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Adjuncts to Blood Component Therapies for the Treatment of Bleeding in the Intensive Care Unit

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ABSTRACT

Patients who are critically ill following surgical or traumatic injury often present with coagulopathy as a component of the complex multisystem dysfunction that clinicians must rapidly diagnose and treat in the intensive care environment. Failure to recognize coagulopathy while volume resuscitation with crystalloid or colloid takes place, or an unbalanced transfusion strategy focused on packed red blood cell transfusion can all significantly worsen coagulopathy, leading to increased transfusion requirements and poor outcomes. Even an optimized transfusion strategy directed at correcting coagulopathy and maintaining clotting factor levels carries the risk of a number of transfusion reactions including transfusion-related acute lung injury, transfusion-related circulatory overload, anaphylaxis, and septic shock. A number of adjunctive strategies can be used either to augment a balanced transfusion approach or as alternatives to blood component therapy. Coupled with an appropriate and timely laboratory testing, this approach can quickly diagnose a patient's specific coagulopathy and work to correct it as quickly as possible, minimizing the requirement of blood transfusion and the pathophysiologic effects of excessive bleeding and fibrinolysis. We will review the literature supporting this approach and provide insight into how these approaches can be best used to care for bleeding patients in the intensive care unit. Finally, the increasing use of several novel oral anticoagulants, novel antiplatelet drugs, and low–molecular weight heparin to clinical practice has complicated the care of the coagulopathic patient when these drugs are involved. Many clinicians familiar with heparin and warfarin reversal are not familiar with the optimal way to reverse the action of these new drugs. Patients treated with these drugs for a wide variety of conditions including atrial fibrillation, stroke, coronary artery stent, deep venous thrombosis, and pulmonary embolism will present for emergency surgery and will require management of pharmacologically induced postoperative coagulopathy. We will discuss optimized strategies for reversal of these agents and strategies that are currently under development.

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Intensive care unit patients are critically ill and may bleed because of multiple causes related to their primary disease and/or acquired coagulopathy. Patients admitted to the intensive care unit following surgical and/or traumatic injury present with a multitude of hemostatic

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changes that may occur following resuscitation and are frequently coagulopathic. The pathophysiology of bleeding in the intensive care unit is multifactorial and includes fibrinolysis, consumption of coagulation factors, dilutional changes, hypothermia, and other potential factors [1,2]. With the growing and extensive use of anticoagulants for ischemic cardiovascular disease, atrial fibrillation, venous thromboembolism, mechanical heart valves, or ventricular assist devices, patients may also have preexisting hemostatic derangements that necessitate management and reversal of the specific anticoagulation agents. However, depending on the anticoagulant, a specific reversal strategy or antidote may not exist. This is particularly important with the factor Xa inhibitor novel direct oral anticoagulants; low–molecular weight heparin; and the P2Y12 receptor antagonists that include clopidogrel, prasugrel, and ticagrelor.

Although allogeneic blood transfusions are classically used as the primary management strategy in bleeding patients, the role of adjuncts to blood component therapies is increasingly being used [3-5]. Specifically, factor concentrates represent important therapeutic options to manage bleeding and will be reviewed. The increasing use of algorithm-based management protocols in bleeding patients is also an important part of adjunctive hemostasis strategies. This commentary will focus on pharmacologic agents and selected factor concentrates for managing bleeding in the intensive care unit.

Antifibrinolytic Agents

Multiple studies from large-scale trials, pooled meta-analyses, and retrospective evaluations have consistently shown the importance of antifibrinolytic agents as a critical pharmacological adjunct to blood component therapies as part of a multimodal strategy to manage bleeding patients. Furthermore, data from the Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage 2 study of tranexamic acid lend important support to this concept that will be reviewed [6]. Data from trauma studies using thromboelastography and thromboelastometry for fibrinolysis detection also support the role of fibrinolysis as an important contributor to coagulopathy [7]. In particular, the use of antifibrinolytic agents for bleeding continues to evolve as an important therapeutic management strategy [6,8,9].

Although different agents inhibit fibrinolysis, the mainstay of agents are the lysine analogs that include epsilon aminocaproic acid and tranexamic acid (TXA). Plasminogen and its active form plasmin bind to lysine residues in cross-linked fibrin to cause clot lysis. The currently used antifibrinolytic agents competitively inhibit the degradation of fibrin by binding to the same lysine binding sites on plasminogen/plasmin. Plasmin also contributes to coagulopathy during fibrinolysis by multiple mechanisms including cleavage of platelet receptors, fibrinogen, and other plasma proteins [10]. Aprotinin, a polypeptide that is a direct inhibitor of plasmin and other proteases, is not currently available in the United States but still used in some European countries. TXA is the agent most extensively studied and used throughout the world. Epsilon aminocaproic acid, used mainly in the United States, has been withdrawn from some countries for anecdotal evidence related to rhabdomyolysis and kidney injury [11] and may not be available. Inhibition of fibrin degradation is considered one of the critical effects of TXA; modulating plasmin is also another important effect. Plasmin can activate multiple inflammatory responses by activating complement first, ultimately leading to the activation of mononuclear and polymorphonuclear inflammatory cells [12–14].

One of the most widely quoted studies in trauma patients was an international blinded randomized trial of more than 20 000 adult trauma patients (Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage 2). In the study, 2 g of TXA (1 g load, 1 g infusion over 8 hours) administered within 3 hours of the acute injury reduced all-cause mortality (14.5% vs 16.0% placebo) [15]. Notably, there were no significant differences in transfusion requirements between the groups, potentially suggesting that TXA's ability to reduce inflammatory "cross talk" following traumatic injury may be another important consideration. However, it is possible that this effect may be only applicable to certain types of injuries with a potentially limited amount of blood loss, and further studies are needed to evaluate its effectiveness in major postsurgical and traumatic bleeding episodes.

Numerous meta-analyses of randomized controlled trials in noncardiac and cardiac surgical patients consistently report decreased bleeding and a reduction in transfusion with lysine analogs. Safety data, however, are limited, and prothrombotic and proconvulsant effects of TXA are concerns. In the largest randomized clinical trial, Myles et al [16] evaluated patients scheduled for coronary artery surgery to receive aspirin or placebo and TXA or placebo. The authors used a composite end point of death and thrombotic complications (nonfatal myocardial infarction, stroke, pulmonary embolism, renal failure, or bowel infarction) within 30 days after surgery. They studied 4662 patients, of which 4631 underwent surgery and included 2311 TXA-treated patients and 2320 to receive placebo. Primary outcome events occurred in 16.7% (386 patients) in the TXA treatment arm and 18.1% (420 patients) in the placebo group (relative risk, 0.92; 95% confidence interval, 0.81-1.05; $P = .22$). Patients treated with TXA had a significant reduction of blood product transfusions during hospitalization, with 4331 U of blood products transfused in the TXA group compared with 7994 U administered in the placebo arm ($P < .001$). Bleeding complications including major hemorrhage/cardiac tamponade leading to reoperation occurred in 1.4% of the TXA treated group compared with 2.8% in placebo ($P = .001$). Postoperative seizures were greater in the TXA-treated patients: 0.7% compared with 0.1% in placebo ($P = .002$).

The consistent finding of postoperative seizures reported with TXA also has been reported following hypothermic circulatory arrest [17]. Other reports note an increase in seizures from 1.3% to 3.8% following TXA therapy in cardiac surgical patients also associated with receiving ≥4 g of TXA [18]. The ability of TXA to antagonize glycine as well as block gamma-aminobutyric acid receptors in the specific aspects of the frontal cortex is one of the potential mechanisms [19]. Furthermore, only a few studies have determined the pharmacokinetics of TXA in cardiac surgical patients especially with cardiopulmonary bypass [20]. Because of variability of dosing of TXA and the lack of pharmacokinetic/pharmacodynamic studies, higher doses of TXA may be administered. Despite these considerations and concerns regarding safety, TXA has a track record of safety and has been administered at doses of ~4 g/d orally for 5 days to reduce heavy menstrual bleeding without an increased risk of seizures or thromboembolic events seen in these patients [21].

Fibrinogen

Fibrinogen is a critical coagulation factor required for clot formation and for clot strength based on normal thromboelastometry and thromboelastometry measurements [3,22]. In patients with ongoing hemorrhage, it is the first factor to decrease below a critical level, and low levels have been associated with bleeding [23,24]. Traditionally, older transfusion guidelines recommended treating fibrinogen when levels were <100 mg/dL (1 g/L) [25]. However, fibrinogen levels at these lower concentrations can potentially influence coagulation testing based on clot determination such as prothrombin time and partial thromboplastin times. Although not supported by controlled trial evidence, current recommendations frequently suggest that fibrinogen should be normalized to ~200 mg/dL (2 g/L) in bleeding patients who require therapy [22,26-30]. In a prospective cohort study of 517 injured patients in which ROTEM was used to rapidly diagnose and manage fibrinogen repletion therapy, hypofibrinogenemia was associated with poor outcomes [31]. In the United States, fibrinogen is typically repleted by cryoprecipitate, which is a multidonor product that many countries do not use. Instead, these other countries use fibrinogen concentrates for repletion therapy. Cryoprecipitate also contains other hemostatic proteins including von Willebrand factor, factor XIII, factor VIII, and fibronectin [32]. Fibrinogen concentrates are available as pasteurized, lyophilized products that undergo purification, viral inactivation, and pathogen removal processes [33]. They do not need to be screened for blood type and can be used for immediate use in emergencies. RiaSTAP (CSL Behring) is the only fibrinogen concentrate globally available

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