Published in final edited form as:

Transfus Med Rev. 2017 October ; 31(4): 258–263. doi:10.1016/j.tmr.2017.04.001.

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 multi-system 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 employed 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 utilized to care for bleeding patients in the ICU.

Finally, the increasing use of several novel oral anticoagulants (NOACs), novel anti-platelet 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 post-operative coagulopathy. We will discuss optimized strategies for reversal of these agents and strategies that are currently under development.

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Keywords

antifibrinolytics; apixaban; bleeding; dabigatran; factor concentrates; factor VIIa; fibrinogen; hemorrhage; prothrombin complex concentrates; rivaroxaban

Introduction

Intensive care unit patients are critically ill and may bleed due to multiple causes related to either 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 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 utilized.(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. Further, data from the CRASH-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 (EACA) 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. EACA, 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.

One of the most widely quoted studies in trauma patients was an international blinded randomized trial of over 20,000 adult trauma patients (CRASH-2). In the study, 2 g of TXA (1 g load, 1 g infusion over 8 hours) administered within three hours of the acute injury reduced all-cause mortality (14.5% versus 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 post-surgical 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 (RCT), Myles et. al. evaluated patients scheduled for coronary-artery surgery to receive aspirin or placebo and TXA or placebo.(16) The authors used a composite endpoint of death and thrombotic complications (nonfatal myocardial infarction, stroke, pulmonary embolism, renal failure, or bowel infarction) within 30 days after surgery. They studied 4,662 patients of which 4,631 underwent surgery and included 2,311 TXA-treated patients and 2,320 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 to 1.05; $P=0.22$). Patients treated with TXA had a significant reduction of blood product transfusions during hospitalization with 4,331 units of blood products transfused in the TXA group compared to 7,994 units administered in the placebo arm ($P<0.001$). Bleeding complications including major hemorrhage/cardiac tamponade leading to reoperation occurred in 1.4% of the TXA treated group compared to 2.8% in placebo ($P=0.001$). Postoperative seizures were greater in the TXA treated patients 0.7% compared to 0.1% in placebo ($P=0.002$).

The consistent finding of postoperative seizures reported with TXA also have 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 grams of TXA.(18) The ability of TXA to antagonize glycine as well as

blocking gamma-aminobutyric acid (GABA) receptors in the specific aspects of the frontal cortex is one of the potential mechanisms.(19) Further, 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/day orally for five 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 multi-donor product that many countries do not use. Instead, these other countries utilize 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 under different trade names in Europe and is licensed in some countries for multiple indications including the treatment of acute bleeding episodes with acquired hypofibrinogenemia. In the US, fibrinogen concentrates are only licensed for management of patients with congenital hypofibrinogenemia or afibrinogenemia.

Dosing strategies for fibrinogen

Fibrinogen can be dosed based on the level of bleeding and initial plasma fibrinogen concentration using an initial dose of ~2 g, with repeat administration dependent upon bleeding status and as a part of multimodal therapy. (34–36) The increasing use of point-of-care testing in trauma and surgery with thromboelastometry (ROTEM device, TEM International, Munich, Germany) or thromboelastography (TEG, Haemonetics Corp., Braintree, MA, USA) has allowed for specific management of targeted coagulation factor repletion.(37, 38) Several tests are used that measure the fibrin/fibrinogen contribution to clot strength. One test has been used extensively, the FIBTEM assay, determines fibrinogen

levels and is used to calculate fibrinogen doses as reported in clinical trials.(34, 36, 39) The fibrinogen dose can be calculated as follows:

$$\text{Fibrinogen concentrate dose (g)} = (\text{target FIBTEM MCF [mm]} - \text{actual FIBTEM MCF[mm]}) \times (\text{bodyweight[kg]}/70) \times 0.5 \text{ g/mm}$$

Normal maximum clot firmness (MCF) values are 9–25 mm and correlate with normal fibrinogen levels. Target MCF of 22 mm are used in aortic surgery patients, however, and are achieved using mean fibrinogen doses of 5.7 g.(35) It should be noted that TEG fibrinogen determinations and ROTEM FIBTEM use different assays to determine fibrinogen levels and therefore the amplitude of the clot is not comparable, and algorithms are using TEG and ROTEM parameters are not interchangeable.(40, 41) Also, the target values are different between the two tests due to a difference in platelet inhibitors of abciximab (TEG) compared to cytochalasin (ROTEM).

Clinical studies evaluating the role of fibrinogen replacement

Fibrinogen repletion, primarily with the use of fibrinogen concentrates for acquired bleeding has been reported in clinical settings that include surgery, trauma, and obstetrics. Multiple reviews have been reported with analysis of studies, repletion levels and other information. (3, 22) However most of this previously reviewed data are based on retrospective analyses, observational studies, and other analyses. Recently, a small number of randomized placebo-controlled clinical trials have been reported that will be considered as follows.

Several recent randomized placebo-controlled clinical trials evaluated the role of fibrinogen concentrates as a hemostatic agent in cardiac surgical patients.(42–44). In two studies, fibrinogen was dosed using a thromboelastometry FIBTEM MCF parameter target of 22 mm, and in the most recent study fibrinogen repletion was targeted to achieve a post-infusion plasma level of 2.5 g/L. The Zero-Plasma Trial (ZEPLAST) study was a single-center, prospective, randomized, placebo-controlled, double-blinded study that evaluated 116 cardiac surgical patients with a cardiopulmonary bypass duration >90 minutes. Following protamine administration, patients received fibrinogen concentrates initially, then potentially PCCs if bleeding persisted. The patients in the study were at moderate risk for bleeding. The authors reported a reduction in transfusions for fibrinogen treated patients with mean fibrinogen levels of 2.5 g/L and none of the patients triggered PCC administration. A subsequent post hoc analysis of the ZEPLAST study suggested a fibrinogen concentrate dose of ~2 g might be sufficient to prevent bleeding in cardiac surgery. However, the risk of bleeding in ZEPLAST was less than in the patients included in the recent REPLACE study. The REPLACE study included major aortic surgery compared with lower risk patients in the ZEPLAST study.

The randomized evaluation of fibrinogen versus placebo in complex cardiovascular surgery trial (REPACE) study was another blinded randomized clinical trial of fibrinogen concentrates in patients undergoing elective aortic surgery with cardiopulmonary bypass. After initially qualifying with excessive bleeding, fibrinogen concentrates were administered to patients who then followed a standardized algorithm for allogeneic blood product

transfusion if bleeding continued. The study was a multicenter international evaluation including 519 patients from 34 centers of which 152 (29%) met inclusion criteria. More allogeneic blood product units were administered during the first 24 h in the group receiving fibrinogen concentrates, 5.0 (2.0–11.0), when compared with placebo, 3.0 (0.0–7.0), $P=0.026$. Fewer patients avoided transfusion in the fibrinogen concentrate group (15.4%) compared with placebo (28.4%), despite increased plasma fibrinogen concentrations. Comparing the two studies, in ZEPLAST mean cardiopulmonary bypass duration was 110 minutes (± 40), whereas 80% of the REPLACE patients exceeded 120 minutes bypass time required hypothermic circulatory arrest. ZEPLAST was a single institution study, with lower risk surgical patients, and only a few surgeons involved with less surgical variability. Of note adherence to a complex transfusion algorithm occurred in 100% of ZEPLAST patients compared to 68% of patients in REPLACE. Of note is that earlier studies also demonstrating efficacy of fibrinogen in cardiac surgery were single center studies. Other important considerations include preemptive administration of fibrinogen in ZEPLAST compared to REPLACE that used a complex step involving weighing swabs from the field to trigger randomization (only if 60–250g over 5 minutes after protamine and “surgical hemostasis”). In REPLACE, there was no difference in bleeding between groups, and it was not clear what triggered the greater number of fresh frozen plasma transfusions in the fibrinogen concentrate group at 2 of the 4 study sites. The ZEPLAST study in contrast, excluded 649 of 768 eligible patients due to emergency surgery, known coagulopathy (including antiplatelet agents other than aspirin), pregnancy, low antithrombin levels, autoimmune disorders, Hct $<35\%$ or a BSA $<1.7\text{m}^2$. Only 3 of the 119 subsequently enrolled were not dosed. Fresh frozen plasma was totally avoided in the ZEPLAST study, which is ironic as this was the product associated with increased transfusion in the treatment arm of the REPLACE trial ($p=0.02$). A major limitation of both studies is that dosing of only 15% in ZEPLAST study or 26% of the REPLACE study populations limits the extrapolation of either study to the readers’ daily practice.

Because of the expected critical role of fibrinogen in postpartum hemorrhage (PPH), preemptive treatment with fibrinogen concentrates were evaluated in a multicenter blinded controlled trial of subjects with severe PPH randomized to receive either a single dose 2 g fibrinogen or placebo.⁽⁴⁵⁾ Postpartum RBC transfusion was the primary outcome, and secondary outcomes included a composite outcome of ‘severe PPH’ that included transfusion of ≥ 4 units of RBCs, need for procedural intervention including embolization or hysterectomy, or maternal death. A total of 249 women were randomized, and RBC transfusion occurred in 25 (20%) of the fibrinogen group and 26 (22%) of the placebo group with no differences in any predefined secondary outcomes.⁽⁴⁵⁾

Prothrombin complex concentrates

Prothrombin complex concentrates (PCCs) are purified lyophilized coagulation factors that include coagulation factors II, VII, IX and X in variable concentrations depending upon the manufacturer.⁽⁴⁶⁾ The original PCCs first available in the United States were originally for hemophilia management and include Profilnine SD [Grifols, Barcelona, Spain], Bebulin VH [Baxter], and FEIBA (Factor Eight Inhibitory Bypassing Activity) VH [Baxter].⁽⁴⁶⁾ The first two PCCs contain low factor VII levels while FEIBA contains factor VII in an activated

form (VIIa). Bebulin contains heparin in low concentrations, and should not be administered if heparin-induced thrombocytopenia is suspected. For warfarin reversal, the four component PCCs contain all four vitamin K-dependent coagulation factors as well as proteins C and S, with minimal levels of antithrombin.(46) In the United States, there is only one four component PCC currently available (Kcentra, CSL Behring), however in other countries, this agent is called Beriplex P/N (CSL Behring, Marburg, Germany). This product also contains small concentrations of heparin. Other four component PCCs available in most countries include both Beriplex P/N and Octaplex (Octapharma, Vienna, Austria), and others is listed in table 1.(5, 46–48) Multiple international guidelines recommend the use of four component PCCs rather than plasma or fresh frozen plasma as a primary treatment for the emergent reversal of warfarin.(5) Advantages of PCCs for acute warfarin reversal include ease of storage, rapid INR correction, small infusion volume (~20 ml per 500IU), and viral inactivation and/or nanofiltration.(5) One report from the United Kingdom National Health Service suggested that PCCs for emergency warfarin reversal were more cost-effective than plasma.(49)

Kcentra, the only four component PCC available in the United States, is approved and indicated for the reversal of vitamin K antagonists in the setting of coagulopathy or bleeding and, therefore, can be administered when urgent surgery is required in patients taking warfarin. In other countries where four component PCCs have been widely available for many years, they are increasingly administered to facilitate factor repletion in managing bleeding in the perioperative setting and in the intensive care unit. A number of management algorithms for bleeding patients include PCC administration based on algorithms that include laboratory testing with or without point-of-care coagulation monitoring. However, in bleeding patients in the intensive care unit and other settings, a multimodal approach is important to include management of additional causes of bleeding such as hypofibrinogenemia, acquired platelet defects especially following extracorporeal circulation, thrombocytopenia, and importantly, considering surgical sources of bleeding. The increasing role of PCCs as part of coagulation treatment algorithms for bleeding in the perioperative setting and in the intensive care unit has become commonplace, but additional studies are important to further evaluate their efficacy and potential safety. However, in the patient with ongoing hemorrhage and bleeding, clinicians should always consider massive transfusion protocols with blood product administration in addition to potential adjunct therapies including PCCs.

In contrast to fibrinogen concentrate there are no randomized control trials of perioperative prothrombin complex concentrate use other than for the reversal of vitamin K antagonists. Details of an on-going study of FFP versus PCCs for the treatment of post cardiac surgical bleeding can be found at www.clinicaltrials.gov (NCT02557672). In the United States, four factor PCC is licensed only for reversal of vitamin K antagonists.

Recombinant activated factor VIIa

Although recombinant activated factor VIIa (rFVIIa, NovoSeven®, Novo Nordisk) was initially considered to be a potential universal procoagulant for non-hemophilia bleeding, increasing studies with randomized and placebo-controlled evaluation suggested this may

not be the case.(50) The effects of rFVIIa are based on tissue factor (TF) binding that occurs locally at the site of vascular injury. Once rFVIIa binds to TF, it catalyzes the Xase complex to initiate hemostasis and thrombin generation. Although rFVIIa has been extensively reported for nonhemophilia bleeding as a potential universal hemostatic agent for life-threatening hemorrhage, there is little efficacy in the multiple reports.(51) However, in selected cardiac surgical patients, efficacy has been demonstrated reducing bleeding, allogeneic blood transfusion requirement, and reexploration in the intensive care unit.(52) In one study, high-risk cardiac surgical patients who bled in the intensive care unit with chest tube drainage rates of > 200 ml/hr following cardiac surgery were randomized to placebo (n=68), 40 mcg/kg rFVIIa (n=35), or 80 mcg/kg rFVIIa (n=69). Fewer patients receiving rFVIIa group underwent a re-operation for bleeding (P=0.03) or required allogeneic transfusions (P=0.01) although the authors recommended caution due to an increase in the number of critical serious adverse events including stroke.(53) Other recommendations and guidelines for off-label use with life-threatening hemorrhage have been previously reviewed. (54, 55)

Controversy continues regarding the risk to benefit profile of rFVIIa and the efficacy for life-threatening hemorrhage. An FDA-MED-Watch database noted thromboembolic events in off-label use included 54% of the events as arterial thrombosis (e.g., stroke or MI).(56) Venous thromboembolism occurred in 56% of patients and was considered the cause in 72% of the 50 reported deaths. In a larger cohort of 4119 patients and 349 healthy volunteers, the thromboembolic event rate was 11.1%.(57) Only arterial thromboembolic event rates were higher following rFVIIa vs placebo (5.5% vs 3.2%) compared to venous thromboembolic events (5.3% vs 5.7%), and were higher among the elderly, likely reflecting the studies in intracranial hemorrhage.(57) Given the severity and seriousness of complications associated with rFVIIa we advocate for a multi-modal approach that addresses several components of coagulopathy prior to administration of highly active procoagulants such as rFVIIa.

In patients with major hemorrhage in the intensive care unit, additional factors should always be considered including management of potential bleeding sites, hypothermia, acidosis, and dilutional changes.(58) Patients following surgery, trauma or medically ill patients all may have acquired coagulopathy upon ICU admission, and multiple blood volumes may have been lost.

Massive transfusion coagulopathy is often initially managed by a standardized transfusion approach.(58, 59) However, many centers increasingly employ goal-directed therapy with the use of specific blood components or factor concentrates as therapeutic modalities.(29) When these patients are admitted to the intensive care unit, temperature, acid-base balance, and lactatemia should be first evaluated and treated.

Critical role of Multimodal therapy

Although fibrinogen and other coagulation factor concentrates are increasingly reported as important therapeutic agents for the hemorrhaging patients, therapy must be multimodal and include hemodynamic and hemostatic resuscitation with other components as needed. In addition to providing substrate for clot formation, there is increasing evidence about the role

of antifibrinolytics in trauma and surgical patients as previously mentioned, and TXA being the agent most often implicated from various studies.

Reversal of direct novel oral anticoagulants

Four novel direct oral anticoagulants (NOACs) are approved as anticoagulation agents for stroke prevention in patients with nonvalvular atrial fibrillation and venous thromboembolism. These include dabigatran (a direct thrombin inhibitor); and rivaroxaban, apixaban, and edoxaban (direct factor Xa inhibitors). Although bleeding is a complication of any anticoagulation agent, specific reversal agents, also known as antidotes, are being developed for the specific NOACs. Even though the risk of bleeding compared with vitamin K antagonists (e.g., warfarin) is decreased with the NOACs, strategies for managing bleeding and anticoagulation reversal continue to be established especially related to direct factor Xa inhibitors. For dabigatran, idarucizumab, a monoclonal Fab fragment that specifically binds to dabigatran to reverse its activity, is currently approved in many countries and approved for bleeding patients requiring emergency surgery or procedural interventions. (60) Andexanet, a Factor Xa decoy, is currently under investigation for emergency bleeding reversal. (61) However, andexanet only reverses rivaroxaban or apixaban for approximately three hours, and then the elimination of the molecule matches its normal renal and hepatic elimination.

There are reports of off-label PCC use for potential bleeding management in NOAC treated patients. No reports provide controlled evidence of efficacy. Reports include case studies, surrogate biomarker endpoints in healthy volunteers, and one study that used a bleeding endpoint to assess reversal.(47, 62) At least one registry trial is underway to assess outcomes in bleeding patients taking NOACs requiring urgent care and given PCCs or other agents. Most studies report significant restoration of thrombin generation for Xa inhibitors and less effect on prothrombin times. Part of the problem of bleeding patients taking antiXa agents is the ability to rapidly measure drug levels with the Xa inhibitors. Nevertheless, in one study in normal volunteers deliberately anticoagulated with rivaroxaban, in which serial antiXa levels were obtained, the infusion of 4-factor PCC failed to have any effect on anti-Xa levels compared with saline.(63) For dabigatran, the direct thrombin inhibitor, assessment of the anticoagulant effect is easier with more standard tests including partial thromboplastin times, thrombin times, and the most sensitive diluted thrombin times.(64, 65) There is no evidence that PCCs exert a reversal effect on dabigatran.

One of the most sensitive assays to determine restoration of hemostatic capability is a test called thrombin generation that uses a fluorometric assay based on tissue factor activation of either plasma and or platelet rich plasma. This critical test has been increasingly used in both experimental models as well as management of bleeding patients but is not readily available for clinical use at the time of this writing. Also, these tests have all been studied in volunteers to determine the ability of PCCs to restore thrombin generation. Overall, PCCs have the ability to restore thrombin generation in vitro in patients taking apixaban, edoxaban, and rivaroxaban. However, most doses of PCC and FEIBA tested increased thrombin generation over baseline values due to the relatively short half-life of the anticoagulation agents compared to the longer half-lives of the factors being infused. One

particular noteworthy study evaluated a 5 mm punch biopsy in healthy subjects receiving a single dose of 60 mg edoxaban. The authors noted that four factor PCC produced a dose-dependent reversal of edoxaban's effect on bleeding duration, bleeding volume, and thrombin generation and normalized values to baseline levels before anticoagulation using a 50 IU/kg dose of PCC.(62) However, the confidence intervals for duration of bleeding overlapped with the results following saline infusion.(62) The PT was only partially reversed and this is a consistent finding in all of the studies exploring PCCs as a potential reversal agent for antiXa agents.(62) In the volunteers who received PCCs, there were no safety issues and no thromboembolic events. Of particular importance, although the hemostatic challenge was only a 5 mm skin biopsy, this is the only study to evaluate an in vivo bleeding parameter associated with attempted NOAC reversal using a four factor PCC.(62)

Summary and opportunities for future investigation

Procoagulant therapies are critical therapeutic approaches for managing bleeding in an intensive care unit setting. Although allogeneic blood products and factor concentrates are used in managing bleeding and other coagulopathic states, PCCs, fibrinogen concentrates, and antifibrinolytic agents are included in bleeding algorithms especially using point of care testing. Although clinical trials are lacking, PCCs are increasingly being used off-label for treatment of bleeding, as part of transfusion algorithms, but also for factor repletion in bleeding patients in the intensive care unit. Further, in critically ill patients especially with preexisting ventricular dysfunction, the small volumes required for administration is another potential advantage. PCCs are part of bleeding management algorithms in other countries where PCCs have been available for many years, however additional randomized studies are needed. They are also the therapy of choice for acute warfarin reversal.

Although PCCs are increasingly used off-label for managing life-threatening bleeding with the oral antiXa agents, additional studies are needed to determine their potential efficacy beyond volunteer and in vitro studies. Although fibrinogen concentrates are used for hypofibrinogenemia outside of the United States, cryoprecipitate is still the mainstay of therapy in this country. Additional studies are needed comparing fibrinogen concentrates with cryoprecipitate when critically ill patients bleed as the two products are distinctly different. Although several recent cardiac surgical studies have failed to show the ability of fibrinogen to reduce bleeding and allogeneic blood transmission, any study targeting a single factor as a therapeutic target may be problematic due to the multiplicity for causes of bleeding. Additional studies evaluating approaches for managing bleeding in the intensive care unit setting are needed, and should include a multi-modal approach.

Acknowledgments

Conflict of Interest

JHL: serves on research steering committees or advisory boards for Boehringer-Ingelheim, CSL Behring, Grifols, Instrumentation Laboratories, Janssen, Leading Biosciences, and Pfizer.

KG: research support Octapharma.

QJQ: funding, NIGMS T32 GM08600, Duke University Medical Center. RRB: none.

IW: funding, NIH, Grant number: R01HL121232–01. Research support: CSL Behring, Fresenius, Terumo BCT, Zimmer-Biomet.

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Highlights

- Factor concentrates do not require cross matching, are highly purified, and are increasingly used for treating bleeding in critically ill patients
- Fibrinogen is a critical hemostatic protein that is the sole source for fibrinogen repletion in countries where cryoprecipitate is not available
- Prothrombin complex concentrates are approved for multiple indications but in the United States for reversal of warfarin for emergency bleeding and/or procedural interventions
- Prothrombin complex concentrates are increasingly used off label for bleeding based on specific transfusion algorithms often using viscoelastic metric analysis
- As part of multimodal strategies to treat bleeding anti-fibrinolytics should be considered in critically ill patients were bleeding

Table 1.

Variations in PCC composition^a.

	3F-PCC		4F-PCC					
	Behulin® (Baxter)	Profilnine (Grifols)	Proplex-T ^b (Baxter)	Beriplex P/N® (CSL Behring)	Kaskadil® (LFFB ^c)	Octaplex® (Octapharma)	Cofact® (Sanquin)	PPSB-HT Nichiyaku (Nihon)
Factor II	24–38	50	50	31	37	10–40	14–35	20
Factor VII	<5	n/a	400	16	10	10–40	7–20	20
Factor IX	24–38	60	100	29	25	20–31	25	20
Factor X	24–38	50	50	41	40	10–40	14–35	20
Protein C				35		10–40		15
Protein S				25		10–40		
Protein Z				36				
Antithrombin III				0.6			<0.6	
Heparin	<0.15 IU/IU FIX		<1.5	0.5	5	4–15	None	

3F-PCC, 3-factor PCC; 4F-PCC, 4-factor PCC; FIX, factor IX; IU, international units; PCC, prothrombin complex

^aComposition in international units/ml (IU/ml)

^bConcentration not specified

^cLFFB Laboratoire Français du Fractionnement et des Biotechnologies, France. From reference 47.