased the frequency of surgical reexploration (OR, 0.37; 95% CI, 0.25-0.55; and OR, 0.44; 95% CI, 0.22-0.90, respectively). These two treatments also significantly decreased the proportion of patients receiving any allogeneic blood transfusion. Aprotinin did not increase the risk of perioperative MI. Levi and coworkers[5] suggest that pharmacologic strategies that decrease perioperative blood loss in cardiac surgery, in particular aprotinin and lysine analogs, also decrease mortality, the need for rethoracotomy, and the proportion of patients receiving a blood transfusion. Aprotinin's ability to reduce the need for allogeneic blood transfusion in cardiac surgery was confirmed in the recent International Study of Peri-Operative Transfusion (ISPOT) meta-analysis, which included 45 trials with 5805 patients.[2] Combining all doses of aprotinin, the overall OR was 0.31 (range, 0.25-0.39; $p = 0.0006$).[12]

Aprotinin has been extensively evaluated in multiple double-blind, placebo-controlled, multicenter studies in cardiac surgery and orthopedic surgery and is currently the only agent approved in the US for reducing bleeding in CABG surgery. Aprotinin has not been associated with an increased risk of MI, graft closure, stroke, or renal dysfunction from US studies and may in fact be associated with a decreased risk of stroke. The mechanism of action is complex, but aprotinin displays anti-inflammatory properties because of its complex array of protease inhibition. As with any polypeptide, there is a risk of anaphylaxis that is influenced not only by prior exposure but also by time since prior exposure. Aprotinin has also been shown to be safe and effective in reducing blood loss in many orthopedic procedures.[13-19] Because tissue injury and contact activation can occur with major orthopedic surgery, multiple studies have examined the efficacy and safety of aprotinin. Further, because orthopedic surgical patients are a potential risk for prothrombotic complications, including deep venous thrombosis, the patients represent an important model to evaluate adverse effects of hemostatic agents.

EPSILON-AMINOCAPROIC ACID AND TRANEXAMIC ACID

Epsilon-aminocaproic acid (EACA) and tranexamic acid (TA) are synthetic lysine analogs that inhibit plasminogen- and/or plasmin-mediated fibrinolysis. TA is 10 times more potent than EACA. The lysine analog antifibrinolytics have been studied mostly prophylactically to

prevent blood loss and decrease bleeding in cardiac surgery with CPB. A recent meta-analysis of 12 randomized trials in patients undergoing cardiac surgery showed that TA decreased the proportion of patients receiving allogeneic RBC transfusions.[12] In the same meta-analysis, only three studies of EACA (118 patients) were eligible, and the OR was not significant.[20] Unfortunately, there are little prospectively analyzed safety data regarding the use of these agents. In the ISPOT meta-analysis, which included 12 cardiac trials, there was no increased risk of MI, but these are retrospective analyses of studies not designed to carefully evaluate specific safety issues. Although the data from randomized controlled trials are much more limited for EACA, the pooled analysis of four trials in cardiac surgery (total of 548 patients) shows a significant increase in perioperative MI (OR, 2.5; 95% CI, 1.06-5.86; $p = 0.035$).[20] In noncardiac surgery, three randomized controlled trials have evaluated TA in orthopedic surgery.[21-23] All showed a significant decrease in transfusion requirements. None showed any increase in deep vein thrombosis (DVT) or pulmonary embolus; there were 6 of 97 (6.2%) events in the TA patients versus 9 of 94 (9.6%) events in the placebo patients (OR, 0.71; 95% CI, 0.26-1.96; $p = 0.51$). Three trials in patients undergoing liver transplantation used TA prophylactically to reduce blood loss; there were no thrombotic complications in the TA or control groups.[24,25] Although thrombosis in major vessels is not uncommon in patients with liver disease, there have remained concerns that EACA may exaggerate this tendency, because the fibrinolytic state in liver transplantation is usually self-limited. Kang and coworkers[26] gave EACA to 20 patients undergoing liver transplantation; no thrombotic episodes were noted in this study compared with three events in 77 (3.9%) control patients. Munoz and associates[27] performed a meta-analysis from 52 randomized clinical trials published between 1985 and 1998 involving the use of EACA ($n = 9$) or aprotinin ($n = 46$) in cardiac surgery. The primary outcomes were total blood loss, RBC transfusion rates and amounts, reexploration, stroke, MI, and mortality. Unfortunately, there were five times as many aprotinin studies as there were EACA studies, and most of the EACA studies report primary CABG patients who do not bleed excessively. The authors report identical decreases in total postoperative transfusions with EACA (61% reduction vs. placebo) and high-dose aprotinin (62% reduction). In these studies, the data from the aprotinin-treated patients involve a series of repeat sternotomy, valvular surgeries, and more complex patients compared to the small number of EACA-treated primary CABG surgery patients. Although both drugs reduced rates of reexploration to similar degrees, this effect was significant only with high-dose aprotinin. Finally, most of the methods used to study the incidence of adverse events in the EACA-treated patients do not conform to the rigorous evaluation of FDA-sponsored clinical studies to evaluate safety issues with aprotinin.

DESMOPRESSIN

Desmopressin is used for the prevention and treatment of bleeding in patients with von Willebrand disease (VWD) or mild hemophilia A and further in patients with an impaired function of primary hemostasis, such as in patients with uremia, liver cirrhosis, or aspirin-associated bleeding. 1-Desamino-8-D-arginine vasopressin (DDAVP) is an analog of the hormone arginine vasopressin that is mainly a V2 agonist. The V1 receptor-mediated effects produce vasoconstriction. Although DDAVP administration at 0.3 μg per kg is the recommended dose, this will increase FVIII levels, von Willebrand factor (VWF) levels (especially the high-molecular-weight multimers), and tissue plasminogen activator levels by 2- to 20-fold. DDAVP has not been consistently proven to be effective in decreasing in perioperative blood loss and was not associated with a favorable effect on other clinical outcomes; rather, it was associated with a 2.4-fold increase in the risk of MI.[28] A recent meta-analysis of 12 randomized controlled trials with DDAVP in cardiac surgery reported an incidence of MI of 4.4 percent in the DDAVP-treated group versus 1.6 percent in the placebo-treated group (OR, 2.07; 95% CI, 0.74-5.85; $p = 0.19$).[2] Cattaneo and Mannucci[28] pooled data from double-blind placebo-controlled trials that evaluated the hemostatic efficacy of DDAVP in cardiac, vascular, and orthopedic surgery. Total thrombotic events (i.e., MI, stroke, arterial thrombosis, venous thromboembolism) were reported in 3.4 percent of the DDAVP-treated patients and 2.7 percent of the placebo-treated patients ($p = 0.38$). The authors pooled data from 17 randomized controlled trials in cardiac ($n = 15$) and vascular ($n = 2$) surgery that specifically mentioned the presence or absence of thrombotic events. The incidence of MI was 3.9 percent (28 of 716 patients) in the DDAVP-treated group and 3.1 percent (20 of 646 patients) in the placebo group for an OR of 1.25 (95% CI, 0.72-2.14; $p = 0.43$). In orthopedic surgery, only three of the five published randomized controlled trials were assessed for DVT. There were four cases of DVT and/or pulmonary embolism in the DDAVP group (3.7%) and five in the placebo group (4.3%), for an OR of 0.82 (95% CI, 0.24-2.78; $p = 0.75$).[30-32]

Recombinant coagulation products. Coagulation products used to manage bleeding in patients with hemophilia, VWD, or acquired inhibitors to antihemophilic factor include antihemophilic factor concentrates, F IX concentrates, FVIIa, and F IX.[4] Although these agents are specifically approved for patients with hematologic disorders, they are also used to manage acute bleeding episodes in patients during cardiac and noncardiac surgery.

Currently, the agent most often reported is recombinant activated FVIIa (rFVIIa; NovoSeven, Novo Nordisk, Princeton, New Jersey), which is approved in the treatment of patients with hemophilia with inhibitors who are bleeding and to facilitate hemostasis in life-threatening, refractory bleeding in complex clinical situations. The prohemostatic effect of rFVIIa is mediated in part by forming a complex with tissue factor (TF).[33] TF is a membrane-bound glycoprotein expressed on subendothelial cells after tissue injury.[34] Circulating FVIIa accounts for approximately 1 percent of circulating FVII and is inactive until bound with TF. FVIIa binds to TF to activate FX to FXa, leading to the generation of thrombin (FIIa) and subsequent fibrin formation and PLT activation.[33] Administering rFVIIa to patients with multiple hemostatic abnormalities has been postulated to have many different effects including additional thrombin generation on the surface of activated PLTs and at the local site of injury.[35] Multiple case reports describe the application of rFVIIa for life-threatening and refractory bleeding despite hemostatic factors and PLTs in patients with both preexisting and acquired hemostatic disorders, during both cardiac and noncardiac surgery.[36,37] 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. Although 90 μg per kg is usually the initial starting dose in patients with hemophilia, lower doses of 30 to 45 μg per kg have been reported in surgical patients to be effective. Additional studies are needed to further evaluate dosing, safety, and efficacy in perioperative use of rFVIIa.

SUMMARY

Hemostatic agents improve hemostasis by multiple mechanisms that include improving primary hemostasis, stimulating thrombin generation and/or fibrin formation or inhibiting fibrinolysis. Although hemostatic factors are mainstays of therapy, pharmacologic agents are important adjuncts as blood products become increasingly in short supply and as newer longer-acting anticoagulants and PLT inhibitors are increasingly being used, and alternative therapies need to be considered for refractory bleeding when prophylactic therapy is not possible. Aprotinin has been extensively studied for prophylactic administration, with both safety and efficacy. Lysine analog fibrinolytic inhibitors also have been extensively studied, with TA demonstrated to be effective. There is a paucity of safety data, however, involving these agents. DDAVP increases VWF and is often used as a hemostatic agent with little data demonstrating efficacy, especially for the treatment of bleeding in surgical patients. Because coagulation in vivo proceeds by the TF and FVII(a) pathway, rFVIIa has been developed as a prohemostatic agent with multiple reports suggesting its efficacy for refractory life-threatening hemorrhage in uncontrolled clinical studies with severe and complicated coagulation defects. At present, a more general use of this agent for bleeding patients without an apparent coagulation defect is the subject of current clinical trials.

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