INVITED ARTICLE

Hemostatic Agents in Critically Ill Patients

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Introduction

Coagulation disorders and hemorhage are common in critically ill patients due to myriad causes. These include blood loss, hemodilution, acquired platelet dysfunction, coagulation factor consumption in extracorporeal circuits, activation of fibrinolytic, fibrinogenolytic and inflammatory pathways, hypothermia, etc. Coagulation defects in critical patients may be either congenital or acquired. Acquired coagulopathy are often present in the critically ill as a result of prescribed oral anticoagulants (for example, warfarin, dabigatran, rivaroxaban, apixaban, edoxaban) and anti-platelet agents (for example: P2Y12 receptor inhibitors-clopidogrel, prasugrel, orticagrelor). Hemorrhagic shock remains a leading cause of mortality in patients especially with trauma despite tremendous progress in acute care medicine.[1]

Management of bleeding and coagulopathy should include identifying patients at risk, understanding the impact of various invasive interventions on hemostasis, institution of allogeneic blood and factor testing, utilizing point-of-care laboratory and understanding the limitations of monitoring techniques, concentrate-based therapies and use various hemostatic agents.[1] While treating coagulopathy, it has to be kept in mind that both hyper- and hypocoaguable states often coexist and hemostasis is a balance between these two.

To understand mechanism of various haemostatic agents, it is imperative to review the basic physiology of hemostasis. The process of hemostasis, is a complex and finely tuned interaction between various plasma proteins, platelets, blood flow, and the endothelium. Five components are crucial in the maintenance and regulation of hemostasis. These include: (1) endothelial cells; (2) platelets for plug formation; (3) coagulation factors for formation of insoluble fibrin clot; (4) coagulation inhibitors; and (5) fibrinolysis. The whole process can be categorized into:

- Primary hemostasis which is platelet aggregation and platelet plug formation
- Secondary hemostasis which is the deposition of insoluble fibrin.

Platelets are activated in a series of processes and the activated platelets adhere to the site of injury and to each other, forming a plug. Along with this, insoluble fibrin is generated by the coagulation cascade. This forms a mesh that is incorporated into and around the platelet plug. This mesh increases the strength and stabilizes the blood clot. These two processes act simultaneously and are mechanistically intertwined. The fibrinolysis pathway plays the role of "check point" in hemostasis regulating thrombus formation.[2,3]

Hemostatic agents can be broadly divided into:

- Pharmacological systematic hemostatic agents
- Clotting factor concentrates.

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Pharmacological Systemic Hemostatic Agents

Antifibrinolytic Agents

Antifibrinolytic drugs should ideally be used where there is hyperfibrinolysis, for example cardiopulmonary bypass, orthotopic liver transplantation, urological, orthopaedic operations, etc. Antifibrinolytic agents are lysine analog and protease inhibitors. Protease inhibitors for example aprotinin and nafamosta, inhibit serine proteases. Lysine analogs, for example tranexamic acid, ε-aminocaproic acid reversibly combine with plasminogen.[4]

Aprotinin

Aprotinin is a broad-spectrum protease inhibitors, reduces fibrinolysis and stabilizes platelet function. Multiple randomized control trial showed its efficacy in reducing blood loss and transfusion requirements in patients undergoing cardiothoracic, liver transplant and orthopedic surgeries.[5–8] Aprotinin also has potential anti-inflammatory effect. This effect of aprotinin encouraged a more systemic use in infants undergoing cardiac surgery. However, several studies showed that use of aprotinin was associated with an increased risk of renal failure, myocardial infarction, heart failure, stroke, encephalopathy and mortality.[9,10] Blood Conservation Using Antifibrinolytics in a Randomized Trial (BART) that looked into the effects of aprotinin, tranexamic acid and epsilon-aminocaproic acid on massive postoperative bleeding and death from any cause at 30 days, had to be terminated early because of a higher mortality in the aprotinin-treated patients.[11] This triggered suspension of manufacturing of aprotinin.

Nafamostat Mesilate

Nafamostat mesilate is synthetic protease inhibitor and inhibits thrombin, factors Xa and XIIa, kallikrein, plasmin and complement factors (C1r, C1s). It also works as an antifibrinolytic, anticoagulant and anti-inflammatory agent.[12] Clinically, it has been used in

the treatment of disseminated intravascular coagulation, acute pancreatitis and as a hemostatic agent in cardiac surgery. Nafamostat mesilate has a low-molecular weight and short half-life of only 8 minutes, which makes it suitable for use as an anticoagulant in extracorporeal circuits during CRRT in patients with a high risk of bleeding.[12,13]

Tranexamic Acid

Tranexamic acid is in clinical practice since 1962. Tranexamic acid is a synthetic derivative of the amino acid lysine and binds the 5 lysine-binding sites on plasminogen. This inhibits plasmin formation and displaces plasminogen from the fibrin surface. It may also directly inhibit plasmin and partially inhibit fibrinogenolysis at higher concentrations.[14] Tranexamic acid is usually given as a bolus dose of 10–15 mg per kg intravenous. As only a small fraction of administered tranexamic acid is metabolized and most is excreted unchanged by the kidney, the dose should be decreased in renal impairment.[15] There are a number of clinical studies that tested its effectiveness in decreasing blood loss and transfusion requirement in surgical and nonsurgical settings. Various studies and meta-analysis in patients undergoing cardiopulmonary bypass, found that tranexamic acid was associated with a reduction in perioperative blood loss and allogenic blood transfusion requirements. However, timing of administration is crucial. It should be given preemptively before bleeding starts. Although there was an initial suspicion, but, tranexamic acid does not seem to be associated with increased risk of thrombotic phenomenon.[16,17] Tranexamic acid has also been successfully used to reduce blood loss in orthopedic surgery particularly in knee arthoplasty and hip replacement.[18,19] Studies evaluating the effect of high-dose tranexamic acid (10–40 mg per kg per hour) in primary orthotopic liver transplantation reported a significant reduction in intraoperative blood loss and transfusion requirements.[20,21] The large multicentric CRASH 2 trial showed a significant reduction in all cause-mortality and bleeding in trauma patients receiving early tranexamic acid if administered over less than three hours of trauma. Another large multicentric trial (WOMAN) conducted in patients with postpartum hemorrhage showed a significant reduction in hemorrhage and need for surgery to treat severe bleeding. Potential side effects when using tranexamic acid, include increased risk of thromboembolic events and neurological side-effects. However, significant incidence of such serious side effect was not observed in those studies. Rapid intravenous administration of tranexamic acid may sometimes cause hypotension and should therefore be administered slowly as an infusion. Some literature reported the potential association of large doses of tranexaemic acid with seizure activity in both adult and pediatric cardiac patients.[22–24]

Epsilon-aminocaproic Acid

Epsilon-aminocaproic acid (EACA) is a competitive inhibitor of plasminogen activation and inhibits plasmin at higher doses. The usual recommended dose is 150 mg per kg as an intravenous bolus before surgery, followed by an infusion of 15 mg per kg per hour during the operation. EACA is largely eliminated unchanged by renal excretion. The terminal elimination half-life for aminocaproic acid is 1–2 hours. It is effective in several situations, such as prophylaxis of bleeding episodes in hemophiliacs, control of menorrhagia, gastrointestinal bleeding, obstetrical bleeding and in bleeding following cardiac and thoracic surgery. Major side effects from EACA include hypotension, cardiac arrhythmias, rhabdomyolysis and thromboembolic events.[4] Several trials have studied the prophylactic administration of EACA in patients undergoing cardiopulmonary bypass. They found that EACA may be useful in reducing blood loss and transfusion. EACA has been studied in noncardiac surgery as well.[25,26] A meta-analysis of three studies including 1691 patient undergoing total knee replacement showed that EACA is as effective as tranaexemic acid in reducing estimated blood loss and transfusion.[27] EACA has also been studied in patients undergoing orthotopic liver transplantation. Data from 1170 consecutive transplants patients showed that EACA decreased intraoperative blood loss and showed a trend toward improved graft and patient survival.[28]

Vasopressin Analogue: Desmopressin

Desmopressin acetate is pharmacologically altered form of naturally occurring vasopressin by deamination of hemicysteine at position 1 and substitution of D-arginine for L-arginine at position 8. Beside antidiuretic action, desmopressin causes the endothelial release of factor VIII and von Willebrand factor into the plasma. The released factors form a complex with platelets and enhance their ability to aggregate. Desmopressin at a dose of 0.3 mg per kg has been used in hemophilia A, von Willebrand's disease, uremic thrombocytopathy, and in perioperative settings. These doses can be repeated at intervals of 12–24 hours, but tachyphylaxis may occur. Side effects correspond with its antidiuretic and vasomotor effects. Hyponatremia, hypertension, tachycardia, nausea, malaise, headache, fatigue, flushing, dizziness are some of the common side effects with desmopressin.[15,29] Few initial studies showed usefulness of desmopressin in patients pretreated with aspirin and undergoing cardiac surgery. But a meta-analysis of 72 trials found that the use of desmopressin in cardiac surgery, resulted in a small decrease in perioperative blood loss, but was not associated with a beneficial effect on other clinical outcomes.[17,30,31] Desmopressin was also tried in several noncardiac surgeries for example spine and orthopedic surgeries which yielded mixed results.[32,33] One of most common agent used in uremic patients with active bleeding is desmopressin. Desmopressin doses for uremic bleeding range from 0.3 μg/kg to 0.4 μg/kg intravenously or subcutaneously. DDAVP administration should not be repeated because of the risk of tachyphylaxis. It is postulated that tachyphylaxis occurs as a result of depletion of factor VIII and vWF endothelial stores.[34]

Estrogens

Estrogen has also been used in uremic bleeding by virtue of its ability to decrease production of l-arginine, which is a precursor of NO. By decreasing production of cGMP, it increases production of thromboxane A2 and ADP. These are crucial contributors to formation of platelet plugs, decrease of antithrombin III and protein S levels, and increase factor VII concentrations. Various studies showed estrogen can decrease bleeding time.[35,36]

Ethamsylate

Ethamsylate acts by reducing thromboxane A2 and prostacyclin biosynthesis and improving platelet homo- and heterotypic adhesiveness. Ethamsylate has been used in dysfunctional uterine bleeding, periventricular hemorrhage in very low-birth weight babies, perioperative scenarios.[37,38]

Clotting Factor Concentrates

Fresh Frozen Plasma

Fresh frozen plasma is the fluid portion of a unit of whole blood that is frozen usually within 8 hours. FFP contains all clotting factors, fibrinogen, albumin, protein C, protein S, antithrombin,

tissue factor pathway inhibitor. Dose of FFP is 10–20 mL/kg which raises factor levels by approximately 20% and that is enough to maintain hemostasis. FFP should be ABO compatible. FFP is used for a planned invasive procedure in the presence of abnormal coagulation tests, reversal of warfarin in the presence of active bleeding or for planned procedure when vitamin K is inadequate to reverse the warfarin effect, during plasma exchange, congenital or acquired factor deficiency with no alternative therapy and as part of massive transfusion protocol.[39]

Prothombin Complex Concentrate

Prothombin complex concentrate (PCC) may be either three-factor (i.e., factors II, IX and X) or four-factor (i.e., factors II, VII, IX and X) concentrates with a concentration approximately 25 times higher than in normal plasma.[40] Indication for PCC are urgent reversal of warfarin, congenital or acquired deficiency of vitamin K-dependent clotting factors and haemophilia B. Various studies compared efficacy of FFP to that of PCC. A systematic review of 14 studies found that PCC is more effective in reversing warfarin and decreasing INR.[41] Dose of PCC is 1–2 mL/kg which is much lower than FFP. Another advantage of PCC over FFP is that PCC does not cause transfusion associated acute lung injury (TRALI).[42]

Recombinant Factor VIIa

Recombinant factor VIIa is produced by transfection of the human factor VII gene into baby hamster kidney cells cultured in bovine albumin. It has an amino acid sequence identical to that of plasma-derived factor VII. rFVIIa binds to the surface of activated platelets and promotes factor X activation and thrombin generation localized at the site of injury without widespread thrombosis. This activation is independent of TF. Standard doses are 90–120 µg/kg given every 2–3 hours till effective hemostasis is achieved.[43,44]

FDA approved used of rFVIIa are:

- Treatment of bleeding episodes in hemophilia A or B patients with inhibitors to factor VIII or factor IX and in patients with acquired hemophilia
- Prevention of bleeding in surgical interventions or invasive procedures in hemophilia A or B patients with inhibitors to factor VIII or factor IX and in patients with acquired hemophilia
- Treatment of bleeding episodes in patients with congenital FVII deficiency
- Prevention of bleeding in surgical interventions or invasive procedures in patients with congenital FVII deficiency

Apart from these, other off-label uses of rFVIIa are spontaneous intracranial hemorrhage, trauma, postpartum hemorhage, cardiac surgery, liver surgery etc.[43,45]

A recent systematic review and meta-analysis of 12 studies including 1244 patients with acquired hemophilia found that rFVIIa is effective in bleeding control with good safety profile.[46] Another meta-analysis evaluated its efficacy and safety for treatment of bleeding in major abdominal, urological and vascular surgery. The study concluded that rFVIIa achieved at least a reduction of bleeding and that the probability of survival was increased in patients responding to rFVIIa. rFVIIa was not associated with an increased risk of thromboembolism compared with placebo.[47] A randomized control trial of 841 patients with intracerebral hemorrhage showed that rFVIIa at dose of 80 µg per kg reduced expansion of the hematoma but did not improve survival or functional outcome after intra cerebral hemorrhage.[48]

The appropriate management of patients with bleeding and coagulopathy remains a major challenge in routine clinical practice. A multidisciplinary approach and adherence to evidence-based guidance are key to improving patient outcomes. Selection of the most appropriate haemostatic pharmacological agents, requires not only consideration of the clinical evidence supporting the efficacy of the various agents, but also the available safety data to ensure that the benefits of this approach are not jeopardized by the risk. Correction of hypothermia, hypocalcemia, metabolic acidosis should precede use of pharmacological hemostatic agents. Dynamic parameters of coagulation may be more useful that static parameter in guiding management. Most studies on hemoststic agents have been carried out in trauma and perioperative settings. Further investigations are required to evaluate efficacy and safety of these hemostatic agents in more complex, critically care settings.

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